Potential Role of Combination Therapy with Sitagliptin, Metformin and Pioglitazone in Diabetes Management in Current Clinical Scenario

Content

Background and Objective of the Survey

Combination therapy with sitagliptin, metformin, and pioglitazone holds significant potential in the management of type 2 diabetes mellitus (T2DM) within the current clinical landscape. Each component of this triple therapy offers distinct mechanisms of action, collectively targeting multiple pathophysiological aspects of T2DM.

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, enhances glycemic control by inhibiting the degradation of incretin hormones, which stimulate glucose-dependent insulin secretion and suppress glucagon secretion. By increasing endogenous incretin levels, sitagliptin improves pancreatic beta-cell function and reduces postprandial glucose excursions.

Metformin, a biguanide, primarily reduces hepatic glucose production and enhances peripheral insulin sensitivity, leading to improved glucose utilization and decreased insulin resistance. It is considered a first-line therapy for T2DM due to its proven efficacy, safety profile, and cardiovascular benefits.

Pioglitazone, a thiazolidinedione, acts as an insulin sensitizer by activating peroxisome proliferator-activated receptor gamma (PPAR-γ) receptors, which regulate gene transcription involved in glucose and lipid metabolism. Pioglitazone improves insulin sensitivity in peripheral tissues, reduces hepatic glucose output, and may also have beneficial effects on cardiovascular risk factors such as lipid profiles and markers of inflammation.

The combination of sitagliptin, metformin, and pioglitazone offers complementary and synergistic effects in T2DM management. By targeting multiple pathophysiological defects underlying insulin resistance and impaired beta-cell function, this triple therapy provides comprehensive glycemic control, allowing for greater reductions in hemoglobin A1c (HbA1c) levels compared to monotherapy or dual therapy.

The objective of the survey is:

To evaluate the potential role of combination therapy with sitagliptin, metformin and pioglitazone in diabetes management in current clinical scenario

Methodology of the Survey

A survey was conducted to evaluate the potential role of combination therapy with sitagliptin, metformin and pioglitazone in diabetes management in current clinical scenario. A total of 150 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
- Sitagliptin
- Pharmacokinetic and Pharmacodynamic Profile and Adverse Drug Reactions
- Fixed dose combination of sitagliptin and metformin
- Trials Assessing Efficacy and Safety of Metformin and Sitagliptin
- Pioglitazone review
- Mechanisms by which pioglitazone may mediate its cardiovascular effects
- Anti-angiogenic, anti-proliferative and anti-inflammatory effects
- Pro-angiogenic and proliferative effects of pioglitazone
- Efficacy and safety of fixed dose combination of Sitagliptin, metformin, and pioglitazone in type 2 Diabetes (IMPACT study): A randomized controlled trial

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[1]

Globally, the prevalence of type 2 diabetes mellitus (T2DM) is on the rise. According to The International Diabetes Federation (IDF), it is projected that 783 million people will be diagnosed with T2DM globally by 2045. This progressive disease is characterized by multiple pathophysiologic abnormalities, including muscle insulin resistance, hepatic insulin resistance, adipocyte insulin resistance, progressive β-cell failure, apoptosis, increased α-cell secretion of glucagon, increased hepatic sensitivity to glucagon, reduced incretin effect due to β-cell resistance to glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), increased renal glucose production, elevated renal tubular glucose reabsorption, brain insulin resistance, and altered neurotransmitter dysfunction, leading to impaired appetite suppression and weight gain, which are collectively referred to as 'Ominous octet'. Recently, it was reported that insulin resistance in muscle and liver, along with β-cell failure, are the core pathophysiologic defects in T2DM. Several antidiabetic agents have been developed to target these defects, leading to improved glucose control in T2DM.

Metformin is commonly used as a first-line therapy, but over time, it often fails to maintain adequate glycemic levels. It has been observed that treatment with a single antihyperglycemic agent is often unsuccessful in achieving and/or maintaining long-term glycemic control in patients with T2DM, leading to the need for combination therapies. Different classes of drugs include thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium-glucose linked transporter-2 inhibitor, GLP-1 receptor agonist, and basal insulin, target different pathways to address the multiple pathophysiology of T2DM. These are recommended in combination with metformin to improve efficacy.

Metformin prevents hepatic gluconeogenesis and glycogenolysis, increases liver and peripheral tissue sensitivity to glucose, and lowers Hb1Ac levels. Sitagliptin, a DPP-4 inhibitor, can raise blood levels of biologically active incretins, stimulating the release of insulin and attenuating the release of glucagon, primarily in response to a meal, which reduces glucose production in a glucose-dependent manner. One of the thiazolidinediones, pioglitazone, is a peroxisome proliferator-activated receptor γ (PPAR-γ) agonist that increases insulin sensitivity by

improving insulin-mediated glucose elimination, leading to decreased plasma insulin concentrations. It has also been demonstrated to improve β-cell responsiveness and increase β-cell function, suggesting that it may have an essential impact on reducing hepatic glucose production. Thus, pioglitazone is commonly used as an add-on medication when metformin, DPP-4 inhibitors, GLP-1 analogs, or their combination do not achieve the desired glycemic target.

Both pioglitazone and sitagliptin efficacy and safety have been well documented, proving that similar antidiabetic effects with distinct mechanisms of action may help to target various facets of ominous octet. Furthermore, the addition of pioglitazone alongside metformin and sitagliptin in triple oral therapy has been effective in glycemic control, addressing insulin resistance and islet β-cell dysfunction, which are the core defects in T2DM. The advantage of combination therapy is that it helps to minimize the adverse effects of high-dose monotherapy and effectively control glycemic levels. Recently, the usage of a fixed-dose combination (FDC) has expanded due to the high compliance and cost-effectiveness of oral hypoglycemic agents.

Sitagliptin[2]

The ever-increasing burden of type 2 diabetes mellitus (T2DM) and inadequate control in the majority of patients has led to a quest for newer therapeutic options. There have been recent exciting advances in the treatment of T2DM, targeting the enteroinsular axis with incretin-based therapies that include the dipeptidyl peptidase IV (DPP-IV) inhibitors. Sitagliptin (MK-0431 [(2R)-4-oxo-4-(3-[trifluoromethyl]-5,6-dihydro[1,2,4]triazolo[4,3-a]-pyrazin-7[8H]-yl)-1-(2,4,5-trifluorophenyl) butan-2-amine]) is an orally active, potent and selective inhibitor of DPP-IV.

Pharmacokinetics and pharmacodynamics[2]

Plasma sitagliptin is well absorbed, with an oral bioavailability of about 87%. The administration of food before dosing showed no significant difference in peak drug levels. Area under the plasma time--concentration curve (AUC) increased dose proportionally over the dose range studied (1.5 -- 600 mg). The half-life for sitagliptin is ~ 8 -- 14 h. Median time to maximal concentration in plasma values (Tmax) across doses ranged from 1 to 6 h. A trend towards a shorter Tmax was noted with increasing sitagliptin dose. Sitagliptin is predominantly cleared

by the kidney, with ~ 80 -- 87% of the drug excreted unchanged in urine. Sitagliptin is probably actively secreted since the renal clearance of sitagliptin is 388 ml/min, much higher than the normal glomerular filtration rate. Approximately 2.3-, 3.8- and 4.5-fold exposure was demonstrated in patients with moderate (creatinine clearance (CrCl) 30 -- 49 ml/min) and severe (CrCl < 30 ml/min) renal insufficiency and end-stage renal disease (ESRD) on dialysis respectively. Dose adjustment of 50 mg daily in patients with moderate renal insufficiency and 25 mg daily in those with severe renal dysfunction or ESRD has been recommended.

About 16% of the drug is metabolized by the liver. A study looking at the pharmacokinetics of sitagliptin in moderate hepatic dysfunction (Child--Pugh's scores ranging from 7 to 9) compared with healthy control subjects found that the mean AUC and Cmax for sitagliptin were numerically, but not significantly, higher in patients with moderate hepatic insufficiency compared with healthy matched control subjects. There was no statistically significant effect on the Tmax, half-life or fraction of the oral dose excreted into urine and renal clearance of sitagliptin. Sitagliptin was well tolerated in this patient population.

Sitagliptin is not a substrate, inducer or inhibitor for cytochrome P450. Age, sex and obesity did not impact the pharmacokinetics of sitagliptin in healthy subjects. Phase I studies in normoglycemic volunteers and patients with diabetes provided proof of predicted pharmacologic characteristics for sitagliptin in humans. Near-maximal glucose-lowering efficacy after single oral doses of sitagliptin was associated with inhibition of plasma DPP-IV activity of ‡ 80%, which occurred at plasma sitagliptin concentrations of ‡ 100 nmol and an augmentation of active GLP-1 and GIP levels of twofold or higher. When the assay is corrected for plasma dilution, the level of DPP-IV inhibition is estimated to be ~ 96%. This degree of DPP-IV inhibition occurred at doses of ‡ 100 mg over a 24-h period, supporting the use of a 100-mg once-daily dosing regimen.

Clinical efficacy[2]

Phase II studies

The safety and efficacy of different doses of sitagliptin were compared with placebo in randomized controlled trials and are summarized in Table 1.

Table 1. Phase II trials.

Study	Baseline therapy	Intervention	Duration (weeks)	n	Average baseline A1c (%)	A1c change (%) compared to placebo	Weight change compared to placebo
Scott, 2007 [56]	Diet and exercise	Sitagliptin 5 – 50 mg b.i.d. Glipizide 5 – 20 mg/day Placebo	12	743	7.9	-0.38 (5 mg) to 0.77 (50 mg b.i.d.) -1 (glipizide)	No significant change (sitagliptin) +1.3 kg (glipizide)
Hanefeld, 2007 [57]	No treatment or drug washout	Sitagliptin 25, 50, 100 mg/day Sitagliptin 50 mg b.i.d. Placebo	12	555	7.7	-0.39 (25 mg) to -0.56% (100 mg)	No significant change
Nonaka, 2008 [58]	Diet and exercise; drug washout	Sitagliptin 100 mg/day Placebo	12	151	7.6	-1.06	-0.7 kg

Phase III studies

Sitagliptin has been evaluated in a number of trials as monotherapy and combination therapy.

In a 24-week, randomized, double-blind study, 1091 drug-naive patients with a mean baseline HbA1c of 8.8% on diet and exercise were randomized to sitagliptin 100 (S100), metformin 1000 or 2000 mg (M1000/M2000), metformin in combination with sitagliptin, or placebo. The placebo-subtracted HbA1c change from baseline was -2.07% (S100/M2000), -1.57% (S100/M1000), -1.30% (M2000), -0.99% (M1000) and -0.83% (S100). The incidence of gastrointestinal adverse experiences as well as amount of weight loss for combination therapy was similar to that with metformin monotherapy at the same dose. There was additive glycemic improvement with the combination therapy with no increase in the adverse events.

Migoya et al. demonstrated that metformin increases total GLP-1 plasma concentrations, possibly by enhancing GLP-1 secretion from enteroendocrine L-cells, while sitagliptin inhibits the degradation of active GLP-1. Thus, the combination of a DPP-IV inhibitor and metformin results in additive increases in active GLP-1 concentrations.

Long-term safety and efficacy of adding sitagliptin or glipizide to ongoing metformin therapy were established in a study with 1072 patients who were randomized to receive sitagliptin or glipizide. After 2 years, the change in HbA1c from baseline of 7.3% was -0.54% with sitagliptin (n = 248) and -0.51% with glipizide (n = 256). The rise in HbA1c from week 24 to week 104 (coefficient of durability; COD) was smaller with sitagliptin (COD (95% CI) 0.16%/year) compared with glipizide (0.26%/year).

A 26-week parallel-group, open-label trial involving patients with T2DM on metformin (‡ 1500 mg daily for ‡ 3 months) with HbA1c between 7.5 and 10.0% evaluated the efficacy of liraglutide and sitagliptin. Change in HbA1c was -1.50% and -1.24% with 1.8-mg and 1.2-mg doses of liraglutide respectively, compared with -0.90% with sitagliptin. Nausea was more common with liraglutide (27% patients on 1.8 mg and 21% on 1.2 mg) than with sitagliptin (5%). There was no difference in the incidence of hypoglycemia between the groups.

In a double-blind, cross over, randomized study with exenatide and sitagliptin in metformin-treated patients, reduction in fasting glucose was similar in the two groups (-15 +/- 4 mg/dL vs. -19 +/- 4 mg/dL) while 2-h postprandial was lower with exenatide compared to sitagliptin (133 +/- 6 mg/dL vs. 208 +/- 6 mg/dL). Exenatide significantly improved the insulinogenic index of insulin secretion, reduced postprandial triglycerides, slowed gastric emptying and reduced total caloric intake compared to sitagliptin. The incidence of nausea and vomiting in the sitagliptin group was 12% and 3% compared to 34% and 24% in the exenatide group.

