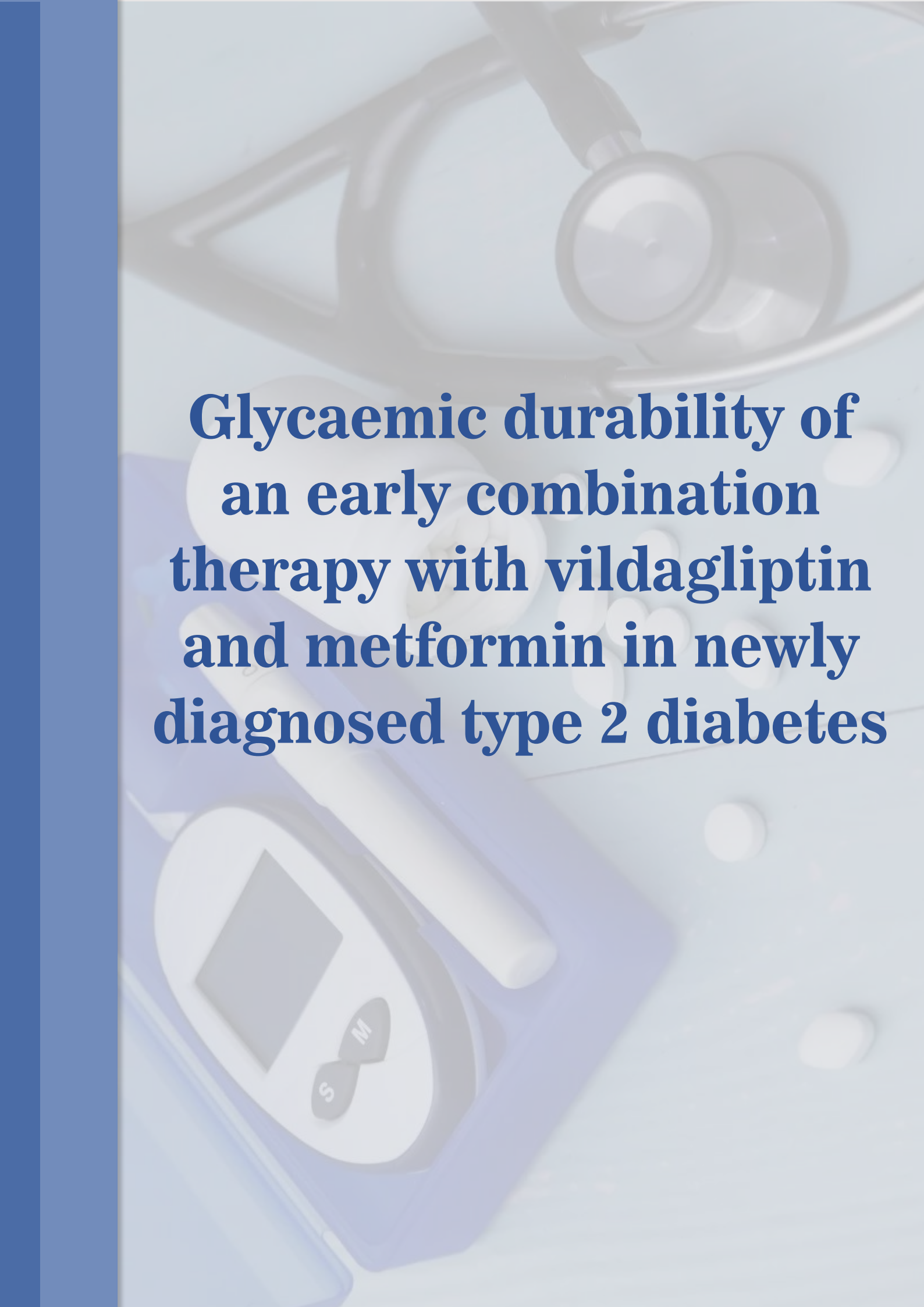
Glycaemic durability of an early combination therapy with vildagliptin and metformin in newly diagnosed type 2 diabetes



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Background and Objective of the Survey

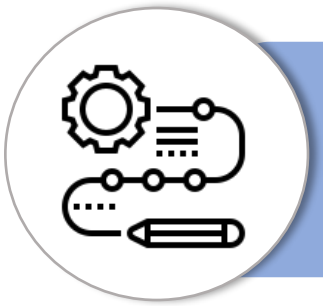
Type 2 Diabetes mellitus (T2DM) is a chronic non-communicable disease that has become a pandemic today. According to the International Diabetes Federation, the global prevalence of T2DM was 9.3% (463 million) in 2019, which is expected to increase to 10.9% (700 million) by 2045. India was estimated to have the second-largest T2DM population in the world at 77 million in 2019; and this is projected to increase to 134 million by 2045.

Although the therapeutic armament for T2DM is growing, lifestyle modification remains the mainstay for its management. Pharmacotherapy initially focused on metformin monotherapy as the starting regimen for T2DM. There was evidence for the efficacy of early combination therapy in patients with higher glycosylated hemoglobin (HbA1c) levels, but this is now also available for patients at lower HbA1c levels. Although intensification of metformin monotherapy with higher doses has improved glycemic control, the increased incidence of gastrointestinal adverse events has contributed to reduced patient compliance.

Therefore, the limitations of the stepwise intensified treatment approach warrant new treatment strategies. Before responsiveness to monotherapy begins to decline, early use of more aggressive combination therapy can be an effective approach. This approach may provide several advantages, including greater glycemic control and the ability to act on different pathological mechanisms involved in glucose dysregulation. Moreover, early interventions are advantageous for slowing the progression of T2DM disease and the associated macrovascular and microvascular complications

The objective of the survey is:

To evaluate the glycaemic durability of an early combination therapy with vildagliptin and metformin in newly diagnosed type 2 diabetes



Methodology of the Survey

A survey was conducted to evaluate the glycaemic durability of an early combination therapy with vildagliptin and metformin in newly diagnosed type 2 diabetes. 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
- Rationale for their use in combination
- Abstracts

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.

Comparison with rosiglitazone[2]

In a noninferiority trial, 786 patients (HbA1c 7.5%–11.0%, mean ∼8.7%) were randomized to vildagliptin 50 mg bid (n = 519) or rosiglitazone 8 mg qd (n = 267) for 24 weeks (-). Mean changes in HbA1c from baseline were −1.1% with vildagliptin vs −1.3% with rosiglitazone, with vildagliptin meeting the noninferiority criterion. Among patients with baseline HbA1c > 9.0% (vildagliptin, n = 166; rosiglitazone, n = 88; mean ∼10.0%), mean reductions were 1.8% vs 1.9%. Overall, vildagliptin was associated with a 0.3-kg reduction in body weight, vs a 1.6-kg increase with rosiglitazone ($p < 0.001$); among patients with baseline BMI ≥ 35 kg/m^2 (vildagliptin, n = 132; rosiglitazone, n = 76; body weight 111–112 kg), vildagliptin patients lost 1.1 kg, compared with a gain of 1.7 kg with rosiglitazone ($p < 0.001$). The frequency of adverse events was similar in the two groups (61.4% and 64.0%), and one case of mild hypoglycemia occurred in each group. Peripheral edema was reported in 2.1% of vildagliptin patients and 4.1% of rosiglitazone patients. Changes in atherogenic lipids consisted of small decreases with vildagliptin and moderate increases with rosiglitazone in triglycerides ($p = 0.01$), total cholesterol ($p \leq 0.003$), and LDL cholesterol ($p \leq 0.003$), with a greater increase in HDL cholesterol occurring with rosiglitazone ($p \leq 0.003$).

Comparison with acarbose[2]

In a noninferiority trial, 661 patients (HbA1c 7.5%–11.0%, mean ~8.6%) were randomized to vildagliptin 50 mg bid (n = 441) or acarbose up to 100 mg tid (n = 220) for 24 weeks (-). Mean changes in HbA1c were 1.4% with vildagliptin and 1.3% with acarbose, with vildagliptin meeting the noninferiority criterion. Among patients with baseline HbA1c >9.0% (vildagliptin, n = 146; acarbose, n = 63; mean ~9.8%), reductions were 2.0% and 2.1%, respectively. Body weight decreased by 0.4 kg with vildagliptin and by 1.7 kg with acarbose ($p < 0.001$). Adverse events occurred in 35% of vildagliptin patients and in 51% of acarbose patients, with a significant reduction in GI adverse events with vildagliptin (12.3% vs 25.5%, $p < 0.001$). No hypoglycemia occurred in either group.

