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The Glycemic Efficacy and Safety Profile of Gliptins: Updated Data in 2020

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ABSTRACT

Background: The earlier update on the safety of gliptins published in 2018 showed that dipeptidyl peptidase-4 (DPP-4) inhibitors have good tolerance and safety profile even in susceptible populations. This review provides recent updates (2018-2020) on the glycemic efficacy and safety profile of gliptins, cardiovascualr safety of gliptins, and their role when used early in diabetes therapy. **Summary:** DPP-4 inhibitors or gliptins is an established class of oral antidiabetic agents in the management of type 2 diabetes with proven efficacy and safety profiles in adults, elderly and young patients. The excellent safety and efficacy of DPP-4 inhibitors are established in type 2 diabetes management even in fragile populations and individuals with varying degrees of renal dysfunction. DPP-4 inhibitors are associated with a good tolerability profile and reduced risk of hypoglycemia. Studies have not shown the involvement of gliptins in cardiovascular adverse events and are considered to be safe for use in terms of cardiovascular events.

Keywords: DPP-4 inhibitors, vildagliptin, alogliptin, cardiovascular benefits, safety and efficacy

Dipeptidyl peptidase-4 (DPP-4) inhibitors or gliptins are antidiabetic agents which act by binding to the enzyme DPP-4 to inhibit the degradation of the incretin, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), with a primary role in glucose homeostasis and glycemic control. DPP-4 inhibitors prolong the activity of endogenous GLP-1 and GIP and may improve postprandial hyperglycemia, without inducing hypoglycemia, in patients with type 2 diabetes mellitus (T2DM).[1]

In the previous update on the safety of gliptins published in 2018, it was suggested that the DPP-4 inhibitors possess good tolerance/safety profile even in the more fragile populations with no gastrointestinal adverse events and minimal chances of hypoglycemia. The review mentioned the occurrence of new adverse event arthralgia; however, until now, there is no definitive evidence about the causality of the relationship.[2]

This comprehensive review aims at discussing the recent updates on the glycemic efficacy and safety profile of gliptins, including their glycemic variability, adverse events and role of gliptins when used early in diabetes therapy.

METHODOLOGY

Authors conducted a review of published literature to assess the glycemic efficacy and safety profile of DPP-4 inhibitors in the treatment of T2DM patients. The search was primarily conducted on PubMed and Google Scholar. In an attempt to identify relevant studies, an extensive literature search of PubMed was performed from January 2018 to July 2020, with the MeSH terms [(((((DPP-4 inhibitors) OR (Gliptins)) OR (DPP-4 inhibitors)) AND (Safety)) AND (tolerance)], (DPP-4 inhibitors) AND (Adverse events), and (((DPP-4 inhibitors) OR (Gliptins)) OR (DPP-4 inhibitors)) AND (glycemic variability), including randomized controlled trials (RCTs), clinical studies, systematic reviews and meta-analyses. In a backward chronological search, the reference lists of all relevant articles were checked for citations that could not be detected in the primary search. A total of 63 articles were selected for the development of the review.

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GLYCEMIC EFFICACY AND SAFETY PROFILE

The DPP-4 inhibitors are oral hypoglycemic agents generally considered to be effective in lowering glucose levels and possess no gastrointestinal adverse effects and minimal risk of hypoglycemia.[2]

A network meta-analysis including data till 2018 compared and evaluated the efficacy and safety of different DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, vildagliptin and alogliptin) compared with placebo and against each other. The results indicated that except alogliptin, all DPP-4 inhibitors led to a decrease of glycated hemoglobin (HbA1c) when compared with placebo. When evaluated for body mass index (BMI) and body weight, it was found that vildagliptin 5 once daily (QD) and linagliptin 5 QD was best placed in reducing the BMI and body weight, respectively.[3]

The EVOLUTION INDIA study assessed the efficacy and safety of evogliptin versus sitagliptin, added to background metformin therapy in Indian patients with uncontrolled T2DM. The study findings demonstrated that mean reduction in HbA1c at 12 weeks in evogliptin and sitagliptin-treated patients were -0.37 (1.06) and -0.32 (1.14), respectively. The results from the study led to the conclusion that evogliptin was noninferior to sitagliptin in HbA1c reduction. It effectively improved glycemic control and was well-tolerated in T2DM patients whose blood glucose was not managed by the use of metformin alone.[4]