In a 26-week randomized, double-blind, double-dummy superiority trial in patients treated with metformin, treatment with exenatide once weekly achieved HbA1c reduction of -1.5% from mean baseline of 8.5, compared to -0.9% for sitagliptin and -1.2% for pioglitazone. Change from baseline weight was -2.3 kg with exenatide, -0.8 kg with sitagliptin and +2.8 kg with pioglitazone. Significant hypoglycemia was not reported in any of the groups. Nausea and diarrhea were the most common side effects, with a greater number reported for exenatide (24 and 18%) compared with sitagliptin (10 and 10%).

The superior glucose lowering with the GLP-1 receptor agonists is believed to be due to the pharmacologically high levels of receptor agonism achieved, with concentrations six- to tenfold that of physiological GLP-1 in addition to slowed gastric emptying. DPP-IV inhibitors, by contrast, achieve a more modest twofold augmentation of GLP-1 levels with sitagliptin and do not significantly impact gastric emptying.

Pharmacokinetic and Pharmacodynamic Profile and Adverse Drug Reactions[3]

Sitagliptin

Sitagliptin is well absorbed orally and has a bioavailability of 87%. There is dose dependent inhibition of DPP-4 activity, and almost 80% of enzyme activity is inhibited for 24 hours at 100 mg.[,] Maximum DPP-4 inhibition is noticed at 100 mg/day dosing, with no additional suppression at 200 mg/day. Sitagliptin has minimal effects on cytochrome P450 enzymes and hence does not appear to have any clinically significant interactions with other medications. Sitagliptin undergoes marginal metabolism in the body and is excreted in the urine by active tubular secretion. Renal function should be monitored during treatment and the dose reduced in modest or severe renal insufficiency, with 50 mg for patients with creatinine clearance of 30 to 50 mL/minute and 25 mg for creatinine clearance <30 mL/minute. Sitagliptin is overall well tolerated. However, in a Cochrane review, a significant increase in all cause infections was described. There have been no reports of severe hypoglycemia with sitagliptin, although headache has been reported more frequently compared with placebo. Interestingly, the Cochrane review suggested that although sitagliptin was not found to cause weight gain, there was more weight loss with placebo treatment.

Pancreatitis has been reported to be increased in patients taking sitagliptin. However, a causal relationship between sitagliptin and pancreatitis has not been established. In a recent large population-based case-control study of type 2 diabetes, the use of incretin-based therapies, including sitagliptin, was reported to be associated with an increased rate of hospitalization secondary to acute pancreatitis. Although a statistical adjustment was made for potential confounders, the groups of incretin therapy users and nonusers were poorly matched. A further concern related to incretin-based therapies is that of premalignant changes in pancreas tissue. These data, which have been subject to some criticism, require validation.[,] A recent joint statement from the ADA/EASD/International Diabetes Federation (IDF) reported that there was insufficient evidence to change existing treatment recommendations and that patients currently on incretin-based therapies should continue to take them as prescribed by their health care professional.

Finally, during the postmarketing surveillance of sitagliptin, allergic reactions including angioedema and exfoliative dermatological reactions such as Stevens-Johnsons syndrome were reported, typically within 3 months of starting treatment. Other common adverse effects reported are nasopharyngitis and upper respiratory tract infections.

Metformin

Metformin is administered orally, demonstrates 50% to 60% bioavailability, and its absorption is reduced and delayed with food. It has a half-life of approximately 6.2 hours and is usually administered 2 to 3 times a day. Almost 85% of the maximal glucose-lowering effect is seen at a dose of 500 mg 3 times daily, but patients may be prescribed up to 2000 mg/day. Metformin is not significantly plasma protein bound and is not metabolized in the body. It is eliminated unchanged in urine by filtration and active tubular secretion, and dose reduction is recommended in renal impairment. Lactic acidosis is a rare but potentially fatal complication of metformin treatment, mainly reported in patients with severe renal insufficiency and those given iodinated contrast medium.[,] Drug interactions have been reported with cimetidine, which increases metformin levels by 40% to 60%, by reducing its renal clearance.[,] There is also the possibility of interactions with cationic drugs such as digoxin and morphine, as they also undergo renal elimination by tubular secretion. Usual side effects of metformin treatment are gastrointestinal, including nausea, vomiting, diarrhea, abdominal discomfort, and flatulence, which become tolerable over time and can be decreased by administering the drug with food.

Fixed dose combination of sitagliptin and metformin[3]

Metformin and sitagliptin have independent glucose lowering properties and may increase GLP-1 levels by working through complementary mechanisms. They also have few pharmacological interactions and a low risk of hypoglycemia, making coadministration an attractive therapeutic prospect. FDC tablets are available in doses of 50 mg sitagliptin + 500 mg metformin or 50 mg sitagliptin + 1000 mg metformin. In a randomized, open-label, 2-part, 2-period crossover study, bioequivalence between FDC and coadministration of corresponding doses of sitagliptin and metformin was established in 48 nondiabetic subjects supporting the efficacy and safety of fixed dose combination treatment. In a placebo-controlled, multipledose, crossover trial in 13 patients with type 2 diabetes, steady state pharmacokinetics of sitagliptin and metformin were not altered by their coadministration, and no drug-related adverse effects were reported. Currently, there are no trials comparing the effect of FDC of sitagliptin and metformin on patient compliance although it might be expected that treatment with an FDC could improve patient compliance compared with treatment with separate agents. Studies comparing patient compliance for FDC with separate coadministration of metformin and glyburide generally report improved treatment adherence when patients were changed from

combination of free doses to FDC.[2] The product information for the FDC advises precaution against lactic acidosis for the metformin component and pancreatitis for the sitagliptin.

Trials Assessing Efficacy and Safety of Metformin and Sitagliptin[3]

Fixed dose combinations (FDCs)

There are 3 trials in which the FDC of sitagliptin and metformin was assessed (Table 1).

Table 2. Efficacy and safety of sita/met fixed dose combination versus comparators.

Treatment (no. of participants)	**Baseline HbA_{1c} In %**	**Change in HbA_{1c} In %**	**Other key efficacy end points**	**Hypoglycemia**	**Significant adverse events**
Sita/Met 50/500 BD to Sita/Met 50/1000 BD (560) or	9.9	−2.4	Fasting glucose, Proinsulin/insulin ratio, HOMA-β, HOMA-IR, lipids	Sita/Met: 2.1% Met: 1.8%	AP: Sita/Met: 1.1%, Met: 3.9% D: Sita: 12%, Met: 16.6%
Met 500 mg BD to Met 1000 mg BD (566)	9.8	−1.8			
Phase A (12 weeks, 492)			Fasting glucose, post-prandial glucose, HOMA-β, lipids	Sita/Met: 2.3% Pio: 2.2%	Edema: Sita/Met: 0.9%, Pio: 6.1%
Sita100 mg OD (244) or	9.0	−1			
Pio 15 mg OD (248)	9.1	−0.9			
Phase B (28 weeks, 455)					
Sita/Met 50/1000 mg BD (224) or		−1.7			

Pio 45 mg OD (231)		−1.4			
Sita/Met 50/500 BD to Sita/Met 50/1000 BD (261) or	8.9	−1.9	Fasting glucose, post-prandial glucose, Fasting and post-prandial proinsulin/insulin, HOMA-β, HOMA-IR, QUICKI, lipids	Sita/Met: 8.4% Pio: 4.3%	D: Sita/Met: 25.3%, Pio: 4.3% N: Sita/Met: 4.6%, Pio: 1.2% V: Sita/Met: 1.9%, Pio: 0%
Pio 30 mg OD to 45 mg OD (256)	8.9	−1.4			

Abbreviations: Sita, Sitagliptin; Met, Metformin; Pio, Pioglitazone; D, Diarrhea; N, Nausea; V, Vomiting; AP, Abdominal pain; OD, once daily; BD, twice daily.

In the study by Reasner et al, FDC of sitagliptin/metformin (sita/met) 50/1000 mg twice daily was compared with metformin 1000 mg twice daily as the initial treatment in patients aged 18 to 78 years with type 2 diabetes for more than 3 years and a mean HbA_{1c} of 9.8%. The primary end point was the effect of 18 weeks of treatment on mean HbA_{1c}, safety, and tolerability. In the study, 484 subjects in the sita/met FDC group and 482 patients in the metformin group completed the protocol. Reduction in HbA_{1c} was 2.4% (95% confidence interval [CI], −2.5 to −2.2) from baseline of 9.9% with sita/met FDC, which was significantly greater than the 1.8% (95% CI, −0.8 to −0.4) from baseline HbA_{1c} of 9.8% with metformin alone. This difference was consistent across all subgroups defined by age, gender, baseline body mass index (BMI), and duration of type 2 diabetes. Around 49% of patients on combination treatment achieved a target HbA_{1c} of <7% compared with 34% on metformin alone. Improvement in HbA_{1c} was greater in patients with a higher HbA_{1c} at baseline. There was also a greater reduction in fasting plasma glucose with the combination treatment (−3.8 mmol/L with combination and −3.0 mmol/L with metformin monotherapy). There was also a significant improvement in β-cell function, as measured by the homeostatic model assessment β (HOMA-β), a surrogate marker of insulin secretion derived from simultaneous blood glucose and insulin levels, with sita/met

FDC compared with metformin monotherapy. At week 18, body weight was reduced by 1.6 kg in both groups. Weight loss was progressive until 12 weeks with a plateau between 12 and 18 weeks. Both sita/met FDC and metformin resulted in small improvement in total cholesterol, HDL cholesterol, triglyceride, and non-HDL cholesterol, and the changes were comparable between groups.

The incidence of hypoglycemia was low and similar in the FDC and monotherapy groups. Overall, gastrointestinal side effects were observed in 20.6% of patients on FDC and 24.6% patients on monotherapy. Diarrhea was the most common gastrointestinal side effect reported, and the incidence was significantly lower in the FDC group. A similar trend was observed for abdominal pain.

In the study by Perez-Monteverde et al, efficacy and safety of FDC of sita/met was compared with pioglitazone in patients who had moderate to severe hyperglycemia. Patients aged 18 to 78 years, with inadequate glycemic control, HbA_{1c} of 7.5% to 12%, and drug naïve within the previous 3 months and not more than 4 weeks cumulatively in the previous 3 years, were randomized to receive for 12 weeks, either sita 100 mg daily or pioglitazone 15 mg daily, titrated up to 30 mg daily after 6 weeks. In the second phase of the trial, patients who had inadequate glycemic control at the end of 12 weeks were switched to sita/met 50/1000 mg FDC twice daily, if they were on sitagliptin and to pioglitazone 45 mg daily if they were on pioglitazone and studied up to week 40. The improvement in HbA_{1c} was comparable between sitagliptin −1.0% (95% CI, −1.2 to −0.9) from a baseline HbA_{1c} of 9% and with pioglitazone −0.9% (95% CI, −1.0 to −0.7) from a baseline HbA_{1c} of 9.1% at the end of 12 weeks of treatment. In both groups, greater benefit was observed in patients with a higher baseline HbA_{1c}. At the end of the second phase of the study, a significantly greater improvement in HbA_{1c} from baseline was observed in the 187 patients in the sita/met FDC group (−1.7%) compared with 200 patients in the pioglitazone group (−1.4%). Similarly, greater improvement was seen with the sita/met FDC for fasting plasma glucose (−2.5 mmol/L with sita/met FDC vs. −2.1 mmol/L with pioglitazone) and 2 hour postmeal glycemia (−5 mmol/L with sita/met FDC vs. −3.8 mmol/lL with pioglitazone). There was a significant improvement in β-cell function (HOMA-β) and proinsulin-insulin ratio with sita/met FDC compared with pioglitazone. There was no change to total and LDL cholesterol in the sita/met FDC group, while an increase was reported with pioglitazone, resulting in a significant difference between groups. The change in triglyceride and HDL cholesterol was not different between groups.

At the end of week 40, although there were higher numbers of adverse events in the sita/met FDC group, this was not significantly different from the pioglitazone group. Gastrointestinal side effects including diarrhea, nausea, vomiting, and abdominal pain were not significantly different between treatment groups (9.5% with FDC of sita/met and 10.9% with pioglitazone). The incidence of edema was significantly higher with pioglitazone (0.9% with sita/met FDC and 6.1% with pioglitazone). Indeed, patients on pioglitazone gained 3.4 kg in body weight while patients on FDC of sita/met lost 1.1 kg. Symptomatic hypoglycemia was rare in both treatment groups, and severe hypoglycemia was not reported. Although biochemical adverse event occurrence of raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was seen in the sita/met FDC group, the change was only mild to moderate, and discontinuation or interruption of treatment was not necessary.

