

# Comparison of Safety and Efficacy of Glimepiride-Metformin and Vildagliptin- Metformin Treatment in Newly Diagnosed Type 2 Diabetic Patients

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## Abstract

**Objectives:** To compare the safety and efficacy of combination of Glimepiride – Metformin with Vildagliptin – Metformin in type 2 diabetic patients with HbA1c between 7.5 to 10.

**Methods:** A randomized, prospective, comparative and interventional study was conducted at Indira Gandhi Medical College, Shimla. The level of hemoglobin A1c (HbA1c), fasting blood sugar (FBS) and postprandial blood sugar (PP) were the primary outcomes, whereas, the evidence of hypoglycemia, quality of life and weight gain were recorded as secondary outcomes. 215 patients newly diagnosed with type 2 diabetes mellitus were randomized into Glimepiride-Metformin group (Group 1) having 111 patients and Vildagliptin-Metformin group (Group 2) having 106 patients. Patients were followed up at 3 month, 12 month, 24 month and then after completion of 30 month of treatment.

**Results:** A comparable FPG, PPPG and HbA1c were observed from baseline at the end of 12 weeks in both groups. However, at the 130-week endpoint a significantly more pronounced reduction in HbA1c was observed in vildagliptin-metformin (1.96%) arm compared to Glimepiride-metformin (1.67%) arm. A similar significant more pronounced reduction was demonstrated in both FPG (48.25% vs. 41.70%) and PPPG (49.40% vs. 42.95%) in vildagliptin-metformin group compared to Glimepiride-metformin group. The proportion of patients who achieved an A1C <7% at 130-weeks was 49% in the vildagliptin group and 41% in the Glimepiride group. Statistically significant more weight gain was observed in Glimepiride arm compared to vildagliptin arm (2.09 kg vs. 0.69 kg) and 8-fold lower incidence was observed in vildagliptin group.

**Conclusion:** Vildagliptin –metformin represent a more effective combination in terms of number of patients achieving guidelines recommended A1C target of less than 7% at the end of 30 months, less weight gain, and a lower risk of hypoglycemia in newly diagnosed type 2 diabetic patients with moderate hypoglycemia.

## Introduction

Diabetes mellitus (DM) is one of the most common chronic disorders attaining epidemic proportion, worldwide. As per International Diabetes Federation (IDF) there were 366 million people with diabetes in 2011; by 2030 the number will rise to 552 million all over the world.<sup>1</sup> India is one of the epicenters of the global diabetes epidemic and has the second highest

number of people with the disease in the world with 69.2 million individuals as of 2015 and this number is set to increase to 109.5 million by 2030.<sup>1</sup> The primary objective of treatment of type 2 diabetes (T2DM) is to achieve

and maintain good glycemic control to minimize the long-term micro- and macro vascular complications.<sup>2</sup> Though, to accomplish this objective, requires attention too many factors beyond glycemic control, however,

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Treating type 2 diabetes early is especially important because early and aggressive blood glucose reduces the diabetes related morbidity and mortality.<sup>7,8</sup> Up to 50-80% of  $\beta$ -cell function has already been lost<sup>9</sup> and nearly 32.55% of patients already have some sort of complications at diagnosis of T 2 diabetes;<sup>10</sup> so early diabetes as currently defined is already a late stage in the natural course of Type 2 diabetes.

A proactive approach, adding a second agent to treat diabetes aggressively from the time of diagnosis is critically important.

Vildagliptin is new classes of oral hypoglycemic agents. It is highly selective dipeptidyl peptidase-4 (DPP-4) inhibitors and increases the levels of glucagon like peptide-1 (GLP-1) by preventing the degradation of endogenous glucagon-like peptide-1 and glucose-dependent insulinotropic peptide (GIP).<sup>11</sup> Vildagliptin lowers blood glucose by increasing insulin secretion and decreasing glucagon secretion and is effective either as monotherapy or combination with other oral agents.<sup>12</sup> Vildagliptin displays good adverse effect profiles and does not cause weight gain and severe hypoglycemia.<sup>11,12</sup>

Glimepiride; a second generation sulfonylurea is a potent oral hypoglycemic agent. It is commonly prescribed as a monotherapy or in combination therapy with other oral agents.<sup>13</sup> Glimepiride though effective in lowering glucose, is associated with weight gain and severe hypoglycemia.<sup>13</sup>

In present study we compared the combination of Glimepiride-metformin treatment to vildagliptin-metformin treatment in newly diagnosed treatment naïve type 2 diabetic patients with moderate hyperglycemia and evaluated over 130 weeks.

