Positioning of **Vildagliptin + Glimepiride + Metformin** in Management of Type 2 Diabetes Mellitus Management

Content

Background and Objective of the Survey

The combination of vildagliptin, glimepiride, and metformin holds a strategic position in the management of type 2 diabetes mellitus (T2DM), particularly in patients who require multiple mechanisms of action to achieve glycemic control.

Vildagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that enhances glycemic control by increasing insulin secretion and decreasing glucagon release in a glucose-dependent manner. Glimepiride belongs to the sulfonylurea class of medications and acts by stimulating insulin secretion from pancreatic beta cells. Metformin, a biguanide, primarily reduces hepatic glucose production and enhances peripheral insulin sensitivity.

The combination of vildagliptin, glimepiride, and metformin offers complementary mechanisms of action to target multiple pathways involved in the pathogenesis of T2DM. Vildagliptin and glimepiride act synergistically to stimulate insulin secretion, while metformin improves insulin sensitivity and reduces hepatic glucose output. This triple combination therapy allows for more comprehensive glycemic control, particularly in patients with inadequate response to monotherapy or dual therapy.

Furthermore, the combination of vildagliptin, glimepiride, and metformin provides flexibility in dosing and titration to individualize treatment according to patients' glycemic targets, tolerability, and risk of hypoglycemia. It also simplifies treatment regimens by combining multiple agents into a single tablet, enhancing convenience and adherence for patients.

The objective of the survey is:

To evaluate the positioning of Vildagliptin + Glimepiride + Metformin in management of type 2 diabetes mellitus management

Methodology of the Survey

A survey was conducted to evaluate the positioning of Vildagliptin + Glimepiride + Metformin in management of type 2 diabetes mellitus management. 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
- Vidagliptin
- Metformin
- Glimepiride

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]

Type 2 diabetes (T2DM) is a chronic and complex disease which involves multiple pathophysiological defects, including impaired islet function and insulin resistance, resulting in impaired glucose tolerance and inappropriately high fasting hepatic glucose production. While insulin resistance remains essentially unchanged over time, the deficit in islet function is a progressive process with quantitative and qualitative abnormalities in insulin and glucagon secretion kinetics, paralleled by a substantial reduction in the maximum capacity to secrete insulin. These defects in islet function are present early on and worsen with the natural history of the disease. Indeed, most individuals who are insulin resistant never develop T2DM because normal islets adapt to insulin resistance both by increasing glucose-potentiated insulin secretion and by increasing α-cell sensitivity to the suppressive effects of glucose. Thus, the first patent characteristic of T2DM is inadequate islet compensation rather than absolute hypoinsulinemia or absolute hyperglucagonemia.

Despite clear evidence that maintenance of glycemic levels as close to normal as possible reduces the risk of diabetic complications, optimal control is seldom achieved and maintained in patients with T2DM). While all oral antidiabetic agents initially lower blood glucose effectively, none of them are able to address all the anomalies involved in the pathogenesis of T2DM, to stop the decline in beta-cell function, and to achieve durable glycemic control.

Established management of T2DM starts with lifestyle changes, ie, introducing a healthier diet and increasing physical activity in order to improve glucose utilization and promote weight loss. This is accompanied by rapid or even concomitant introduction of an oral antidiabetic agent. Metformin is widely used as the first-line antidiabetic drug of choice. Metformin reduces hepatic glucose output, primarily by inhibiting gluconeogenesis, and, to a lesser extent, increases tissue sensitivity to insulin. Beneficial clinical properties of metformin include weight control, a low risk of hypoglycemia and favorable effects on the lipid profile and the fibrinolytic pathway. Metformin was reported to be equally effective in lowering glucose in non-obese and obese patients and can thus be used independent of an individual's BMI. More importantly, it is the only drug which has demonstrated beneficial effects on cardiovascular events, as reported in the UKPDS substudy of overweight patients. In this study, metformin

was also associated with reduced all-cause mortality, which was not seen in patients with equally well controlled blood glucose treated with sulfonylureas or insulin.

Metformin is therefore recommended by all guidelines as first-line therapy for T2DM. The International Diabetes Federation (IDF) suggests to use metformin in all cases inadequately controlled by non-pharmacological treatments (IDF, on line) while a recent consensus document of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends to prescribe metformin at diagnosis, together with lifestyle interventions).

Upon progression of the disease, progressive loss of β-cell function and mass makes it difficult for patients to maintain glycemic control with monotherapy. In the UKPDS only about 50% of patients were still adequately controlled on monotherapy after 3 years (UKPDS-49). Even if somewhat better durability of glycemic control was achieved with TZD over 4 years in the ADOPT trial, high rates of secondary failure have been reported with all current oral hypoglycemic drugs (OADs), including following successful initial metformin therapy.

As a result, combination therapy involving agents with complementary mechanism of action is the next logical step in the management of T2DM. Established treatment options for metformin monotherapy failure include the addition of sulfonylureas (or glinides), thiazolidinediones, acarbose, or insulin. Since metformin lowers plasma glucose without affecting insulin secretion, it is often combined with an agent stimulating insulin secretion, like a sulfonylurea. Adding a sulfonylurea to metformin has thus been the conventional and the gold standard combination therapy for decades. However, while previous therapeutic goals made this combination quite attractive, the lower glycemic targets for intensification of therapy substantially increase the risk of hypoglycemia (particularly in patients with mild hyperglycemia or in the older and more fragile patients) resulting in symptoms or increased food intake to avoid or treat them. Therefore, the need for more glucose-sensitive agents as alternative combination therapies was warranted.

Recently, newer agents, which induce a glucose-dependent stimulation of insulin secretion became available and can provide an attractive alternative for use in combination with metformin. Such a novel therapy for T2DM is based on pharmacological inhibition of the enzyme dipeptidyl peptidase IV (DPP-4), which is responsible for the rapid inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic

peptide (GIP). These intestinally derived peptides are released rapidly after eating, ie, in the presence of glucose or nutrients in the gut.

By stabilizing endogenous incretin hormones at physiological concentrations, DPP-4 inhibitors increase the sensitivity to glucose of both insulin and glucagon secretion (ie, increase insulin secretion and suppress glucagon secretion in a glucose-dependent manner), thereby lowering glucose levels. DPP-4 inhibitors are thus the first oral agents addressing the dual α- and β- islet cells dysfunction present in T2DM.

Vidagliptin

Pharmacologic overview[2]

Vildagliptin is rapidly absorbed after oral administration, with approximately dose-proportional pharmacokinetics. No dosage adjustment is necessary based on age, gender, body mass index (BMI), food intake, presence of hepatic impairment, or concomitant use of commonly used drugs. Bio-equivalence of the fixed-dose combination of vildagliptin and metformin with the individual components has been shown; the effect of food in decreasing metformin exposure was smaller with the metformin component in the fixed-dose combination than has been reported with metformin alone, and the fixed-dose combination can thus be administered in the same manner as metformin alone.

Vildagliptin monotherapy trials[2]

Vildagliptin has been evaluated as monotherapy in treatment-naïve T2DM patients in randomized, double-blind dose-ranging and comparative trials, including comparisons with metformin, rosiglitazone, and acarbose; in subjects with impaired glucose tolerance; and in T2DM patients with mild hyperglycemia.

Dose-ranging studies[2]

In one dose-ranging study, 354 patients (HbA1c 7.5%–10.0%, baseline average 8.4%) were randomized to vildagliptin 50 mg qd (n = 88), 50 mg bid (n = 83), or 100 mg qd (n = 91) or to placebo (n = 92) for 24 weeks. Placebo-subtracted mean changes from baseline in HbA1c were

0.5%, 0.7%, and 0.9%, respectively, in the three vildagliptin dose groups (all $p \leq 0.01$ vs placebo). Placebo-subtracted reductions from baseline fasting plasma glucose (FPG; baseline average 10.5 mmol/L) were 0.6, 1.3, and 1.3 mmol/L, respectively ($p < 0.001$ for latter two dose groups). Adverse events occurred with similar frequency with vildagliptin (55.8%–59.3%) and placebo (57.6%). There was no significant change in weight, and no episodes of hypoglycemia occurred with vildagliptin treatment. In a second dose-ranging study, 632 patients (HbA1c 7.5%–11.0%, baseline 8.4%) were randomized to vildagliptin 50 mg qd (n = 163), 50 mg bid (n = 152), or 100 mg qd (n = 157) or to placebo (n = 160) for 24 weeks (-). Changes in HbA1c from baseline were −0.3% with placebo vs −0.8%, −0.8%, and −0.9% with vildagliptin 50 mg qd, 50 mg bid, and 100 mg qd, respectively ($p < 0.01$ for all). Body weight decreased by 0.3–1.8 kg across all groups. Mild hypoglycemia occurred in 2 patients (1.2%) receiving vildagliptin 50 mg qd, in 1 patient (0.6%) receiving 100 mg qd, and in none of the patients receiving 50 mg bid or placebo.

Impaired glucose tolerance[2]

In a randomized, double-blind trial, 179 subjects with IGT (2-h glucose 9.1 mmol/L, HbA1c 5.9%) were randomized to vildagliptin 50 mg qd (n = 90) or placebo (n = 89) for 12 weeks (-). Compared with placebo, vildagliptin significantly increased levels of GLP-1 and GIP and reduced glucagon levels. Postprandial insulin levels were unaffected, and vildagliptin treatment was associated with a significant reduction in prandial glucose excursion (incremental area under the curve [AUC] −1.0 mmol/L/h, $p < 0.001$), representing a 32% reduction vs placebo. β-cell function, assessed by insulin secretory rate (ISR) relative to glucose measured as ISR $AUC_{0–2\ h}$/glucose $AUC_{0–2\ h}$, was significantly increased (+6.4 pmol/min/m^2/mM, $p = 0.002$) with vildagliptin. Adverse event profiles were similar for vildagliptin and placebo. No cases of hypoglycemia were reported. Change in body weight was −0.6 kg with vildagliptin and −0.1 kg with placebo.

Mild hyperglycemia[2]

A total of 306 patients with T2DM and mild hyperglycemia (HbA1c 6.2%–7.5%) were randomized to vildagliptin 50 mg qd (n = 156) or placebo (n = 150) for 52 weeks followed by a 4-week washout period. At baseline, HbA1c and FPG were 6.7% and 7.1 mmol/L,

respectively, in the vildagliptin group and 6.8% and 7.2 mmol/L, respectively, in the placebo group. At 52 weeks, changes in HbA1c were −0.2% with vildagliptin vs +0.1% with placebo (between-group difference $p < 0.001$); FPG did not change significantly with vildagliptin (+0.2 mmol/L) and increased with placebo (+0.5 mmol/L, $p < 0.001$; between-group difference $p = 0.032$). Compared with patients on placebo, vildagliptin patients had a significant reduction in 2-hour postprandial glucose (−0.9 mmol/L, $p = 0.012$) and significantly improved β-cell function assessed as ISR $AUC_{0–2\,h}$/glucose $AUC_{0–2\,h}$ (+5.0 pmol/min/m^2/mM, $p < 0.001$).

Additional characterization of the effect of vildagliptin on model-assessed β-cell function showed that the 0.3% reduction in HbA1c and significantly reduced glucose $AUC_{0–2h}$ (−1.7 mM/h, $p = 0.002$) were accompanied by significantly increased fasting insulin secretory tone (+34.1 pmol/min/m^2, $p < 0.001$), glucose sensitivity (+20.7 pmol/min/m^2/mM, $p < 0.001$), and rate sensitivity (163.6 pmol/m^2/mM, $p = 0.015$), with total insulin secretion (ISR $AUC_{0–2\,h}$) and a potentiation factor (expressing relative potentiation of insulin secretory response to glucose) during meals remaining unchanged. Body weight decreased by 0.5 kg with vildagliptin and by 0.2 kg with placebo. Adverse events were similar in the two groups; hypoglycemia occurred in none of the vildagliptin patients and in one placebo patient.

After this study of 52 weeks, a washout period of 4 weeks was built in, followed by continuation of therapy in a subgroup of patients (n = 131). None of the effects of vildagliptin treatment at 52 weeks were present after the 4-week washout period, suggesting absence of a potential disease-modifying effect over 1 year of treatment. The potential for such an effect is suggested by preclinical studies showing that GLP-1, incretin mimetics, and DPP-4 inhibitors inhibit apoptosis, augment β-cell function, and increase β-cell mass in rodent models with a high rate of β-cell turnover. However, results of the 52-week extension after the 4-week washout following the core 52-week study (total 104 treatment weeks and 4 weeks washout period) suggest that vildagliptin treatment may attenuate deterioration of β-cell function over 2 years of treatment in mild hyperglycemia. Among the 131 patients in the extension study (vildagliptin, n = 68; placebo, n = 63), vildagliptin patients had a significant reduction vs placebo in HbA1c after the second 52-week treatment period (−0.5%, $p = 0.008$). Placebo-adjusted changes from core study baseline values in FPG, glucose $AUC_{0–2\,h}$, and ISR $AUC_{0–2\,h}$/glucose $AUC_{0–2\,h}$ tended to be greater after 2 years than after 1 year of vildagliptin treatment. After the second washout period (week 112), the placebo-adjusted change from week 0 to week 112 in ISR $AUC_{0–2\,h}$/glucose $AUC_{0–2\,h}$ was 3.2 pmol/min/m^2/mM ($p = 0.058$) and the placebo-adjusted change in HbA1c was −0.3% ($p = 0.051$), indicating an attenuated rate of loss of

glycemic control in the absence of active treatment. Adverse events were similar in the two groups; two placebo patients and no vildagliptin patients had hypoglycemia. Body weight did not change significantly in placebo patients (−0.3 kg) and decreased significantly in vildagliptin patients (−1.1 kg, p = 0.026) compared with core study baseline.