A head-to-head prospective, open-label, randomized, active-control trial comparing teneligliptin with sitagliptin as an add-on to metformin and/or sulfonylurea in patients with T2DM was conducted. It was suggested that teneligliptin provided similar glycemic control as compared to sitagliptin and reduced HbA1c, fasting blood glucose (FBG) and postprandial blood glucose (PPBG) values significantly within 12 weeks of treatment. The results showed that at the end of 12 weeks, statistically significant lowering was seen in both teneligliptin and sitagliptin arms in HbA1c (-1.19 ± 1.16% $p < 0.0001$ and -0.92 ± 0.95%, $p < 0.0001$), FBG (-28.3 ± 63.0 mg/dL, $p = 0.01$ and 022.9 ± 47.4 mg/dL, $p < 0.006$) and PPBG (-41.3 ± 85.4 mg/dL, $p = 0.006$ and -54.7 ± 85.6 mg/dL, $p = 0.0005$). According to the results, both gliptins were found to be safe and well-tolerated with no differences in the adverse events rate in Indian patients with T2DM. However, post-hoc comparisons have shown that the percentage of patients reaching the target HbA1c <7% after 12 weeks of treatment was in favor of teneligliptin compared with sitagliptin.[5]

Another phase 4, randomized, placebo-controlled national study was conducted in Japan over 52 weeks in 102 patients (≥60 years) on stable treatment with basal insulin and metformin or α-glucosidase inhibitors. The participants were randomized (1:1) to be administered linagliptin 5 mg QD or placebo with the primary endpoint being the change in HbA1c after 24 weeks of treatment. The findings of the study showed that significant HbA1c reductions with linagliptin versus placebo were observed in elderly patients at 24 weeks (95% confidence interval [CI] -0.96, -0.45, $p < 0.0001$) and maintained at 52 weeks. Linagliptin was effective in improving glucose control in Japanese patients aged ≥60 years with T2DM on stable glucose-lowering therapy with basal insulin and was well-tolerated in elderly patients with no adverse events reported.[6]

In a study comprising of 458 participants who were not at HbA1c goal on a submaximal dose of metformin, when a DPP-4 inhibitor like sitagliptin was added while metformin dose was being increased, the intervention resulted in improved glycemic response. The findings of the study showed that following 20 weeks of treatment, the least-squares mean changes from baseline in HbA1c were -12.1 mmol/mol (-14.0, -10.1) (-1.10% [-1.28, -0.93]) and -7.6 mmol/mol (-9.6, -5.6) (-0.69% [-0.88, -0.51]) with sitagliptin and placebo, respectively. The between-group differences in the least-squares mean changes from baseline HbA1c was -4.5 mmol/mol (-6.5, -2.5) (-0.41% [-0.59, -0.23]); $p < 0.001$. These findings suggested that the use of sitagliptin led to the achievement of HbA1c target with similar safety and tolerability as compared to increasing metformin dose alone.[7]

Similar results were obtained in a study which analyzed pooled data from two 52-week Phase III studies assessing the efficacy and safety of once daily combinations of empagliflozin/linagliptin as exclusive therapy or add-on to metformin in patients with T2DM. Adverse events were evaluated descriptively in patients who took ≥1 dose of the study drug. The findings showed that empagliflozin or linagliptin as monotherapy or add-on to metformin for 52 weeks was well-tolerated in T2DM patients, with a safety profile similar to individual components, including a low risk of hypoglycemia. The percentage of patients with confirmed hypoglycemic adverse events was low in all groups (1.1-2.2%); however, no patient required any assistance. Events consistent with urinary tract infection were described in a similar percentage of patients in all groups (11.4-13.8%); events consistent with genital infection were stated in increased proportions of patients on empagliflozin/linagliptin or

empagliflozin (4.0-6.5%) than linagliptin 5 mg (2.6%). Also, the risks of hypersensitivity reactions and adverse events related to loss of volume were low across all treatment groups.[8]