## Material and Methods

### Patient population

Consecutive patients of T2DM attending Medicine OPD at IGMC, Shimla, were screened for possible enrolment in the study. All patients who fulfilled the inclusion criteria (age  $\geq 18$  years, newly diagnosed type 2 diabetic patients with HbA1c between 7.5 to 10 and newly diagnosed type 2 diabetic patients with HbA1c >10% not willing to insulin therapy) were included. This study complies with WHO diagnostic criteria for diabetes mellitus, i.e., a random or casual plasma glucose concentration  $\geq 200$  mg/dl or fasting plasma glucose  $\geq 126$  mg/dl or 2-hour plasma glucose  $\geq 200$  mg/dl during standard 75 g oral glucose tolerance test.<sup>14</sup> Patients were excluded if they had Type 1 diabetes mellitus, acute complication of diabetes like hyperglycemia hyperosmolar state/diabetic ketoacidosis, significant renal

or liver disease, congestive heart failure, acute coronary syndrome, age <18 years and > 80 years and pregnancy. Due informed consent was taken from each participant and ethical clearance from the institution’s ethical committee was obtained.

**Study design**

The study was a randomized, prospective, comparative and interventional study.

**Study duration**

Study was started in February 2013 with follow up done till July 2015.

**Randomization procedure**

After base line clinical and lab investigations patients were randomized to assign group 1 or group 2 treatment through Block Randomization Technique. Allocation sequence was generated by the person not involved in the study. Randomization for Group 1 and Group 2 were concealed using Sequentially

Numbered Opaque Sealed Envelope (SNOSE) technique.

**Intervention**

Patients randomized to group 1 were treated with Glimepiride 2 mg OD and Metformin 1 gm BD and group 2 with Vildagliptin 50 mg BD and Metformin 1 gm BD. Due to difficult geographical terrain, patients were advised to come for follow up between 3 to 6 month at their convenience and study participants were followed up at 3, 12, 24 and 30 months. Patients who failed to respond with study drugs were switched over to insulin therapy. The doses of drugs were adjusted during follow up depending upon patient’s A1C levels and the drugs and their dosages were recorded in both the study groups. On completion of 30 months of intervention, the specified outcome parameters were reassessed.

**Data collection**

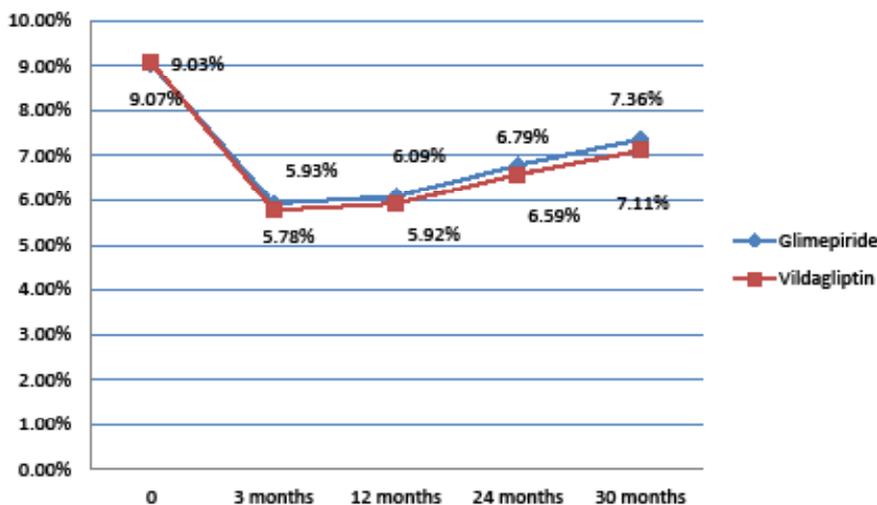
Name, age, sex, contact number, educational status and occupation