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

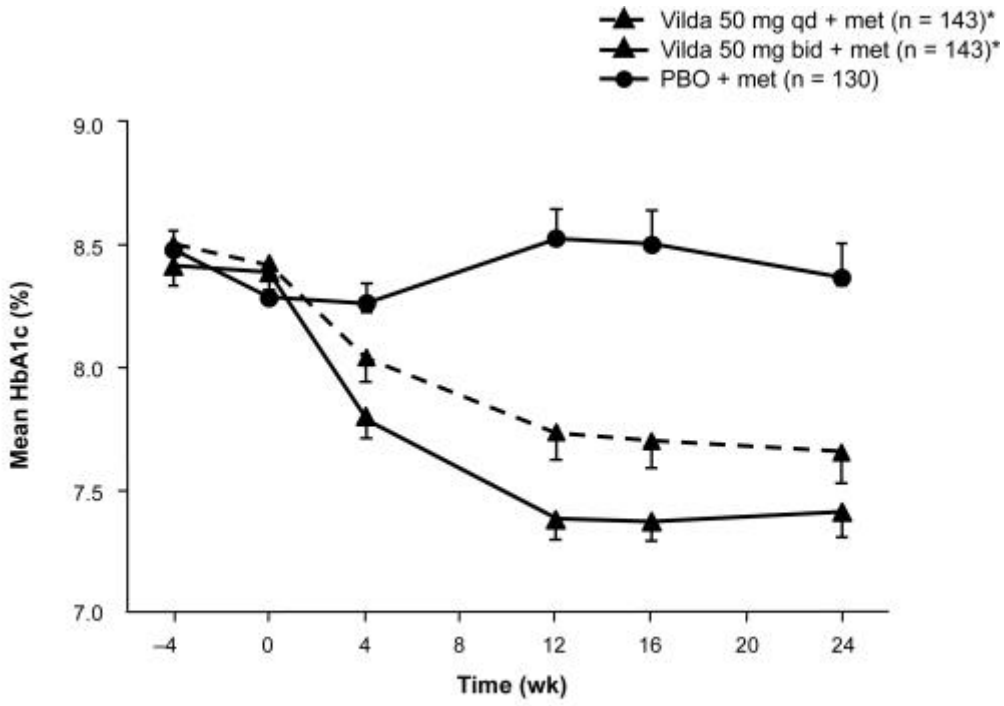
Adapted from *Summary of Clinical Safety*, 5 December 2007. Table 4–1g.

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 pioglitazone vs placebo[2]

A total of 463 patients with inadequate glycemic control on thiazolidinedione treatment (HbA1c 7.5%–11.0%, mean 8.6%–8.7%) were randomized to vildagliptin 50 mg qd (n = 147) or 50 mg bid (n = 158) or to placebo (n = 158) plus maximum-dose pioglitazone at 45 mg qd for 24 weeks. Changes in HbA1c were −0.8% with vildagliptin qd and −1.0% with vildagliptin bid, vs −0.3% with pioglitazone/placebo ($p \leq 0.001$ for both comparisons). Adverse events were similar in frequency in all groups (48.7%–55.5%). Mild hypoglycemia occurred in none of the patients with vildagliptin qd, in one patient (0.6%) with vildagliptin bid, and in 3 patients (1.9%) with pioglitazone/placebo. Body weight increased by 1.4 kg with placebo/pioglitazone and by an additional 0.1 kg with vildagliptin qd and an additional 1.3 kg with vildagliptin bid ($p = 0.003$ vs placebo/pioglitazone). No consistent or dose-related changes in lipids were observed with the addition of vildagliptin to pioglitazone.

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.

Initial combination with pioglitazone[2]

A total of 607 treatment-naïve patients (HbA1c 7.5%−11.0%, mean ~8.7%) were randomized to vildagliptin 100 mg qd (n = 154), pioglitazone 30 mg qd (n = 161), vildagliptin 50 mg qd plus pioglitazone 15 mg qd, or vildagliptin 100 mg qd plus pioglitazone 30 mg qd for 24 weeks). Changes in HbA1c were −1.1% with vildagliptin alone, −1.4% with pioglitazone alone, −1.7% with the 50 mg/15 mg combination ($p < 0.05$ vs pioglitazone alone), and −1.9% with the 100 mg/30 mg combination ($p < 0.001$ vs pioglitazone alone). The target HbA1c level of <7.0% was achieved in 43%, 43%, 54%, and 65% of patients, respectively ($p < 0.001$for the 100 mg/30 mg combination vs both monotherapy groups). Among patients with baseline HbA1c > 9.0% (average ~10.0%), reductions were 1.5% with vildagliptin alone (n = 46), 1.8% with pioglitazone alone (n = 54), 2.3% with the 50 mg/15 mg combination (n = 49), and 2.8% with the 100 mg/30 mg combination (n = 54) ($p < 0.001$ for the higher-dose combination vs pioglitazone alone). Among patients aged ≥65 years, reductions were 1.3% with vildagliptin alone (n = 17), 1.2% with pioglitazone alone (n = 19), 1.7% with the 50 mg/15 mg combination (n = 15), and 2.3% with the 100 mg/30 mg combination (n = 21) ($p < 0.001$ for the higher-dose combination vs pioglitazone alone). Changes in body weight (mean 80–82 kg) were +0.2 kg with vildagliptin monotherapy, +1.5 kg with pioglitazone monotherapy, +1.4 kg with the 50 mg/15 mg combination, and +2.1 kg with the 100 mg/30 mg combination. Adverse event rates were comparable in all groups (45.8%–51.6%). Rates of edema were 5.2% with vildagliptin

alone, 9.3% with pioglitazone alone, 3.5% with the 50 mg/15 mg combination, and 6.1% with the 100 mg/30 mg combination. Hypoglycemia occurred in one patient (0.7%) receiving vildagliptin monotherapy and in one (0.7%) receiving the 100 mg/30 mg combination.

Metformin

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).

Pharmacogenomics of metformin[3]

Considerable interindividual heterogeneity in clinical efficacy and the pharmacokinetic disposition of metformin has been reported in the treatment of diabetic patients. This may be explained by variability in genetic polymorphisms of cation transporters. It was first reported that individuals carrying polymorphisms of the OCT1 gene SLC22A1 display an impaired effect of metformin in lowering blood glucose levels, consistent with the great reduction of hepatic metformin uptake observed in OCT1/ mice. However, these results have not been confirmed in the long-term follow-up of a large observational cohort of patients treated with metformin. Conversely, variants in the MATE1 gene SLC47A1 enhance the effect of metformin on glycated hemoglobin (HbA1c) and glucose tolerance in T2D patients. In MATE1 mice, urinary excretion of metformin is significantly decreased, suggesting that MATE1 is essential for renal clearance of the drug. Among new candidate genetic determinants of metformin response, single nucleotide polymorphisms have been identified in the AMPK subunit genes, PRKAA1, PRKAA2 and PRKAB2, and the LKB1 gene STK11. In addition, a recent genome-wide association study showed association between a large locus on chromosome 11, encompassing several genes, and glycemic variability in response to metformin therapy. This locus includes the ataxia telangiectasia mutated (ATM) gene, and it was suggested as the most likely candidate given its association with insulin resistance and T2D. However, additional studies are needed to clearly delineate genetic influences on the clinical response to metformin.

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.

Inhibition of hepatic gluconeogenesis[3]

An important breakthrough in the understanding of the molecular mechanism underlying metformin action was the demonstration that metformin-induced AMPK activation is associated with the inhibition of glucose production in primary hepatocytes. The role for AMPK in mediating the action of metformin was initially supported by the reduction in metformin's effect on glucose production in primary hepatocytes treated with compound C, an AMPK inhibitor that is now recognized to be nonselective. Thereafter, it was reported that, ablation of liver kinase B1 (LKB1, the upstream kinase that phosphorylates and activates AMPK) in the liver prevented the antihyperglycemic effects of metformin in high-fat-fed mice, also supporting the involvement of the kinase in the inhibition of glucose production by the drug. In this study, it was shown that LKB1/AMPK signaling controls the phosphorylation and nuclear exclusion of the transcriptional coactivator cAMP-response element-binding protein (CREB)-regulated transcription coactivator 2 (CRTC2, also known as TORC2) (Shaw *et al*., 2005), a pivotal regulator of gluconeogenic gene transcription in response to fasting. In addition, AMPK activation by metformin has also been reported to be involved in the transcriptional regulation of hepatic gluconeogenic enzyme genes by different mechanisms: (i)

dissociation of the CREB-CBP (CREB-binding protein)-TORC2 transcription complex, through the phosphorylation of the transcriptional coactivator CBP via atypical protein kinase (ii) increased expression of the orphan nuclear receptor small heterodimer partner, and (iii) induction of SIRT1-mediated CRTC2 deacetylation. However, the impact of reduction in gluconeogenic gene expression in metformin action has been recently disputed. Forced increase in gluconeogenic enzymes expression did not counteract the metformininduced reduction in glucose output, this being in line with the emerging concept that transcriptional expression of PEPCK and G6Pase only weakly influences hepatic glucose output in patients with T2D.

Regulation of lipid metabolism[3]

Another effect of metformin is to improve lipid metabolism by reducing hepatic steatosis as demonstrated in rodent liver and also reported in a clinical study. It was also recently reported that metformin exerts a beneficial effect on circulating lipids by lowering plasma triglycerides, through a selective increase in VLDL-triglyceride uptake and fatty acid oxidation in brown adipose tissue. The metformin-induced reduction in tissue lipid storage is consistent with an increase in both fatty acid oxidation and inhibition of lipogenesis, presumably mediated by AMPK activation. Further support for a role of AMPK in the mechanisms of metformin action on lipid metabolism was recently provided in knockin mouse models in which ACC1 and ACC2 were rendered insensitive to AMPK phosphorylation. These mice are refractory to the lipidlowering and insulin-sensitizing effects of metformin, showing that metformin-induced reduction in blood glucose levels depends on its ability to lower cellular fatty acid levels through the AMPK-dependent phosphorylation of ACC. Thus, the inhibition of hepatic glucose production by metformin may be, at least in certain conditions, secondary to the effects of the drug on ACC. These observations offer a potential explanation for the lack of metformin action on blood glucose levels in liver-specific LKB1-knockout mice fed on a high-fat diet. Indeed, impaired metformin-induced AMPK phosphorylation in the absence of LKB1 would prevent ACC phosphorylation and the ability of metformin to improve insulin sensitivity and lower blood glucose. Therefore, metformin can acutely suppress hepatic glucose output by acting on distinct metabolic pathways via AMPK-independent and AMPK-dependent mechanisms in the context of insulin resistance.

