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Study the effect of Dipeptidyl Peptidase 4 Inhibitors as an Antidiabetic in Type 2 Diabetes Mellitus (T2DM)

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ABSTRACT

Dipeptidyl peptidase IV is a key regulator of insulin- stimulating hormones, glucagon-like peptide and glucose dependent insulinotropic polypeptide. Thus it is a promising target for treatment of type 2 Diabetes mellitus. Inhibition of plasma Dipeptidyl peptidase IV enzyme lead to enhanced endogenous glucagon like peptide-1, GIP activity which ultimately results in the potentiating of insulin secretion by pancreatic cell and subsequent lowering blood glucose level, HbA [1c], glucose secretion, liver glucose production. One of the principal goals of diabetes management is to attain haemoglobin HbA [1c] treatment goals and prevent the onset or decrease the rate of occurrence of Microvascular conditions.^{2, 6} numerous treatment options are available for management of Type 2 Diabetes mellitus, various class of DPP IV inhibitor being explored such as Sitagliptin and Vildagliptin successfully launched. Several other novel DPP IV inhibitors are in pipeline, Unless there are clear contraindications, metformin monotherapy is prescribed, and if HbA [1c] targets are not attained after 3 months, 1 of several classes of agents could be added, such as sulfonylurea's, Thiazolidinediones, dipeptidyl peptidase-4 inhibitors, - glucagon like peptide-1 receptor agonists, or basal insulin.^{2,6} Despite the broad range of therapeutic options, the attainment of HbA [1c] goals among patients with diabetes remains challenging, with just slightly more than half (52%) of diabetes patients attaining the common HbA [1c] goal of < 7.0%. The present review summarizes latest preclinical and clinical trial data of different DPP IV inhibitors with a special emphasis on their DPP8/9 fold selectivity and therapeutic advantages over GLP-1 based approach.

Keywords: Diabetes 2, Dipeptidyl Peptidase-4, glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1.

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INTRODUCTION

Diabetes is a growing epidemic. The prevalence of diabetes in the United States nears 30 million, and future projections estimate that one in three adults could have diabetes by 2050 if current trends continue¹. Type 2 diabetes mellitus (T2DM), characterized by insulin resistance and progressive β -cell dysfunction², accounts for >90% of diagnosed cases³. In association between chronic hyperglycemia and the development of vascular complications have been established². Strict glycaemic control may help reduce the risk of micro vascular complications and correct the pathophysiological damage chronic hyperglycemia exerts on β -cells and insulin secretion². Guideline from American Diabetes Association (ADA) is based on a stepwise approach to establish glycaemic control⁴. For most adults with T2DM, a glycosylated haemoglobin (HbA1c) goal of <7% is recommended. For patients who can tolerate a more stringent HbA1c target without significant hypoglycemia or other adverse effects, a goal of <6.5% is recommended. However, less stringent glycaemic goals (>7%) may be appropriate for patients with more advanced disease, extensive comorbid conditions, or a history of severe hypoglycemia⁴. Metformin is the preferred initial pharmacological therapy for Type 2 Diabetes mellitus^{4, 5}. Metformin lowers basal and postprandial plasma glucose concentrations by decreasing hepatic glucose production and intestinal glucose absorption and increasing peripheral glucose uptake and utilization⁶. When used as monotherapy in treatment of patients with Type 2 Diabetes mellitus⁴, metformin reduced HbA1c by 1.4%⁷. Metformin is also associated with weight reduction or weight neutrality⁶. For patients taking metformin but still experiencing hyperglycemia after ~3 months, the ADA recommends adding a second pharmacological agent. Should a patient still not meet the individualized HbA [1c] goal after another ~3 months, a third oral antidiabetic drug (OAD) or insulin may be added⁴. Combining medications with complementary mechanisms of action may help address the numerous factors underlying dysfunctional glycaemic control². Guidance from the ADA regarding which agents to choose in dual therapy regimens is flexible and even less prescriptive for triple therapy regimens. Although this emphasizes the importance of tailoring pharmacological treatment to an individual patient's needs, this also underlines the complexity in clinical choices, in part due to the wide variety of available agents⁴. Although the therapeutic profiles of traditional agents, such as metformin, sulfonylurea's, and Thiazolidinediones (TZDs) are well established in monotherapy and combination regimens, additional insights about the newer agents, the dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose co transporter 2 (SGLT2) inhibitors, are needed as clinical use continues to increase. The following is a review of the efficacy and safety of combination therapy including DPP-4 inhibitors and/or SGLT2