In the study by Wainstein et al, efficacy and safety of FDC of sita/met 50/1000 mg twice daily was compared with pioglitazone 45 mg per day after 32 weeks of treatment. Studied were patients with type 2 diabetes between 18 and 78 years and HbA_{1c} of 7.5% to 12% who were not on any oral antidiabetics (OAD) in the 3 months prior to screening and not more than 4 weeks cumulatively in the previous 3 years. At the end of 32 weeks, the least squares mean change from baseline in HbA_{1c} was significantly lower in both treatment groups. In the 210 patients completing treatment (of 261 recruited) in the sita/met FDC group, HbA_{1c} improved by 1.9% (95% CI, −2.0 to −1.7) from a baseline HbA_{1c} of 8.9%, while in the 204 patients completing treatment (of 256 recruited) in the pioglitazone group, HbA_{1c} improved by 1.4% (95% CI, −1.5 to −1.3) from a baseline HbA_{1c} of 8.9%. In the population of patients with an $HbA_{1c} \geq 10\%$, there was significantly greater reduction of HbA_{1c} from baseline with sita/met FDC than with pioglitazone. The reduction of HbA_{1c} with sita/met FDC was more rapid than with pioglitazone. There was also more rapid and sustained reduction in fasting plasma glucose with maximal effect by 4 weeks with sita/met FDC (−3.1 mmol/L) compared with pioglitazone (−2.4 mmol/L). There was also a more significant improvement in the 2-hour postmeal glucose with sita/met FDC (−5.7 mmol/L) than with pioglitazone (−4.6 mmol/L). In the sita/met FDC group, there was a more significant decrease from baseline in the fasting pro-insulin/insulin ratio and increase from baseline in HOMA-β. However, there was greater reduction from baseline in insulin resistance measured as homeostasis model assessment-insulin resistance (HOMA-IR) and increase from baseline in insulin sensitivity, measured as quantitative insulin sensitivity check index (QUICKI) with pioglitazone. Unlike the previous trial, fasting total

cholesterol, LDL cholesterol, and triglycerides were not changed from baseline with sita/met FDC but were reduced following treatment with pioglitazone.

There were numerically more adverse effects with sita/met FDC, mainly from a significantly higher incidence of gastrointestinal side effects including, diarrhea, nausea, vomiting, and abdominal pain/discomfort (25.6% with sita/met FDC and 14.3% with pioglitazone). The incidence of hypoglycemia, although numerically higher with sita/met FDC, was not statistically significant. Similar to the previous study, there was no report of severe hypoglycemia. A significantly higher rate of peripheral edema was seen in the pioglitazone group (7% with pioglitazone and 1.1% with sita/met FDC). Similar to the previous study, patients on pioglitazone gained 3.0 kg in body weight while those on sita/met FDC lost 1.4 kg. Patients on the FDC lost most of the weight in the first 8 weeks of treatment with a more gradual decline over the remainder of the treatment period. A mild increase in ALT levels was reported in 3 patients in the sita/met FDC group compared with none in the pioglitazone group. Of the 3 cases reported, ALT was >3 times upper limit of normal in 1 subject who was discontinued from the study, and levels settled within 7 days of stopping the study drug.

Dual therapy

In addition to the trials with sita/met FDC, there have been trials where coadministration of metformin and sitagliptin as dual therapy has been compared against either monotherapy with metformin or with metformin alongside another agent such as glipizide, rosiglitazone, saxagliptin, or exenatide (Table 2).

Table 3. Efficacy of dual therapy versus comparators.

Treatment (no. of participants)	**Baseline HbA_{1c} In %**	**Change in HbA_{1c} In %**	**Other key efficacy end points**	**Hypoglycemia**	**Significant adverse events**
1. Sita: 50 + Met: 500 BD (183), or	8.8	−1.4	Fasting glucose, proinsulin/insulin ratio, post-meal	1. 2.2%	1. GI: 24.7%*

2. Sita: 50 + Met 1000 BD (180), or	8.8	−1.9	glucose, HOMA-β, HOMA-IR, lipids	2. 1.1%	2. GI: 17.9%
3. Sita: 100 OD (178), or	8.9	−0.66		3. 1.1%	3. GI: 25.3%
4. Met: 500 BD (179), or	8.9	−0.82		4. 0.5%	4. GI: 15.9%
5. Met: 1000 BD (179), or	8.7	−1.13		5. 0.6%	5. GI: 15.1%
6. PL: (169)	8.7	0.17		6. 0.6%	6. GI: 10.8%
1. Sita: 50 + Met: 500 BD (101), or		−1.4	Fasting glucose, proinsulin/insulin ratio, post-meal glucose, HOMA-β, HOMA-IR, lipids	1. 2.6%	1. GI: 29.5%*
2. Sita: 50 + Met 1000 BD (98), or		−1.7		2. 4.9%	2. GI: 33%
3. Sita: 100 OD (65), or		−1.2		3. 1.1%	3. GI: 20.7%
4. Met: 500 BD (80), or		−1.1		4. 1.6%	4. GI: 20.9%
5. Met: 1000 BD (95)		−1.3		5. 2.2%	5. GI: 33%
1. Sita 100 + Met ≥ 1500 OD (464), or	7.96	−0.67	Fasting glucose, proinsulin/insulin ratio, post-meal glucose, HOMA-β, HOMA-IR, QUICKI	1. 1.3%	No significant difference including GI side effects
2. Met ≥ 1500 + PL (237)	8.03	−0.02		2. 2.1%	
1. Met ≥ 1500 + PL (94), or	9.1	0	Fasting glucose, Post-meal glucose, HOMA-β, HOMA-IR, QUICKI, lipids	1. 0%	No significant difference including GI side effects
2. Met ≥ 1500 + Sita	9.3	−1		2. 1%	

100 mg OD (96)					
Phase A (24 weeks)			Fasting glucose, lipids	Phase B	Change in body weight:
1. Met ≥ 1500 + PL (237), or	8.0	−0.7%		1. 1.7%	1. −0.9 Kg
2. Met ≥ 1500 + Sita 100 OD (464)	8.0	−0.9%		2. 13%	2. +1.5 Kg
Phase B (to 54 weeks)					AP:
1. Met + Sita 100 OD (for Sita, 391), or	7.9				1. 20%
2. Met + Glip up to 20 mg OD (for placebo, 164)	7.9				2. 5.1%
1. Met ≥ 1500 + Sita 100 mg OD (386), or	7.6	−0.51%	Fasting glucose, proinsulin/insulin ratio, HOMA-β, HOMA-IR, QUICKI	1. 5%	Change in body weight: 1. −1.5 Kg 2. +1.1 Kg
2. Met ≥ 1500 + Glip up to 20 mg OD (412)	7.7	−0.56%		2. 32%	1. F: 3.1% 2. F: 0.9% 1. Dizz: 3.7% 2. Dizz: 2.1%
1. Met ≥ 1500 + Sita 100 mg OD (94), or	7.8	−0.73	Fasting glucose, proinsulin/insulin ratio, post-meal glucose, HOMA-	1. 1%	1. E: 1% 2. E: 5% 3. E: 1% 1. GI: 9%

2. Met ≥ 1500 + Rosi 8 mg OD (87), or	7.7	−0.79	β, HOMA-IR, QUICKI, lipids	2. 1%	2. GI: 7% 3. GI: 9%
3. Met > 1500 + PL (92) OD	7.7	−0.22		3. 2%	
1. Met 1500–3000 + Sita 100 OD (374), or	7.7	−0.62	Fasting glucose, fasting insulin, C-peptide, glucagon, HOMA-2β	–	In both groups: Nasopharyngitis (4%), UTI (5.3%–5.7%), Influenza (5.7%–5.8%)
2. Met 1500–3000 + Saxa 5 OD (365)	7.7	−0.52			
1. Met 1500–2000 + Exen 2/wk + PL (160), or	8.6	−1.5	Fasting glucose, blood pressure, lipids, quality of life	1. 1%	Change in body weight: 1. −2.3 Kg 2. −0.8 Kg 3. +2.8 Kg
2. Met 1500–2000 + Sita 100 OD + PL (166), or	8.5	−0.9		2. 3%	1. N/D: 24%/18% 2. N/D: 10%/10% 3. N/D: 5%/7%
3. Met 1500–2000 + Pio 45 OD + PL (165)	8.5	−1.2		3. 1%	4. E: 8%

Abbreviations: GI, Gastrointestinal—including abdominal pain, nausea, vomiting; PL, Placebo; AP, Abdominal pain; F, Fatigue; Dizz, Dizziness; E, Edema; N, Nausea; D, Diarrhea; Glip, Glipizide; Rosi, Rosiglitazone; Saxa, Saxagliptin; Exen, Exenatide; Pio, Pioglitazone.

The trial by Goldstein et al was a double-blind placebo-controlled study of 1091 patients with type 2 diabetes for a mean duration of 4 years, aged 18–78 years, a mean HbA1C of 8.8% (range 6.3%–11.9%) with or without treatment with OADs. Patients were randomized to receive 1 of 6 treatment regimens: sitagliptin 100 mg + metformin 1000 mg (sita100/met1000), or sitagliptin 100 mg + metformin 2000 mg (sita100/met2000), or metformin 1000 mg (met1000), or metformin 2000 mg (met2000), or sitagliptin 100 mg (sita100) or placebo daily for 24 weeks. Patients already on OADs were allowed a wash out period, while others were allowed direct entry after comparable run in periods. The efficacy of treatment, measured as placebo-adjusted reduction in HbA_{1c} (−1.4% in sita100/met1000, −1.9% in sita100/met2000) and proportion of patients achieving HbA_{1c} < 7% (66% in sita 100/met2000, 43% in sita100/met1000, 38% in met2000, 23% in met1000, 20% in sita100, and 9% in the placebo group) was significantly greater in the coadministration groups compared with respective monotherapy groups. Also the magnitude of response on HbA_{1c} with combination drugs was additive compared with the effects with each individual treatment. There was a significant improvement in fasting plasma glucose with coadministration compared with monotherapy. There was a significant improvement in β cell function, measured as HOMA-β and insulin resistance, measured as HOMA-IR with combination treatment.

The combination treatment was deemed safe, as the serious adverse events rate with combination treatment was comparable to placebo. The incidence of hypoglycemia was low and similar across all treatment groups. Gastrointestinal side effects including diarrhea, nausea, abdominal pain, and vomiting were related to the dose of metformin, both with monotherapy and coadministration. Loss of weight was observed in all treatment groups except monotherapy with sitagliptin.

Following the initial trial, an additional 885 patients (161 in sita100/met2000, 160 in sita100/met1000, 153 in met2000, 147 in met1000, and 141 in sita100) continued into a 30-week continuation period. At the end of 54 weeks, least squares mean changes in HbA_{1c} from baseline were −1.8% in sita100/met2000, −1.4% in sita100/met1000, −1.3% in met2000, −1.0% in met1000, and −0.8% in sita100. HbA_{1c} was substantially reduced with both low and high dose combination treatment at 54 weeks. Although the improvement in HbA_{1c} continued through 24 weeks, in most treatment groups, a nadir was seen at week 30. The improvement was greater for subjects with a higher baseline HbA_{1c}. Similar to the results at 24 weeks, improvement was seen at 54 weeks in fasting and postprandial glucose and HOMA-β, with

larger improvement in coadministration groups. Weight was reduced in all treatment groups except sitagliptin monotherapy.

Five hundred and seventeen patients completed a further 50 week extension study. At the end of 104 weeks the improvement in HbA_{1c} was preserved in all treatment groups (−1.7% in sita100/met2000, −1.4% in sita100/met1000, −1.3% in met2000, −1.1% in met1000 and −1.2% in sita100). The improvement with high dose coadministration was larger than monotherapy with either single agent. Both coadministration and monotherapy had similar adverse effect profile.

The trial by Charbonnel et al was a double-blind placebo-controlled study in which 701 patients aged 18 to 78 years with type 2 diabetes, mean duration of 6.2 years, with mild to moderate hyperglycemia (mean HbA_{1c} 8%, range 6.4%–11.0%) while taking metformin at 1500 mg/day were randomly assigned to receive sitagliptin 100 mg/day (464 patients) or placebo (237 patients) for 24 weeks. Patients on other OADs were changed over to metformin monotherapy with dose titration and eventually established on 1500 mg/day. Sitagliptin was found to be more efficacious compared with placebo at the end of 24 weeks. There was an improvement in the primary end point, HbA_{1c} (−0.67%, −0.77% to −0.57%, *P* 0.001 from baseline) with sitagliptin compared with placebo. There was also a significant increase in patients achieving a HbA_{1c} < 7% (47% vs. 18.3%, $P < 0.001$) and a significant improvement in fasting plasma glucose (−1.4, −1.7 to −1.1, $P < 0.001$) from baseline with sitagliptin at 24 weeks. There was also a significant improvement in fasting insulin, fasting C-peptide, and β cell function measured as HOMA-β ($P < 0.001$). No significant effect was seen with sitagliptin on insulin resistance measured as HOMA-IR, although it resulted in a significant increase in the measure of insulin sensitivity (QUICKI). In the patients treated with sitagliptin, there was a significant decrease in plasma glucose, with an increase in C-peptide 2 hours after a standard meal. The study also investigated the effect of treatment on lipid profile. There was a statistically significant decrease in total cholesterol and triglycerides and increase in HDL cholesterol with sitagliptin compared with placebo while LDL cholesterol levels were unaffected. Rates of discontinuation of treatment for adverse effects and gastrointestinal side effects were similar in both groups. Some nonspecific side effects including nasopharyngitis, urinary tract infection, arthralgia, back pain, and cough were reported more commonly with sitagliptin, although the overall incidence was small. Weight loss was observed in both groups and not statistically significant between sitagliptin and placebo.