The results of a double-blind, randomized, controlled parallel-group study comparing 1 and 5 mg doses of a DPP-4 inhibitor (linagliptin) demonstrated similar clinical efficacy and safety profile of the drug in young patients equivalent to adult patients. The DPP-4 inhibitor was well-tolerated and led to a dose-dependent DPP-4 inhibition accompanied by the corresponding lowering of the HbA1c and fasting plasma glucose (FPG) levels in young people with T2DM. The higher dose was favored over lower dose in terms of efficacy and safety profile.[9]

The DPP-4 inhibitors are also considered to be both efficacious and well-tolerated across a wide range of renal function; however, sometimes, dose adjustment may be needed to control drug exposure.[10] The CompoSIT-R study was a prospective, randomized clinical trial comparing the efficacy and safety of the DPP-4 inhibitor sitagliptin with the sodium-glucose cotransporter-2 (SGLT2) inhibitor dapagliflozin in patients with T2DM and mild renal insufficiency. The findings showed that in T2DM patients with mild renal insufficiency, sitagliptin optimized blood glucose management to a greater extent than dapagliflozin. After 24 weeks, the between-group difference in the least square mean (95% CI) changes from baseline in HbA1c was -0.15% (-0.26, -0.04) (-1.67 mmol/mol [-2.86, -0.48]), p = 0.006, meeting the prespecified criteria for declaring both noninferiority and superiority of sitagliptin versus dapagliflozin. This study provided concrete evidence based on which clinicians could take informed patient-centered decisions for the treatment of T2DM patients. DPP-4 inhibitors are preferred choice in patients with T2DM and renal disease owing to their efficacy and good tolerability across the renal disease spectrum. In T2DM patients with mild renal insufficiency who were poorly controlled on metformin ± sulfonylureas, treatment with sitagliptin compared with dapagliflozin demonstrated enhanced glycemic efficacy and increased percentage of patients achieving the glycemic goal and a good safety profile.[11]

When compared with other treatments, DPP-4 inhibitors were linked with a larger variation in HbA1c level, and a higher response rate of patients achieving the HbA1c goal of <7%. The occurrence of adverse events in the two groups did not differ significantly, and DPP-4 inhibitors did not lead to an increased rate of hypoglycemia.[12] DPP-4 inhibitors significantly reduce HbA1c levels in T2DM patients with moderate-to-severe renal injury. It has been established that DPP-4 inhibitors did not increase the risk of hypoglycemia and adverse events.[13]

A systematic review and meta-analysis of 15 RCTs to assess ethnic differences in efficacy and safety of a potent DPP-4 inhibitor alogliptin concluded that it is more effective in improving glycemic levels in Asian population as compared to other ethnic populations. It was hypothesized that BMI value was a primary contributor to the differential glycemic effects of DPP-4 inhibitors. The studies with Asian population were on lower-BMI groups as compared with those of non-Asian population.[14] The results of a meta-analysis previously had shown that in some cases, the baseline BMI was significantly linked with HbA1c-reducing efficacy in patients being given DPP-4 inhibitors.[15] It has been proven that DPP-4 adipokine is significantly present in the visceral fat of obese people, and its release into circulation is also increased. Hence, DPP-4 activity is raised in obese individuals. As it is evident that the circulating DPP-4 level and activity are increased in obese individuals, the efficacy of DPP-4 inhibitors in non-Asian patients with high BMI should be lower than in Asian patients, which has also been proven in various studies.[14]

The results of the SUPER study, evaluating the efficacy of a DPP-4 inhibitor as add-on treatment in Chinese T2DM patients inadequately controlled by insulin ± metformin, showed that add on DPP-4 inhibitor, saxagliptin 5 mg QD, led to a substantial improvement in glycemic control without increasing the risk of hypoglycemia and was also well-tolerated in Chinese patients with T2DM uncontrolled by insulin and/or metformin.[16] Cumulative evidence from 30 RCTs concluded that saxagliptin has similar efficacy compared with most oral antidiabetic drugs and may be more effective than acarbose and may also have a better safety profile than both acarbose and sulfonylureas. The results of the study showed that compared with placebo, saxagliptin reduced HbA1c (weight mean difference [WMD] -0.52%, 95% CI -0.60 to -0.44) and FPG (WMD -13.78 mg/dL, 95% CI -15.31 to -12.25), and increased the proportion of patients achieving HbA1c <7% (risk ratio [RR] 1.64, 95% CI 1.53-1.75). Saxagliptin was also similar to other DPP-4 inhibitors but inferior to liraglutide and dapagliflozin on glycemic control. It significantly reduced the occurrence of overall adverse events compared with acarbose (RR 0.71, 95% CI 0.57-0.89) and liraglutide (RR 0.41, 95% CI 0.24-0.71) when added to metformin. Another advantage was that saxagliptin did not increase the risk of arthralgia, heart failure, pancreatitis and other adverse events.[17]