Summary of pooled monotherapy results[2]

Pooled 24-week data from monotherapy arm show that vildagliptin is effective across the range of levels of hyperglycemia and baseline BMI values and in older and younger patients. For all patients receiving 50 mg bid (n = 1569), change in HbA1c from baseline was −1.0%, including changes of −0.6% in those with baseline HbA1c ≤ 8.0% (n = 543), −0.9% for baseline HbA1c > 8.0–9.0% (n = 490), −1.6% for baseline HbA1c > 9.0%–10.0% (n = 362), and −1.9% for baseline HbA1c > 10.0% (n = 174) (p < 0.001 for all compared with baseline). Reductions from baseline HbA1c (8.6%–8.7%) according to BMI with vildagliptin 50 mg bid were 1.1% and 0.9% for <30 kg/m^2 (n = 819) and >30 kg/m^2 (n = 748), respectively, and 1.1% and 1.0% for <35 kg/m^2 (n = 1202) and >35 kg/m^2 (n = 365), respectively (p < 0.001 for all vs baseline). Reductions with 50 mg bid were 1.1% in both patients aged <65 years (n = 1326, baseline 8.7%) and those aged >65 years (n = 243, baseline 8.4%).

Changes in fasting lipids with vildagliptin treatment were minor, consisting of reductions of 0.6%, 2.7%, and 2.0% in triglycerides, total cholesterol, and LDL cholesterol, respectively, and an increase of 3.9% in HDL cholesterol at the 50 mg bid dose. Rates of peripheral edema were similar to that seen with placebo, consisting of 0.9% with vildagliptin 50 mg qd (n = 655), 1.3% with vildagliptin 50 mg bid (n = 2251), 2.0% with metformin up to 2000 mg/d (n = 252), 4.1% with rosiglitazone 8 mg/d (n = 267), 7.9% with pioglitazone 30 mg/d (n = 216, in a monotherapy arm in a combination study discussed below), and 1.2% with placebo (n = 586). There was a low risk of hypoglycemia, and rates of other clinical adverse events were comparable to those seen with placebo (Table 1).

Table 1: Incidence of adverse events (≥5%) and incidence of hypoglycemic events in vildagliptin monotherapy trials (pooled data at 24 weeks)

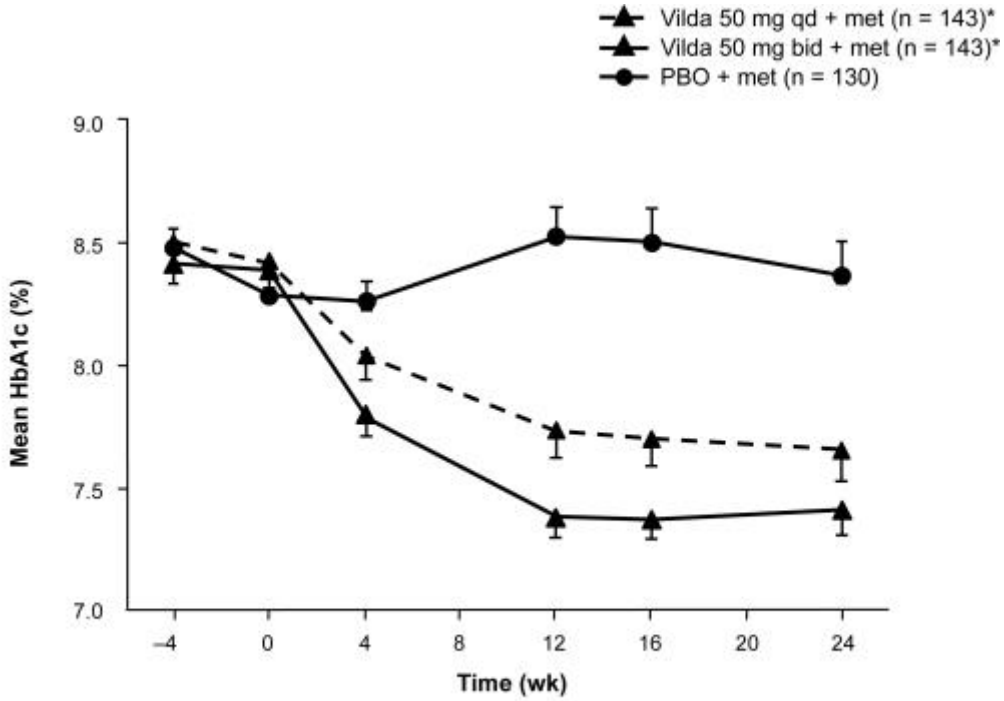
	No (%)					
	Vildagliptin 50 mg qd (n = 655)	**Vildagliptin 50 mg bid (n = 2251)**	**Metformin ≤1g bid (n = 252)**	**Rosiglitazone 8 mg qd (n = 267)**	**Acarbose ≤100 mg tid (n = 220)**	**Placebo (n = 586)**
Adverse events in ≥ 5% of patients						
Nasopharyngitis	37 (5.6)	128 (5.7)	13 (5.2)	20 (7.5)	14 (6.4)	36 (6.1)
Headache	35 (5.3)	112 (5.0)	13 (5.2)	14 (5.2)	1 (0.5)	23 (3.9)
Dizziness	29 (4.4)	105 (4.7)	10 (4.0)	11 (4.1)	9 (4.1)	20 (3.4)
Upper respiratory tract infection	11 (1.7)	75 (3.3)	5 (2.0)	8 (3.0)	11 (5.0)	20 (3.4)
Diarrhea	10 (1.5)	64 (2.8)	57 (22.6)	7 (2.6)	6 (2.7)	12 (2.0)
Nausea	10 (1.5)	53 (2.4)	23 (9.1)	2 (0.7)	0	13 (2.2)
Hypoglycemic events						
≥1 event	2 (0.3)	7 (0.3)	0	1 (0.4)	0	1 (0.2)
Discontinued due to event	0	0	0	0	0	0
Grade 2 event	0	0	0	0	0	0

Combination therapy[2]

Vildagliptin has been assessed in randomized, double-blind trials as add-on therapy to metformin, SU, thiazolidinedione, and insulin treatment and in initial combination with pioglitazone.

Add-on to metformin vs placebo[2]

A total of 544 patients with inadequate glycemic control (HbA1c 7.5%–11.0%; mean 8.3%–8.4%) on a metformin regimen of ≥1500 mg/d were randomized to vildagliptin 50 mg qd (n = 177) or 50 mg bid (n = 185) or placebo (n = 182) while continuing on metformin for 24 weeks; metformin in all patients was titrated up to ≥2000 mg/d by study baseline, and the mean study dose was 2100 mg/d (-). HbA1c was reduced by a mean of 0.7% with the addition of vildagliptin 50 mg qd and by 1.1% with vildagliptin 50 mg bid compared with metformin/placebo (both $p \leq 0.001$) (Figure 1). FPG (baseline 9.7–10.1 mmol/L) was reduced by 0.8 mmol/L ($p = 0.003$) and 1.7 mmol/L ($p < 0.001$), respectively, with vildagliptin 50 mg qd and bid. In predefined analyses, the addition of vildagliptin 50 mg bid produced changes in HbA1c vs metformin/placebo of −1.3% vs −0.2% in patients aged ≥65 years (vildagliptin, n = 20; metformin/placebo, n = 22; baseline ~8.3%), −0.8% vs +0.2% in those with baseline BMI ≥ 30 kg/m^2 (vildagliptin, n = 103; metformin/placebo, n = 86; baseline ~8.3%), and −1.3% vs 0.0% in those with baseline HbA1c >9.0% (vildagliptin, n = 29; metformin/placebo, n = 29. The HbA1c target of <7.0% was reached in 54% of vildagliptin 50 mg bid patients, 50% of vildagliptin 50 mg qd patients, and 14% of metformin/placebo patients starting treatment with HbA1c ≥8.0% and in 31%, 22%, and 13%, respectively, of those starting at HbA1c > 8.0%–8.5% (-). Improved β-cell function with the addition of vildagliptin was shown by significant increases in adjusted mean ISR $AUC_{0–2\ h}$/glucose $AUC_{0–2\ h}$ with vildagliptin qd (n = 53; +6.9 pmol/min/m^2/mM) and bid (n = 57; +7.3 pmol/min/m^2/mM) vs metformin/placebo (n = 54; +1.6 pmol/min/m^2/mM; $p \leq 0.001$ for both comparisons); adjusted mean changes in 2-hour postprandial glucose were −1.9, −2.3, and −0.1 mmol/L, respectively ($p \leq 0.001$ for both vs metformin/placebo).



*p < 0.001 vs PBO; Mean ± SE primary IT T population (intention-to-treat).
HbA1c, glycosylated hemoglobin; ITT, intention-to-treat; met, metformin; PBO, placebo; vilda, vildagliptin.

Figure 1: Mean HbA1c ± SE in patients receiving vildagliptin qd or bid or placebo as an add-on to metformin therapy (≥1500 mg/d). Reproduced with permission from –. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Care*, 30:890–5. Copyright © 2007 American Diabetes Association.

There were no significant changes in body weight from baseline (mean 93–95 kg) with vildagliptin qd (−0.4 kg) or bid (+0.2 kg) and a significant decrease with metformin/placebo (−1.0 kg, $p < 0.001$) (-). Among patients with baseline DPB ≥ 90 mmHg and SBP ≥ 140 mmHg (vildagliptin 50 mg bid, n = 57; metformin/placebo, n = 59), reductions in DBP were −4.0 mmHg with vildagliptin 50 mg bid ($p < 0.05$) and −0.9 mmHg with metformin/placebo (p = NS) and reductions in SBP were −9.8 ($p < 0.05$) and −6.3 ($p < 0.05$), respectively. Vildagliptin had a neutral effect on fasting lipids; changes for vildagliptin qd, vildagliptin bid, and metformin/placebo were, respectively, +1.0% ($p = 0.014$ vs metformin/placebo), +4.8%, and +18.4% for triglycerides; −1.6%, −1.8%, and +1.7% for total cholesterol; +0.4%, +1.8%, and +0.7% for LDL cholesterol; and −0.6%, +0.2%, and +2.0% for HDL cholesterol. Adverse events occurred with similar frequency in all treatment groups (63.3%–65.0%), with GI adverse events occurring in 9.6% of patients ($p = 0.022$ vs metformin/placebo) on vildagliptin qd,

14.8% of those on vildagliptin bid, and 18.2% of those on metformin/placebo. Mild hypoglycemia occurred in one patient in each group (0.6% with vildagliptin qd, 0.5% with vildagliptin bid, and 0.6% with metformin/placebo).

Add-on to insulin vs placebo[2]

A total of 296 patients with inadequate glycemic control on insulin (HbA1c 7.5%–11.0%, baseline ~8.4%, mean duration of insulin use ~6 years) received vildagliptin 50 mg bid (n = 144) or placebo (n = 152) plus ongoing insulin for 24 weeks; the mean daily insulin dose at baseline was 81.2–81.9 U, and dose adjustments were permitted during the study. The change in insulin dose was +1.2 U in the vildagliptin group and +4.1 U in the insulin/placebo group. Changes in HbA1c were −0.5% with vildagliptin and −0.2% with insulin/placebo ($p = 0.01$); among patients aged ≥65 years (vildagliptin, n = 42; insulin/placebo, n = 41; baseline 8.4%), changes were −0.7% with vildagliptin add-on and −0.1% with insulin/placebo. Vildagliptin was associated with significant reductions in number of hypoglycemic episodes (113 vs 185, $p < 0.001$) and number of severe events (0 vs 6, $p < 0.05$). The change in body weight was +1.3 kg in vildagliptin/insulin patients and +0.6 kg in insulin/placebo patients.