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; $p \leq 0.01$). 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.

Pharmacokinetics/Pharmacodynamics (Pk/Pd) and mode of action (MoA) of metformin and vildagliptin, and rationale for their use in combination

PK/PD and MoA of metformin[1]

Metformin is absorbed mainly from the small intestine, with a 60% bioavailability; the plasma half life is estimated at 1.5–4.9 hours. The drug is not significantly metabolized, and 90% is eliminated unchanged in urine in 12 hours by glomerular filtration and tubular secretion. It is distributed in most tissues, with higher concentrations in liver, kidneys, salivary glands and the intestinal walls. The drug can be removed by hemodyalisis.

Metformin has been available for treating diabetes since the 1950s, but despite decades of medical use, the mechanism of action of the drug at the molecular level is still not fully understood but is related to an action on AMP kinase.

The glucose-lowering effect of metformin is mainly due to decreased basal hepatic glucose output and -to a lesser extent- enhanced peripheral glucose uptake (with muscle as its main site of action). The latter action on muscles is likely indirect and explained by the overall improved metabolic state. Additional actions that contribute to the glucose-lowering effect are the increased intestinal use of glucose and decreased fatty acid oxidation.

The most feared and widely publicized adverse effect of biguanide therapy is lactic acidosis, likely resulting from the action of biguanides to interfere with non-oxidative glucose metabolism. Lactic acidosis could occur in energy-compromised individuals leading to increased lactate production and/or reduced lactate clearance, such as in liver disease, renal dysfunction or other illness causing tissue hypoxia (such as cardiac or respiratory dysfunction). It has a high mortality, but is extremely rare with metformin, the overall incidence being estimated at one case per 30,000 patient-years. This rate of lactic acidosis events is actually almost similar to that reported in patients with T2DM not taking metformin indicating that lactic acidosis occurs in metformin-treated patients when energy metabolism is further altered in patients where it was already severely compromised.

The most common dose-limiting adverse effects of metformin are gastrointestinal (abdominal discomfort, metallic taste and anorexia, nausea or diarrhea but these effects are minimized with gradual upward titration and concomitant administration with meals, overall leading to drug discontinuation in less than 5%–10% of the patients. However gastrointestinal discomfort is often the single factor that prevents the use of higher, more efficacious doses of metformin.

PK/PD and MoA of vildagliptin[1]

Vildagliptin is well and rapidly absorbed after oral administration. About 70% of the orally administered vildagliptin is metabolized, hydrolysis being the main pathway, and renal excretion being the main route of elimination (85%), with some of the oral dose excreted in the urine as unchanged drug (23%). Food ingestion does not alter the pharmacokinetics of vildagliptin. Vildagliptin does not inhibit or induce the major P450 enzymes and shows no drug interactions with commonly used medication (such as glyburide, metformin, pioglitazone,

digoxin, warfarin, simvastatin, valsartan, amlodipine, ramipril). Age, gender, BMI, and race do not affect the pharmacokinetics of vildagliptin.

Vildagliptin selectively inhibits DPP- 4 activity, resulting in increased levels (2- to 4-fold) of the two key glucoregulatory incretin hormones GLP-1 and GIP, allowing the pancreatic islet cells to better sense and more appropriately respond to raised glucose levels.

The increased levels of active endogenous incretin hormones result in better post-prandial and fasting glucose control by stimulating insulin secretion, reducing glucagon levels and suppressing overnight hepatic glucose production, which all contribute to the clinical effect to lower HbA_{1c}.

Further evidence for an improvement of islet function with vildagliptin, with an increase of both α- and β-cell responsiveness to glucose, come from a number of recent studies. In addition, vildagliptin treatment leads to a more efficient β-cell insulin processing, providing further evidence for an amelioration of the abnormal β-cell function in patients with T2DM. Previous data in rodents showed that vildagliptin increases pancreatic β-cell mass by markedly stimulating β-cell replication and inhibiting apoptosis, similar to the beneficial effects reported for parenterally administered GLP-1 agonists. These animal data on beta cell protection still need to translate into durable glycemic control in humans, which can only be demonstrated in long term clinical trials.

These primary effects of vildagliptin to enhance incretin hormone levels also lead to improved insulin mediated glucose disposal which may be due in part to reduced glucose toxicity and in part to reduced stored triglycerides in muscle and liver. A similar improvement in insulin sensitivity and β-cell function, leading to improved postprandial glycemia, has recently been shown in subjects with impaired fasting glucose after 6 weeks of treatment with vildagliptin 100 mg/day. Furthermore, the known effects of vildagliptin on incretin levels and islet function in type 2 diabetes were reproduced in another study conducted in 179 subjects with impaired glucose tolerance over 12 weeks, with a 32% reduction in postprandial glucose excursions and no evidence of hypoglycemia or weight gain.

Vildagliptin shows no action on gastric emptying or any evidence for delayed glucose absorption or delayed appearance of drugs co-administered in interaction studies.

Interestingly, treatment with vildagliptin for 4 weeks improved postprandial plasma triglyceride after a fat-rich meal, and this was achieved mainly through a decrease in

intestinally derived apo B-48-containing particles. These results indicate that vildagliptin treatment reduces postprandial atherogenic TRLs in the circulation and suggest that it may protect against weight gain in patients with T2DM by extracting less fat from the gut.

The clinical profile of vildagliptin has been extensively assessed in the development program, providing evidence of its glucose-lowering efficacy across a wide range of clinical uses: as monotherapy or initial combination therapy in treatment-naive patients), as add-on therapy with the most commonly prescribed classes of oral hypoglycemic drugs, and in combination with insulin in patients with long-standing disease. In monotherapy, vildagliptin produced consistent reductions from baseline in HbA_{1c} of approximately 1%, sustained out to one year, was weight-neutral and well-tolerated, and had a low incidence of hypoglycemia and no episodes of severe hypoglycemia. Vildagliptin 100 mg daily was as effective as rosiglitazone 8 mg daily without the weight gain. When compared with metformin 2000 mg daily, statistical noninferiority was not established but treatment with vildagliptin 100 mg daily for 1 year reduced HbA_{1c} by 1.0% ($p < 0.001$) with a more favorable gastrointestinal (GI) tolerability than metformin. Furthermore, the efficacy and safety profiles of vildagliptin in elderly patients (who had a high prevalence of co-morbidities and mild renal insufficiency) were comparable to those in younger patients, including a very low (0.8%) incidence of hypoglycemia and no severe hypoglycemic episode. In this regard, a recent study of vildagliptin added to existing insulin therapy is interesting: hypoglycemia was significantly less frequent and less severe with vildagliptin than with placebo, despite improved glycemic control in those receiving vildagliptin. In addition, recent data further confirmed the low hypoglycemic risk at the other end of the disease spectrum. In recently diagnosed patients with mild hyperglycemia (n =306; baseline $HbA_{1c} \approx 6.7\%$, FPG $\approx$ 7.1 mmol/L and nearly half of the patients over age 65) 52-week treatment with vildagliptin elicited a modest but statistically significant reduction in A1C (−0.3%), primarily due to a reduction of postprandial glucose and at least in part reflecting improved beta-cell function. Treatment with vildagliptin was weight neutral (−0.5 kg from baseline) and was well tolerated with no episode of hypoglycemia over one year in the vildagliptin group. This low hypoglycemic potential of vildagliptin likely reflects the glucose-dependent nature of both the insulinotropic and the glucagonostatic effects of GLP-1.

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.

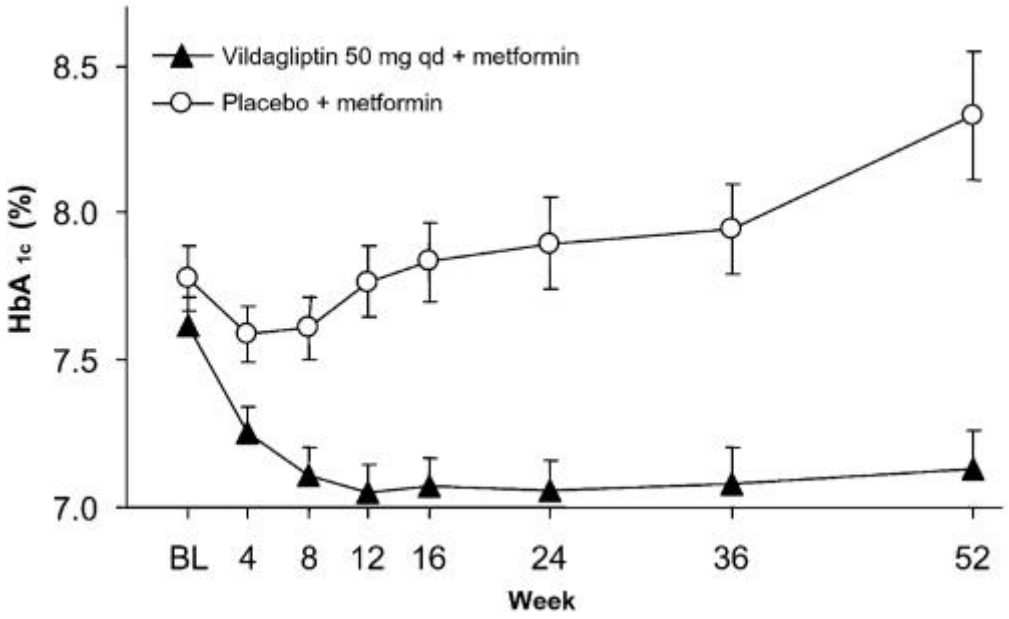


Figure 2: Mean (± SE) HbA_{1c} during 52-week treatment with vildagliptin (50 mg qd, closed triangles, n = 42) and placebo (open circles, n = 29) in metformin-treated patients with T2DM. The between-group difference in HbA1c from baseline to endpoint was −1.1 ± 0.2% ($p < 0.0001$). Copyright © American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