of the patients were noted. Family history of diabetes if any was also noted. Dietary history and history of smoking and alcohol were recorded. At baseline, the patient’s history was recorded and a thorough physical examination conducted. Anthropometric measurements: weight, height, waist (at the level of anterior superior iliac spine in standing position) and body mass index (weight in kilogram divided by height in meter square) were recorded. Fasting plasma glucose, post prandial plasma glucose, A1C and blood pressure were recorded. Plasma glucose levels were measured by using glucose oxidase and A1C was measured by radioimmunoassay. All patients underwent routine blood tests i.e. complete hemogram, liver and kidney functions and lipid profile at base line. X-ray chest and thyroid function test were done where clinically indicated. Patient’s telephone number and address were recorded and they were advised to follow at 3-6month

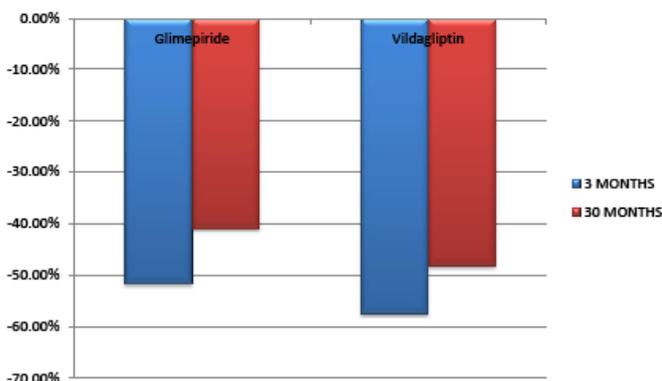
**Table 1: Demographic and risk factor profile at baseline**

Variable	Group 1 (100) (Glimepiride-Metformin)	Group 2 (100) (Vildagliptin-Metformin)
Age (years)	49.41 (±8.87)	50.88 (±9.30)
Sex (M)	59 (59%)	60 (60%)
Height (cm)	160.4 (±8.90)	160.86 (±8.02)
Weight (kg)	67.97 (±8.48)	69.48 (±10.27)
Waist (cm)	92.27 (±8.08)	93.50 (±7.74)
BMI (kg/m <sup>2</sup> )	26.44 (±2.74)	26.81 (±3.15)
FPG mg/dl	187.85 (±34.81)	202.60 (± 67.70)
PPPG mg/dl	295.90 (±55.89)	307.10 (70.96)
A1C	9.03%	9.07%
Family H/O HTN	5 (5%)	10 (10%)
Family H/O DM	30 (30%)	23 (23%)

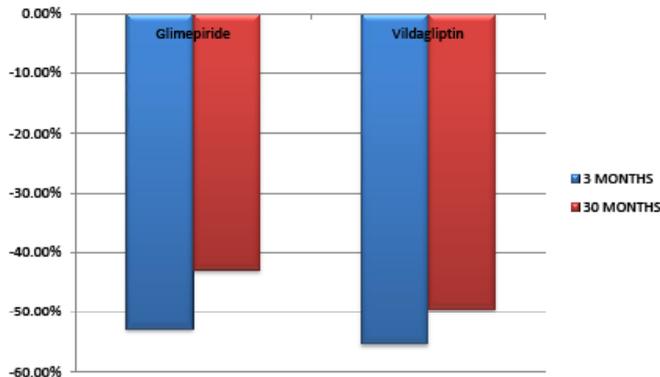
Key: BMI – Body mass index; HTN – Hypertension; DM- Diabetes Mellitus; FPG- Fasting Plasma Glucose; PPPG- Post-Prandial Plasma Glucose; A1C- Glycated hemoglobin