In the study by Raz et al, 159 patients with type 2 diabetes with HbA_{1c} between 8% and 11% were on metformin (≥1500 mg/day) for the first phase of the trial. Patients who were compliant with a fasting plasma glucose between 7.2 and 15.5 mmol/L were randomized to receive, in addition to metformin, either sitagliptin 100 mg daily or placebo for 30 weeks. At 18 weeks, patients on sitagliptin had significantly lower HbA_{1c}, and they were more likely to achieve a HbA_{1c} < 7% at both 18 weeks and 30 weeks. Adverse events including hypoglycemia were similar between the 2 groups. Changes in body weight were similar in both groups.

There are some trials in which dual therapy with metformin and sitagliptin has been compared with other hypoglycaemic treatments. The trial by Karasik et al was a continuation of the trial by Charbonnel et al. In the trial, 544 of the patients completing the initial study were recruited, and patients on placebo were switched to glipizide 5 mg daily and titrated to 15 mg daily for another 30 weeks. Change in HbA_{1c} from baseline at the end of the trial was −0.7% with sitagliptin and −0.9% with glipizide. Hypoglycemia was more common with glipizide (16% against 1% with sitagliptin). Patients on sitagliptin lost 0.9 kg while patients on glipizide gained 1.5 kg in body weight.

Nauck et al performed a noninferiority trial comparing safety and efficacy of sitagliptin to glipizide when added to ongoing treatment with metformin (≥1,500 mg/day). Seven hundred and thirty-nine patients with type 2 diabetes with inadequate glycaemic control on metformin monotherapy with HbA_{1c} 6.5% to 10% were randomized to receive sitagliptin 100 mg daily or glipizide 5 mg daily titrated up to 20 mg daily. Improvement in HbA_{1c} at 54 weeks was comparable between the 2 groups (−0.51% with sitagliptin and −0.56% with glipizide). In all, 63% of patients on sitagliptin and 59% of patients on glipizide achieved HbA_{1c} < 7%. There were more adverse events in patients on glipizide. Also patents on glipizide experienced more hypoglycemia (32% in patients on glipizide vs. 5% in patients on sitagliptin). Patients on sitagliptin lost 1.5 kg, while those on glipizide gained 1.1 kg in body weight. Sitaglitin was found to be noninferior to glipizide when added to metformin and, with respect to adverse effects, was better tolerated.

In the study by Scott et al, 273 patients on metformin (≥1500 mg/day) with a mean HbA_{1c} of 7.7% were randomized to receive sitagliptin 100 mg daily, rosiglitazone 8 mg daily, or placebo for 18 weeks. At the end of 18 weeks changes in HbA_{1C} were −0.73% with sitagliptin and −0.79% for rosiglitazone and −0.22% with placebo and both changes were significant against placebo. Significantly more patients achieved a HbA_{1c} <7% with sitagliptin (55%) compared

with rosiglitazone (38%). Adverse effects, gastrointestinal side effects, and rates of hypoglycemia were comparable among the groups. Patients on sitagliptin and placebo lost 0.4 kg and 0.8 kg of body weight respectively, while there was a gain of 1.5 kg with rosiglitazone.

In the study by Scheen et al, patients with inadequate glycaemic control on stable doses of metformin (1500–3000 mg/day) were randomized to receive either sitagliptin 100 mg daily (n = 398) or saxagliptin 5 mg daily (n = 403) for 18 weeks. Improvement of HbA_{1c} was achieved at 8 weeks and was maintained with both treatment groups throughout the study. Reduction in mean HbA_{1c} at 18 weeks was 0.62% with sitagliptin/metformin and 0.52% with saxagliptin/metformin. There was similar weight loss with both drugs. Class specific side effects of DPP-4 inhibitors including influenza, urinary tract infections, and nasopharyngitis were commonly reported adverse events. At the end of the trial, noninferiority was established between the 2 treatment arms.

The study by Bergenstal et al compared the efficacy and safety of exenatide (at 2 mg daily, n = 160), sitagliptin (at 100 mg daily, n = 166), and pioglitazone (45 mg once daily, n = 165) when added to stable doses of metformin for 26 weeks. The largest reduction in HbA_{1c} from baseline was seen with exenatide (−1.5%), while the reduction with sitagliptin was 0.9%, and with pioglitazone, 1.2%. Also fasting plasma glucose was significantly improved with exenatide (−1.8 mmol/L) compared with sitagliptin (−0.9 mmol/L) but not when compared with pioglitazone (−1.5 mmol/L). Weight loss was most prominent with exenatide (−2.3 kg), which was significantly more compared with sitagliptin (−0.8 kg) and pioglitazone (2.8 kg). There were no reports of major hypoglycemia with any of the treatment arms.

Pioglitazone review[4]

There has been much discussion about the cardiovascular safety of TZDs over the last few years since the findings of a meta-analysis of 42 trials, in which Nissen et al compared the risk for MI associated with rosiglitazone with that of placebo or other antihyperglycemic agents. Rosiglitazone was associated with a significant 43% increased risk for MI (P = 0.03). Since then several studies have shown some risk of increased myocardial infarction associated with rosiglitazone use.

The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study was the first randomized, double-blind outcome study in patients with type 2 diabetes managed

with diet and/or oral blood glucose-lowering drugs and/or insulin who had a history of macrovascular disease, assessing the effect of pioglitazone on the secondary prevention of macrovascular events. A total of 5238 patients were randomized with the cohort of patients, a typical type 2 diabetic population at high risk of further macrovascular events. The average time of observation was 34.5 months. Treatment with pioglitazone reduced the secondary endpoint of combined all-cause mortality, non-fatal myocardial infarction, and stroke by 16%. However the primary outcome composite consisting of death, myocardi a l infarction, stroke, acute coronary syndrome, leg amputation or coronary/leg vascularization was not statistically less although a declining trend was seen. Another subgroup analysis from PROactive demonstrated that pioglitazone reduced the risk of recurrent stroke significantly in high-risk patients with T2D. However the criticism for PROactive was that the choice of its primary composite end-point, which included peripheral vascular disease was a physician driven rather than disease-driven outcome. In a meta-analysis of 94 trials that excluded the PROactive trial pioglitazone was associated with a reduced all-cause mortality with no relevant effect on coronary events.

The CHICAGO study (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) tested the hypothesis that pioglitazone would have a beneficial effect for reducing CIMT progression, compared with glimepiride. Treatment with pioglitazone produced improvement in several parameters, such as systolic blood pressure and lipid levels, including a 14% increase in HDL cholesterol, and reduced CIMT progression, compared with glimepiride. However, only the beneficial effect on HDL cholesterol predicted its beneficial effect for reducing CIMT progression. Data from the CHICAGO study indicate that the progression of carotid artery intima-media thickness, a marker of atherosclerosis and a surrogate end point for cardiovascular disease, was slowed more with pioglitazone than glimepiride in a racially diverse population of men and women with diabetes mellitus type 2.

The PERISCOPE Trial (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) compared the effects of an insulin sensitizer pioglitazone, with an insulin secretagogue, glimepiride, on the progression of coronary atherosclerosis in patients with type 2 diabetes. A total of 543 patients underwent coronary intravascular ultrasonography and were randomized to receive glimepiride, or pioglitazone, for 18 months with titration to maximum dosage, if tolerated. Atherosclerosis progression was measured by repeat intravascular ultrasonography examination in 360 patients at study completion. In patients with type 2 diabetes and coronary artery disease, treatment with

pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis compared with glimepiride.

The risk of developing congestive heart failure or worsening of present heart failure is a constant feature of the thiazolidinediones. The PROactive studies as well as other studies show increased risk for congestive heart failure with pioglitazone. However the risk is small and some some large studies show non significant increases in heart failure risk.

Pioglitazone's cardiovascular effects may be linked in part to its effects on lipid metabolism. The PROactive and CHICAGO studies as well as other studies show that pioglitazone significantly lowers triglycerides (11%–15%) and increases HDL(9%–14%)(5–9). Even though pioglitazone increases LDL (5%–7%), the quality of LDL may be altered so as to be less artherogenic. Pioglitazone improves insulin resistance in T2DM in association with mobilization of fat and toxic lipid metabolites out of muscle.

Mechanisms by which pioglitazone may mediate its cardiovascular effects[4]

Taken together, animal and human data suggest that pioglitazone may be beneficial in terms of improving cardiovascular outcomes. However the mechanisms attributed to these cardiovascular effects are controversial. PPAR-γ agonists have widespread effects involving, inflammation, atherosclerosis, obesity and diabetes.

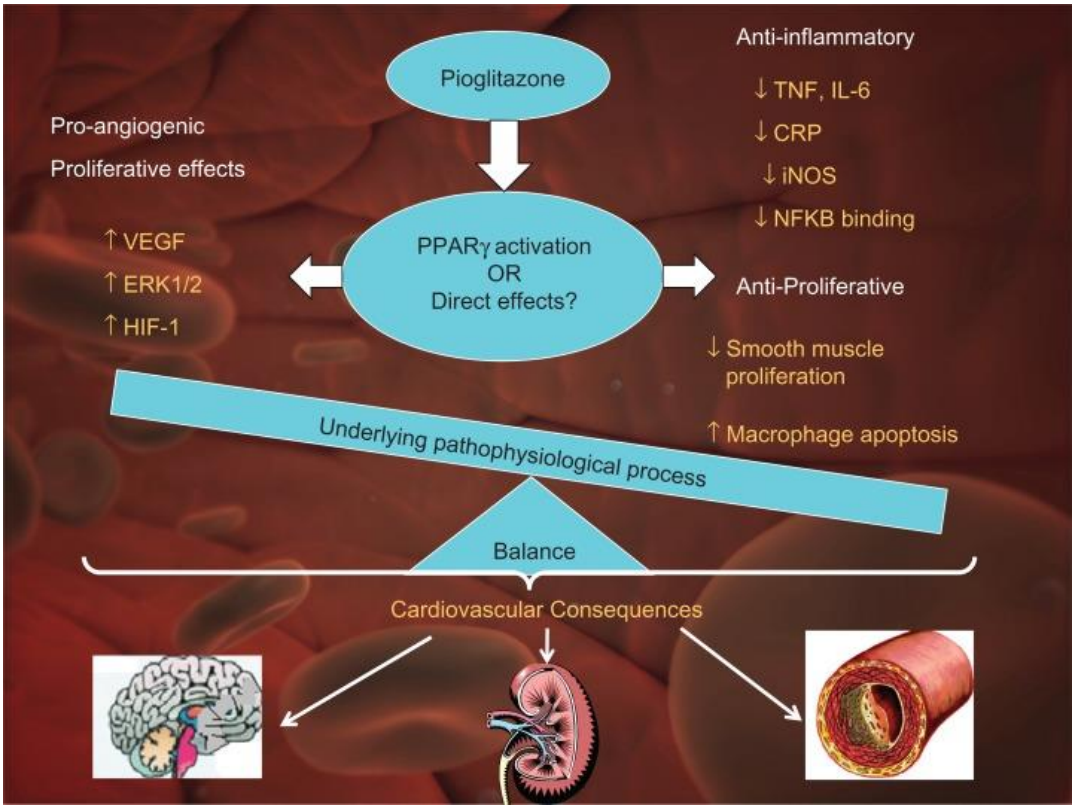


Figure 1. Mechanisms underlying cardiovascular effects of pioglitazone.

Note: The cardiovascular effects of pioglitazone may be due in part to PPAR activation and in part due to direct effects. The cardiovascular outcome is dependant upon the balance between proangiogenic and anti-inflammatory, anti-angiogenic effects, interacting with the underlying pathophysiological process.

Abbreviations: ERK; Extracellular signal regulated kinase, HIF; Hypoxia inducible factor-1, VEGF; Vascular endothelial growth factor, NFKB; Nuclear factor Kappa-B.

Anti-angiogenic, anti-proliferative and anti-inflammatory effects[4]

Thiazolidinediones have been shown to decrease post angioplasty neointimal hyperplasia in both animals and humans⁻ PPAR-γ ligands have been shown to inhibit and stimulate angiogenesis. Pioglitazone has been shown to have anti-proliferative effects in humans, decreasing in-stent neointimal proliferation. Pioglitazone inhibits the effects of inflammation such as decreasing bFGF in obese non-diabetes patients.· Pioglitazone decreases urinary TGF-beta1 excretion in diabetes and obese non-diabetes patients. Pioglitazone decreases inflammatory responses in adipose tissue/cells induced by monocytes/macrophages by acting

on either or both cell types. Another study demonstrated that activation of PPARgamma and PPAR beta/delta by pioglitazone in neurons triggers diverse neuroprotective mechanisms. A recent study showed that pioglitazone decreases urinary TGF-beta1 excretion in type 2 diabetics, which may be partly contributed to its direct reno-protection. Thus a review of the literature suggests that pioglitazone may have vasculoprotective effects in several organs such as heart, kidney and brain.