In an extension of this trial, 96 patients on vildagliptin 50 mg bid continued on treatment and 104 in the insulin/placebo group switched to vildagliptin 50 mg qd plus ongoing insulin for an additional 28 weeks (total 52 weeks) (-). During the extension phase, the average insulin dose increased by approximately 2 U. At 52 weeks, the efficacy of vildagliptin 50 mg bid in reducing HbA1c was maintained (−0.5%); in patients receiving vildagliptin 50 mg qd, the change between week 24 and week 52 was −0.4%. In patients aged ≥65 years receiving 50 mg bid, the change in HbA1c at 52 weeks was −0.9%, compared with −0.24% in younger patients, indicating that overall efficacy primarily reflected the effect in older patients. There was no significant change in body weight with continued 50 mg bid treatment (+0.3 kg during the extension; +1.8 kg over 52 weeks) or during the extension in patients switched to 50 mg qd (+0.5 kg). The rate of hypoglycemic events per patient-year was 1.80 in the 50 mg bid group and 1.78 in the 50 mg qd group, compared with 2.66 in the insulin/placebo group during the core study; in the elderly patients, event rates were 2.1 and 2.3 in the vildagliptin groups, compared with 3.3 in insulin/placebo patients during the core study.

Pharmacokinetics of metformin[3]

The optimal oral metformin dose for many diabetic patients is ~2 g/day. After a single oral dose, metformin is rapidly distributed to many tissues following partial absorption by the small intestine, but the luminal concentration in the gastrointestinal tract remains high. The peak plasma concentration occurs in 3 hr (increasing from 1.0 to 1.6 mg/ml [about 6 to 10 mM] after a 0.5 g dose and to ~3 mg/ml [about 18 mM] after a 1.5 g dose) with a mean plasma half-life of about 20 hr. When the human metformin dose of 20 mg/kg/day orally is translated to the mouse equivalent dose of 250 mg/kg/day, according to the normalization to body surface area, murine plasma levels of metformin of up to 1.7 mg/ml (about 10 mM) are achieved. This is in the range achieved when conventional antidiabetic doses are used in humans. Biodistribution studies in mice using 14C-labeled metformin showed accumulation mainly in the gastrointestinal tract, kidney, and liver. It is important to note that being supplied directly by blood coming from the portal vein, the liver may contain a concentration of orally administered metformin substantially higher than in the general circulation and other organs. Metformin liver concentrations of greater than 180 mmol/kg wet weight and 250 mmol/kg wet weight in normal and diabetic rodents, respectively, can be achieved after a single dose of 50 mg/kg.

Cellular uptake of metformin[3]

Metformin is an unusually hydrophilic drug that mostly exists in a positively charged protonated form under physiological conditions. These physicochemical properties make rapid and passive diffusion through cell membranes unlikely. Indeed, transport of metformin involves an active uptake process via solute carrier organic transporters. The intestinal absorption of metformin is primarily mediated by the plasma membrane monoamine transporter (PMAT, SLC29A4 gene), which is localized on the luminal side of enterocytes. Organiccation transporter 1 (Oct1, SLC22A1 gene) is expressed on the basolateral membrane of enterocytes and may be responsible for the transport of metformin into the interstitial fluid. The primary mediator of hepatic metformin uptake is OCT1 and possibly OCT3 (SLC22A3 gene), expressed at the basolateral membrane of hepatocytes. The clearance of metformin is dependent on renal elimination, as metformin does not undergo relevant biotransformation in the liver or biliary excretion. In the kidney, metformin is taken up into renal epithelial cells by OCT2 (SLC22A2 gene), expressed on the basolateral membrane, and excreted into the urine

via multidrug and toxin extrusion 1 and 2 (MATE1 gene SLC47A1 and MATE2 gene SLC47A2).

Metformin and treatment of type 2 diabetes[3]

Metformin exerts its glucose-lowering effect primarily by decreasing hepatic glucose production through suppression of gluconeogenesis and enhancing insulin suppression of endogenous glucose production and, to a lesser extent, by reducing intestinal glucose absorption and possibly improving glucose uptake and utilization by peripheral tissues, such as skeletal muscle and adipose tissue. Of note, it has been reported that metformin does not improve peripheral insulin sensitivity, and improvements in insulin sensitivity in muscle may be related to the use of higher doses of metformin than clinically relevant. Additionally, metformin may also improve glucose homeostasis by interacting with the incretin axis through the action of glucagon-like peptide 1 (GLP-1). A recent study has found evidence that metformin and phenformin antagonize the action of the counter-regulatory hormone glucagon to suppress hepatic glucose production. Furthermore, Fullerton and colleagues recently showed that metformin-induced improvements in insulin action operate through alterations in hepatic lipid homeostasis via the inhibitory phosphorylation of acetyl CoA carboxylase (ACC) by AMPK.

Use of Metformin as first-line therapy[4]

As noted, metformin is preferred by most guideline committees as the initial therapy in individuals not able to achieve glycaemic targets despite diet and other lifestyle interventions. So widespread is its current use that virtually all diabetes drug development programmes include a series of studies involving the addition of the investigational compound to background metformin therapy. The drug's efficacy was best illustrated by DeFronzo *et al*, in a 1995 report. In 'protocol 1' of this study, 289 obese participants with uncontrolled diabetes, treated with diet alone, were assigned to receive metformin or placebo (forced titration from 850 mg daily to 850 mg thrice daily if fasting plasma glucose exceeded 7.8 mmol/l and side effects were tolerable). At 29 weeks, metformin resulted in a lower mean fasting plasma glucose of 10.6 vs 13.7 mmol/l with placebo ($p < 0.001$); compared with corresponding baseline values, fasting plasma glucose was reduced by 2.9 mmol/l in the metformin group and

increased by 0.3 mmol/l in the placebo group. With metformin, mean HbA1c decreased from 8.4% (68.3 mmol/mol) to 7.1% (54.1 mmol/mol), while, with placebo, it increased from 8.2% (66.1 mmol/mol) to 8.6% (70.5 mmol/mol; p <0.001).

The drug's efficacy is dose-dependent, as demonstrated by Garber and colleagues, who investigated the pharmacodynamic effects with different dosing regimens vs placebo, over 14 weeks in 451 individuals with type 2 diabetes. The minimal efficacious dose of metformin was 500 mg daily and maximal efficacy was achieved at a dose of 2000 mg daily. While some patients may benefit from doses as high as 2500 mg daily, in this study, overall, there were no major differences in fasting plasma glucose and HbA1c when compared with the proximate lower daily dose of 2000 mg. At 500 mg, metformin decreased fasting plasma glucose by an adjusted mean value of 1.1 mmol/l and HbA1c by 0.9% (9.8 mmol/mol; placebo-subtracted); at 2000 mg, the corresponding reductions were 4.3 mmol/l and 2.0% (21.9 mmol/mol; p ≤0.01). In both the studies by DeFronzo *et al*, and Garber *et al*, the drug was well tolerated with mild gastrointestinal (GI) side effects predominating and no increased risk of hypoglycaemia.

Since these original trials, follow-up and short-term studies (usually 3–6 months) using metformin have demonstrated mean HbA1c reductions on the order of 1% (10.9 mmol/mol) to 1.5% (16.4 mmol/mol), depending, in part, on the baseline value. In head-to-head trials, the drug has been shown to be equipotent to sulfonylureas, thiazolidinediones and glucagon-like peptide-1 (GLP-1) receptor agonists, and, in general, more potent than dipeptidyl peptidase-4 (DPP-4) inhibitors.

A Diabetes Outcome Progression Trial was a long-term randomised, double-blind, controlled clinical trial comparing the durability of glycaemic-control efficacy of a sulfonylurea (glibenclamide, known as glyburide in the USA and Canada), metformin and a thiazolidinedione (rosiglitazone), as initial treatment for recently diagnosed type 2 diabetes. After 5 years, progression to monotherapy 'glycaemic failure' (liberally defined as fasting plasma glucose >10.0 mmol/l) was least with rosiglitazone (15% of participants), intermediate with metformin (21%) and greatest with glibenclamide (34%). Similar results were found when using the alternative and perhaps more conventional glycaemic failure definition of plasma glucose >7.8 mmol/l. As compared with glibenclamide, metformin was associated with a 46% (p < 0.001) relative reduction in the risk of monotherapy failure. However, the durability of glycaemic control with metformin was not as great as with rosiglitazone (63% less monotherapy failure than glibenclamide and 32% less than metformin; p <0.001 for both).

Optimal glucose control, as measured by the time mean HbA1c was maintained at <7% (53.0 mmol/mol), was highest with rosiglitazone (57 months) intermediate for metformin (45 months) and lowest for glibenclamide (33 months). This landmark study once again illustrated the progressive nature of type 2 diabetes, as was initially reported by the UK Prospective Diabetes Study (UKPDS) in 1998. It also serves as a reminder that metformin, though seemingly better in attenuating this progression than insulin secretagogues, does not appear to substantially preserve beta cell function. This could also be considered as one conclusion of the Diabetes Prevention Program (DPP), which found that the transition from impaired glucose tolerance to type 2 diabetes was attenuated the most with lifestyle change, which had nearly twice as potent an effect as metformin.

Rationale for the combination of vildagliptin and metformin[1]

Because an incretin-based therapy acts by different mechanisms than metformin, combined therapy with metformin and a DPP4 inhibitor like vildagliptin was expected to be of considerable interest for the treatment of type 2 diabetes. Firstly, additive effects on plasma glucose lowering should be seen, which was first demonstrated with a combination of metformin and GLP-1 infusion in T2DM patients. Furthermore, beyond the additive effects of the drugs, the attractive potential of this combination would be to achieve the glucose lowering effect with beneficial effects on ß-cell function, without promoting weight gain or increasing the risk of hypoglycemia and without exacerbating the GI side effects of metformin. Clinical studies have indeed confirmed these expectations as outlined below.

An additional interesting aspect regarding the combination of metformin and a DPP4 inhibitor comes from the following recent research findings. Firstly, it was indicated that metformin increases plasma active GLP-1 in obese nondiabetic subjects, suggesting that metformin may have the additional property of inhibiting DPP IV activity. This increase in active GLP-1 with metformin was further confirmed by a number of studies, while the underlying mechanism is still the subject of debate: the increase could reflect a stimulation of GLP-1 secretion from intestinal L cells, an inhibition of renal GLP-1 excretion or an increased transcription/translation of the proglucagon gene, as well as an effective inhibition of DPP IV activity.

The clinical potential of this mechanistic research further emerged when Dunning et al compared the effects of vildagliptin on plasma levels of intact GLP-1 in drug-naïve patients

with T2DM versus patients receiving concomitant metformin. Relative to patients receiving no concomitant OAD, the effects of vildagliptin to increase plasma levels of both fasting and postprandial active GLP-1 were clearly and consistently enhanced in patients receiving concomitant metformin, a finding that likely extends to DDP4 inhibitors in general. The fact that vildagliptin substantially enhances the incretin effect in patients receiving concomitant metformin may underlie the pronounced efficacy of vildagliptin to decrease FPG, PPG and HbA1c in metformin-treated patients, as further discussed below.

Clinical data on combination therapy of vildagliptin and metformin[1]

The efficacy of a drug when combined with other agents can be different from that of the same drug prescribed as monotherapy: when used in combination, most drugs reduce HbA_{1c} to a lesser extent than in monotherapy. Furthermore, patients failing metformin monotherapy could have different characteristics and show a different response to hypoglycemic agents. Therefore, to reliably assess the efficacy of a new drug in combination with metformin, it is important to get data in patients insufficiently controlled with metformin monotherapy at stable, maximally tolerated doses. The efficacy and safety of the vildagliptin/metformin combination was studied accordingly in 2 placebo-controlled and 1 active-controlled trials.

The combination of vildagliptin plus metformin was initially evaluated in a 12-week phase II study with a 40-week, double-blind, placebo-controlled extension. In this population starting from a relatively low baseline HbA_{1c} of 7.6% and treated with metformin for a mean duration of 28 months and at a mean daily dose of 1.8 g/day, vildagliptin 50 mg daily added to metformin reduced mean HbA_{1c} by 1.1% relative to metformin/placebo after 52 weeks of treatment ($p < 0.001$). This reflected deterioration of glycemic control in patients receiving metformin alone and a stable HbA1c of ~7.1% maintained from week 12 to week 52 in patients treated with vildagliptin plus metformin, suggesting that the addition of vildagliptin prevented the progressive deterioration in glucose control seen in patients treated with metformin/placebo (Figure 2). The percentage of patients achieving the target of HbA_{1c} <7% at study end was 41.7% with vildagliptin plus metformin and 10.7% with placebo plus metformin (significant between-group difference) and the percentage of patients achieving a target of ≤6.5% was 21.4% with vildagliptin versus none with placebo. Two patients receiving vildagliptin during the core phase (out of 107 patients) experienced one episode of hypoglycemia and there were no hypoglycemic episodes during the extension. The lowering of fasting plasma glucose (FPG)

from baseline persisted in patients who took vildagliptin 50 mg qd plus metformin, and was significantly greater than in those taking placebo plus metformin (between group difference of 1.1 mmol/L). Body weight was unchanged with vildagliptin, showing no difference to placebo (+0.04 kg). Fasting triglycerides, as well as total and LDL cholesterol, were modestly improved with vildagliptin compared to placebo. Interestingly, additional analyses showed that the maintenance of efficacy over 52 weeks was associated with a sustained improvement in both insulin secretion and dynamic insulin sensitivity. Furthermore, vildagliptin significantly improved the efficiency of insulin processing by the β-cells, providing further evidence that vildagliptin treatment ameliorates abnormal β-cell function in patients with T2DM.