**Fig. 3: Comparison of HbA1c over 30 months between two groups**



**Fig. 1: Comparison of reduction in fasting blood sugar at 3 and 30 months between glimepiride and vildagliptin**



**Fig. 2: Comparison of reduction in post prandial blood sugar at 3 and 30 months between glimepiride and vildagliptin**

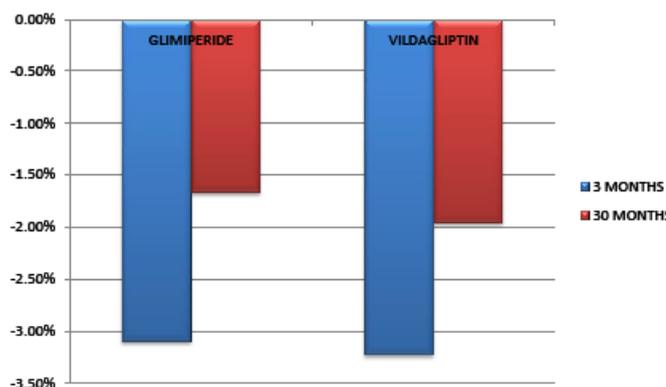


Fig. 4: Comparison of reduction in HbA1c at 3 and 30 months between glimepiride and vildagliptin

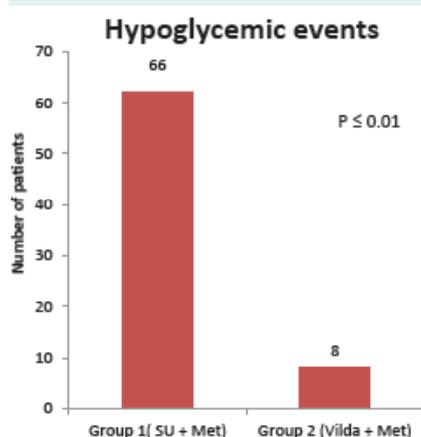


Fig. 5: Comparison of hypoglycemic events within two groups

intervals. At base line, patients were educated regarding the symptoms of hypoglycemia and about the corrective measure if hypoglycemia occurs.

#### Follow up

FPG, PPPG and HbA1c were recorded during each follow up period and patients were enquired about anorexia, nausea, gastrointestinal intolerance and any other symptoms experienced after starting the study drug. Symptoms of minor as well as major hypoglycemia were noted. Subjective feeling of wellbeing i.e. quality of life was enquired.

Hypoglycemia:<sup>15</sup> "Any abnormally low plasma glucose concentration that exposes the subject to potential harm" and defined as:

Biochemically: Based on documented blood glucose levels < 70 mg/dl.

Overall hypoglycemia: any event classified by study investigators as such (from history: patient had one or other symptom of hypoglycemia and symptom resolved on taking sugar

without knowing the blood glucose level).

#### Statistical analysis

Data was analyzed using Epi Info version 3.4.3. Discrete values were expressed as percentage and continuous variables as mean  $\pm$  SD. Student t test was applied to assess the significance of difference in mean values and chi-square test was for evaluation of frequencies of variable. 'p' value < 0.05 was considered significant.

#### Results

A total of 217 patients were enrolled for the study, out of which 111 were enrolled in the Group 1 (Glimepiride-Metformin) and 106 patients were enrolled in group 2 (Vildagliptin-Metformin). However, in group 1, 8 patients were lost during follow up at 3 months and 3 patients had to be shifted to insulin because of the unsatisfactory treatment response. Finally, 100 patients completed the entire study period in this group.

Similarly in group 2, 4 patients were lost to follow up at 3 months whereas, 2 patient required insulin, thus a total of 100 patients completed study period in this group.

The demographic and risk factor profile of the patient population among the Group 1 and Group 2 were similar and shown in Table 1.

#### Efficacy of glucose control

In group 1, there was a significant ( $p < 0.01$ ) decline of 51.63% in the level of mean FBG from 187.85 ( $\pm 34.81$ ) mg/dl at baseline to 90.86 ( $\pm 18.95$ ) mg/dl at 3 months. At 30 months, mean FBG was 109.50 ( $\pm 18.28$ ) mg/dl, which showed a significant ( $p < 0.01$ ) reduction (41.70%) from baseline. The mean change in