Pro-angiogenic and proliferative effects of pioglitazone[4]

There is however contradictory evidence that suggests that pioglitazone also has proangiogenic and proliferative effects. Diabetic mice with induced unilateral hind limb ischemia, when treated with pioglitazone showed normalization of VEGF, up-regulation of eNOS activity, and partial restoration of blood flow recovery. In mice treated with pioglitazone, VEGR-receptor-2 positive endothelial progenitor cells (EPCs) were up-regulated and migratory capacity was increased. *In vivo* angiogenesis was increased two-fold.

Efficacy and safety of fixed dose combination of Sitagliptin, metformin, and pioglitazone in type 2 Diabetes (IMPACT study): a randomized controlled trial[1]

Background

Due to the progressive decline in β-cell function, it is often necessary to utilize multiple agents with complementary mechanisms of action to address various facets and achieve glycemic control. Thus, this study aimed to evaluate the efficacy and safety of a fixed-dose combination (FDC) of metformin/sitagliptin/pioglitazone (MSP) therapy vs. metformin/sitagliptin (MS) in type 2 diabetes mellitus (T2DM).

Methods

In this phase 3, multicenter, double-blind study, patients with T2DM who exhibited inadequate glycemic control with HbA1c of 8.0–11.0% while taking ≥1500 mg/day metformin for at least 6 weeks were randomized to receive either FDC of MSP (1000/100/15 mg) or MS (1000/100 mg) per day for 24 weeks. The primary outcome measure was the change in HbA1c, and secondary outcomes included changes in fasting plasma glucose (FPG), postprandial

plasma glucose (PPG), and body weight from baseline to 24 weeks along with safety and tolerability.

Results

Among the 236 patients randomized, 207 (87.71%) successfully completed the study. All baseline characteristics were comparable between the FDC of MSP and MS groups. There was a subsequent significant reduction of HbA1c in FDC of MSP (− 1.64) vs. MS (− 1.32); between groups was [− 0.32% (95% CI, − 0.59, − 0.05)], $P = 0.0208$. Similar reductions were found in FPG [− 13.2 mg/dL (95% CI, − 22.86, − 3.71)], $P = 0.0068$, and PPG [− 20.83 mg/dL (95% CI, − 34.11, − 7.55)], $P = 0.0023$. There were no significant changes in body weight. A total of 27 adverse effects (AEs) and one severe AE were reported, none of which were related to the study drug.

Conclusion

The FDC of MSP demonstrated significant efficacy in managing glycemic indices and could serve as a valuable tool for physicians in the management of Indian patients with T2DM.

References:

1. Subbarayan, Sreevidya; Kipnes, Mark (2011). *Sitagliptin: a review. Expert Opinion on Pharmacotherapy, 12(10), 1613–1622.*
2. Ballav C, Gough SC. Safety and efficacy of sitagliptin-metformin in fixed combination for the treatment of type 2 diabetes mellitus. *Clin Med Insights Endocrinol Diabetes*. 2013;6:25-37.
3. Desouza CV, Shivaswamy V. Pioglitazone in the treatment of type 2 diabetes: safety and efficacy review. *Clin Med Insights Endocrinol Diabetes*. 2010;3:43-51.
4. Aashish, M., Arindam, N., Siddiqi, S.S. *et al.* Efficacy and safety of fixed dose combination of Sitagliptin, metformin, and pioglitazone in type 2 Diabetes (IMPACT study): a randomized controlled trial. *Clin Diabetes Endocrinol* **10**, 3 (2024).

Survey Form

1) How often do you prefer to prescribe triple Combination therapy in patient with type 2 DM?

A. Frequently
B. Not much frequently

2) In which patient profile do you consider the triple combination therapy?

A. Patients not controlled with the dual combination therapy
B. Newly diagnosed patient with HbA1C≥9%

3) Do you concomitantly prescribe Sitagliptin with Pioglitazone and Metformin?

A. Yes
B. No

4) How often do you prefer Sitagliptin concomitantly with Pioglitazone and Metformin in patients with type 2 DM?

A. Frequently
B. Not much frequently

5) In your clinical practice, which patient profile benefits the most from administration of Sitagliptin concomitantly with Metformin and Pioglitazone in diabetes management?

A. Lean Uncontrolled Diabetics
B. Diabetics with H/O Hypoglycemia
C. Diabetics associated with Nonalcoholic fatty liver disease (NAFLD)

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

A. Superior
B. Comparable
C. Inferior
D. Uncertain

7) Do you believe that, pioglitazone-based combination therapy should be used earlier compared other available triple drug combinations in the treatment of T2DM considering its major impact against Insulin resistance?

A. Yes
B. No

8) Do you believe that, Pioglitazone not only improve glycaemic control but also improve CV outcomes in uncontrolled T2DM?

A. Yes
B. No

9) Have you noticed the protective effects of Pioglitazone in patients associated with various Cardiovascular conditionsfrom the given options?

A. Stroke
B. Myocardial infarction
C. Chronic kidney disease

10) As per your clinical experience, administration of Sitagliptin concomitantly with Metformin and Pioglitazone is:

A. Generally, well tolerated
B. Associated with a low incidence of hypoglycaemia
C. Associated with no meaningful change in body weight

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

A. Superior
B. Comparable
C. Inferior
D. Uncertain

12) Which particular feature(s) of Pioglitrazone-based combination therapy has potentially beneficial in current clinical scenario?

A. Potent insulin sensitization
B. Preservation of beta-cell function
C. Durable reduction in HbA1c
D. Correction of multiple components of metabolic syndrome
E. Improvement in nonalcoholic fatty liver disease

13) How often do you experience any adverse effect like edema/fluid retention?

A. Never
B. Occasionally
C. In every patient

14) In your clinical practice, in T2DM management with step-down approach will you prefer to use Sitagliptin concomitantly with Metformin and Pioglitrazone?

A. Yes
B. No

15) In your experience, how often did you observe weight gain in patients administered with Sitagliptin concomitantly with Metformin and Pioglitrazone?

A. Never
B. Occasionally
C. In every patient

16) In your current clinical practice, in which T2DM cases do you consider to step-down in antihyperglycemic treatment?

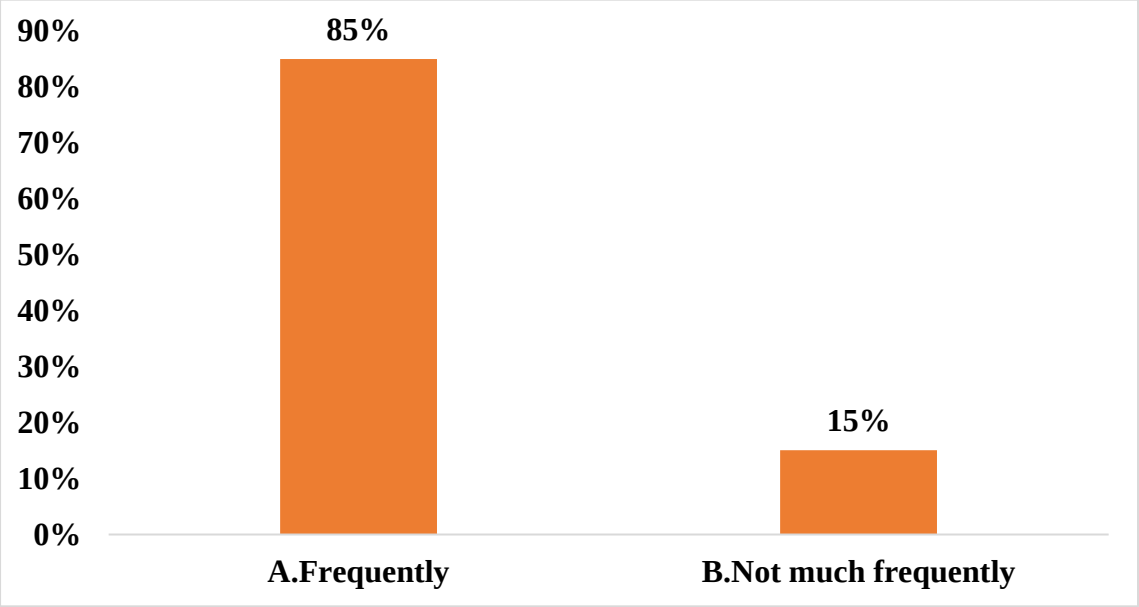
A. with significant weight reduction irrespective of its origin
B. with complex insulin regimens where re-evaluation of this treatment was missed
C. with continuously decreasing renal function
D. among elderly patients with comorbidities

Survey Findings

1) How often do you prefer to prescribe triple Combination therapy in patient with type 2 DM?

A. Frequently

B. Not much frequently

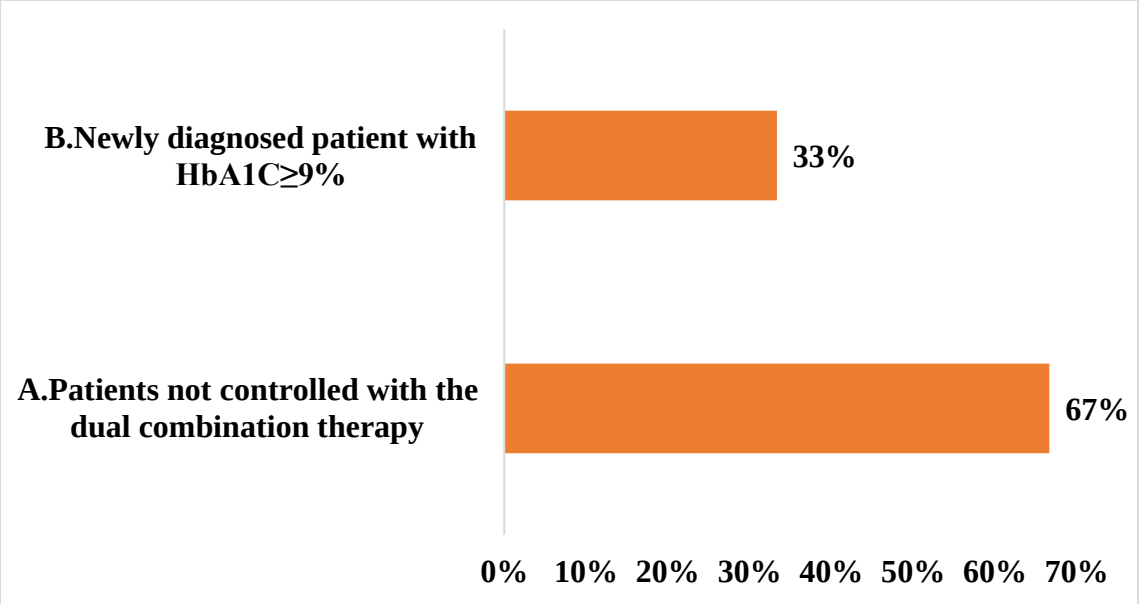


According to majority of doctors, 85%, they frequently prefer to prescribe triple combination therapy in patient with type 2 DM.

2) In which patient profile do you consider the triple combination therapy?

A. Patients not controlled with the dual combination therapy

B. Newly diagnosed patient with HbA1C≥9%

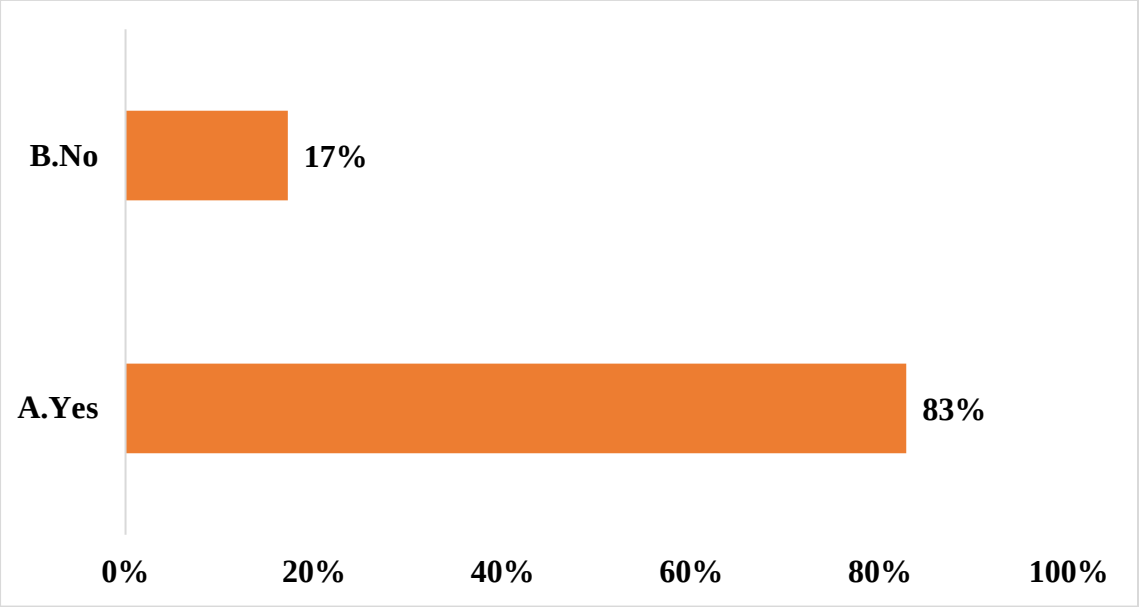


As per 67% of doctors, patients not controlled with the dual combination therapy are considered for the triple combination therapy.