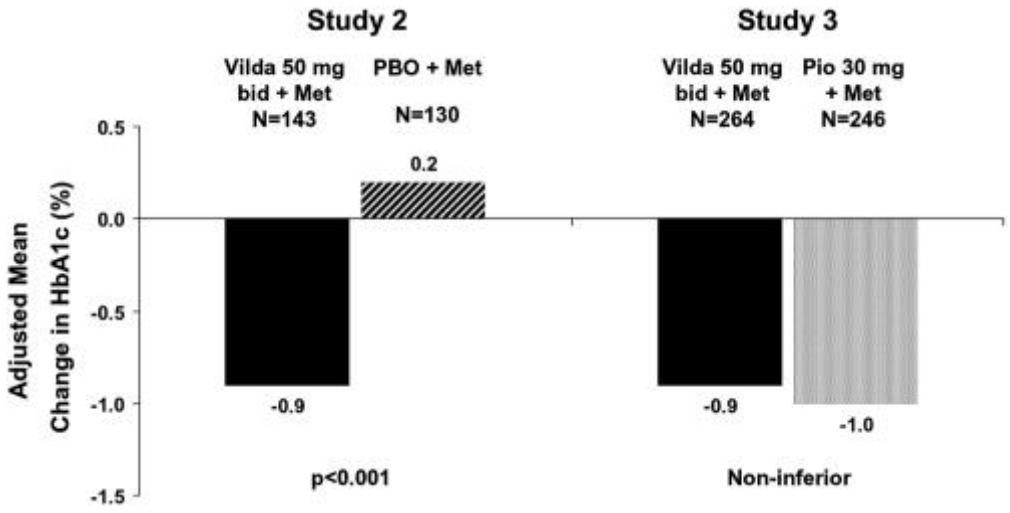


Figure 3: Study 2 – Adjusted mean change from baseline to endpoint in HbA_{1c} after 24 weeks of treatment with vildagliptin (50 mg bid) or placebo in metformin-treated patients with T2DM (p < 0.001).

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).

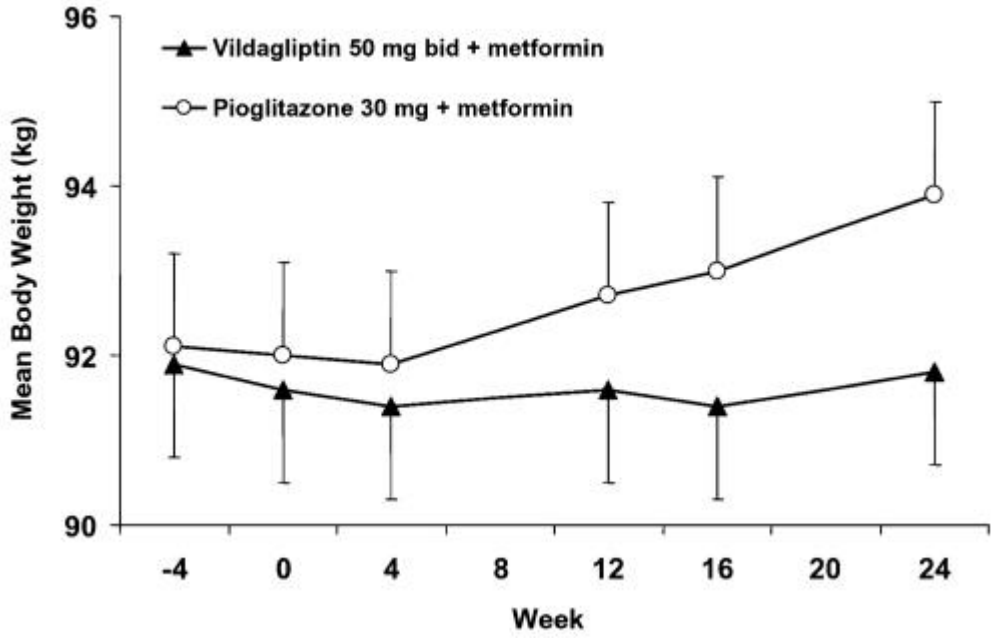


Figure 4: Study 3 – Time-course of mean body weight during 24-week treatment with vildagliptin (50 mg bid, closed triangles, n = 264) or pioglitazone (30 mg qd, open circles, n = 246) in T2DM patients continuing their previous stable metformin dose regimen (Derived from data of).

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.

References:

1. Halimi S, Schweizer A, Minic B, Foley J, Dejager S. Combination treatment in the management of type 2 diabetes: focus on vildagliptin and metformin as a single tablet. Vasc Health Risk Manag. 2008;4(3):481-492. doi:10.2147/vhrm.s2503
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4. Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use in type 2 diabetes. Diabetologia. 2017;60(9):1586-1593.

Survey Form

1) What is your opinion on current unmet needs in the management of glycaemic control with monotherapy?

a) Delays in achieving glycaemic targets
b) Switching from monotherapy to combination therapy
c) Delay in treatment intensification
d) Exposure to avoidable hyperglycaemia

2) In what percentage of your patients uncontrolled diabetes with metformin/diet you prefer to start combination therapy?

a) <10%
b) 11-20%
c) 21-30%
d) >40%

3) In your opinion, advantages of FDC therapy in T2DM management include

a) Lowering pill burden
b) Improving glycemic control with better efficacy
c) Better treatment adherence

4) What is your opinion on early glycaemic control improves long-term glycaemic durability and reduces the risk of associated complications?

a) Yes
b) No

5) What is your opinion on early achievement of HbA1c level within the glycemic target is a determinant of long-term glycemic durability?

a) Yes
b) No

6) In your opinion, early initiation of combination therapy helps

a) In earlier achievement of glycemic goals

b) Sustained glycemic control

c) Better preserves β-cell function

d) Delays the deterioration of glycemic control

7) What percentage of patients you prefer to early initiation of combination therapy?

a) <10

b) 11-20%

c) 21-30%

d) >30%

8) What percentage of patients you prefer combination of a vildagliptin with metformin?

a) <10

b) 11-20%

c) 21-30%

d) >30%

9) At what HbA1c level would you initiate treatment with metformin + vildagliptin?

a) HbA1c 7.0 to 7.5

b) HbA1c 7.6% -8.0

c) HbA1c 8.1% - 8.5%

d) HBA1c > 8.5%

10) What is your opinion on choice of exploring the combination of a vildagliptin with metformin?

a) Supports glucose-dependent β-cell stimulation by vildagliptin

b) Concomitant insulin sensitisation by metformin

c) Well established favourable safety profile of both drugs

d) All the above

11) How much reduction in HbA1c with metformin + vildagliptin FDC in Indian type 2 diabetes patients?

a) 0.25%-0.5%
b) 0.75%-1.0%
c) 1.25%-1.5%
d) >1.5%

12) How would you rate the tolerability of early initiation of combination therapy of metformin + vildagliptin FDC?

a) Excellent
b) Good
c) Fair
d) Poor

13) In your opinion is Vildagliptin the best, effective, affordable, and safe gliptin to be used on combination with metformin?

a) Yes
b) No

14) In your opinion, early use, and synergistic effects of combination therapy of metformin + vildagliptin FDC could have a potential moderating effect on cardiovascular outcomes?

a) Yes
b) No

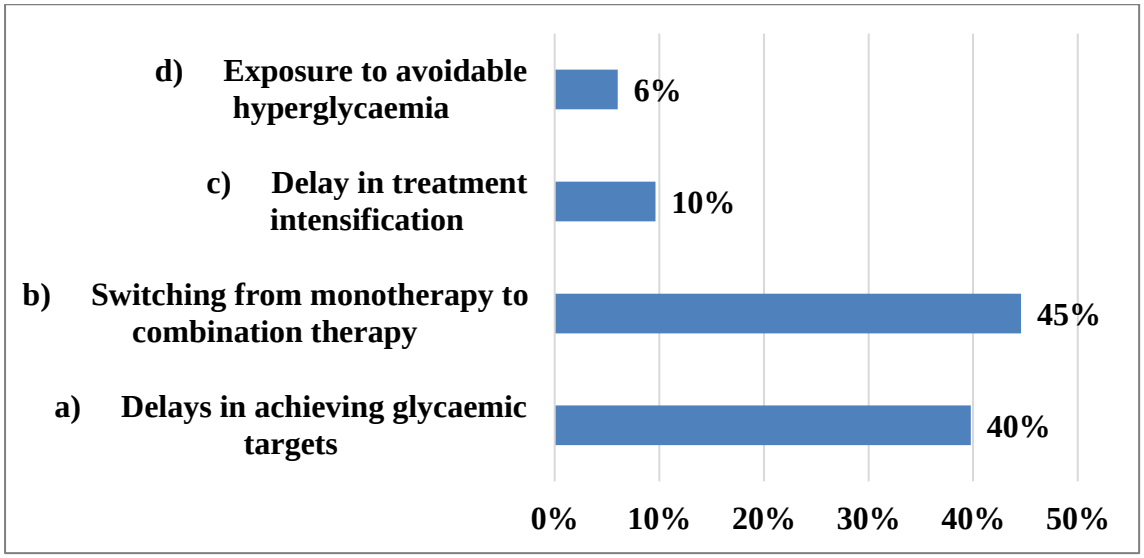
15) Use of combination therapy of metformin + vildagliptin may?

a) Help promote adherence to OAD therapy
b) Improved clinical outcomes
c) GI tolerability
d) All the above

Survey Findings

1) What is your opinion on current unmet needs in the management of glycaemic control with monotherapy?

a) Delays in achieving glycaemic targets
b) Switching from monotherapy to combination therapy
c) Delay in treatment intensification
d) Exposure to avoidable hyperglycaemia



In the opinion of 45% of doctors, the current unmet needs in the management of glycaemic control can be met with switching from monotherapy to combination therapy.