Another open-label, phase 3 exploratory study evaluated the efficacy and safety of a once-weekly novel DPP-4 inhibitor, trelagliptin, in Japanese T2DM patients when switched over from once daily sitagliptin therapy. Of the 14 patients receiving the study drug, the blood glucose did not show any marked changes from baseline at major assessment points in the meal tolerance test, and a reduction in blood glucose was seen at several other assessment points. Mild-to-moderate adverse events were reported in approximately 43% of the patients, and most were not related to the study drug. It was indicated that it is possible to transition from a once daily DPP-4 inhibitor to trelagliptin in T2DM patients with stable glycemic control in combination with diet and exercise therapy without any significant influences on glycemic control or safety.[18]

When used as monotherapy, the efficacy and safety of once-weekly DPP-4 inhibitor omarigliptin can improve glycemic control over 54 weeks. A study was conducted among people with T2DM not on glucose-lowering medications, or who were washed off monotherapy or low-dose dual therapy. The results showed that from a mean baseline HbA1c of 8.0-8.1%, the least-squares mean (95% CI) change from baseline in HbA1c at Week 24 (primary endpoint) was -0.49% (-0.73, -0.24) in the omarigliptin group and -0.10% (-0.34, 0.14) in the placebo group, for a between-group difference of -0.39% (0.59, -0.19) ($p < 0.001$).[19]

A systematic review and meta-analysis, including 11 clinical trials, offered a conclusion based on a subgroup analysis that omarigliptin possessed homologous efficacy and safety compared to other antihyperglycemic agents. It revealed that omarigliptin had a favorable efficacy and safety as monotherapy or added on to other antihyperglycemic agents. The results of the meta-analysis showed that in comparison with the control group, omarigliptin was linked with a considerably stronger reduction in HbA1c and FPG. The study findings did not reveal any significant differences in adverse events, serious adverse events, hypoglycemic events between omarigliptin and control group.[20]

In a systematic review and meta-analysis, the results of the 6-minute walk test and peak oxygen consumption suggested that DPP-4 inhibitors or GLP-1 receptor agonists improved patients' exercise tolerance and did not reduce patients' quality of life, with high heterogeneity among the results. The authors have concluded that DPP-4 inhibitors or GLP-1 receptor agonists can improve exercise tolerance in heart failure patients, and do not appear to increase the incidence of all-cause death or severe adverse events and do not decrease health-related quality of life.[21] It has been revealed in many studies that GLP-1 can use microvasculature and stimulate mitochondrial activity in muscle.[22-24] During exercise, microvasculature plays a crucial role in ensuring an adequate supply of oxygen and nutrients so that adenosine triphosphate (ATP) is generated in the mitochondria.[25] When DPP-4 GLP-1 pathway is targeted, an increase in GLP-1 levels ensures oxygen and nutrient supply to the muscles further stimulating mitochondrial activity. With improved microvasculature function, oxygen consumption is also improved. These cascading events may be potentially responsible for improved oxygen tolerance.[21] Another study has also shown that exercise tolerance is also improved as DPP-4 inhibitors activate the GLP-1 receptor signalling.[24] A systematic review and meta-analysis conducted to evaluate safety and tolerability profile of DPP-4 inhibitors versus sulfonylurea treatment in adult T2DM patients suggested a better safety profile for DPP-4 inhibitors than sulfonylureas and the effect was better for treatment regimens including metformin. The findings of the meta-analysis reported that DPP-4 inhibitors in combination with metformin reduced global adverse events (RR: 0.90; 95% CI, 0.86-0.94; $p < 0.0001$; $I^2 = 83\%$; 17 studies), cardiovascular events (RR: 0.54; 95% CI, 0.37-0.79; $p = 0.002$; $I^2 = 0\%$; 6 studies), hypoglycemia (RR: 0.17; 95% CI, 0.13-0.22; $p < 0.00001$; $I^2 = 76\%$; 17 studies) and severe hypoglycemic events (RR: 0.10; 95% CI, 0.05-0.19; $p < 0.00001$; $I^2 = 0\%$; 12 studies). The mean difference of the weight shift was 1.92 kg in favor of DPP-4 inhibitors in combination with metformin compared with sulfonylureas in combination with metformin. Besides, monotherapy with DPP-4 inhibitors also reduced the rates of hypoglycemia (RR: 0.31; 95% CI, 0.24-0.41; $p < 0.00001$; $I^2 = 0\%$) and severe hypoglycemic events (RR: 0.26; 95% CI, 0.10-0.66; $p = 0.004$; $I^2 = 0\%$) and patients did not gain weight.[26]