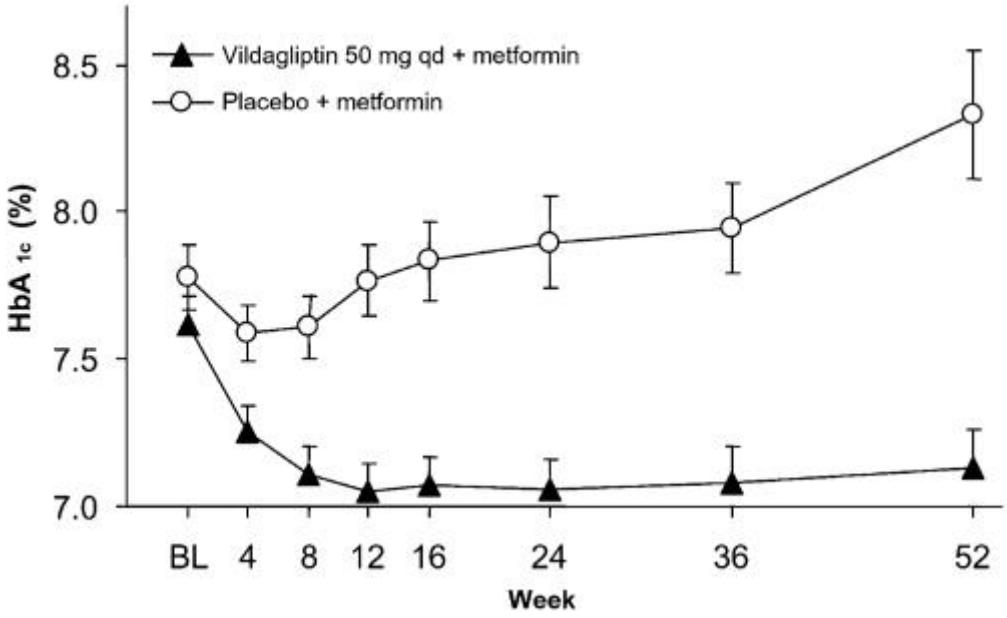


Figure 2: Mean (± SE) HbA_{1c} during 52-week treatment with vildagliptin (50 mg qd, closed triangles, n = 42) and placebo (open circles, n = 29) in metformin-treated patients with T2DM. The between-group difference in HbA1c from baseline to endpoint was −1.1 ± 0.2% ($p < 0.0001$). Copyright © American Diabetes Association. From Diabetes Care, Vol. 27, 2004; 2874–80. Modified with permission from The American Diabetes Association.

The combination of vildagliptin plus metformin was further evaluated in a 24-week phase 3 study conducted in patients with inadequate glycemic control (HbA_{1c} 7.5%–11%) despite a stable metformin dose (≥1500 mg/day, mean daily dose of 2100 mg with a mean duration of metformin use of 17 months) (Bosi et al 2007). Enrollees were randomized to vildagliptin 50 mg daily (given as 50 mg qd, n=177), vildagliptin 100 mg daily (given as 50 mg bid, n=185), or placebo (n=182). The demographic and diabetic background characteristics of the 3 groups were well balanced at baseline, with a mean age of 54 years, a mean BMI of 32.8 kg/m^2, a

mean disease duration of 6.2 years and a mean HbA_{1c} of 8.4% (Table 2). Relative to placebo the addition of vildagliptin to metformin resulted in significant and dose-related reductions in HbA_{1c} (−1.1 ± 0.1% and −0.7 ± 0.1% with vildagliptin 100 mg daily and 50 mg daily, respectively; $p < 0.001$ vs placebo for both), and in fasting plasma glucose (−1.7 ± 0.3 mmol/L [$p < 0.001$ vs placebo] and −0.8 ± 0.3 mmol/L [$p = 0.003$ vs placebo], respectively). The percentage of patients achieving the target of HbA_{1c} ,7% at study end was 35.5% with vildagliptin 100 mg daily plus metformin compared to 9.4% with placebo plus metformin and percentage of patients achieving a target of ≤6.5% was 18.2% with vildagliptin 100 mg daily plus metformin versus 3.1% with placebo plus metformin (both $p < 0.001$). In addition, treatment with vildagliptin elicited significant reductions from baseline in 2-hour postprandial glucose relative to placebo: −2.3 ± 0.6 mmol/L and −1.9 ±0.6 mmol/L with vildagliptin 100 mg and 50 mg daily ($p = 0.001$ vs placebo for both). Again, these effects were associated with significant improvements in measures of β-cell function: the β-cell function index, expressed as insulin secretory rate/glucose, increased significantly by 3-fold relative to placebo in both vildagliptin groups ($p < 0.001$). In patients aged ≥65 years, a pre-planned subgroup analysis showed a mean reduction from baseline in HbA_{1c} of 1.3 ± 0.2% with vildagliptin 100 mg/d compared to a small increase of 0.2 ± 0.1% with placebo.

Table 2: Patients' baseline characteristics: addition of vildagliptin in patients with inadequate glycemic control on maximum tolerated doses of metformin alone

	Study 1[a] Extension population		**Study 2[b] Randomized population**			**Study 3[c] Randomized population**	
	Vilda 50 mg qd + Met	**PBO + Met**	**Vilda 50 mg qd + Met**	**Vilda 50 mg bid + Met**	**PBO + Met**	**Vilda 50 mg bid + Met**	**Pio 30 mg qd + Met**
N	42	29	143	143	130	295	281
Age (years) (mean ± SD)	58.4 ± 9.2	54.3 ± 12.2	54.3 ± 9.7	53.9 ± 9.5	54.5 ± 10.3	56.3 ± 9.3	57.0 ± 9.7
Male/Female (%)	62/38	76/24	57/43	62/38	53/47	62/38	64/36
BMI (kg/m^2) (mean ± SD)	29.6 ± 3.7	29.9 ± 3.6	32.1 ± 5.3	32.9 ± 5.0	33.2 ± 6.1	32.2 ± 5.6	32.1 ± 5.1

HbA_{1c} (mean ± SD)	7.6 ± 0.6	7.8 ± 0.6	8.4 ± 0.9	8.4 ± 1.0	8.3 ± 0.9	8.4 ± 1.0	8.4 ± 0.9
FPG (mmol/L) (mean ± SD)	9.6 ± 1.6	10.1±1.8	9.7 ± 2.2	9.9 ± 2.56	10.0 ± 2.35	10.9 ± 2.6	11.0 ± 2.7
Duration of T2DM (years) (mean ± SD)	5.8 ± 4.2	4.6 ± 3.6	6.8 ± 5.5	5.8 ± 4.7	6.2 ± 5.3	6.4 ± 4.9	6.4 ± 5.2

[a]Study 1: A 52-week study of vildagliptin 50 mg daily added to metformin.

[b]Study 2: A 24-week study of vildagliptin (50 mg daily or 100 mg daily) or placebo added to metformin.

[c]Study 3: A 24-week study of vildagliptin (100 mg daily) or pioglitazone (30 mg daily) added to metformin.

Abbreviations: Vilda, vildagliptin; Met, metformin; PBO, placebo; Pio, pioglitazone.

Vildagliptin did not induce body weight gain (change from baseline of +0.21 and −0.38 kg with vildagliptin 100 and 50 mg daily, respectively, compared to −1.02 kg with placebo). The effect of vildagliptin on fasting lipids was largely neutral, with the exception of fasting triglycerides, which increased less in the vildagliptin treatment groups than in the placebo group (difference from placebo ranging from 14.5% to 18.4%). Effects of vildagliptin 100 mg daily and placebo on blood pressure (BP) were compared and showed modest improvements in BP in both groups with a significant benefit of vildagliptin versus placebo added to metformin.

The incidence of reported adverse events (AEs) was similar among groups (65.0%, 63.3%, and 63.5% of patients receiving vildagliptin 100 mg daily, 50 mg daily, or placebo, respectively). GI side effects were reported less frequently in the vildagliptin treatment groups (14.8% and 9.6% in the 100- and 50-mg daily groups, respectively) than in the placebo group (18.2%). One patient in each of the 3 groups experienced a mild hypoglycemic event, which did not lead to discontinuation. Discontinuations due to AEs were overall marginally more frequent with vildagliptin (4.4% and 4.5% respectively with 100 and 50 mg/d) than placebo (2.2%) (not driven by any specific AE), while serious AEs (SAEs) were marginally more common with placebo (4.4%) than with vildagliptin (2.7% and 2.3% with 100 and 50 mg daily, respectively), and there were no deaths.

An additional active-controlled study assessed the combination therapy of vildagliptin and metformin: a 24-week, multicenter, double-blind, randomized study, comparing vildagliptin (100 mg daily, given as equally-divided doses, n = 295) and pioglitazone (30 mg daily, given

as a single qd dose, n = 281) in patients with inadequate glycemic control (HbA_{1c} 7.5%–11%) despite metformin monotherapy (used for an average of 43 months) at a stable dose (mean dose at baseline >2000 mg/day).

The groups were well balanced at baseline, with a mean age, BMI, HbA_{1c}, and FPG of ~57 years, 32.1 kg/m^2, 8.4%, and 10.9 mmol/L, respectively. Patients were predominantly Caucasian, with mean disease duration of 6.4 years. When added to a stable dose of metformin, both vildagliptin 100 mg and pioglitazone 30 mg daily were equally effective in decreasing HbA_{1c} (by 0.9 ± 0.1% and 1.0 ± 0.1%, respectively) from identical baseline values (8.4 ± 0.1%) with statistical non-inferiority of vildagliptin to pioglitazone being established (Figure 3). The decrease in A1C in the pre-defined subgroup of patients with baseline A1C >9.0% was more substantial, as expected, and similar in vildagliptin-treated patients (baseline=9.8%; mean change = −1.5 ± 0.2%) and in those receiving pioglitazone (baseline = 9.7%; mean change= −1.5 ± 0.2%). The percentage of patients who achieved the endpoint of HbA_{1c} ≥6.5% was comparable in those receiving vildagliptin (19.7%) and pioglitazone (17.9%). Pioglitazone decreased FPG (−2.1 ± 0.1 mmol/L) to a greater extent than vildagliptin (1.4 ± 0.1 mmol/L), but only pioglitazone increased body weight (+1.9 ± 0.2 kg: between-group difference=−1.6 ± 0.3 kg, $p < 0.001$) (Figure 3). In the more obese patients (with BMI >35 kg/m^2), the mean change in body weight from baseline to endpoint was +0.1 ± 0.5 kg in patients receiving vildagliptin (baseline=110.6 kg, n = 73), and +2.6 ± 0.5 kg in pioglitazone-treated patients (baseline=110.3 kg, n=70; between-treatment difference −2.5 ± 0.7 kg [$p < 0.001$]). On the other hand, the efficacy tended to be more pronounced with pioglitazone in the obese patients (mean baseline BMI of 36 kg/m2) with a mean change in HbA_{1c} of −1.2% ±0.1% versus −0.8% ± 0.1% with vildagliptin, while the reverse was true in non obese patients (mean baseline BMI 27 kg/m^2) in whom the decrease in HbA_{1c} was somewhat greater in those receiving vildagliptin (1.0% ±0.1%) than pioglitazone (0.7% ± 0.1%).

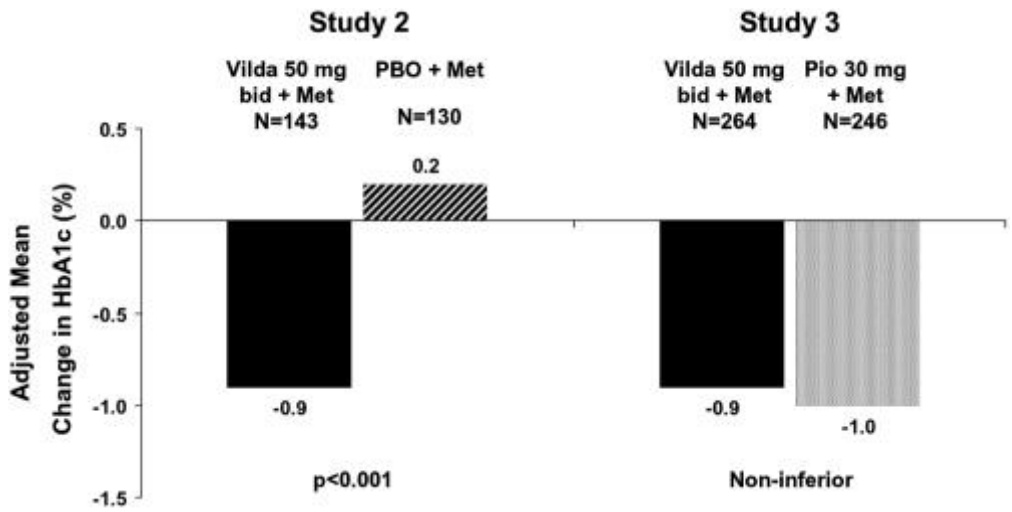


Figure 3: Study 2 – Adjusted mean change from baseline to endpoint in HbA_{1c} after 24 weeks of treatment with vildagliptin (50 mg bid) or placebo in metformin-treated patients with T2DM ($p < 0.001$).