inhibitors, with a focus on triple combination regimens incorporating these agents. Dipeptidyl peptidase-4 (DPP-4) inhibitors are gaining attention as a novel class of antihyperglycemic agents based on the incretin effect. Sitagliptin was the first available agent, followed by vildagliptin, saxagliptin, linagliptin and Alogliptin⁸. DPP-4 inhibitors achieve glycemic control through inhibition of the dipeptidyl peptidase-4 enzyme, which contributes to the rapid degradation of incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which are released after food intake and then exert glucose-lowering effects through stimulating insulin secretion and by pancreatic² -cells and inhibiting glucagon secretion by pancreatic \pm cells in a glucose dependent manner⁹. There are two major obstacles in developing GIP-based anti-diabetic drugs, including rapid degradation by DPP-4 enzyme and severely low incretin activity in patients with type 2 diabetes¹⁰. GLP-1 is also rapidly inactivated by DPP-4 enzyme in the circulation, but its incretin effects are still largely retained in patients with type 2 diabetes¹⁰. Therefore, DPP-4 inhibitors improve glycaemic control in patients with type 2 diabetes in a glucose-dependent manner through inhibiting inactivation of GIP and GLP-1 and then exerting their various biological activities. Inhibition of DPP-4 can also reduce postprandial glucagon secretion from pancreatic \pm cells and potentially will increase² cell mass, induce small islets, and stimulate islet neogenesis¹¹.

Table 1: Treatment of Type 2 Diabetes Mellitus:

	Monotherapy	Add	Add
Obese	Metformin	Sulfonylurea	Insulin or glitazone or exenatide
Non obese	Sulfonylurea or metformin	Metformin or sulfonylurea	Insulin or glitazone or exenatide
Elderly	Low dose secretagogues	Switch to simple insulin regimen	
Asians	Glitazone	Metformin	Insulin or exenatide or sulfonylurea