A novel xanthine DPP-4 inhibitor, yogliptin, targeting type 2 diabetes was assessed in a randomized, double-blind, parallel, placebo-controlled phase I single-dose escalation and the findings showed that it was well-tolerated in healthy participants, with no dose-limiting toxicity observed in the range from 2.5 to 600 mg. Additionally, yogliptin also exhibited plasma DPP-4 inhibitory activity for 3 days when given in a single dose of 25-200 mg and for 1 week when given in a single dose of 400 mg. Hence, it was suggested that once-weekly dosing of yogliptin was possible in T2DM patients.[27]

PREFERENCE 4 study was conducted to compare treatment satisfaction of four classes of oral hypoglycemic agents including DPP-4 inhibitors,

α-glucosidase inhibitors, biguanides and sulfonylureas. The DPP-4 inhibitor was the most preferred option in terms of treatment satisfaction. In this study, the mean total and the three subscale scores at Week 4 suggested that patients were most satisfied with the DPP-4 inhibitor treatment. Furthermore, increased satisfaction sustained with high adherence, HbA1c improvement and few adverse events over 12 weeks gave a good indication of the popularity of DPP-4 inhibitors for their ability to restore β-cell dysfunction with limited risk of hypoglycemia. The PREFERENCE 4 study provided a ground for basing clinical judgments in optimal drug selection for patients with T2DM.[28] The TRINITY trial assessed the patient preference for treatment with the oral once-weekly DPP-4 inhibitor, trelagliptin and oral once daily alogliptin given for 8 weeks each in patients with T2DM. The findings suggested that patients preferred once-daily alogliptin compared with once-weekly trelagliptin even though patient satisfaction and HbA1c levels were similar across treatments. However, both the treatments demonstrated favorable safety and tolerability profiles.[29] When 10 clinical trials were systematically reviewed and underwent analysis, it was concluded that DPP-4 inhibitor teneligliptin improved blood glucose levels and β-cell function with low risks of hypoglycemia in T2DM patients.[30]

EARLY INITIATION THERAPY WITH GLIPTIN

Early treatment intensification is linked with sustained glucose management and delayed diabetes complications. The current guidelines for the management of hyperglycemia in T2DM recommend the use of metformin as first-line therapy with further intensification and second-line therapy only when glycemic control is not achieved.[31,32] However, frequently the treatment intensification is delayed, which may be the reason for the loss of glycemic control and exposure to avoidable hyperglycemia.[33] In the UK Prospective Diabetes Study, it was established that early treatment to reduce glycemia using metformin was linked with lowering of myocardial infarction, diabetes-related deaths and all-cause mortality and long-term continued benefit following 10 years of treatment.[34] Some other studies have also highlighted the significance of attaining early blood glucose control in the first 12 months of diagnosis as an approach towards improving long-term glycemic durability and lowering of complications associated with diabetes.[35]

Existing evidence has suggested that the combination therapy, including DPP-4 inhibitor and other antidiabetes drugs, showed a significant decrease in HbA1c ($p < 0.001$) and a similar risk of hypoglycemia ($p > 0.05$). When compared with monotherapy, initial combination therapy including DPP-4 inhibitors also resulted in significant HbA1c reductions, a similar risk of hypoglycemia and similar risks of other adverse events.[36]