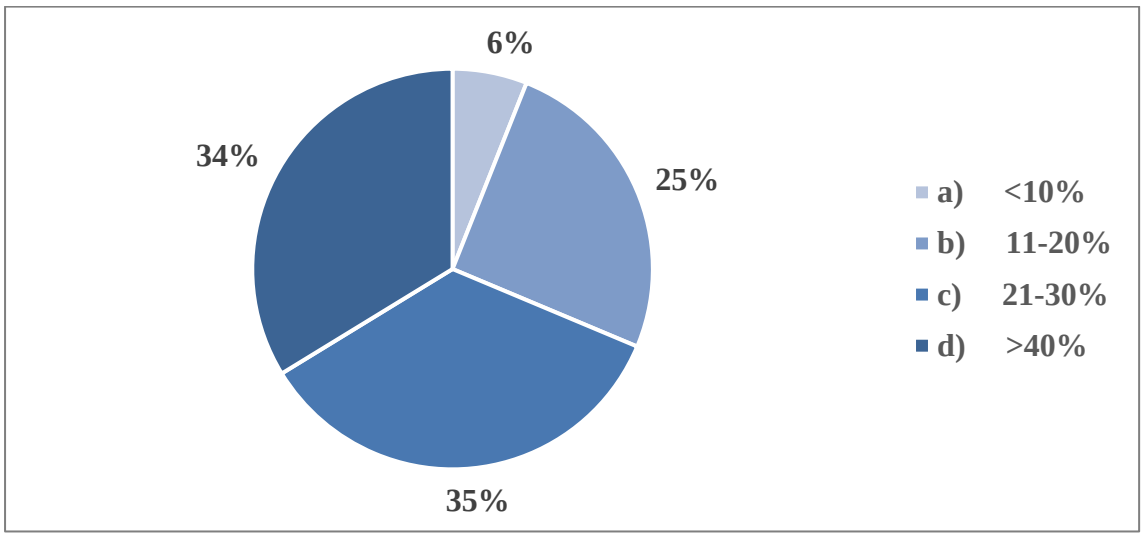
2) In what percentage of your patients uncontrolled diabetes with metformin/diet you prefer to start combination therapy?

a) <10%

b) 11-20%

c) 21-30%

d) >40%



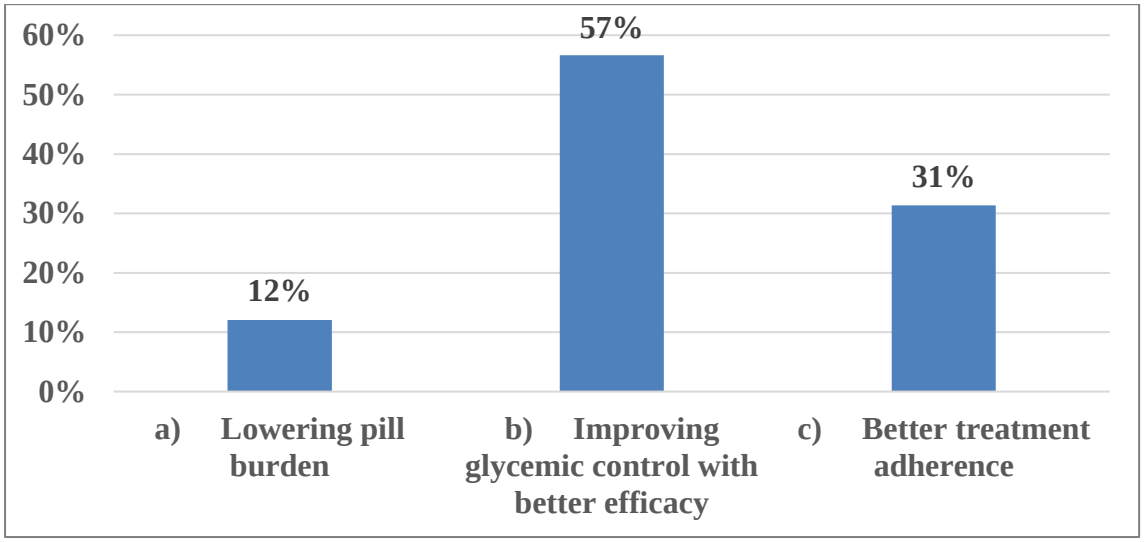
As per 35% of doctors, 21-30% of their patients uncontrolled diabetes with metformin/diet they prefer to start combination therapy.

3) In your opinion, advantages of FDC therapy in T2DM management include

a) Lowering pill burden

b) Improving glycemic control with better efficacy

c) Better treatment adherence

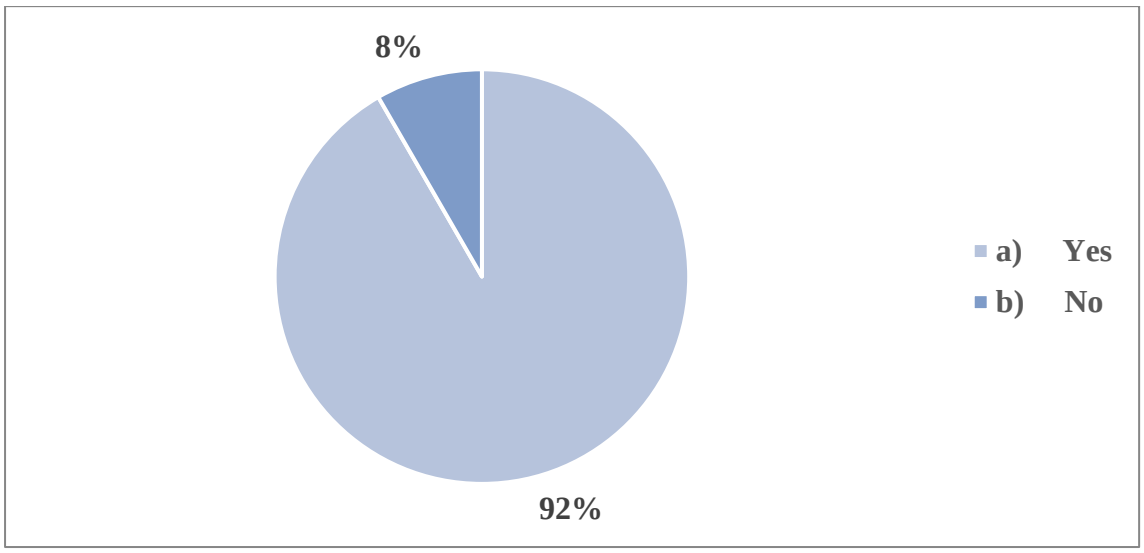


According to 57% of doctors, the advantages of FDC therapy in T2DM management include improving glycemic control with better efficacy.

4) What is your opinion on early glycaemic control improves long-term glycaemic durability and reduces the risk of associated complications?

a) Yes

b) No

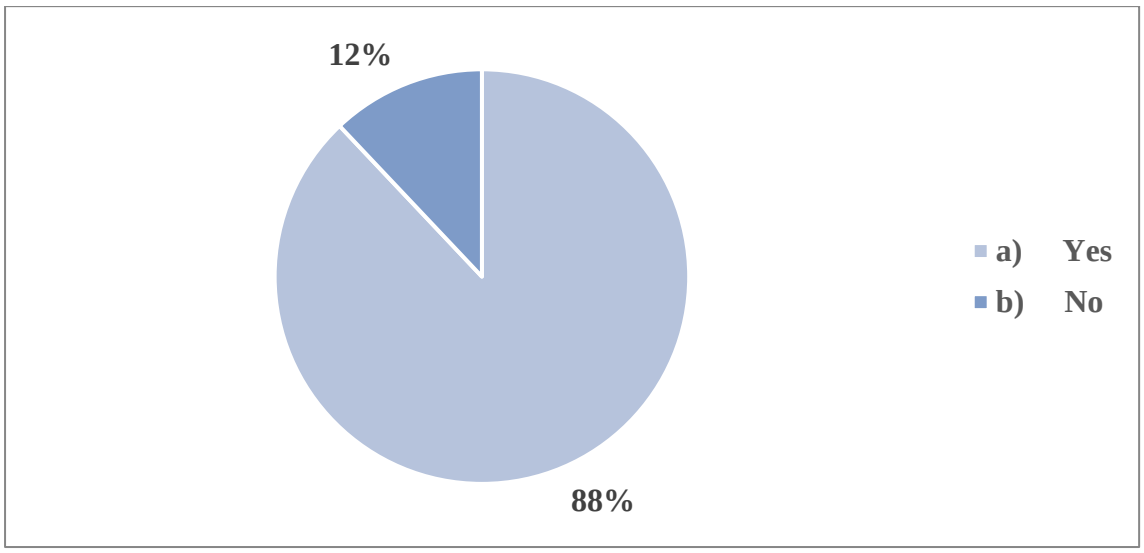


In the opinion of majority of doctors, 92%, early glycaemic control improves long-term glycaemic durability and reduces the risk of associated complications.