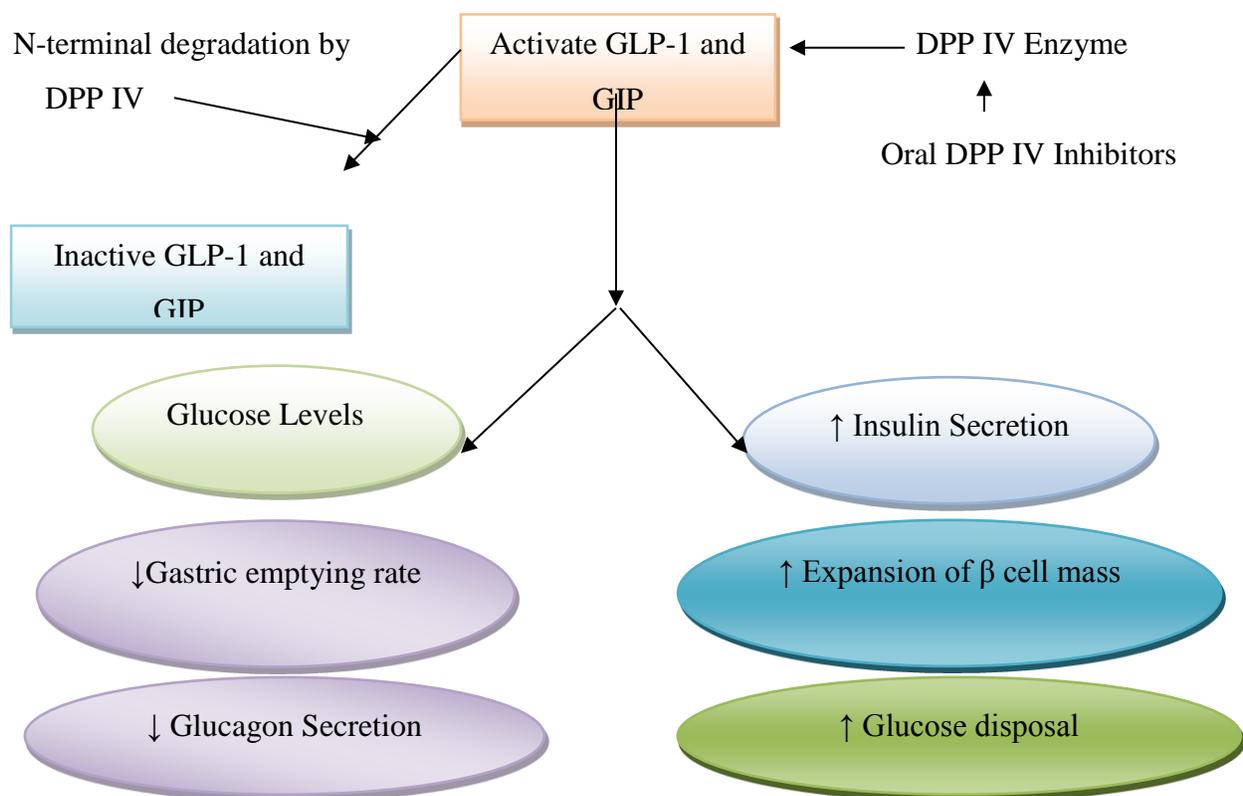


Figure 1: Physiological action of GLP-1 and GIP and their modulation by oral DPP IV inhibitors. Schematic representation of the effect of oral DPP IV inhibitors on GLP-1 AND GIP is increased upon inhibition of plasma DPP IV by oral DPP IV inhibitors.

MATERIALS AND METHOD

Dipeptidyl peptidase 4 inhibitors:

Dipeptidyl peptidase 4 (DPP-4) inhibitors prevent the degradation of gastrointestinal incretin glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), resulting in improved glycaemic control by increasing levels of GLP-1 and GIP³⁻⁵. The efficacy and safety of DPP-4 inhibitors and insulin combination therapy has been evaluated in several previous studies, including systematic reviews and meta-analyses based on findings from randomized controlled trials (RCTs). However, these are only limited data comparing DPP-4 inhibitors with other antihyperglycemic agents in combination with insulin, especially head-to-head comparisons, and no systemic reviews or meta-analyses have been published. Therefore, aim of our current systematic review and meta-analysis was to evaluate the efficacy and safety of DPP-4 inhibitors compared with placebo or other antihyperglycemic agents in combination with insulin therapy. Overall, the effects of DPP-4 inhibitors of clinical atherosclerosis remain unclear, especially in patients at early stage of vascular dysfunction. Previous studies investigating

endothelial function have reported heterogeneous effects of DPP-4 inhibitors, both in healthy volunteers¹¹⁻¹² and in patients with Type 2 Diabetes Mellitus¹³⁻¹⁷. These heterogeneous results may be attributable to the methods applied and variances in the populations studied. Furthermore, differences in glucose control between study arms could have prevented firm conclusions from being drawn about the pleiotropic effects of DPP-4 inhibition versus effects resulting from the reduction of hyperglycemia, which is suggested to improve endothelial function¹⁸. The present study, we assessed the short-term effects of the DPP-4 inhibitor linagliptin compared with an active comparator (the sulphonylurea, Glimperide) and with placebo on measures of macro- and Microvascular endothelial function in healthy patients with uncomplicated T2D who were representative of a primary prevention population (i.e., had no history of pre-existing cardiovascular disease).

Mechanism of action: DPP-4 inhibitors:

There is continued interest in the role of incretin hormone responses and deficiencies in T2DM⁸ Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are major incretin hormones, critical for glucose-dependent insulin secretion⁹. GLP-1 additionally acts to suppress glucagon release, stimulate b-cell proliferation, and delay gastric emptying⁹. Under normal physiologic conditions, GLP-1 and GIP are rapidly broken down by the exopeptidase DPP-4 enzyme⁸⁻¹⁰. There is mixed evidence as to whether GLP-1 secretion is also decreased in patients with Type 2 Diabetes Mellitus¹¹. However, it is theorized that the impaired incretin effect is partly due to a decreased postprandial GLP-1 response and reduced insulinotropic response¹²⁻¹³. DPP-4 inhibitors selectively inhibit the DPP-4 enzyme and thereby slow the degradation of GLP-1 and GIP and increase their concentrations in circulation⁸⁻¹⁴. In glucose-dependent manner, DPP-4 inhibitors improve b-cell sensitivity to glucose, increase insulin secretion, and decrease glucagon secretion¹⁵.