Administering two or more agents in combination therapy is a critical approach. In a randomized, double-blind, parallel-group study of newly diagnosed patients with T2DM (VERIFY), it was seen that early intervention with combination therapy of vildagliptin + metformin provides more significant and sustainable long-term benefits compared with the current standard-of-care initial metformin monotherapy.[37]

GLYCEMIC VARIABILITY

Glycemic variability is an essential aspect of blood glucose management, and DPP-4 inhibitors have been reported to have the ability to improve glycemic control and to reduce glucose fluctuations, by increasing active serum GLP-1 and GIP concentrations through a glucose-dependent insulin secretion.[38]

DPP-4 inhibitors are potential therapeutic agents for use in combination with metformin as they complement each other's mechanism of action. In a pilot study, a comparison of glycemic variability with high metformin dose versus low metformin dose and DPP-4 inhibitor combination was conducted in Japanese T2DM patients with inadequate glucose control despite the low-dose metformin monotherapy. The results indicated that low metformin + DPP-4 inhibitor might reduce post-breakfast glycemic variability to a more considerable extent than high metformin in T2DM patients receiving low-dose metformin monotherapy. The study results suggested that the combination of metformin and DPP-4 inhibitor has a better effect on improving post-breakfast glycemic excursions.[39]

An open-label, parallel-group, exploratory study examining the effects of two DPP-4 inhibitors on glycemic variability in patients with type 2 diabetes recommended that once-weekly trelagliptin and once-daily alogliptin improved glycemic control and reduced glycemic variability without inducing hypoglycemia.[38] An open-label, randomized study conducted among women with T2DM, suggested that both vildagliptin and gliclazide modified release similarly lowered the mean amplitude of glycemic excursions in them after 24 weeks of treatment.[40] However, in a trial including 20 T1DM patients, the findings showed that DPP-4 inhibitor (linagliptin) was not effective in reducing HbA1c and glycemic variability in relatively well-controlled type 1 diabetes.[41]

Following Roux-en-Y gastric bypass surgery (RYGB), in patients with diabetes and mild hyperglycemia a short course of DPP-4 inhibitor such as sitagliptin was found to provide small but significant glucose-lowering effect, with no identified improvement in β-cell function in a 4-week randomized trial.[42] In a randomized crossover study, 11 women who had undergone RYGB and had documented hypoglycemia were evaluated to investigate the effects of acarbose, sitagliptin, verapamil, liraglutide and pasireotide on post-bariatric hypoglycemia after the bypass. It was found that sitagliptin lowered nadir glucose values while acarbose and pasireotide reduced post-bariatric hypoglycemia.[43]

In a study assessing the efficacy of vildagliptin as add-on therapy to short-term continuous subcutaneous insulin infusion (CSII) with CSII monotherapy, the findings showed that the mean blood glucose (BG) concentrations during the whole treatment period were less and the time to attain target blood glucose levels was reduced in the CSII + vildagliptin group compared with the CSII group (9.89 ± 3.37 vs. 9.46 ± 3.23 mmol/L, $p < 0.01$; 129 ± 4 vs. 94 ± 5 h, $p < 0.01$, respectively). The authors concluded that short-term CSII with vildagliptin as add-on therapy might be a potentially beneficial alternative regimen for the management of uncontrolled blood glucose in T2DM patients.[44]

EFFECTS ON CARDIOVASCULAR OUTCOME

Type 2 diabetes mellitus heightens the risk of major cardiovascular complications by two-folds in patients without pre-existing cardiovascular disease, often resulting in fatal outcomes. Even though it has been established that improved glycemic control leads to a reduction in microvascular diabetic complications, ambiguity about the role of a specific glucose-lowering approach or a specific medicinal agent in terms of cardiovascular safety persists.[45]

Cardiovascular adverse events following the use of DPP-4 inhibitors have been suspected since DPP-4 inhibitors were launched in 2006. However, in a study, cardiovascular events after taking DPP-4 inhibitors were detected in only 1% of total 307 adverse event reports. An analysis of spontaneous adverse drug reports data did not reach any conclusive association between DPP-4 inhibitors and cardiovascular adverse events, owing to a small number of cardiovascular adverse events reports.[46]