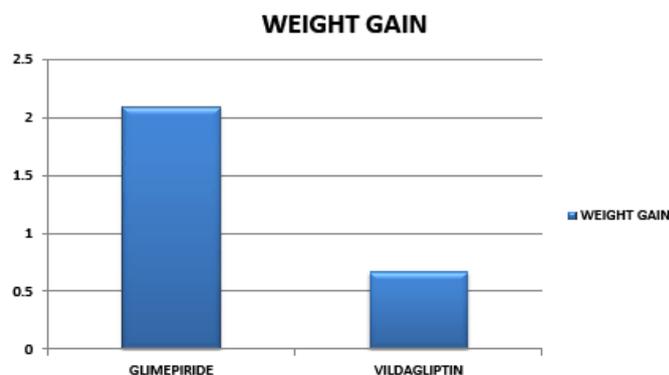


Fig. 6: Comparison of weight gain between two groups

PPPG level from baseline of 295.90 ( $\pm 55.89$ ) mg/dl was 139.32 (11.78) mg/dl at the end of 3 month. This exhibited a percentage decline of 52.81%, which was highly significant statistically ( $p < 0.01$ ). Similarly, a significant ( $p < 0.01$ ) decline (42.95%) in PPPG level was observed at the end of 30 month from baseline of 295.90 ( $\pm 55.89$ ) mg/dl to 168.80 ( $\pm 29.60$ ) mg/dl (Figures 1 and 2). The mean HbA1c level exhibited a 3.10% decline from baseline of 9.03% to 5.93% at 3 months which was statistically highly significant ( $p < 0.01$ ). A significant ( $p < 0.01$ ) reduction of 1.67% was observed at the end of study (from 9.03% to 7.36%) (Figures 3 and 4). The proportion of patients who achieved HbA1c < 7 were 83% on completion of 3 months of treatment and 31% at the end of study.

In group 2, a significant ( $p < 0.01$ ) decline of 57.44% in mean FBG from a baseline of 202.60 ( $\pm 67.70$ ) mg/dl to 86.22 ( $\pm 8.66$ ) mg/dl at the end of 3 months was observed. The fasting plasma glucose remained significantly decreased by 48.25% from a baseline of 202.60 ( $\pm 67.70$ ) to 104.84 ( $\pm 7.72$ ) at the end of 30 month. The PPPG decreased significantly (55.34%) from a mean of 307.1 ( $\pm 70.96$ ) mg/dl to 137.15 ( $\pm 13.73$ ) mg/dl at 3 months ( $p < 0.01$ ). At 30 months, the mean value of PPPG was 155.39 ( $\pm 33.34$ ) mg/dl, thus reduction observed from baseline to end of treatment was 49.40%, a highly significant difference ( $p < 0.01$ ) (Figures 1 and 2). The mean HbA1c was decreased significantly from 9.07 to 5.84% ( $\downarrow$  by 3.23%) at 3 month and from 9.07% to 7.11% ( $\downarrow$  by 1.96%) at the end of 30 months (Figures 3 and 4). The proportion of patients who achieved HbA1c < 7 were 84 % on completion of 3 months of treatment and 39% at the end of study.

The comparison of the levels of FBS, PPPG and HbA1c of two groups revealed that there was no significant difference at baseline ( $p>0.05$ ). At 3 months, the levels of FBS and HbA1c exhibited significant difference among two groups (significantly lower in vildagliptin compared to Glimepiride) having  $p$  values of 0.05 and 0.03, respectively, however a non-significant difference ( $p$  value=0.93) in the level of PPPG. At 30 months all these variables (FPG, PPPG 7 HbA1c) showed significant difference ( $p<0.01$ ) among the two groups (significantly lower in vildagliptin compared to Glimepiride).

#### **Incidence of hypoglycemia**

The overall incidence of hypoglycemia (minor) was higher in patients treated with Glimepiride-metformin combination as compared to the patients treated with Vildagliptin-Metformin combination. A total of 66 patients experienced at least 1 episode of hypoglycemia in group 1 as compared to 8 patients in group 2 ( $p<0.01$ ) (Figure 5). All episodes were minor except for 9 episodes in Glimepiride which were recorded to be of moderate in intensity.

#### **Changes in body weight**

In present study, a variation in body weight had been observed among the two treatment groups. A significant weight gain was observed in group 1 (2.07 kg) as compared to (.69 kg) in group 2 ( $p<0.01$ ) at the end of study (Figure 6).