Study 3 – Adjusted mean change from baseline to endpoint in HbA_{1c} after 24 weeks of treatment with vildagliptin (50 mg bid) or pioglitazone (30 mg qd) in metformin-treated patients with T2DM; the between group difference was 0.10 ± 0.08% (95 CI: −0.05, −0.26).

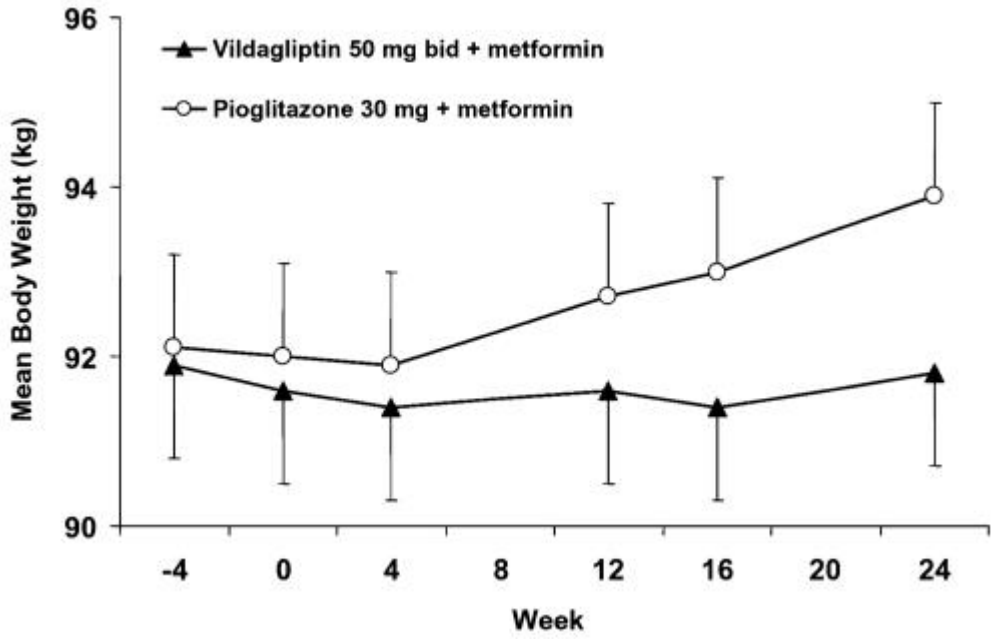


Figure 4: Study 3 – Time-course of mean body weight during 24-week treatment with vildagliptin (50 mg bid, closed triangles, n = 264) or pioglitazone (30 mg qd, open circles, n =

246) in T2DM patients continuing their previous stable metformin dose regimen (Derived from data of).

Fasting lipid levels were similar in the two treatment groups at baseline. Total-cholesterol, LDL-cholesterol and non-HDL cholesterol decreased in patients receiving vildagliptin and increased in pioglitazone-treated patients (with between-group differences of −6.9% ± 1.3% for total cholesterol, −10.2% ± 2.4% for LDL cholesterol, and −4.9% ± 1.9% for non-HDL cholesterol, all $p < 0.001$). Conversely, fasting triglycerides decreased more (between-treatment difference of 9.3% ± 3.2%, $p = 0.004$) and HDL-cholesterol increased more (between-treatment difference of −13.8% ± 1.6%, $p < 0.001$) in pioglitazone-treated patients. AEs were reported by 60% of patients receiving vildagliptin and by 56.4% of pioglitazone-treated patients; SAEs were reported by 2.0% and 4.6% of patients receiving vildagliptin and pioglitazone, respectively. Mild hypoglycemia was reported by 1 patient in the vildagliptin group (0.3%) and by no patient receiving pioglitazone.

In summary, the 3 double-blind, controlled studies evaluating combination therapy with vildagliptin and metformin showed statistically significant and clinically meaningful reductions in HbA_{1c} when vildagliptin was added to metformin of ~1% (Figure 4), that were evident across all demographic and disease subgroups. In patients with T2DM inadequately controlled with metformin, the addition of vildagliptin (100 mg daily) was equally effective as that of pioglitazone (30 mg daily). Efficacy was well preserved over 52 weeks in the placebo-controlled extension. Fasting and post prandial plasma glucose were significantly reduced; and the beneficial effects on glucose control was clearly accompanied by consistent improvements of parameters for β-cell function. The effects on fasting lipids were neutral and, in contrast to the pioglitazone/metformin combination (especially in the more obese patients) there was no weight gain. Overall the tolerability profile was good, with in particular no exacerbation of GI tolerability and there was no increased risk of hypoglycemia with vildagliptin and metformin combination therapy.

Vildagliptin as a fixed combination product with metformin – opportunities for improvement of adherence[1]

While early and aggressive treatment with multiple drug combinations becomes increasingly common in the management of T2DM, adding more medications may however translate into reduced adherence to treatment. Subsequently, efforts have been made to simplify the treatment

regimen with fixed-combination tablets to help improving treatment adherence in patients with T2DM who frequently take multiple medication. For this reason, vildagliptin and metformin have recently been made available in a single tablet.

This new galenical formulation combines fixed doses of vildagliptin and metformin in 2 dosage strengths of 50/850 and 50/1000 mg of vildagliptin and metformin, and was developed based on 4 additional pharmacokinetic (PK) studies: 3 cross-over design PK studies in healthy subjects, to assess if the fixed combination tablet was bioequivalent to the free combination of the active components, and 1 cross-over design PK study to assess the effect of food on the absorption of the fixed combination tablet.

These PK studies demonstrated that the fixed combination tablets are bioequivalent to the co-administered vildagliptin and metformin as free combinations. The efficacy and safety of the new combination tablet can thus be based on the data already available in T2DM patients insufficiently controlled with metformin monotherapy.

Glimepiride

Glimepiride has a molecular weight of 491 kd and is practically insoluble in water. Glimepiride is administered orally once daily starting at 1 mg/d, with titration based on glucose concentrations in the blood and urine; the recommended dosage in the United States is 8 mg/d.g Once-daily dosing is considered an advantage, as dosing frequency influences treatment compliance, and patients with type 2 diabetes are frequently receiving medications for concomitant disorders such as hypertension or dyslipidemia. A study in 91 patients taking oral antidiabetic medicines reported mean compliance rates of 79% with once-daily dosing, compared with 38% with thrice daily dosing.[5]

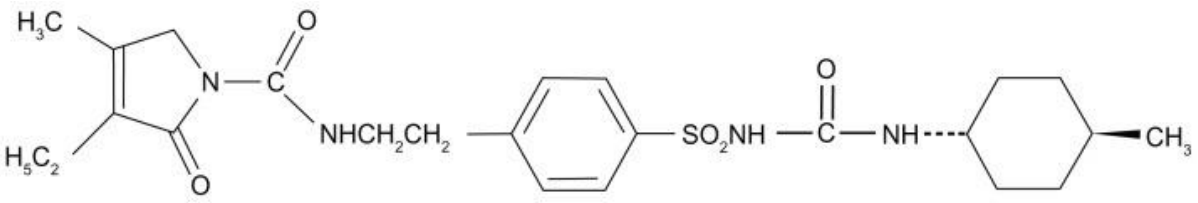


Figure 5. Chemical structure of glimepiride

Pharmacology and Pharmacokinetics

Glimepiride is a long-acting SU and, like other SUs, exerts its insulin-secreting effect via a pancreatic beta-cell receptor, resulting in a reduced likelihood of the opening of transmembrane potassium (KAi,) channels. The resulting depolarization opens voltage-dependent calcium channels and leads to calcium influx into the cell. In the presence of glucose, the elevated intracellular calcium levels trigger insulin secretion. The SU receptor on the KArp channel is composed of 2 units, comprising 1 pore-forming channel and 2 regulatory subunits. Different SUs attaches to different sites on the regulatory subunits, with distinct binding kinetics. Glimepiride has been shown to have a 2.5 to 3-fold lower binding affinity for the SU receptor compared with glibenclamide, but when other kinetic binding parameters were investigated, it was found that glimepiride had a 2.5- to 3-fold faster rate of association and an 8- to 9-fold faster rate of dissociation at the receptor site compared with glibenclamide. Glimepiride has also been shown to be specifically incorporated into a 65kd polypeptide in the beta-cell membrane, providing evidence of a novel binding site and confirming the observation that different SUs bind to different subunits of the SU-receptor complex. However, this 65-kd polypeptide has not yet been cloned or further characterized.[5]

Glimepiride is rapidly and completely absorbed after oral administration and is unaffected by food intake. There is no evidence of accumulation in the circulation after multiple doses. Glimepiride is completely metabolized by hepatic oxidative biotransformation; the hepatic cytochrome P450 2C9 isozyme transforms glimepiride to the cyclohexyl hydroxymethyl derivative (Ml), which is further metabolized by cytosolic enzymes to the carboxyl derivative (M2). After a single dose, the elimination half-life of glimepiride is 5 hours, increasing to 9 hours after multiple doses.[5]

Table 3. Pharmacokinetic properties of glimepiride

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 M_1 (hydroxyl) metabolite and then to inactive M_2 (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).

Pharmacodynamic Effects

Pancreatic effects[6]

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.'

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. 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 ($P < 0.05$).

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.

Extrapancreatic effects[6]

The extrapancreatic 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.

Advantages of glimepiride compared to other Sus[6]

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.

Efficacy and Safety Profile[5]

In a randomized clinical comparison involving 304 patients with type 2 diabetes, glimepiride significantly reduced fasting plasma glucose levels in a dose-dependent manner compared with placebo (P -c 0.001). Equivalent metabolic control was achieved with glimepiride and gliclazide in a multicenter, randomized, open-label, parallel-group study. Analysis of 6 multicenter studies involving >2400 patients whose diabetes was poorly controlled with diet and exercise found that glimepiride was as effective in producing metabolic control as glipizide and glibenclamide. Blood glucose levels were more rapidly reduced over the first few weeks of treatment with glimepiride compared with glipizide ($P < 0.05$).19 Overall, results of efficacy studies indicated at least therapeutic equivalence between glimepiride, glibenclamide, gliclazide, and glipizide. However, glimepiride achieved metabolic control at the lowest dosage

relative to other SUs (l-8 mg/d) and was able to provide maximal glycemic control with once-daily dosing.

A review of the data from controlled clinical trials in 2013 patients in the United States found that the incidence of treatment-emergent adverse events was similar between glimepiride, glibenclamide, gliclazide, glipizide, and placebo. A review of the data from 20 clinical studies involving >6500 patients reported an incidence of adverse events during glimepiride treatment similar to that with other SUszl Glucose-stimulated insulin release was preserved in isolated human islets in the presence of glimepiride but not in the presence of chlorpropamide or glibenclamide. These results suggest that pancreatic beta-cells maintain their capacity for glucose-stimulated insulin release in the presence of all 3 agents, but less so with chlorpropamide or glibenclamide. Such glucose-dependent insulin secretion is a desirable feature in an oral antidiabetic agent.