5) What is your opinion on early achievement of HbA1c level within the glycemic target is a determinant of long-term glycemic durability?

a) Yes

b) No



According to majority of doctors, 88%, early achievement of HbA1c level within the glycemic target is a determinant of long-term glycemic durability.

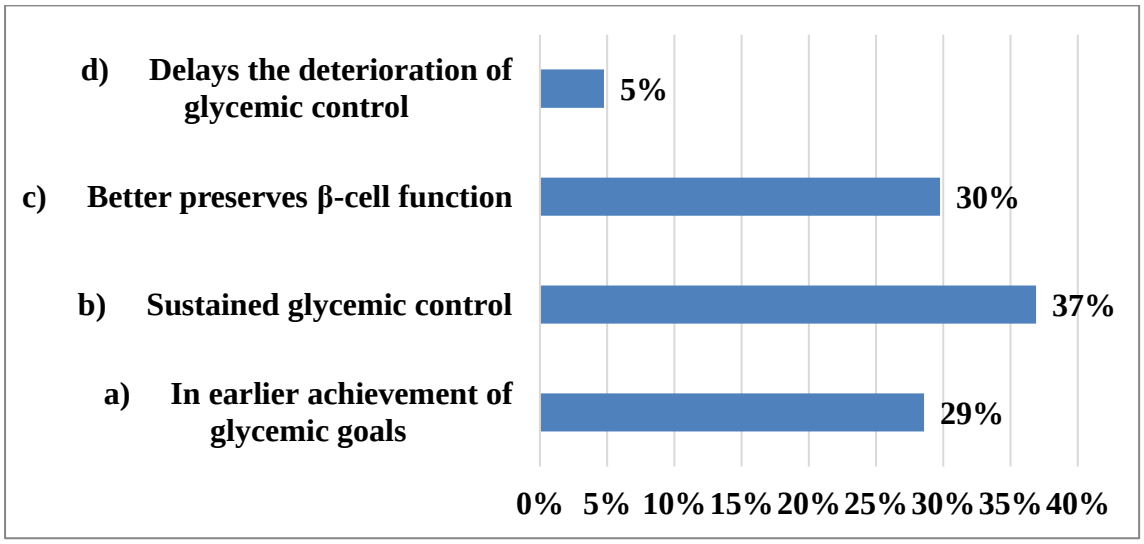
6) In your opinion, early initiation of combination therapy helps

a) In earlier achievement of glycemic goals

b) Sustained glycemic control

c) Better preserves β-cell function

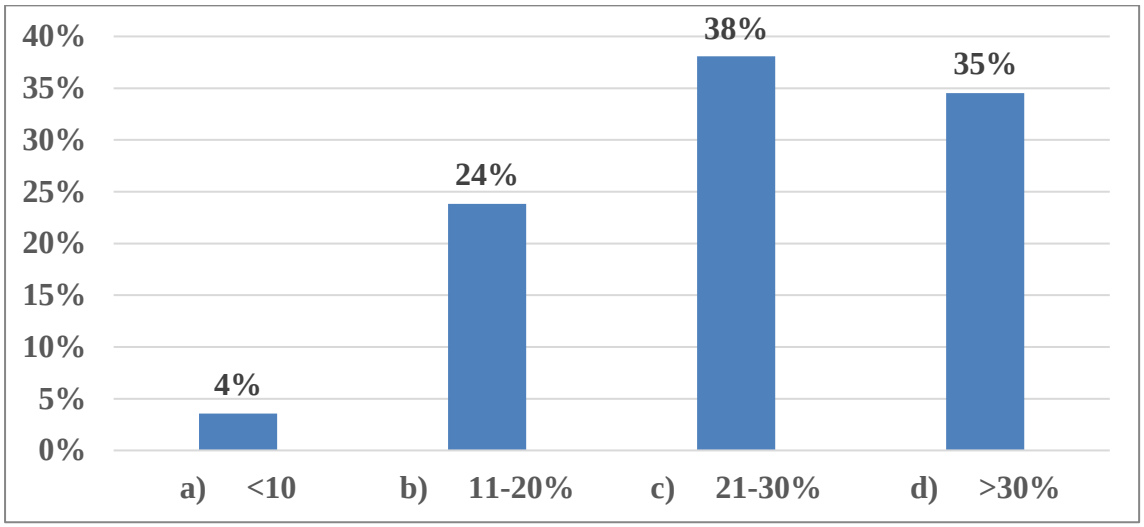
d) Delays the deterioration of glycemic control



As per 37% of doctors, early initiation of combination therapy helps in sustained glycemic control.

7) What percentage of patients you prefer to early initiation of combination therapy?

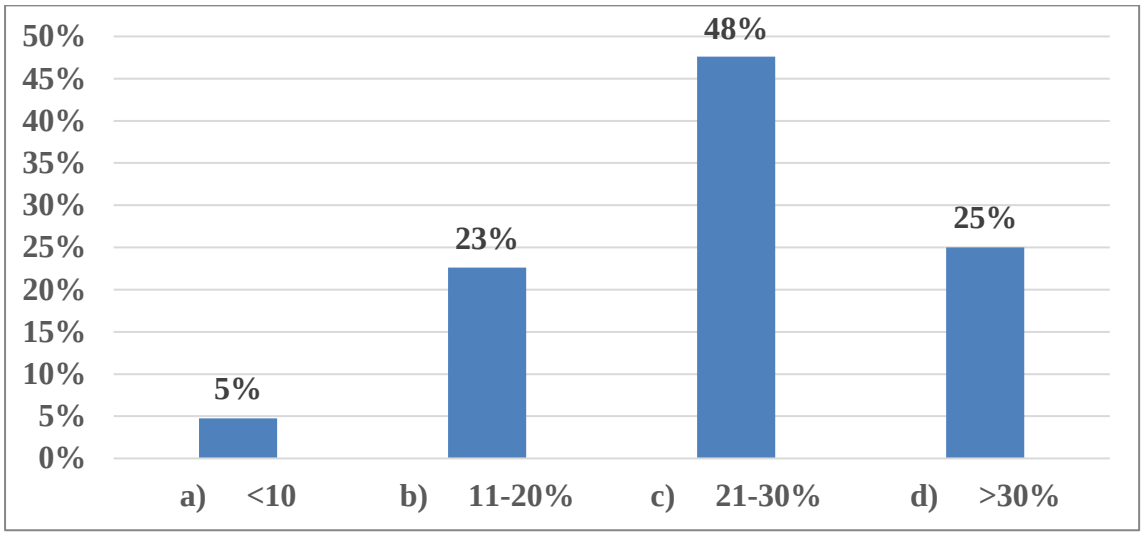
a) <10
b) 11-20%
c) 21-30%
d) >30%



38% of doctors prefer 21-30% of patients for early initiation of combination therapy.

8) What percentage of patients you prefer combination of a vildagliptin with metformin?

a) <10
b) 11-20%
c) 21-30%
d) >30%



48% of doctors prefer 21-30% of patients for combination of a vildagliptin with metformin.

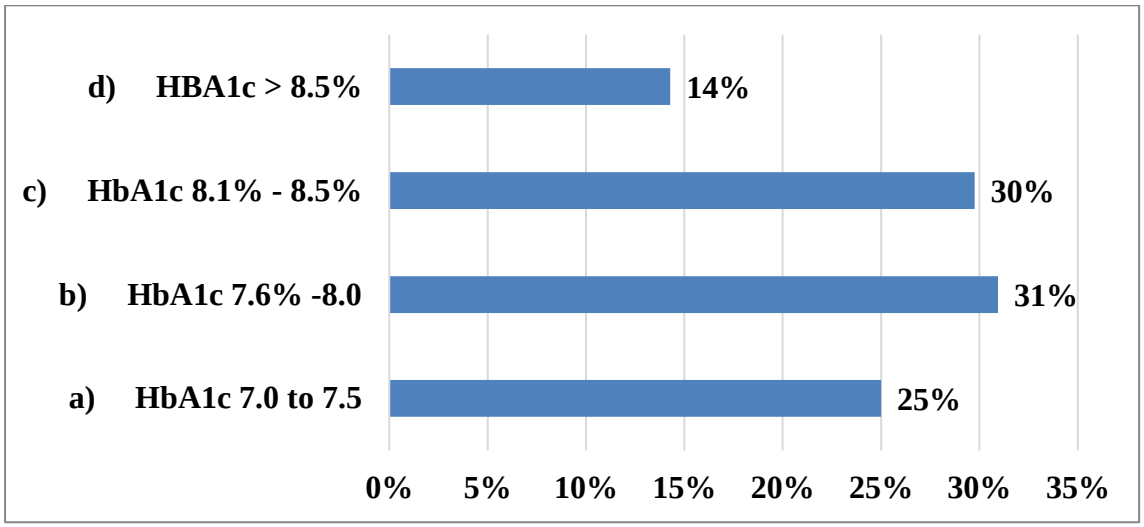
9) At what HbA1c level would you initiate treatment with metformin + vildagliptin?