#### **Treatment outcome**

On completion of 3 months of treatment, out of 100 patients in group 1, 60% of patients were switched on to metformin and pioglitazone combination, while 40% needed the initial combination of Glimepiride and metformin. All patients were followed up till 30 months and it was observed that there was gradual increase in the HbA1c levels from 18 months onwards to the end of study and escalation of therapy was needed. Consequently, at 30 months, 72% patients needed three medicines (Glimepiride + metformin and Pioglitazone), 4% patients required the addition of fourth drug (DPP-4 inhibitor or acarbose inhibitor), 2% patients were shifted to pre-mix insulin and 22% patients required metformin and Pioglitazone to achieve glycemic control (A1C  $<7\%$ ).

In group 2, on completion of 3

months of treatment, of 100 patients, 80% were switched on to combination of metformin and Pioglitazone (vildagliptin discontinued) and only 20% of patients required the combination of vildagliptin and metformin. Though, there was also gradual increase in the A1C levels from 18 month onwards, however it was quite small, Consequently, at the end of 30 month, 65 % of patients needed escalation of therapy from two drugs to three drugs (vildagliptin + metformin+ Pioglitazone), 4% patients required the addition of fourth drug (Sulphonylurea or acarbose inhibitor) and 1% were shifted to pre-mix insulin and remaining 30% were able to maintain their glycemic control with two drugs (metformin+ pioglitazone).

#### **Cost-effectiveness**

The two groups differ in their cost effect, as treatment with vildagliptin group was 4.3 fold costlier than with sulphonylurea till 3 months of treatment. However, this difference lessens to 2.0 fold and 2.50 fold in 24 months and 30 months respectively, as more number of patients were able to maintain on metformin and pioglitazone in group 2 compared to group 1 with the progress of treatment duration. The difference in the cost between vildagliptin and Glimepiride decreases at the end of the study because more number of patients in Glimepiride group needed escalation of therapy compared to vildagliptin group.

#### **Discussion**

The primary results of our study showed that the initial combination therapy at the time of diagnosis provided significant and durable glycemic control up-to 130 weeks period; second that the combination of vildagliptin - metformin improved the durability of glycemic control better than Glimepiride- metformin combination at 30 month (A1c 7.11 vs. 7.31  $p<0.001$ ) and displays a favorable adverse effect profile with no weight gain and less episodes of hypoglycemia. The better glycemic control in the later part of study period in vildagliptin-metformin group could not be explained by difference in baseline characteristics and difference in drug adherence and body composition.

In our study A1C decreased significantly at the end of 3 months

in both groups (from 9.03% to 5.93% decreased by 3.10%) in group1 and (from 9.07% to 5.84% decreased by 3.23%) in group 2 (Figure 3) and 84% and 85% of the patients achieved the target of A1C  $<7\%$ . Similar reductions were observed in FPG and PPPG levels at the end of 3 months. Similar reduction in glycemic parameters were observed in various previous studies and support the results of our study.<sup>16,17</sup>

At the end of study period (120 weeks), all three parameters (FPG, PPPG and A1C) remained significantly lowered compared to baseline values in both groups. Consistent with the results of our study, the durability in glycemic control with initial combination therapy was also observed in other previous studies and supports the results of our study<sup>16-19</sup>. The reduction in glycemic levels in Glimepiride- metformin was associated with significantly higher incidence of hypoglycemia (66% vs. 8%) and weight gain (2.07 kg vs. 0.69 kg) (Figures 5 and 6) and consistent with the results reported in various previous studies.<sup>16,17,19</sup>