In vivo findings also suggest protective and restorative characteristics, evidenced by improved b-cell mass and morphology with treatment¹⁶. Clinical trials have demonstrated the efficacy of DPP-4 inhibitor monotherapy in patients with Type 2 Diabetes Mellitus, and indirect comparisons of individual agents suggest comparable efficacy among the class¹⁷. Importantly, DPP-4 inhibitors are associated with a low risk of hypoglycaemia, weight neutrality, and a rare occurrence of major adverse effects⁴.

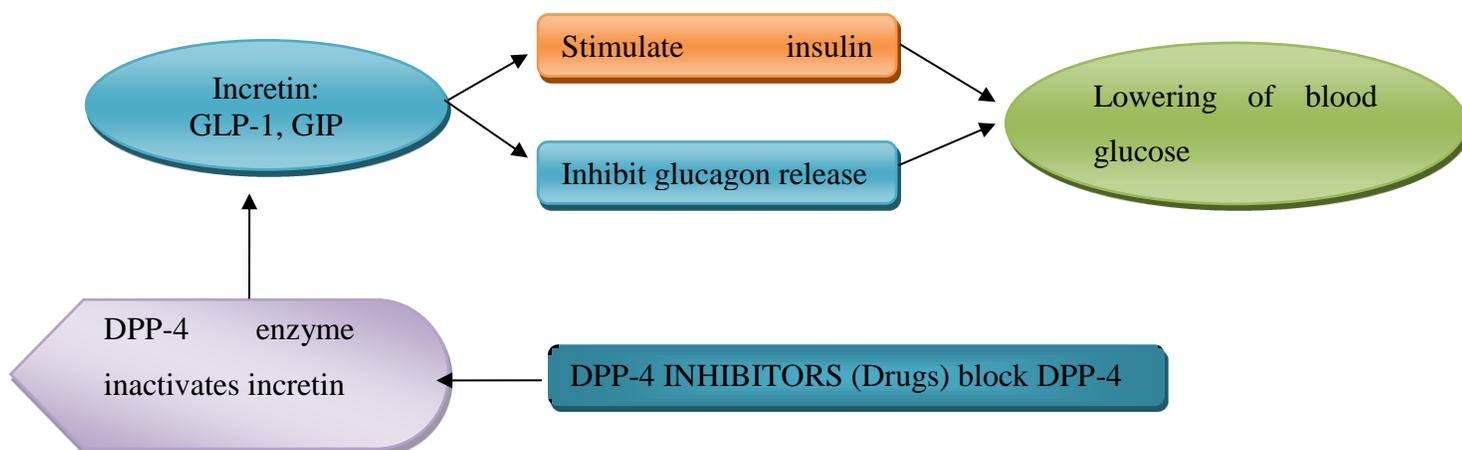


Figure 2: Efficacy of DPP-4 inhibitors in combination therapy:

Alogliptin:

12.5 and 25 mg/day has been studied in various combination therapies. When used as add-on to background metformin, Alogliptin 12.5 or 25 mg significantly decreased HbA1c and fasting plasma glucose (FPG) from baseline to 26 weeks versus placebo ($p < 0.001$ for each Alogliptin dose)²². Similar improvements were observed in the proportion of patients reaching HbA1c $\leq 7\%$ with the addition of Alogliptin 12.5 mg (52.0%) or 25 mg (44.0%) versus placebo (18%, $p < 0.001$ for each dose)²². Add-on Alogliptin 12.5 or 25 mg to metformin was no inferior to (each $p < 0.001$), and Alogliptin 25 mg was statistically superior to ($P = 0.010$) add-on Glipizide to metformin in reducing HbA1c from baseline to 104 weeks²³. Decreases in FPG from baseline with Alogliptin 25 and 12.5 mg were also statistically significantly greater compared with add-on Glipizide starting at weeks 16 and 26, respectively, and continued throughout 104 weeks²³. In a separate evaluation of Alogliptin 12.5 or 25 mg added to background glyburide 10 mg for 26 weeks, dual therapy with Alogliptin was associated with significant improvements of HbA1c compared with glyburide monotherapy and numerical improvements in secondary glycemic measures²⁴. As part of triple oral therapy regimen, either added as dual therapy with Pioglitazone to background metformin or as add-on to background Pioglitazone and metformin²⁸, Alogliptin 12.5 and 25 mg triple oral therapy regimens were associated with significant beneficial effects on glycemic parameters compared with dual therapy arms at 26 weeks (all $p < 0.01$). Study findings in patients receiving insulin with or without metformin or in patients receiving Pioglitazone with or without metformin or a sulfonylurea also showed the addition of Alogliptin 12.5 or 25 mg to significantly improve HbA1c by week 4 and sustain glycemic control through week 26 ($p < 0.001$ vs. placebo)²⁹⁻³⁰. When used as initial combination therapy with metformin or Pioglitazone in treatment-naïve patients, Alogliptin 12.5 or 25 mg was associated with statistically significant

improvements in HbA1c and FPG from baseline at 26 weeks versus monotherapy with individual components (all $p < 0.05$)²⁵⁻²⁶. Similar and significant improvements were also observed in the percentage of patients achieving HbA1c $\leq 7\%$ with Alogliptin initial combination therapy (all $p < 0.05$ vs. individual components)²⁵⁻²⁶.

Linagliptin:

5 mg/day have been shown to be efficacious in reducing HbA1c and FPG from baseline when administered as initial combination therapy with metformin for 24 weeks in treatment of patients ($p < 0.001$ vs. individual monotherapy components)³¹. A similar trend for improved glycemic parameters was also observed with linagliptin 5 mg administered as initial combination therapy with Pioglitazone³² or as add-on therapy in patients continuing metformin^[33]. Compared with add-on Glimepiride to metformin³⁴, add-on linagliptin to metformin provided similar improvements in HbA1c and FPG at 2 years (all $p < 0.01$ for no inferiority; Table 1B). In triple combination therapy, linagliptin 5 mg as add-on to metformin plus a sulfonylurea or a TZD significantly improved key glycemic efficacy outcomes at 24 weeks, with differences from dual therapy reaching statistical significance (all $p < 0.05$)³⁵⁻³⁶. Findings from a separate study of linagliptin as add-on to basal insulin with or without metformin or Pioglitazone showed similar improvements in HbA1c and FPG from baseline at 24 weeks with the addition of linagliptin as a third agent ($p < 0.001$ vs. dual therapy)³⁷. Also reported were outcomes from a subgroup analysis in which no interaction with linagliptin was observed in patients stratified by renal function, type of basal insulin, age, use of OADs, sex, and body mass index. Further analysis of patients stratified by background medication showed the improvement in HbA1c from baseline reached statistical significance with add-on linagliptin versus placebo ($p < 0.01$) in patients taking background metformin, sulfonylurea with or without metformin or insulin alone or in combination³⁸.

Saxagliptin:

In three individual 24-week studies, saxagliptin 2.5 and 5 mg improved HbA1c and FPG from baseline when used as initial combination therapy with metformin in treatment-naïve patients or when used as add-on to background metformin³⁹. In addition, more patients achieved HbA1c $< 7\%$ with saxagliptin as initial combination or add-on therapy (all $p < 0.001$)^{40, 41}. In a comparative analysis versus add-on Glipizide to metformin, add-on saxagliptin 5 mg was no inferior in reducing HbA1c from baseline at 52 weeks⁴². Significantly improved efficacy outcomes have also been observed with dual therapy including saxagliptin 2.5 or 5 mg and a sulfonylurea or TZD⁴³⁻⁴⁴. In combination with insulin with or without metformin, add-on saxagliptin 5 mg demonstrated significant improvements in HbA1c from baseline at 24 weeks ($p <$

0.001 vs. placebo)⁴⁵. Although trend toward improvement in FPG and the proportion of patients achieving HbA1c <7% was observed with the addition of saxagliptin, differences from placebo did not reach statistical significance⁴⁵. As add-on to metformin and a sulfonylurea for 24 weeks, saxagliptin 5 mg significantly decreased HbA1c from baseline compared with placebo add-on ($p < 0.0001$)⁴⁶. Although no significant difference between groups was observed in the change from baseline in FPG, more patients achieved HbA1c <7% with saxagliptin triple therapy (nominal $p < 0.0001$ vs. dual therapy)⁴⁶.