3) Do you concomitantly prescribe Sitagliptin with Pioglitazone and Metformin?

A. Yes

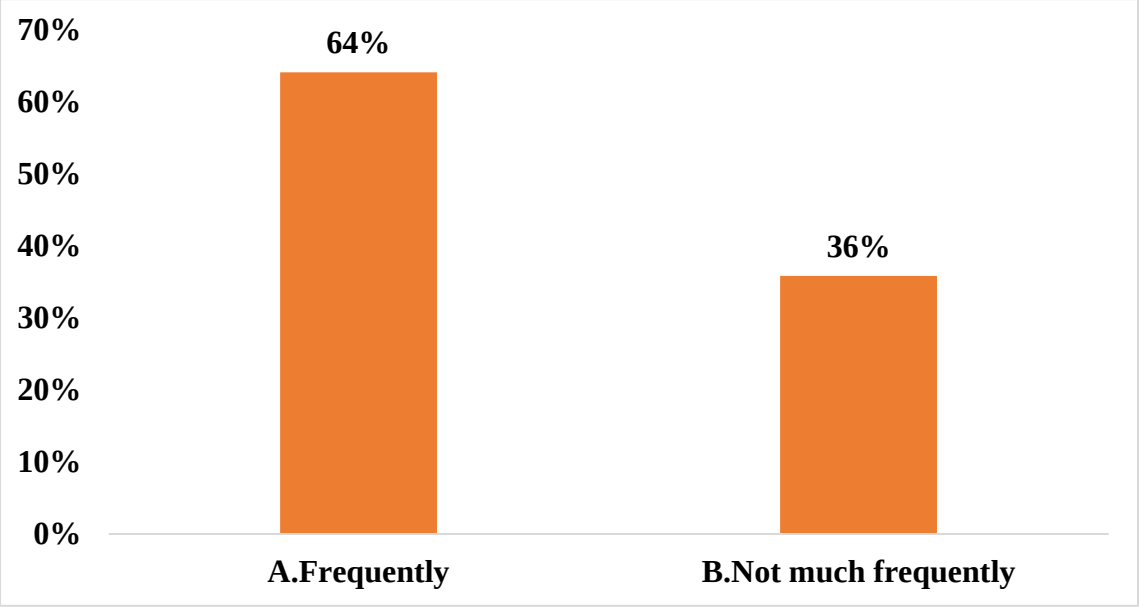
B. No



As per majority of doctors, 83%, they do concomitantly prescribe sitagliptin with pioglitazone and metformin.

4) How often do you prefer Sitagliptin concomitantly with Pioglitazone and Metformin in patients with type 2 DM?

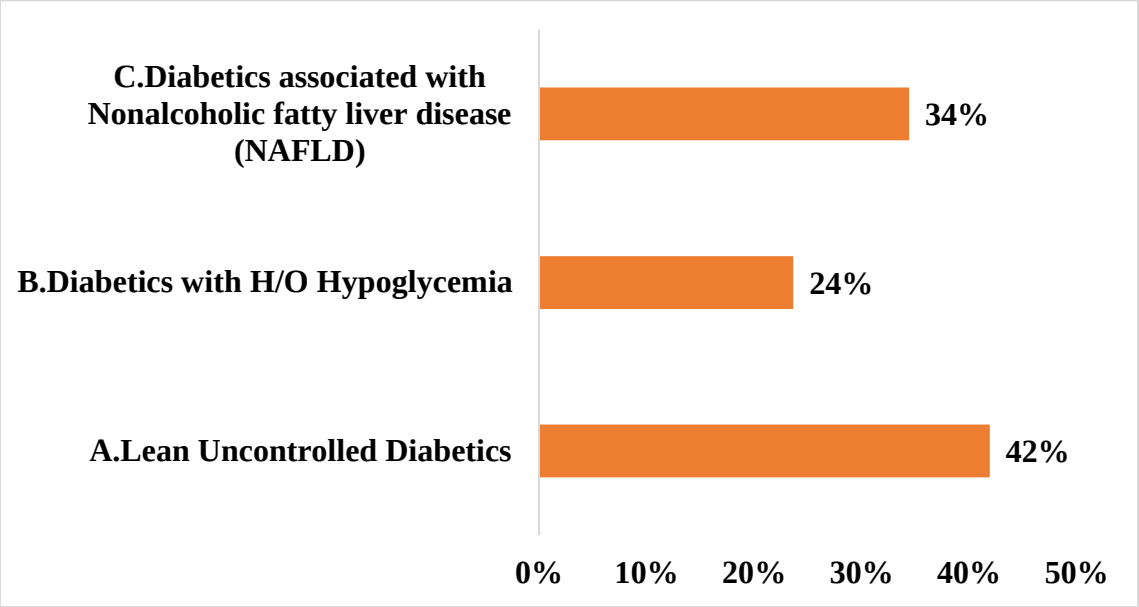
A. Frequently
B. Not much frequently



According to 64% of doctors, they frequently prefer sitagliptin concomitantly with pioglitazone and metformin in patients with type 2 dm.

5) In your clinical practice, which patient profile benefits the most from administration of Sitagliptin concomitantly with Metformin and Pioglitazone in diabetes management?

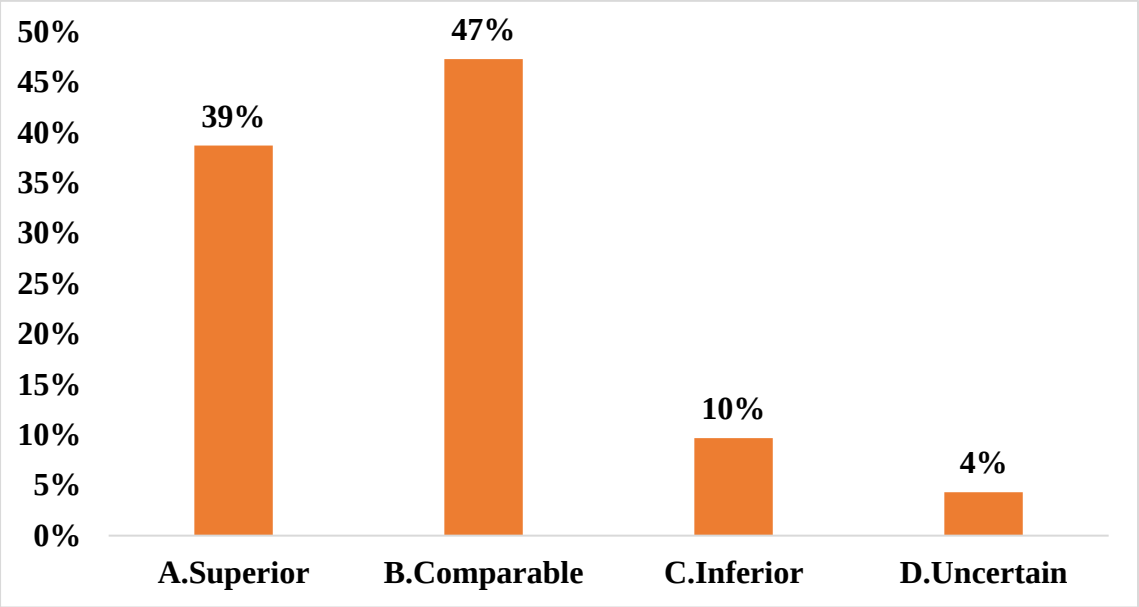
A. Lean Uncontrolled Diabetics
B. Diabetics with H/O Hypoglycemia
C. Diabetics associated with Nonalcoholic fatty liver disease (NAFLD)



According to 42% of doctors, lean uncontrolled diabetics patient profile benefits the most from administration of sitagliptin concomitantly with metformin and pioglitazone in diabetes management.

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

A. Superior
B. Comparable
C. Inferior
D. Uncertain

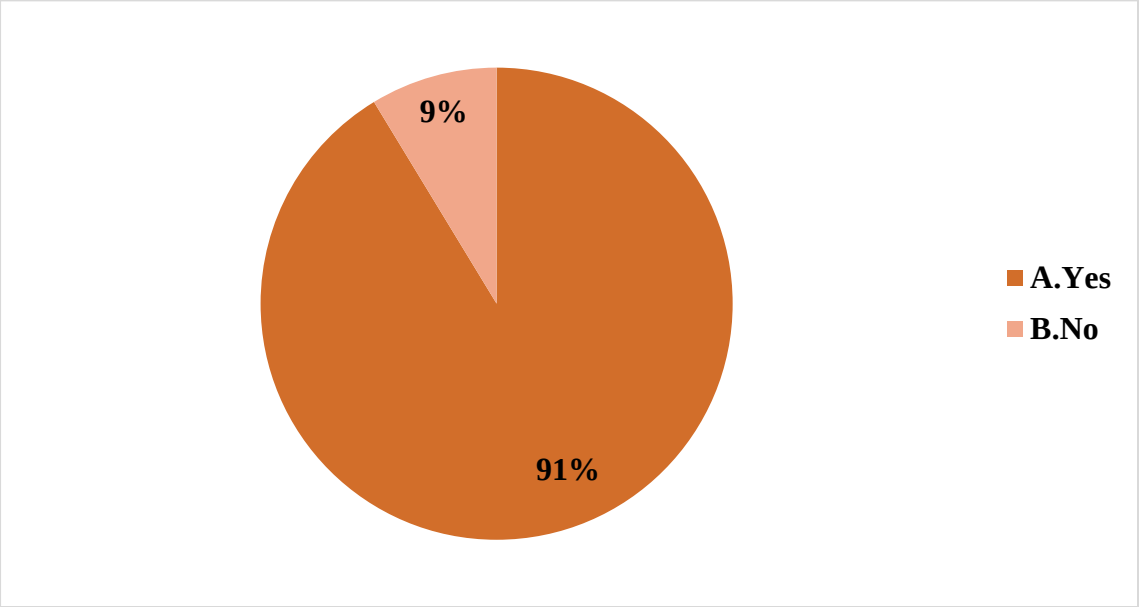


As per 47% of doctors, they perceive the efficacy of administering sitagliptin concomitantly with metformin and pioglitazone compared to other available conventional oral antidiabetic drugs (OADs) as comparable.

7) Do you believe that, pioglitazone-based combination therapy should be used earlier compared other available triple drug combinations in the treatment of T2DM considering its major impact against Insulin resistance?

A. Yes

B. No

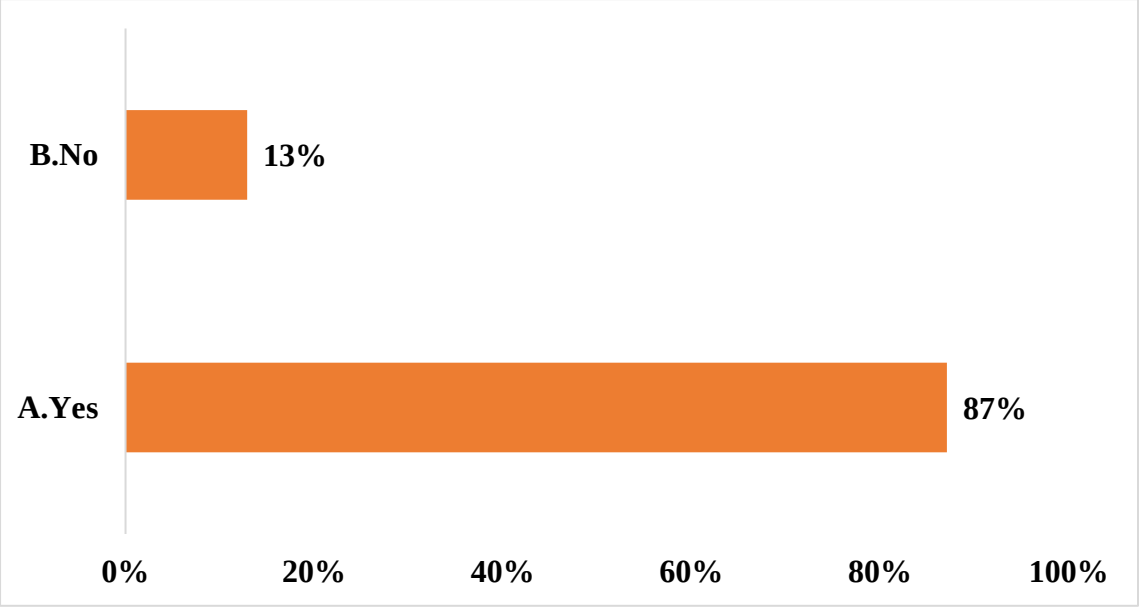


As per majority of doctors, they do believe that pioglitazone-based combination therapy should be used earlier compared other available triple drug combinations in the treatment of T2DM considering its major impact against insulin resistance.