At the end of study period, 39% of participants in vildagliptin- metformin group and 31% in Glimepiride-metformin group achieved the target of A1C  $<7\%$  and comparable with other studies.<sup>20,21</sup> The A1C levels were comparable in both groups up-to 18 month of treatment,<sup>16,21</sup> when A1C start rising in both group, albeit, more pronounced rise in A1C was observed in Glimepiride-metformin group compared to vildagliptin-metformin group that reached at a significant levels at 24 and 30 month (at 24 month A1C 6.79 vs. 6.61  $p<0.001$  and at 30 month A1C 7.36 vs. 7.11  $p<0.001$ ) (Figure 3). At the end of 30 month, A1C decreased by 1.96% from base line (from 9.07% to 7.11%) in vildagliptin group compared to 1.67% reduction in Glimepiride group (from 9.03% to 7.36%) (Figure 4), despite more patients in latter required the addition of another oral agent to maintain the A1C  $<7\%$ . The statistically significant increase in A1C levels in Glimepiride compared to vildagliptin group at 24 and 30 month in this study showed that the combination of vildagliptin and metformin reduced the rate of treatment failure compared with combination of Glimepiride and metformin and is in lieu with previous studies.<sup>22,23</sup> The significant rise in A1C after 24 month of treatment in

drug naïve patients in Glimepiride group is attributed to more pronounced  $\beta$ -cell failure seen with sulphonylurea treatment.<sup>24,25</sup> Similar to our study, better response among Asian diabetic patients to DPP-4 inhibitors has been shown in other studies, resulting into durable glycaemic control.<sup>26,27</sup> Consistent with this; more study participants in Glimepiride group required more escalation of drug therapy compared to vildagliptin group (80% vs. 70% at 30 month).

This study like various previous studies showed that vildagliptin-metformin treatment displays better side effect profiles compared to Glimepiride – metformin treatment with less weight gain and lower incidence of hypoglycemia.<sup>11,12,16,17</sup> Recently several clinical trials have shown strong association between adverse clinical outcome and hypoglycemia.<sup>28</sup> The occurrence of any severe hypoglycemia constitutes a marker of vulnerability to a primary cardiovascular events or death. Cardiovascular events are the major cause of mortality in type 2 diabetic patients, considering the potential C-V risk associated with severe hypoglycemia,<sup>29</sup> the use of medications associated with lower risk of hypoglycemia for the management of blood glucose in type 2 diabetic patients would be prudent.

Cost is a limiting factor for DPP-4 inhibitors use. In this study, the initial 4-fold higher cost in vildagliptin group decreased to 2.75 fold at the end of 30 month. However, the lower

cost in Glimepiride was associated with increased pill burden, increased incidence of hypoglycemia, increased weight gain and more number of patients with target A1C >7%.

In T2D, guidelines recommended glycaemic targets significantly delayed the onset and progression of complications, however, the proportion of patients reaching these targets remains unacceptably low. In guidelines recommended step-up approach, a patient accumulate total glycaemic burden of A1C > 8% for 5 years and A1C > 7 % for 10 years as patient passed through non-pharmacological to monotherapy to combination oral agents.<sup>30</sup> A major, however, less recognized contribution of this glycaemic burden is the response of clinicians to failing antihyperglycaemic treatment as the A1C levels rise inexorably high above 9.0% before combination therapy is attempted by the clinicians.<sup>30</sup> However, recent clinical trials indicate that earlier intervention and timely achievement of glycaemic targets help in reducing the diabetes related chronic complications. Achieving the guidelines recommended glycaemic targets very early (within 12 weeks) and maintaining these targets over prolonged period up to 120 weeks in this study with early use of combination therapy in drug naïve patient favours the early use of combination therapy in the treatment armamentarium of newly diagnosed type 2 diabetic patients with moderate hyperglycemia. Better glycaemic sustainability and good AE

profile was observed with vildagliptin therapy, albeit at a higher cost.

Despite vast expenditure of healthcare resources, management of T2D remains woefully inadequate, and many patients spend long time well outside the recommended glycaemic range. New standard care of clinical practice guidelines entails initial combination therapy earlier in the treatment continuum than previous guidelines. However, resistance to initiate combination therapy at diagnosis, among physicians is widespread. As the principal responsibility for managing T2D continue to shift to primary care setting, PCPs must rise to the challenge of overcoming their own resistance.

Although the present study had limitation in terms of small number of patients, collectively the results indicate that the DPP-4 inhibitors –metformin represent a more effective combination in terms of number of patients achieving guidelines recommended A1C target of less than 7% at the end of 30 months, less weight gain, and a lower risk of hypoglycemia in newly diagnosed type 2 diabetic patients with moderate hypoglycemia.

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