Hypoglycemia[5]

As a consequence of their stimulant effect on insulin secretion, older SUs (eg, glibenclamide) often induce hypoglycemia. The incidence of hypoglycemic events is high in patients with type 2 diabetes, with potentially serious cost implications. A recent study reported 148 cases of severe hypoglycemia in 121 patients surveyed over a 4-year period. An individual drug's pharmacokinetic properties are often the determining factor in its propensity to induce hypoglycemia. Newer agents exert glycemic control with less insulin release and consequently with less tendency to induce hypoglycemia. In a l-year, multicenter, randomized, double-blind, parallel-group comparative tria1, the cumulative occurrence of symptomatic hypoglycemia was 1.7% in the glimepiride group (n = 289) and 5.0% in the glibenclamide group (n = 288) (log rank = 0.015; P = 0.014, Wilcoxon rank sum test). An observational review of the literature by Rosskamp et a1 found no lifethreatening hypoglycemic episodes in 4500 patients with type 2 diabetes who received glimepiride therapy A multicenter, randomized, open-label, parallel-group study in 144 patients reported hypoglycemia as a presenting symptom in 24.0% of glimepiride recipients and 24.6% of gliclazide recipients. A double-blind study in which patients received 24 weeks of treatment with either glimepiride (n = 230) or gliclazide (n = 229) reported similar numbers of patients with hypoglycemic episodes in the 2 treatment groups (11 glimepiride, 6 gliclazide). Under normal conditions, exercise induces significant suppression of endogenous insulin secretion and increases muscular glucose uptake. SUs and

exercise both decrease blood glucose levels, and the extent of the interaction needs to be clearly defined, as the combination of exercise and SU treatment may lead to excessive blood glucose-lowering activity The effects on metabolic control of exercise combined with glimepiride or glibenclamide were examined in a multicenter, randomized, double-blind, parallel-group trial in 167 patients with type 2 diabetes. The trial consisted of 3 phases: a screening phase; a double-blind, parallelgroup stabilization phase; and an open-label, exercise test phase with a 2 x 2 factorial design. Efficacy was assessed in terms of changes from baseline to end point in the area under the plasma concentration-time curve over 1 to 3 hours for blood glucose and insulin. Pairwise comparisons were made using t tests, and the results were presented as the difference of mean changes from baseline to end point between patients with and without exercise in each drug-treatment group. A blood glucose-lowering response to acute exercise was observed in both the glimepiride and glibenclamide groups. Physical exercise did not induce a statistically significant change in serum insulin levels in the glibenclamide group, whereas significant suppression of insulin secretion was observed in the glimepiride group (P < O.OOl>, providing safer levels of circulating insulin.

Insulin-mimetic effects[5]

Because SUs reduce blood glucose concentrations by stimulating the secretion of insulin from pancreatic beta-cells, an inverse relationship between insulin release and glucose concentration would be expected. However, a review of the available data suggests that glimepiride reduces concentrations of blood glucose with little or no increase in circulating insulin. This finding has resulted in speculation that glimepiride exerts extrapancreatic, insulinlike effects on muscle and adipose tissues. Results of a recent study suggest that independent of its insulin secretagogic actions, glimepiride also reduces endogenous glucose production. Reduction of therapeutically induced hyperinsulinemia may be important, as experts have proposed an association between fasting plasma insulin levels and subsequent development of heart disease. However, the direct effects of insulin on the cardiovascular system are still under debate.

Del Guerra *et al* evaluated the direct effects of glimepiride on human pancreatic islets. Pancreatic islet cells were isolated and cultured from the pancreata of 7 human donors. Insulin release was assessed in response to glucose challenge 24 hours after treatment with glimepiride. Cells were incubated with glucose at concentrations of 2.5, 5, 10, or 20 mmol/L; the effect of glimepiride 0, 1, 10, and 100 urnoIL was assessed for each glucose concentration. At all

glucose concentrations, increasing levels of glimepiride caused increases in insulin secretion. Therefore, glimepiride treatment resulted in a physiologic insulin secretion profile, exhibiting biphasic secretion that was dependent on the ambient glucose level.

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Survey Form

1) In your clinical practise, what is the average HbA1c in patients presenting with T2DM?

a) 7-9%
b) 9-11%
c) >11%

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

a) Vildagliptin
b) Sitagliptin
c) Linagliptin
d) Alogliptin
e) Saxagliptin

3) Which is your preferred Sulfonylureas (SU)?

a) Glimepiride
b) Gliclazide
c) Glibenclamide
d) Glipizide

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

a) <25%
b) 26-50%
c) 51-75%
d) >75%

5) In your clinical practise, what percentage of your T2DM patients are controlled on a dual combination therapy?

a) <25%
b) 26-50%
c) 51-75%
d) >75%

6) What is your approach for management in patients with T2DM uncontrolled on dual therapy (Metformin + OHA) not including a SU, in your current clinical practice?

a) Add a SU
b) Increase the dose of the current agents.
c) Any other

7) Would you consider concomitantly using Vildagliptin, Glimepiride & Metformin in patients uncontrolled on dual therapy?

a) Yes
b) No

8) In your clinical experience, what percentage of T2DM patients currently would be concomitantly on Vildagliptin, Glimepiride & Metformin?

a) <10%
b) 10-20%
c) 20-50%
d) >50%

9) As per your opinion what will be the suitable patient profile for Vildagliptin + Glimepiride + Metformin combination therapy?

a) Patients with severe hyperglycemia at the time of diagnosis
b) Patients with uncontrolled hyperglycemia on dual combination therapy
c) Any other

10) As per your opinion, what could be the average duration of Vildagliptin + Glimepiride + Metformin combination Therapy in patients with T2DM?

a) <6 months
b) 6 months to 1 year
c) >1 year to 5 years
d) Life-long

11) What could be the potential side effects of the combination Vildagliptin + Glimepiride + Metformin?

a) Hypoglycemia
b) Weight gain
c) Any other

12) In your opinion, in what age group could the combination of Vildagliptin + Glimepiride + Metformin be preferred?

a) 20-40 years old
b) 40-60 years old
c) >60 years old

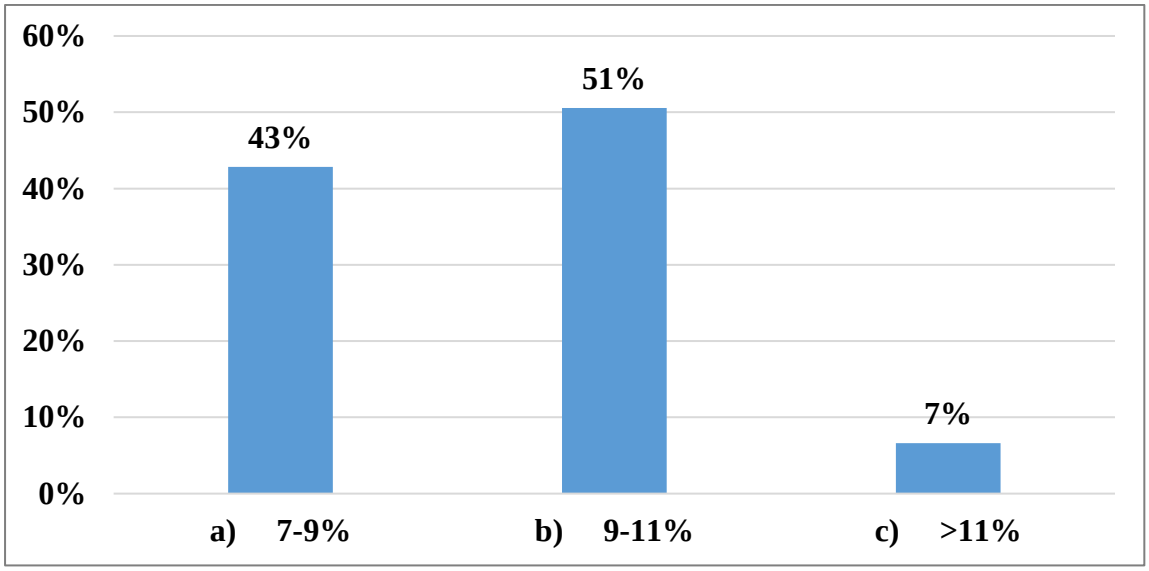
Survey Findings

1) In your clinical practise, what is the average HbA1c in patients presenting with T2DM?

a) 7-9%

b) 9-11%

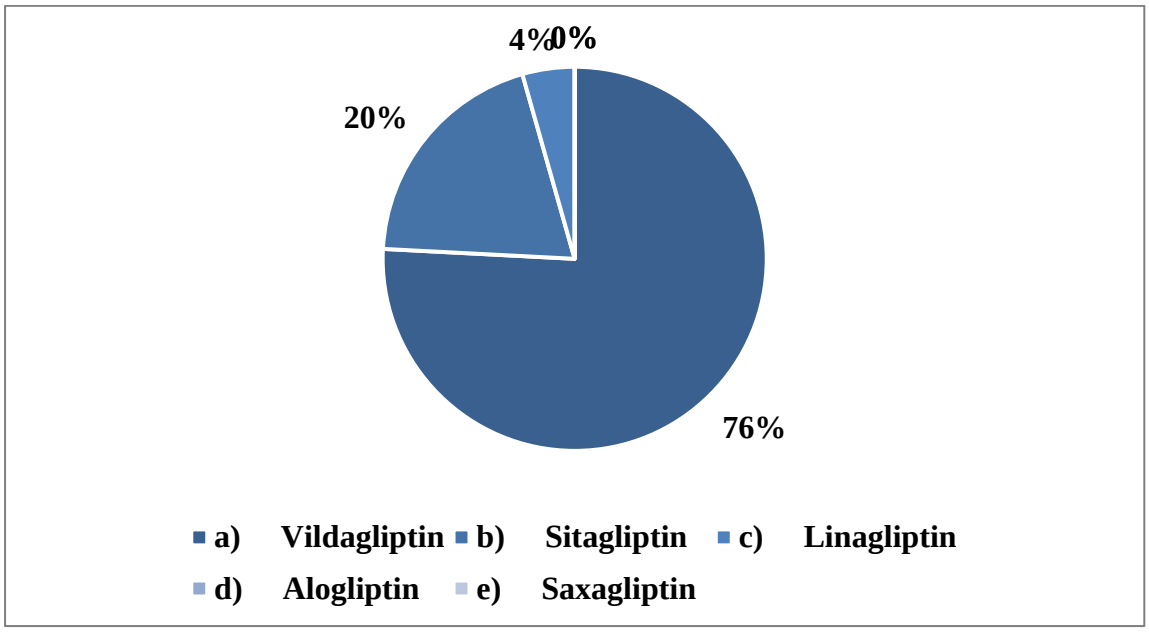
c) >11%



In the clinical practice of 51% of doctors, the average HbA1c in patients presenting with T2DM is 9 - 11%.

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

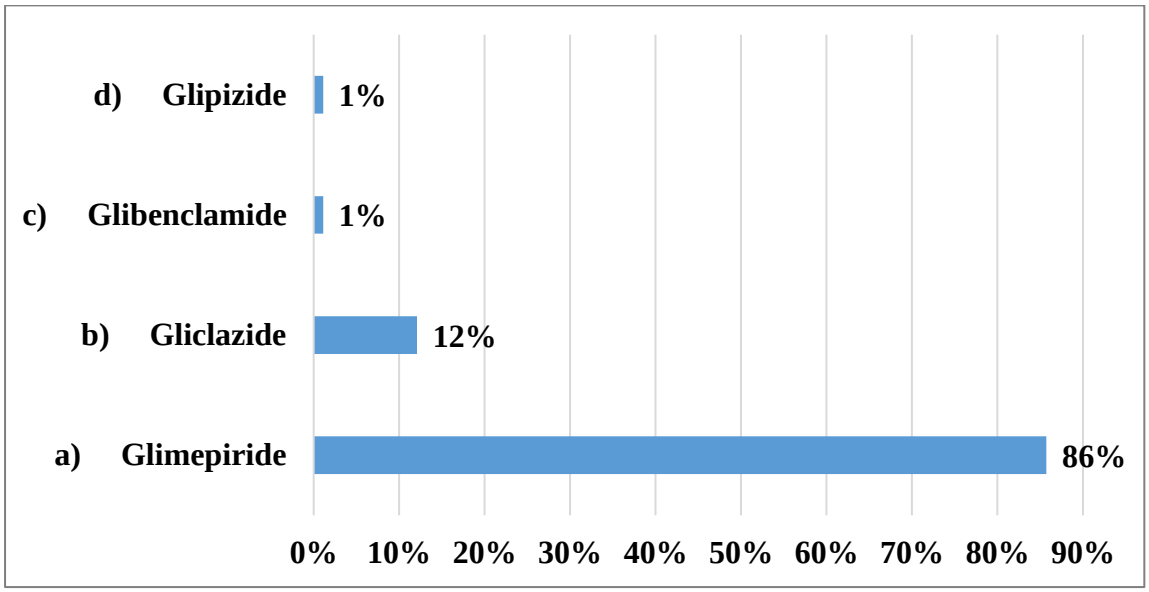
a) Vildagliptin
b) Sitagliptin
c) Linagliptin
d) Alogliptin
e) Saxagliptin



According to majority (51%) of doctors, the most preferred Dipeptidyl peptidase 4 (DPP-4) inhibitor in their current clinical practice is Vildagliptin.

3) Which is your preferred Sulfonylureas (SU)?