Sitagliptin:

As initial combination therapy with metformin or add-on to metformin, Sitagliptin 100 mg was shown to significantly improve HbA1c and FPG from baseline at 24 weeks and increase the proportion of patients achieving HbA1c <7% (all $p < 0.001$ vs. individual monotherapy components)⁴⁷⁻⁴⁸. In comparison with add-on Glipizide to metformin, add-on sitagliptin 100 mg to metformin demonstrated no inferiority for reducing HbA1c from baseline at 52 weeks⁴⁹. In addition, dual therapy with Sitagliptin 100 mg added to Pioglitazone for 24 weeks significantly improved glycemic outcomes compared with Pioglitazone monotherapy ($p < 0.001$; Table 1D)⁴². Sitagliptin has been studied in various triple combination treatment regimens. Findings have shown the addition of sitagliptin 100 mg to Glimepiride, with or without metformin, to significantly improve HbA1c and FPG from baseline at 24 weeks and increase the proportion of patients reaching HbA1c <7% (all $p < 0.001$ vs. placebo)⁴³. In patients continuing insulin with or without metformin, the addition of Sitagliptin 100 mg for 24 weeks was shown to significantly improve glycemic outcomes compared with placebo, including HbA1c, FPG, and the proportion of patients achieving HbA1c <7% (all $p < 0.001$)⁴⁰. In separate study, similar and significant improvements in glycemic efficacy were demonstrated with add-on Sitagliptin 100 mg for 24 weeks to ongoing Pioglitazone and metformin ($p < 0.001$ vs. placebo add-on)⁴⁴.

Safety and tolerability of DPP-4 inhibitors in combination therapy:

Overall, the safety and tolerability profile of dual or triple combination therapy regimens including a DPP-4 inhibitor was similar to that observed with placebo or active comparator regimens, and no major safety concerns emerged²²⁻⁴⁹. Many trials presented here combined DPP-4 inhibitor with metformin. In these instances, neutral or beneficial effect on weight was consistently observed²³. A neutral effect on weight was also observed when DPP-4 inhibitor therapy was added to regimens containing insulin²⁹. Small increases in weight, known side effect of sulfonylurea's and TZDs⁴, were observed when DPP-4 inhibitor regimens included this OADs²⁴. DPP-4 inhibitors are associated with a low risk of hypoglycemia⁴. When combined with metformin or a TZD, a low

incidence of hypoglycemia was consistently observed, and, when combined with insulin, the incidence of hypoglycemia was generally similar to that observed with placebo addition²². The occurrence of hypoglycemic events was generally shown to increase when combined with sulfonylurea^{24, 26}. Importantly, the addition of a DPP-4 inhibitor did not appear to exacerbate known adverse effects of the other components (e.g. gastrointestinal disturbance with metformin, bone fracture with TZD)²⁸ and no increase in the occurrence of cardiovascular (CV) events was observed⁴⁰. Common adverse effects associated with DPP-4 inhibitors include upper respiratory and urinary tract infection, nasopharyngitis, and headache⁴⁴ and the pattern of these events was similar in combination therapy regimens⁴⁷. Certain exfoliative dermal toxicities have also been reported with the DPP-4 inhibitor class. However, overall findings from the presented studies showed no increased risk of skin-related adverse events in DPP-4 inhibitor treatment groups³⁶. In addition, laboratory values, including neutrophils and lymphocyte counts, remained largely unchanged, and the addition of a DPP-4 inhibitor was associated with a neutral or beneficial effect on lipid parameters³⁹. Based on the studies reviewed above, dual combination with DPP-4 inhibitor and metformin or TZD appears to be therapeutically beneficial treatment option because glycemic efficacy was shown to significantly improve compared with monotherapy, without increased hypoglycaemia. Similar outcomes were observed with triple therapy regimens including a DPP-4 inhibitor with metformin and a TZD or insulin, although consideration should be given to weight increases associated with TZD therapy.