8) Do you believe that, Pioglitazone not only improve glycaemic control but also improve CV outcomes in uncontrolled T2DM?

A. Yes

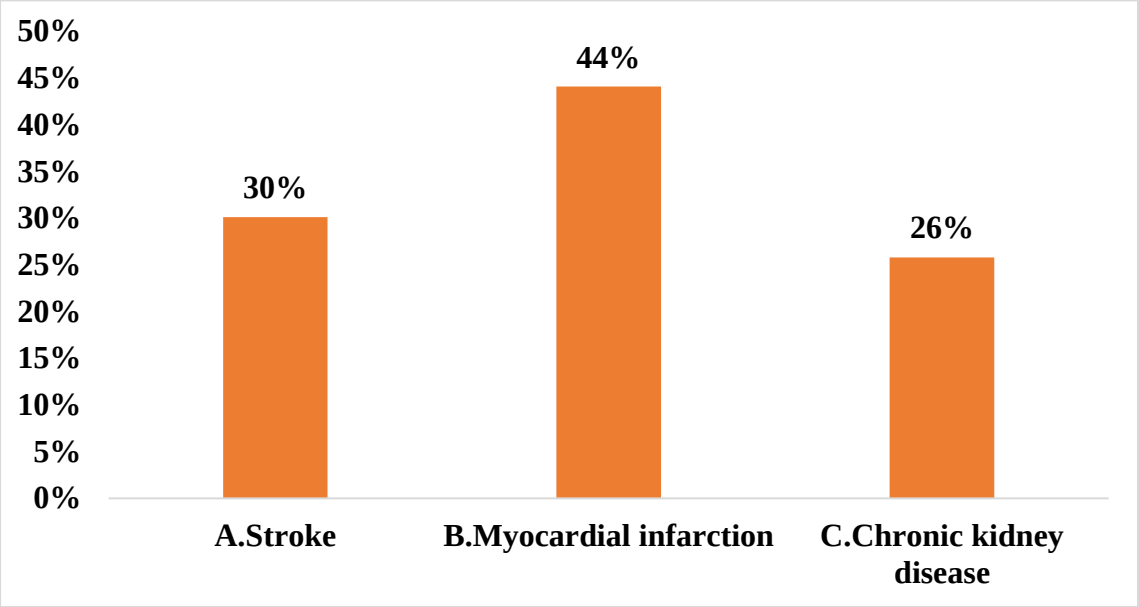
B. No



According to majority of doctors, 87%, they do believe that pioglitazone not only improve glycaemic control but also improve cv outcomes in uncontrolled T2DM**.**

9) Have you noticed the protective effects of Pioglitazone in patients associated with various Cardiovascular conditions from the given options?

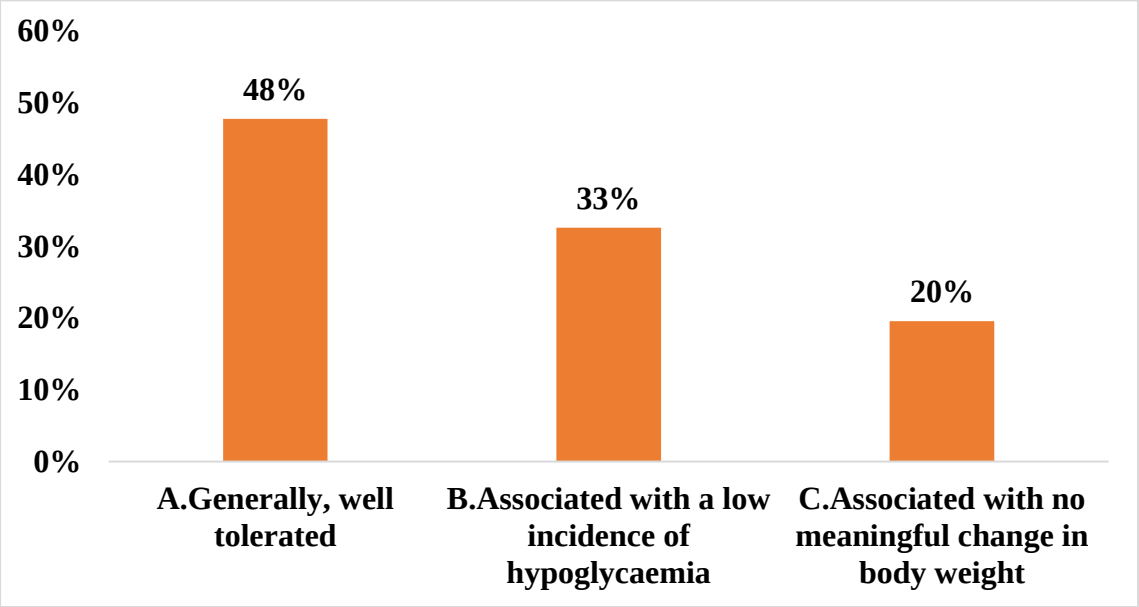
A. Stroke
B. Myocardial infarction
C. Chronic kidney disease



According to 44% of doctors, myocardial infarction is the protective effects of pioglitazone in patients associated with various cardiovascular conditions from the given options.

10) As per your clinical experience, administration of Sitagliptin concomitantly with Metformin and Pioglitazone is:

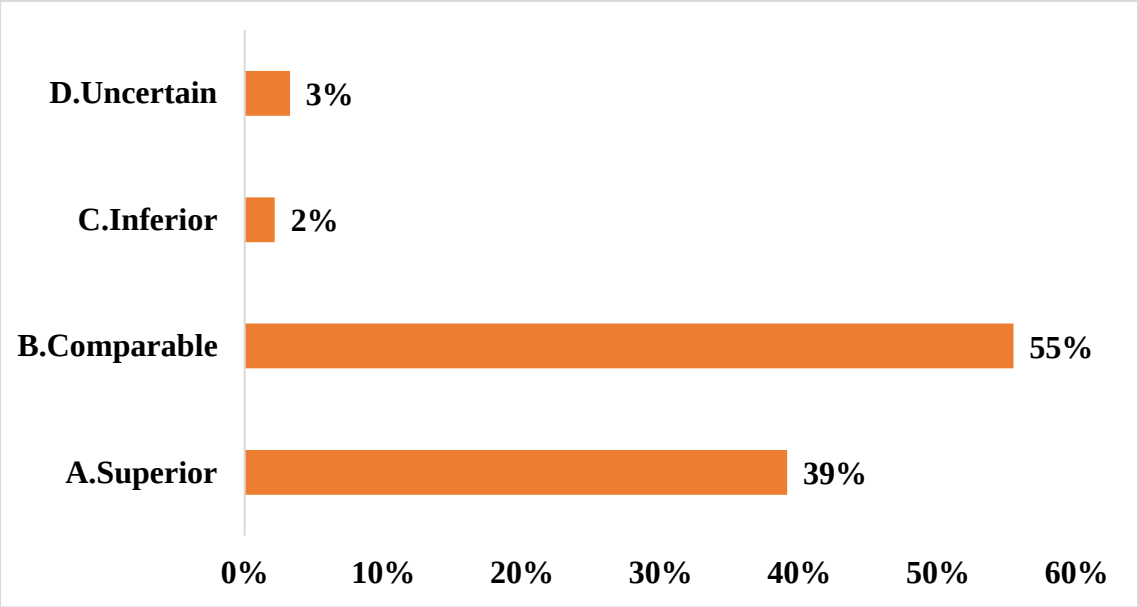
A. Generally, well tolerated
B. Associated with a low incidence of hypoglycaemia
C. Associated with no meaningful change in body weight



According to 48% of doctors, administration of sitagliptin concomitantly with metformin and pioglitazone is generally well tolerated as per their clinical experience.

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

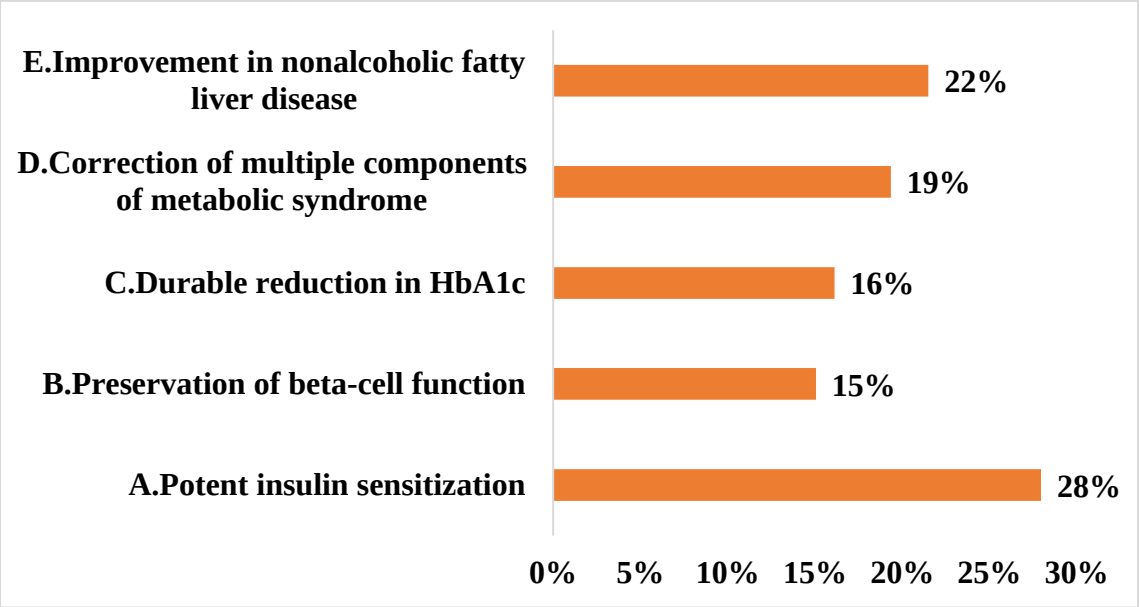
A. Superior
B. Comparable
C. Inferior
D. Uncertain



According to 55% of doctors, they perceive the long-term safety profile of administering sitagliptin concomitantly with metformin and pioglitazone as compared to other available triple combination therapies (conventional) for diabetes management as comparable.

12) Which particular feature(s) of Pioglitrazone-based combination therapy is potentially beneficial in current clinical scenario?

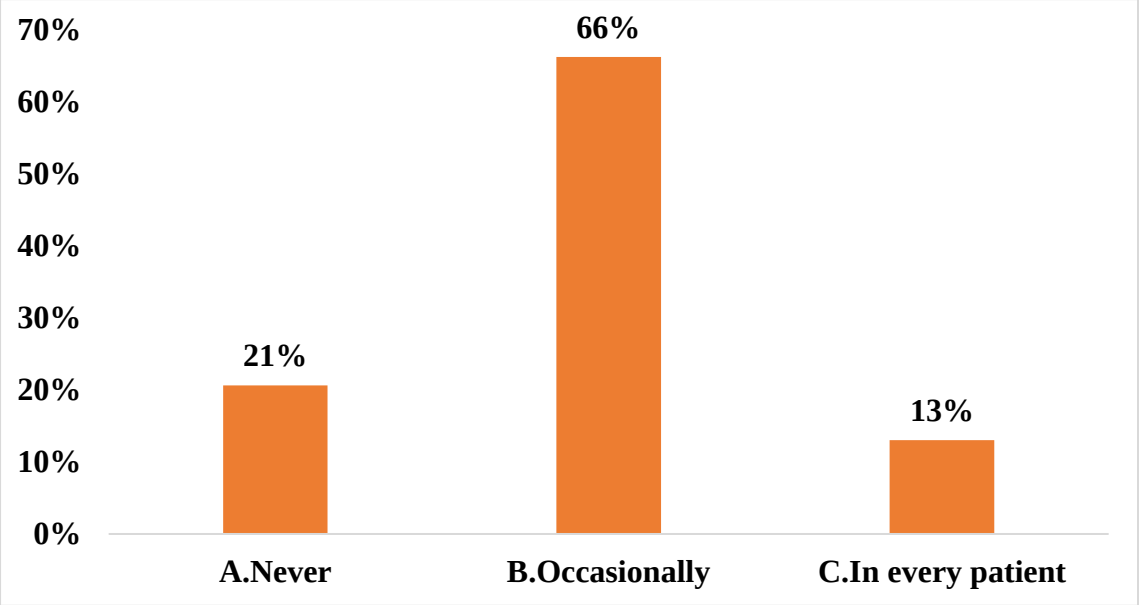
A. Potent insulin sensitization
B. Preservation of beta-cell function
C. Durable reduction in HbA1c
D. Correction of multiple components of metabolic syndrome
E. Improvement in nonalcoholic fatty liver disease



As per 28% of doctors, potent insulin sensitization feature of pioglitrazone-based combination therapy is potentially beneficial in current clinical scenario.