a) HbA1c 7.0 to 7.5

b) HbA1c 7.6% -8.0

c) HbA1c 8.1% - 8.5%

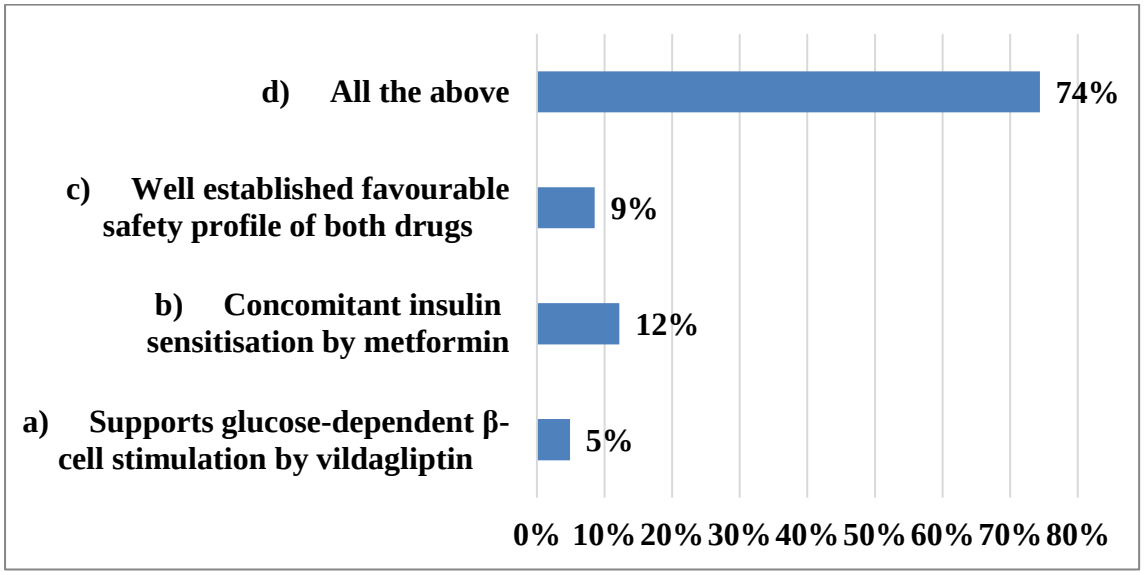
d) HBA1c > 8.5%



36% of doctors initiate treatment with metformin + vildagliptin at HbA1c 7.6% -8.0.

10) What is your opinion on choice of exploring the combination of a vildagliptin with metformin?

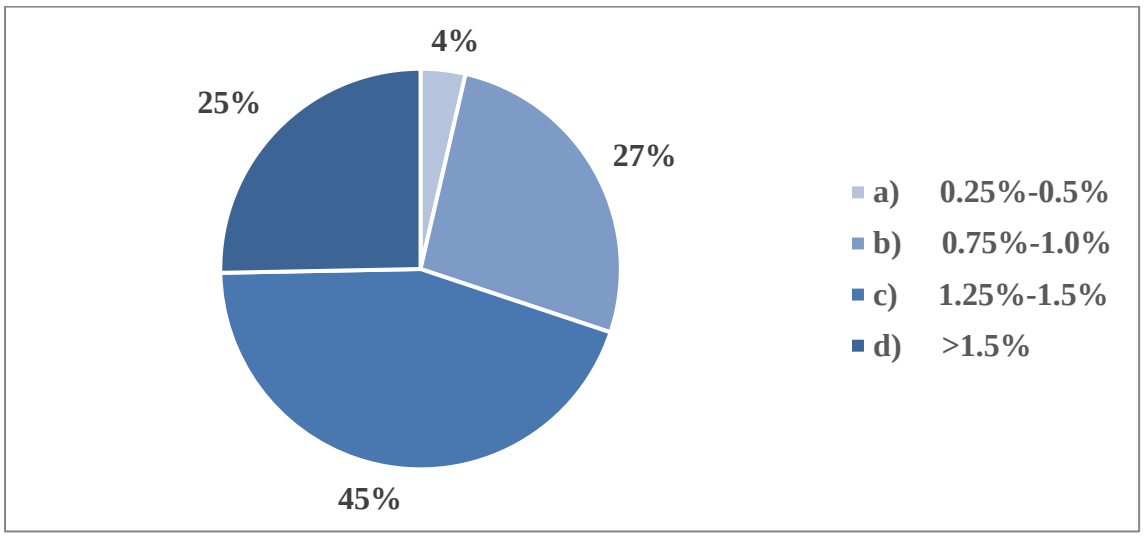
a) Supports glucose-dependent β-cell stimulation by vildagliptin
b) Concomitant insulin sensitisation by metformin
c) Well established favourable safety profile of both drugs
d) All the above



According to majority of doctors, 74%, exploring the combination of a vildagliptin with metformin supports glucose-dependent β-cell stimulation by vildagliptin, concomitant insulin sensitisation by metformin and well established favourable safety profile of both drugs.

11) How much reduction in HbA1c with metformin + vildagliptin FDC in Indian type 2 diabetes patients?

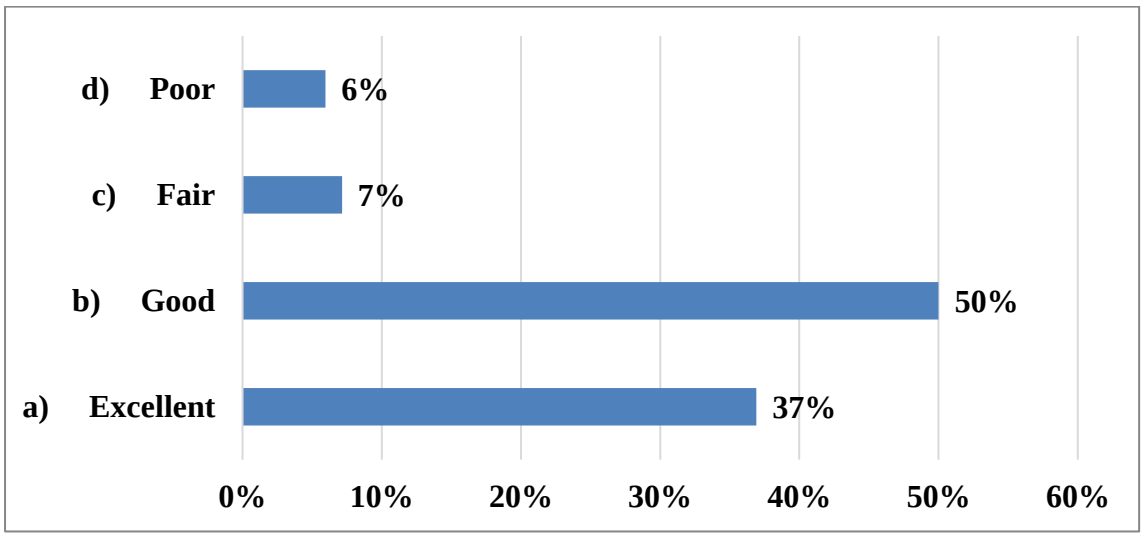
a) 0.25%-0.5%
b) 0.75%-1.0%
c) 1.25%-1.5%
d) >1.5%



45% of doctors have observed a reduction of 1.25%-1.5% in HbA1c with metformin + vildagliptin FDC in Indian type.

12) How would you rate the tolerability of early initiation of combination therapy of metformin + vildagliptin FDC?

a) Excellent
b) Good
c) Fair
d) Poor

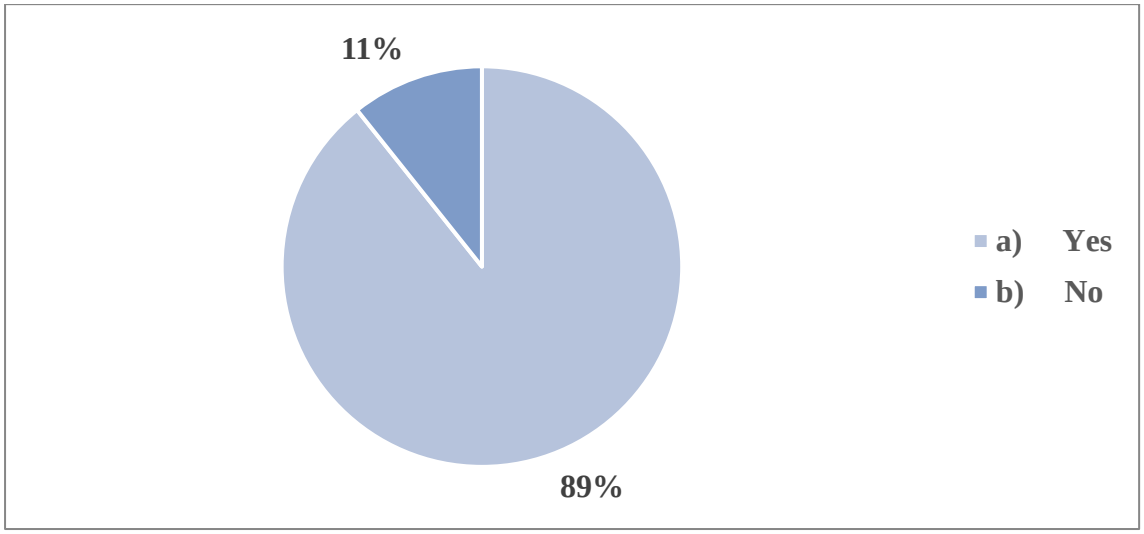


50% of doctors rate the tolerability of early initiation of combination therapy of metformin + vildagliptin FDC as good.