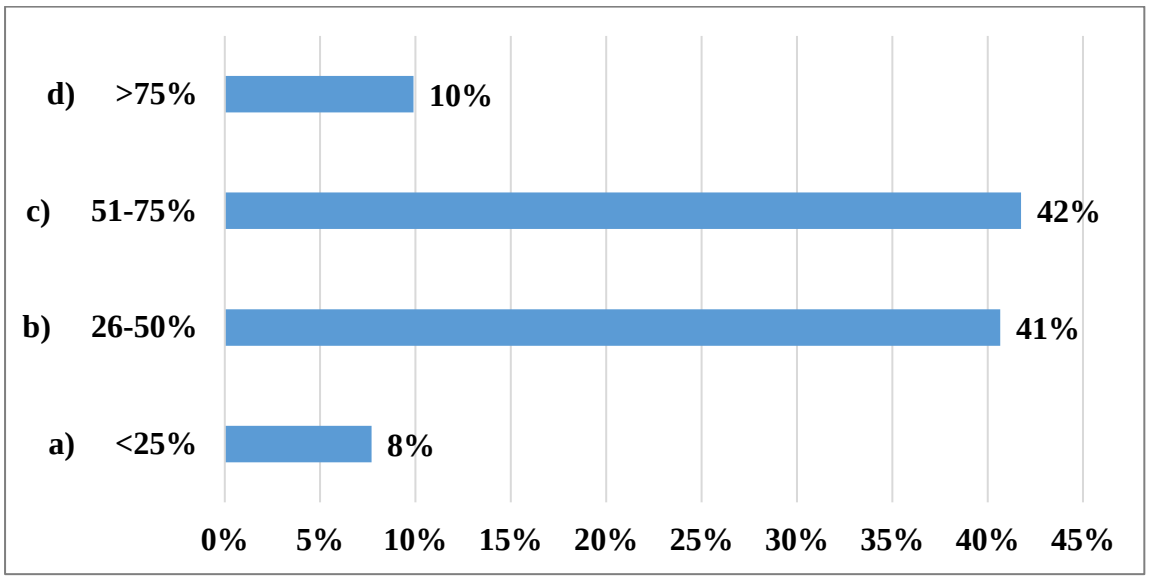
a) Glimepiride
b) Gliclazide
c) Glibenclamide
d) Glipizide



As per majority of doctors, 86%, their preferred Sulfonylureas (SU) is Glimepiride.

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

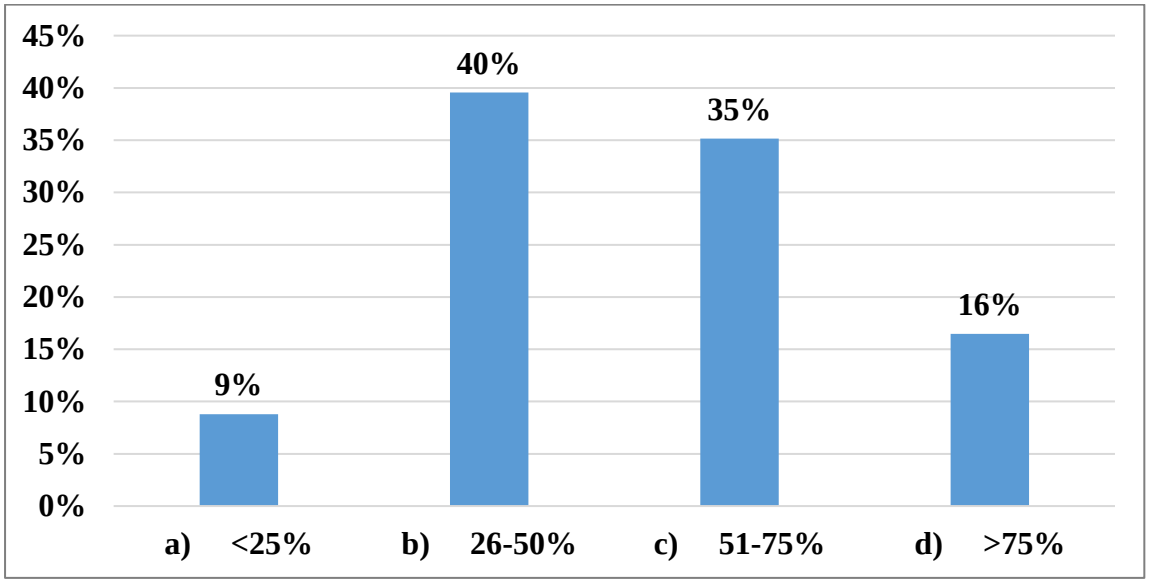
a) <25%
b) 26-50%
c) 51-75%
d) >75%



According to 42% of doctors, they find the to initiate therapy for T2DM with a combination need 51 – 75%.

5) In your clinical practise, what percentage of your T2DM patients are controlled on a dual combination therapy?

a) <25%
b) 26-50%
c) 51-75%
d) >75%



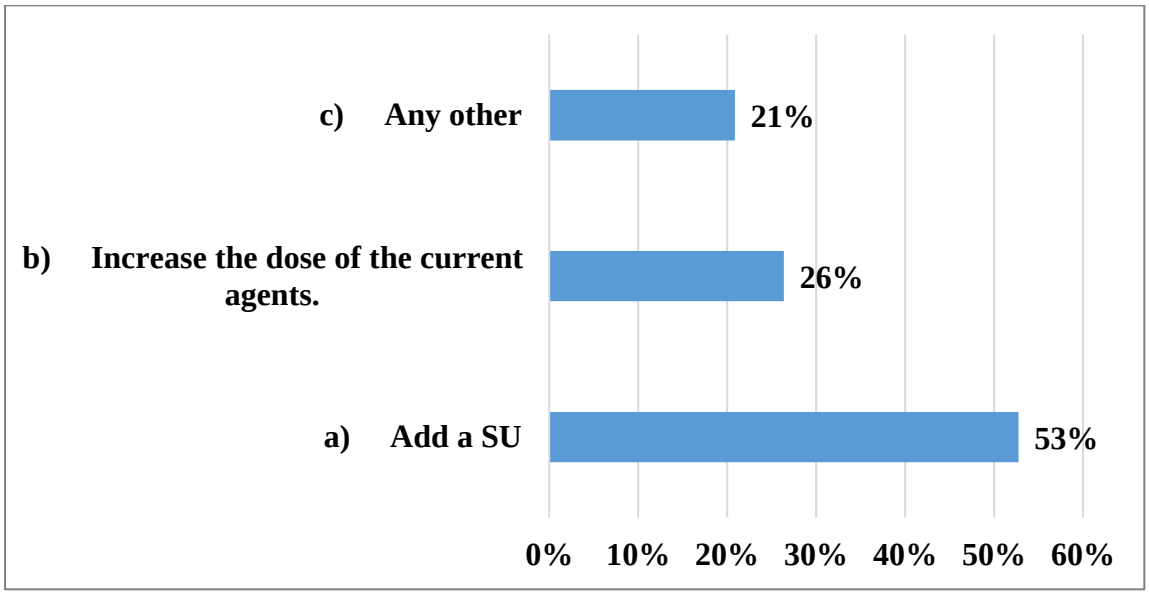
As per 40% of doctors, 26 – 50% of their T2DM patients are controlled on a dual combination therapy.

6) What is your approach for management in patients with T2DM uncontrolled on dual therapy (Metformin + OHA) not including a SU, in your current clinical practice?

a) Add a SU

b) Increase the dose of the current agents.

c) Any other

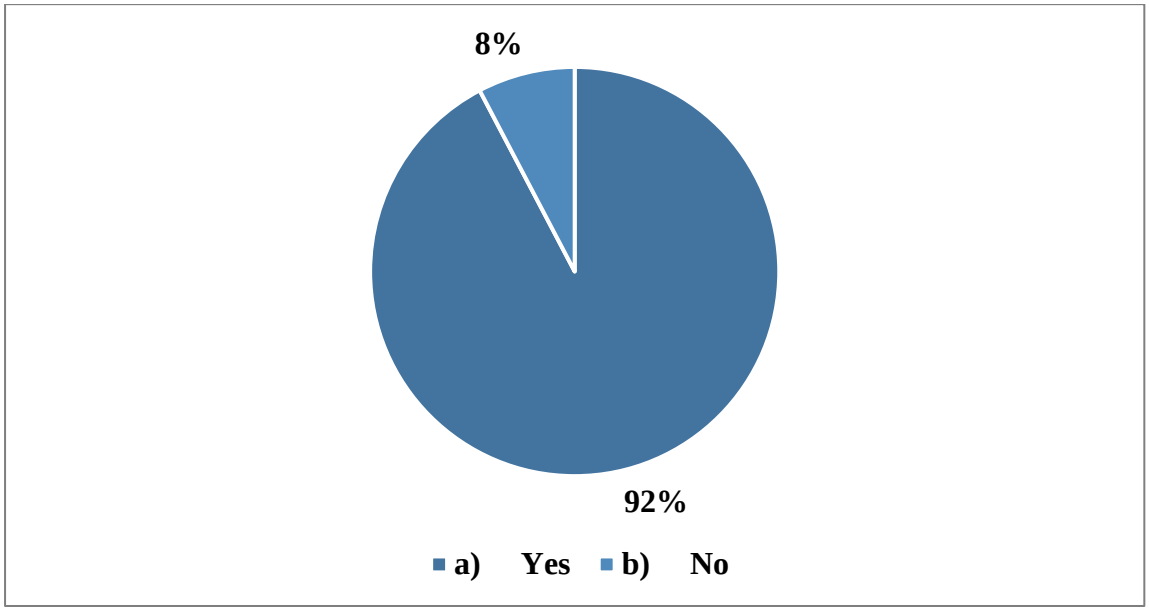


According to 53% of doctors, they manage patients with T2DM uncontrolled on dual therapy (Metformin + OHA) not including a SU, in their current clinical practice by adding a SU.

7) Would you consider concomitantly using Vildagliptin, Glimepiride & Metformin in patients uncontrolled on dual therapy?

a) Yes

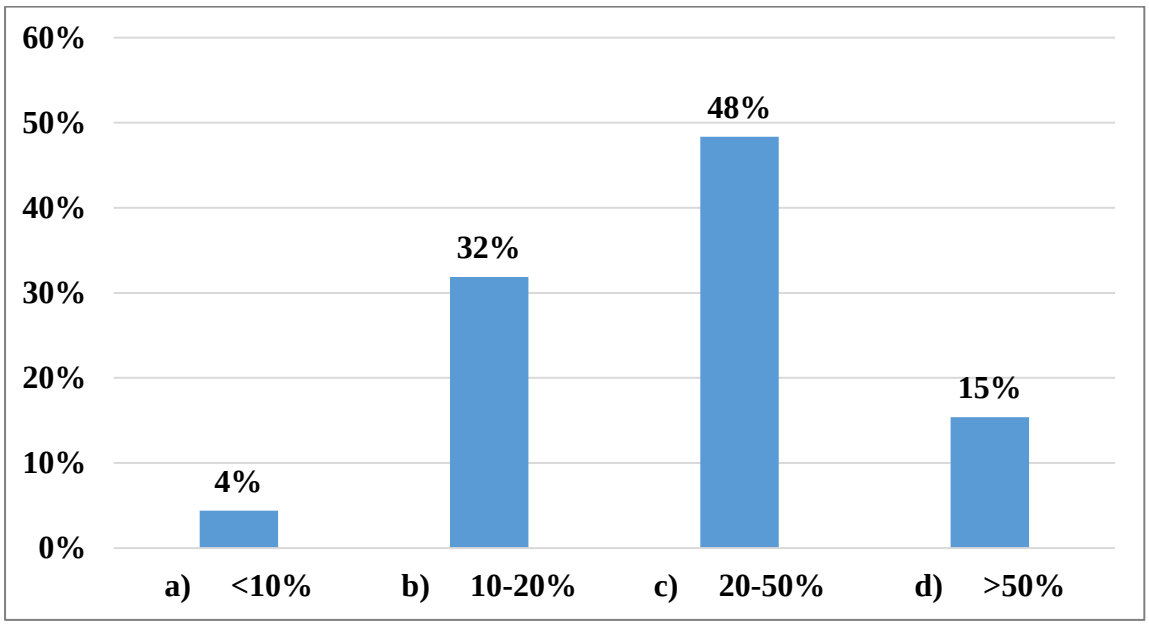
b) No



Majority of doctors, 92%, consider concomitantly using Vildagliptin, Glimepiride & Metformin in patients uncontrolled on dual therapy.