13) How often do you experience any adverse effect like edema/fluid retention?

A. Never
B. Occasionally
C. In every patient

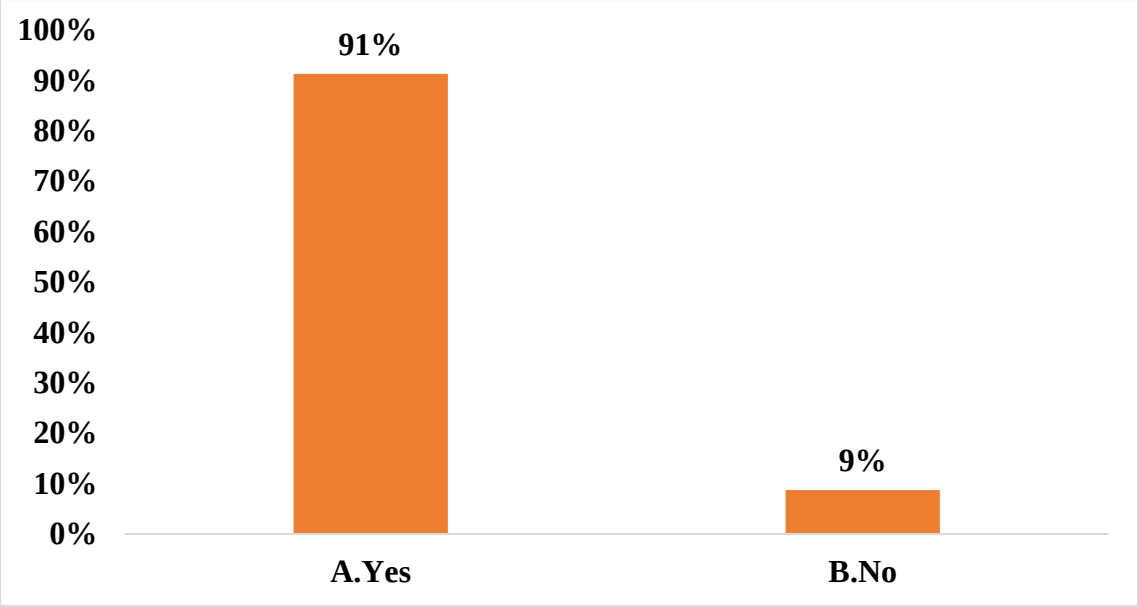


According to 66% of doctors, they occasionally experience any adverse effect like edema/fluid retention.

14) In your clinical practice, in T2DM management with step-down approach will you prefer to use Sitagliptin concomitantly with Metformin and Pioglitrazone?

A. Yes

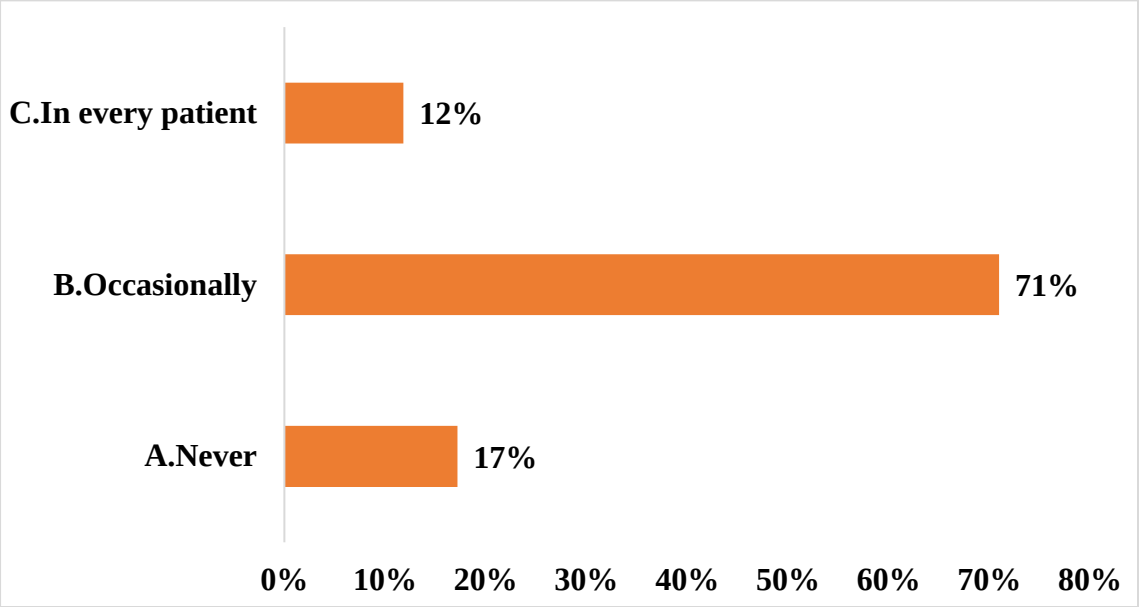
B. No



As per majority of doctors, 91%, in T2DM management with step-down approach they, will prefer using sitagliptin concomitantly with metformin and pioglitrazone.

15) In your experience, how often did you observe weight gain in patients administered with Sitagliptin concomitantly with Metformin and Pioglitrazone?

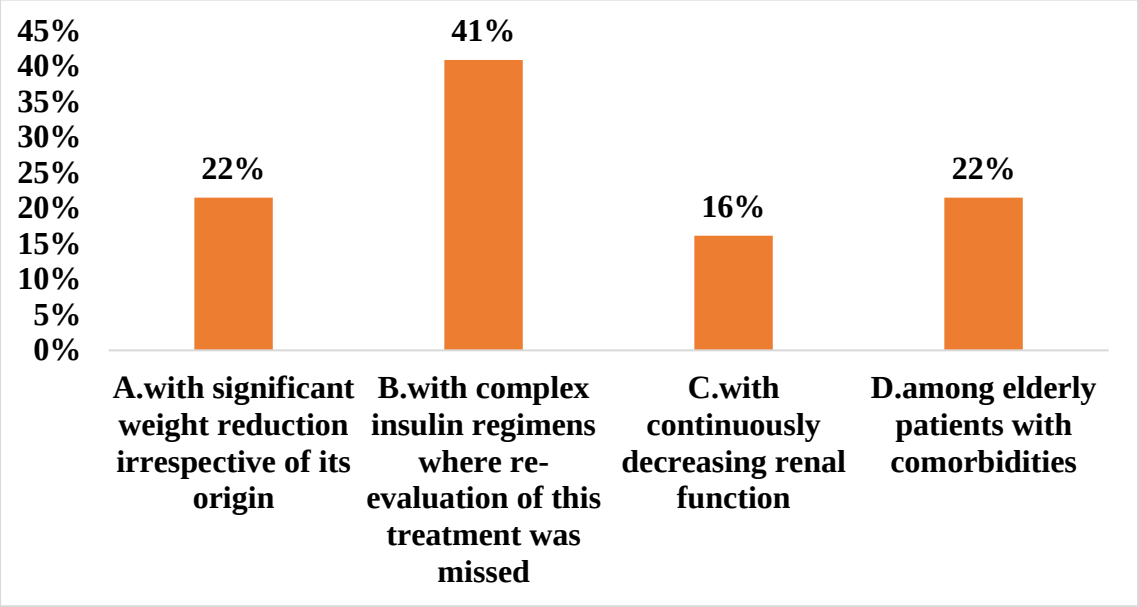
A. Never
B. Occasionally
C. In every patient



According to majority of doctors, 71%, they occasionally observe weight gain in patients administered with sitagliptin concomitantly with metformin and pioglitrazone.

16) In your current clinical practice, in which T2DM cases do you consider to step-down in antihyperglycemic treatment?

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 41% of doctors, they consider to step-down in antihyperglycemic treatment in T2DM cases with complex insulin regimens where re-evaluation of this treatment was missed.

Summary

- According to majority of doctors, 85%, they frequently prefer to prescribe triple combination therapy in patient with type 2 DM.
- As per 67% of doctors, patients not controlled with the dual combination therapy are considered for the triple combination therapy.
- As per majority of doctors, 83%, they do concomitantly prescribe sitagliptin with pioglitazone and metformin.
- According to 64% of doctors, they frequently prefer sitagliptin concomitantly with pioglitazone and metformin in patients with type 2 dm.
- According to 42% of doctors, lean uncontrolled diabetics patient profile benefits the most from administration of sitagliptin concomitantly with metformin and pioglitazone in diabetes management.
- As per 47% of doctors, they perceive the efficacy of administering sitagliptin concomitantly with metformin and pioglitazone compared to other available conventional oral antidiabetic drugs (OADs) as comparable.
- As per majority of doctors, they do believe that pioglitazone-based combination therapy should be used earlier compared other available triple drug combinations in the treatment of T2DM considering its major impact against insulin resistance.
- According to majority of doctors, 87%, they do believe that pioglitazone not only improve glycaemic control but also improve cv outcomes in uncontrolled T2DM**.**
- According to 44% of doctors, myocardial infarction is the protective effects of pioglitazone in patients associated with various cardiovascular conditions from the given options.
- According to 48% of doctors, administration of sitagliptin concomitantly with metformin and pioglitazone is generally well tolerated as per their clinical experience.
- According to 55% of doctors, they perceive the long-term safety profile of administering sitagliptin concomitantly with metformin and pioglitazone as compared to other available triple combination therapies (conventional) for diabetes management as comparable.
- As per 28% of doctors, potent insulin sensitization feature of pioglitrazone-based combination therapy is potentially beneficial in current clinical scenario.

- According to 66% of doctors, they occasionally experience any adverse effect like edema/fluid retention.
- As per majority of doctors, 91%, in T2DM management with step-down approach they, will prefer using sitagliptin concomitantly with metformin and pioglitrazone.
- According to majority of doctors, 71%, they occasionally observe weight gain in patients administered with sitagliptin concomitantly with metformin and pioglitrazone.
- As per 41% of doctors, they consider to step-down in antihyperglycemic treatment in T2DM cases with complex insulin regimens where re-evaluation of this treatment was missed.

Consultant Opinion

Preference for Triple Combination Therapy: A significant majority of doctors, accounting for 85%, frequently prefer prescribing triple combination therapy for patients with T2DM. This indicates a preference for comprehensive treatment strategies to achieve optimal glycemic control.

Criteria for Initiating Triple Therapy: Two-thirds of doctors, or 67%, consider patients who are not adequately controlled with dual combination therapy as candidates for triple combination therapy. This approach highlights the stepwise escalation of treatment based on individual patient needs and response.

Concomitant Prescription of Sitagliptin, Pioglitazone, and Metformin: A majority of doctors, 83%, reported concomitantly prescribing sitagliptin with pioglitazone and metformin, indicating a common treatment regimen in clinical practice.

Beneficial Patient Profiles: Lean uncontrolled diabetic patients are perceived to benefit the most from the administration of sitagliptin concomitantly with metformin and pioglitazone, as reported by 42% of doctors. This suggests that this combination may be particularly effective in certain patient subgroups.

Efficacy Comparison: Nearly half of the doctors, 47%, perceive the efficacy of administering sitagliptin concomitantly with metformin and pioglitazone as comparable to other available conventional oral antidiabetic drugs (OADs). This suggests that the triple combination therapy provides similar efficacy outcomes compared to alternative treatments.

Early Use of Pioglitazone-Based Therapy: The majority of doctors, comprising 87%, believe that pioglitazone-based combination therapy should be used earlier compared to other available triple drug combinations in the treatment of T2DM due to its significant impact against insulin resistance.

Cardiovascular Benefits of Pioglitazone: A notable proportion of doctors, 44%, perceive the protective effects of pioglitazone in patients with various cardiovascular conditions, particularly myocardial infarction. This suggests that pioglitazone may confer cardiovascular benefits beyond glycemic control.

Tolerability and Safety: Almost half of the doctors, 48%, reported that the administration of sitagliptin concomitantly with metformin and pioglitazone is generally well-tolerated, with comparable long-term safety profiles to other available triple combination therapies for diabetes management.

Adverse Effects and Weight Gain: While the majority of doctors perceive the long-term safety profile as comparable, around two-thirds occasionally experience adverse effects like edema/fluid retention, and 71% occasionally observe weight gain in patients administered with the triple combination therapy.

Preference for Step-Down Approach: A significant majority of doctors, 91%, prefer using sitagliptin concomitantly with metformin and pioglitazone in a step-down approach for T2DM management, suggesting a preference for simplifying treatment regimens over time.

Considerations for Complex Insulin Regimens: Forty-one percent of doctors consider stepping down antihyperglycemic treatment in T2DM cases with complex insulin regimens, where re-evaluation of this treatment was missed. This highlights the importance of re-evaluating treatment strategies to optimize patient care.

NOTES

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

Developed by:

Weston Medical Education Foundation of India

CTS-77, Shop No.11, Swapna Siddhi CHS LTD, Akurli Road Near Malad Sahakari Bank
Kandivali (E), Mumbai - 400101. M: 9322615653 I W: www.wmefi.co.in