RESULTS AND DISCUSSION:

For patients who cannot tolerate metformin, initial combination therapy with a DPP-4 inhibitor and a TZD or an SGLT2 inhibitor may also be beneficial²⁶. The more recent studies evaluating the use of triple therapy regimens demonstrate an additive benefit with the inclusion of a DPP-4 inhibitor or SGLT2 inhibitor as a third agent compared with dual therapy arms. Overall, the safety and tolerability profiles of DPP-4 inhibitors or SGLT2 inhibitors in combination with other antihyperglycemic agents were generally consistent with the known effects of individual monotherapy components. Although additional long-term studies are needed, current data suggest that both classes of medication maintain efficacy and tolerability with prolonged exposure. A novel treatment approach is the use of a DPP-4 inhibitor with an SGLT2 inhibitor in triple combination therapy. Each of these medications is appealing for use in combination therapy regimens owing to their demonstrated clinical efficacy, a low incidence of hypoglycemia, and a neutral or beneficial effect on weight. Research also suggests the glucose-lowering actions of a DPP-4 inhibitor plus an SGLT2 inhibitor may be complementary, rather than additive. Current guidelines recommend that

DPP-4 inhibitors be used cautiously, or not at all, in patients with preexisting heart failure until additional data are known. Findings from the ongoing and large-scale Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) study, the Cardiovascular and Renal Microvascular Outcome Study in Patients with Type 2 Diabetes Mellitus at High Vascular Risk (CARMELINA), and the randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study should provide additional insight on the effects DPP-4 inhibitors have on CV outcomes. Research has shown that b-cell dysfunction occurs earlier and more severely than previously believed². Findings have shown that patients with pre-diabetes have already lost ~50% of their b-cell volume, and patients with impaired glucose tolerance may have lost >80% of b-cell function². Although the exact mechanism by which insulin resistance leads to b-cell failure is unknown, initiating pharmacological treatment early may help prevent progressive b-cell decline². There is early evidence, *in vivo*, that indicates a restorative effect on b-cell mass and morphology with DPP-4 inhibitors¹⁶ and a beneficial effect on b-cell function with SGLT2 inhibitors. In combination with another Type 2 Diabetes Mellitus medication with a synergistic mechanism of action, there is potential to delay or possibly prevent the natural progression of b-cell failure and produce a durable treatment effect. There is a clinical need to further evaluate the effects of antidiabetic medications on CV outcomes. Two recently completed CV outcomes trials of DPP-4 inhibitors provide new insight. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) trial (n = 16,492) evaluated the CV safety of saxagliptin in patients with a history of, or at risk of CV events. Outcomes (median follow up of 2.1 years) showed no increased risk of the primary composite end point of CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke in patients treated with saxagliptin versus placebo in addition to standard of care. There was also no significant increase in the occurrence of the secondary composite end point, defined as the primary end point plus hospitalization for heart failure, coronary revascularization, or unstable angina, with saxagliptin compared with placebo.

CONCLUSION:

In conclusion, clinical studies in a variety of patients with Type 2 Diabetes Mellitus support the efficacy, safety, and tolerability of dual and triple combination treatment regimens including a DPP-4 inhibitor and/or an SGLT2 inhibitor. Although a step- wise approach remains the standard treatment algorithm, initiating combination treatment early may help address the multiple sites of dysfunction that occur early in the disease and help prevent future complications. A number of studies have demonstrated the efficacy and tolerability of initial combination therapy in treatment-

naïve patients. For patients with T2DM with inadequate glycaemic control with dual therapy, the addition of a DPP-4 inhibitor and/or an SGLT2 inhibitor is clinically useful as a third agent. Each class consistently produced additive effects on glycaemic parameters compared with dual therapy, without notably affecting the side-effect profile of other agents in combination. More recent studies implementing simultaneous administration of two OADs to metformin potentially highlights a novel approach to triple therapy dosing.

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CONFLICT OF INTEREST:

The authors confirm that this article content has no conflict of interest.

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