8) In your clinical experience, what percentage of T2DM patients currently would be concomitantly on Vildagliptin, Glimepiride & Metformin?

a) <10%
b) 10-20%
c) 20-50%
d) >50%



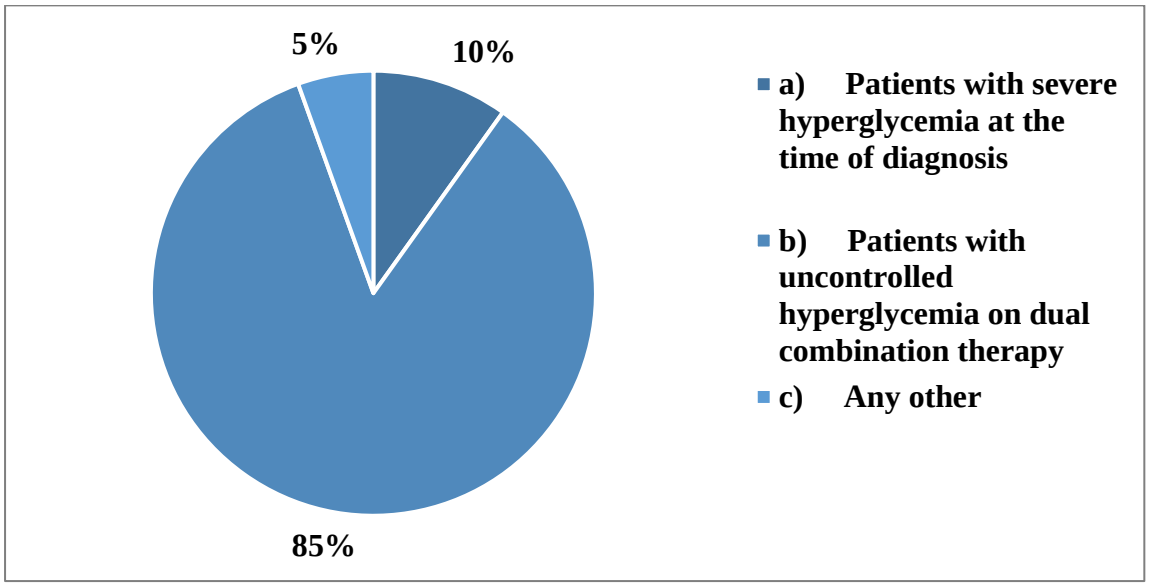
According to 48% of doctors, 20 – 50% of T2DM patients currently would be concomitantly on Vildagliptin, Glimepiride & Metformin.

9) As per your opinion what will be the suitable patient profile for Vildagliptin + Glimepiride + Metformin combination therapy?

a) Patients with severe hyperglycemia at the time of diagnosis

b) Patients with uncontrolled hyperglycemia on dual combination therapy

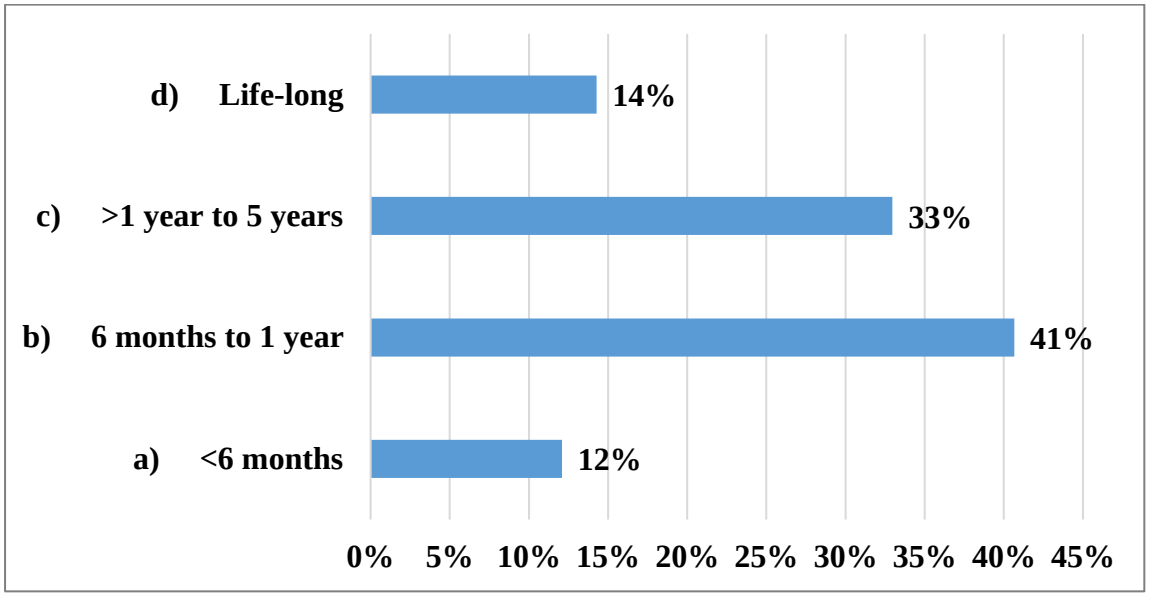
c) Any other



In the opinion of majority of doctors, 85%, the suitable patient profile for Vildagliptin + Glimepiride + Metformin combination therapy will be patients with uncontrolled hyperglycemia on dual combination therapy.

10) As per your opinion, what could be the average duration of Vildagliptin + Glimepiride + Metformin combination Therapy in patients with T2DM?

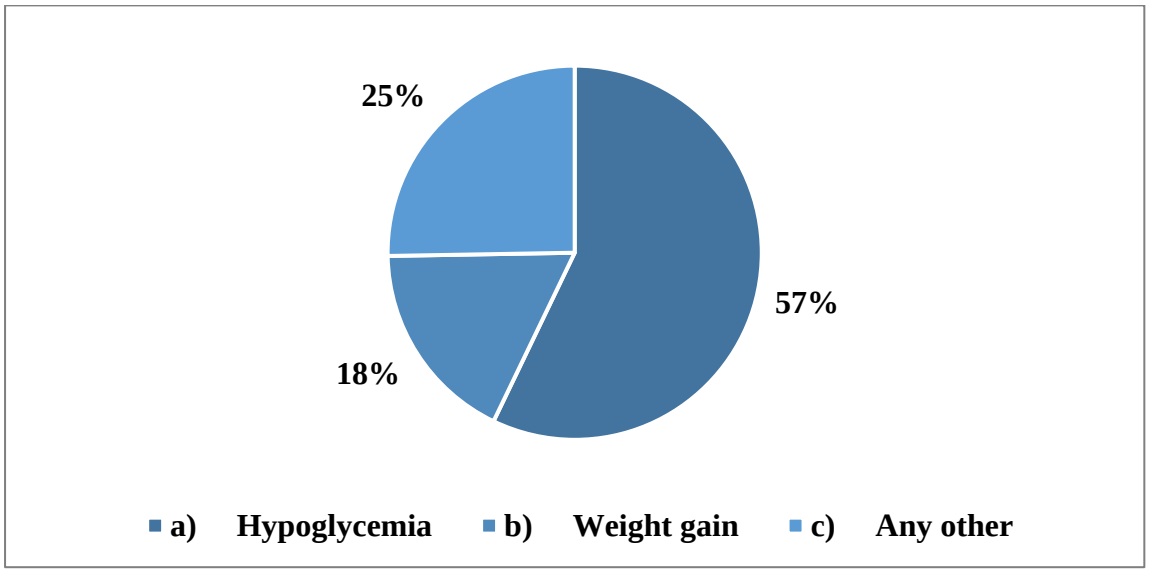
a) <6 months
b) 6 months to 1 year
c) >1 year to 5 years
d) Life-long



According to 41% of doctors, the average duration of Vildagliptin + Glimepiride + Metformin combination Therapy in patients with T2DM could be 6 months to 1 year.

11) What could be the potential side effects of the combination Vildagliptin + Glimepiride + Metformin?

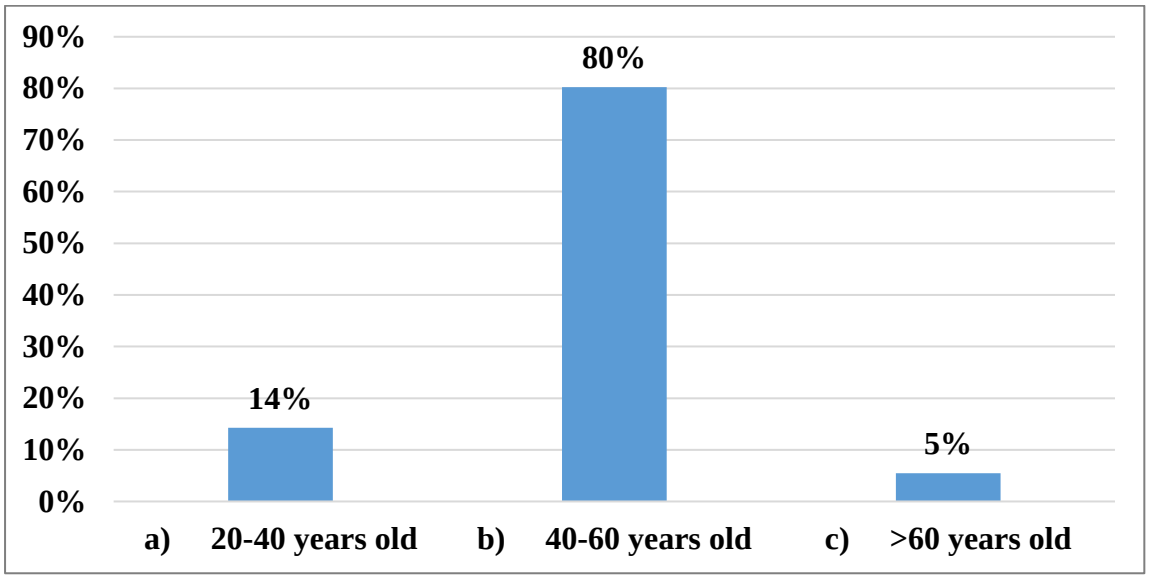
a) Hypoglycemia
b) Weight gain
c) Any other



As per 57% of doctors, the potential side effects of the combination Vildagliptin + Glimepiride + Metformin could be hypoglycemia.

12) In your opinion, in what age group could the combination of Vildagliptin + Glimepiride + Metformin be preferred?

a) 20-40 years old
b) 40-60 years old
c) >60 years old



In the opinion of majority of doctors, 80%, combination of Vildagliptin + Glimepiride + Metformin could be preferred for age group of 40 – 60 years.

Summary

- In the clinical practice of 51% of doctors, the average HbA1c in patients presenting with T2DM is 9 - 11%.
- According to majority (51%) of doctors, the most preferred Dipeptidyl peptidase 4 (DPP-4) inhibitor in their current clinical practice is Vildagliptin.
- As per majority of doctors, 86%, their preferred Sulfonylureas (SU) is Glimepiride.
- According to 42% of doctors, they find the to initiate therapy for T2DM with a combination need 51 – 75%.
- As per 40% of doctors, 26 – 50% of their T2DM patients are controlled on a dual combination therapy.
- According to 53% of doctors, they manage patients with T2DM uncontrolled on dual therapy (Metformin + OHA) not including a SU, in their current clinical practice by adding a SU.
- Majority of doctors, 92%, consider concomitantly using Vildagliptin, Glimepiride & Metformin in patients uncontrolled on dual therapy.
- According to 48% of doctors, 20 – 50% of T2DM patients currently would be concomitantly on Vildagliptin, Glimepiride & Metformin
- In the opinion of majority of doctors, 85%, the suitable patient profile for Vildagliptin + Glimepiride + Metformin combination therapy will be patients with uncontrolled hyperglycemia on dual combination therapy.
- According to 41% of doctors, the average duration of Vildagliptin + Glimepiride + Metformin combination Therapy in patients with T2DM could be 6 months to 1 year.
- As per 57% of doctors, the potential side effects of the combination Vildagliptin + Glimepiride + Metformin could be hypoglycemia.
- In the opinion of majority of doctors, 80%, combination of Vildagliptin + Glimepiride + Metformin could be preferred for age group of 40 – 60 years.

Consultant Opinion

Market Opportunities:

The survey highlights the prevalent use of Vildagliptin as the preferred DPP-4 inhibitor and Glimepiride as the preferred Sulfonylureas (SU). This suggests a significant market opportunity for pharmaceutical companies manufacturing these drugs to further establish their presence in the T2DM treatment landscape.

Value for Healthcare Professionals:

Healthcare professionals should continue to receive education and training on the optimal use of combination therapies for T2DM management. This includes understanding the rationale for combining different classes of drugs and the potential benefits for patients.

Adverse Effect Management:

Given the concern about hypoglycemia associated with the combination of Vildagliptin, Glimepiride, and Metformin, healthcare professionals should be vigilant in monitoring patients for signs of hypoglycemia and provide appropriate education on its prevention and management.

Withdrawal Management:

Clear guidelines should be established for initiating combination therapy in patients with T2DM, particularly in those who are uncontrolled on dual therapy. Healthcare professionals should be equipped with evidence-based protocols for adjusting treatment regimens as needed to optimize glycemic control while minimizing the risk of adverse effects.

Market Positioning:

Pharma companies can capitalize on the preference for combination therapy by developing and marketing fixed-dose combinations that include Vildagliptin, Glimepiride, and Metformin. These products can offer convenience and potentially improve patient adherence to treatment.

Personalized Treatment Decisions:

Healthcare professionals should consider individual patient characteristics, such as age and comorbidities, when selecting combination therapies for T2DM management. Tailoring treatment regimens to meet the unique needs of each patient can optimize glycemic control and improve overall outcomes.

Improving Patient Outcomes:

Emphasizing the importance of combination therapy for patients with uncontrolled T2DM can help improve patient outcomes by addressing multiple pathophysiological mechanisms of hyperglycemia. Healthcare professionals should prioritize achieving and maintaining glycemic control to reduce the risk of complications associated with T2DM.

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