13) In your opinion is Vildagliptin the best, effective, affordable, and safe gliptin to be used on combination with metformin?

a) Yes

b) No

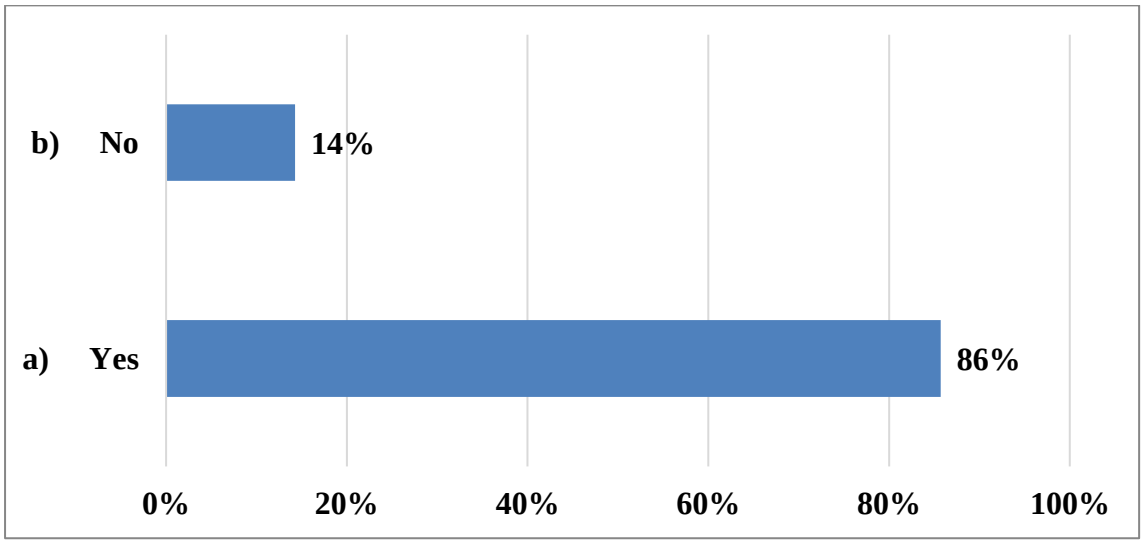


In the opinion of majority of doctors, Vildagliptin is the best, effective, affordable, and safe gliptin to be used on combination with metformin.

14) In your opinion, early use, and synergistic effects of combination therapy of metformin + vildagliptin FDC could have a potential moderating effect on cardiovascular outcomes?

a) Yes

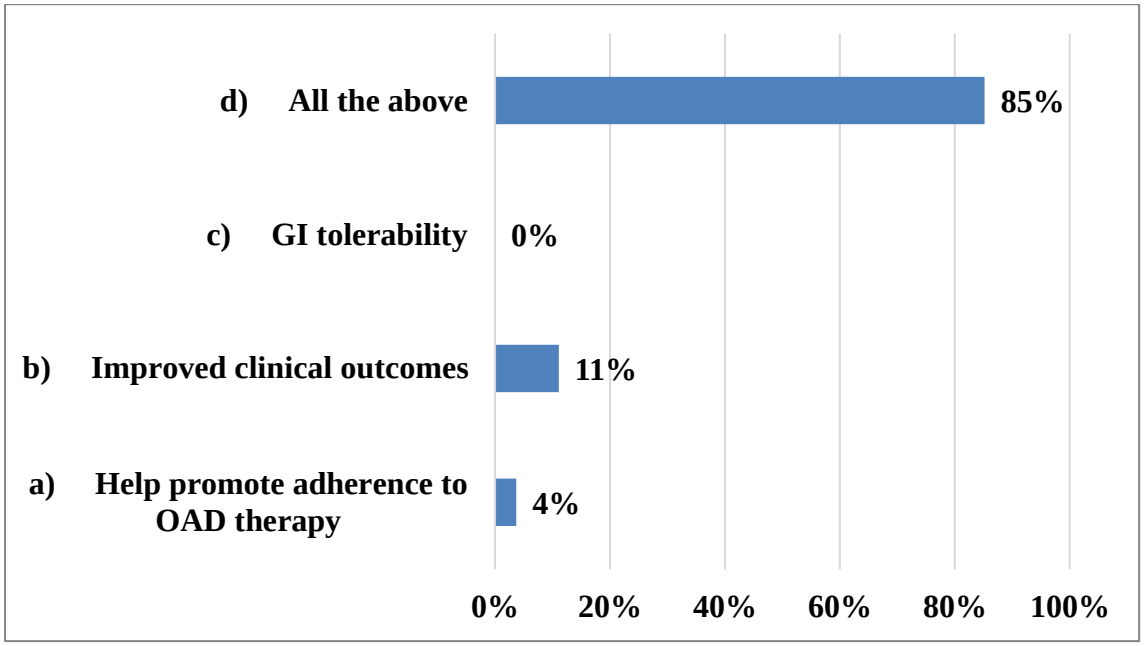
b) No



Majority of doctors, 86%, agree that early use, and synergistic effects of combination therapy of metformin + vildagliptin FDC could have a potential moderating effect on cardiovascular outcomes.

15) Use of combination therapy of metformin + vildagliptin may?

a) Help promote adherence to OAD therapy
b) Improved clinical outcomes
c) GI tolerability
d) All the above



According to majority of doctors, 85%, use of combination therapy of metformin + vildagliptin may help promote adherence to OAD therapy and improved clinical outcomes, along with GI tolerability.

Summary

- In the opinion of 45% of doctors, the current unmet needs in the management of glycaemic control can be met with switching from monotherapy to combination therapy.
- As per 35% of doctors, 21-30% of their patients uncontrolled diabetes with metformin/diet they prefer to start combination therapy.
- According to 57% of doctors, the advantages of FDC therapy in T2DM management include improving glycemic control with better efficacy.
- In the opinion of majority of doctors, 92%, early glycaemic control improves long-term glycaemic durability and reduces the risk of associated complications.
- According to majority of doctors, 88%, early achievement of HbA1c level within the glycemic target is a determinant of long-term glycemic durability.
- As per 37% of doctors, early initiation of combination therapy helps in sustained glycemic control.
- 38% of doctors prefer 21-30% of patients for early initiation of combination therapy.
- 48% of doctors prefer 21-30% of patients for combination of a vildagliptin with metformin.
- 36% of doctors initiate treatment with metformin + vildagliptin at HbA1c 7.6% -8.0.
- According to majority of doctors, 74%, exploring the combination of a vildagliptin with metformin supports glucose-dependent β-cell stimulation by vildagliptin, concomitant insulin sensitisation by metformin and well established favourable safety profile of both.
- 45% of doctors have observed a reduction of 1.25%-1.5% in HbA1c with metformin + vildagliptin FDC in Indian type.
- 50% of doctors rate the tolerability of early initiation of combination therapy of metformin + vildagliptin FDC as good.
- In the opinion of majority of doctors, Vildagliptin is the best, effective, affordable, and safe gliptin to be used on combination with metformin.
- Majority of doctors, 86%, agree that early use, and synergistic effects of combination therapy of metformin + vildagliptin FDC could have a potential moderating effect on cardiovascular outcomes.
- According to majority of doctors, 85%, use of combination therapy of metformin + vildagliptin may help promote adherence to OAD therapy and improved clinical outcomes, along with GI tolerability

Consultant Opinion

Early Combination Therapy:

Encourage early initiation of combination therapy in patients with uncontrolled diabetes on metformin monotherapy or lifestyle interventions to achieve optimal glycemic control and reduce the risk of associated complications.

Advantages of Fixed-Dose Combination (FDC) Therapy:

Educate healthcare providers about the advantages of FDC therapy, including improved glycemic control with better efficacy, which can address the unmet needs in T2DM management.

Importance of Early Glycemic Control:

Emphasize the significance of early glycemic control in improving long-term glycemic durability and reducing the risk of diabetes-related complications, as recognized by the majority of doctors in the survey.

Selection of Combination Therapy:

Consider the combination of vildagliptin with metformin as a preferred option, especially in patients who require early initiation of combination therapy, based on its efficacy, safety profile, and synergistic effects.

HbA1c Targets:

Encourage healthcare providers to initiate treatment with metformin + vildagliptin FDC at HbA1c levels between 7.6% to 8.0%, as recommended by 36% of doctors in the survey, to achieve optimal glycemic control.

Patient Adherence and Tolerability:
Highlight the importance of good tolerability and patient adherence with early initiation of combination therapy, as reported by 50% of doctors, to promote long-term treatment success and improve clinical outcomes.

Cardiovascular Risk Reduction:
Educate healthcare providers about the potential moderating effects of combination therapy with metformin + vildagliptin FDC on cardiovascular outcomes, as recognized by the majority of doctors in the survey.

Patient Education and Support:
Provide patient education and support regarding the benefits of combination therapy, including improved glycemic control, reduced pill burden, and enhanced gastrointestinal tolerability, to promote treatment adherence and optimize clinical outcomes.

By implementing these recommendations, healthcare providers can enhance the management of glycemic control in patients with T2DM, improve treatment adherence, and reduce the risk of diabetes-related complications. Additionally, pharmaceutical companies can capitalize on the market opportunities presented by the demand for effective combination therapies and the potential for improved patient outcomes.

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

Developed by:

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