The CARdiovascular Outcome study of LINAgliptin versus glimepiride in type 2 diabetes (CAROLINA) trial compared the effect of linagliptin and glimepiride on major cardiovascular events in patients with relatively early T2DM and increased cardiovascular risk. The findings showed that the primary outcome (time to the first occurrence of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) occurred in 356 of total 3,023 (11.8%) patients in the linagliptin group and 362 of 3,010 (12.0%) in the glimepiride group (hazard ratio [HR], 0.98 [95.47%, CI, 0.84-1.14]; $p < 0.001$ for noninferiority), meeting the noninferiority criterion but not superiority ($p = 0.76$). The results indicated that among adults with relatively early type 2 diabetes and increased cardiovascular risk, the use of linagliptin is of comparable efficacy and safety as compared with glimepiride.[47]

In a randomized noninferiority trial (CARMELINA trial) including 6,979 patients comparing the effect of linagliptin versus placebo, the findings showed that among patients with T2DM and high cardiovascular risk, linagliptin, compared with placebo, demonstrated noninferiority concerning the risk of major cardiovascular events over 2.2 years.[48] A network meta-analysis of 9 large trials showed that the DPP-4 inhibitors do not pose any additional cardiovascular risk.[49]

The EXAMINE trial randomized 5,380 patients who were 15 to 90 days post-acute coronary syndrome to the DPP-4 inhibitor alogliptin versus placebo and the results showed that DPP-4 inhibition with alogliptin was safe even in the high-risk period after acute coronary syndrome.[50] However, another systematic review and meta-analysis showed DPP-4 inhibitors to have a neutral effect on cardiovascular risk.[51]

A study was conducted to characterize all-cause mortality and major adverse cardiovascular events (MACE) in patients treated with metformin in combination with either sulfonylurea or a DPP-4 inhibitor using data from routine primary care in the UK. The findings showed that combination therapy with metformin + sulfonylurea was linked with a substantially increased risk of all-cause mortality of 36-85% compared with therapies combining metformin and DPP-4 inhibitors. It was also suggested that it might be possible for DPP-4 inhibitors to have a beneficial effect on cardiovascular outcomes beyond their antihyperglycemic properties.[52]

Because of the above discussion, it becomes clear that an oral hypoglycemic agent must be selected after metformin based on its cardiovascular safety and benefits. Based on the inputs from various existing trials, it has been established that DPP-4 inhibitors do not play any substantial role in increasing cardiovascular

outcomes in patients with T2DM suggesting them to be safe to use in terms of cardiovascular events.[53]

ADVERSE EVENTS ASSOCIATED WITH DPP-4 INHIBITOR USE

Frequently occurring adverse effects related to the use of DPP-4 inhibitors occur in 5% of patients who receive them.[54] Three most frequently reported adverse reactions in clinical trials were nasopharyngitis, upper respiratory tract infection (URTI) and headache.[55] URTI, nasopharyngitis and headache with sitagliptin and URTI, urinary tract infection and headache with saxagliptin have been reported.[54] An analysis of 16 studies has shown that DPP-4 inhibitor linagliptin related adverse events have diverse incidence and frequency, ranging from mild-to-moderate intensity. The most frequent adverse event reports were nasopharyngitis with monotherapy at 5 mg and 10 mg dose (31.6% and 29.6%, respectively), gastrointestinal events (>10.0%) with linagliptin in combination.[56]

Genitourinary Infection

A meta-analysis of RCTs and in an extensive pharmacovigilance database, it was shown that combination therapy with a DPP-4 inhibitor appears to reduce the frequency of genitourinary tract infections associated with SGLT2 inhibitors. The findings showed that the frequency of genitourinary infection in the patients on DPP-4 inhibitors/SGLT2 inhibitor combination therapy versus those on SGLT2 inhibitor monotherapy was 0.51 (95% CI 0.28-0.92). An explanation for genitourinary infection protection is both DPP-4 inhibitors and SGLT2 inhibitors may interact as proteins at the membrane level. DPP-4 activity is also present in some yeasts, moulds and bacteria and its inhibition by DPP-4 inhibitors may lead to an alteration of micro-organismal function.[57]

Bone Health and Risk of Fracture

Cumulative evidence from RCTs has demonstrated that the use of DPP-4 inhibitors may not affect the risk of fracture. Similarly, in a meta-analysis based on real-world data, the use of DPP-4 inhibitors was not associated with the risk of fracture.[58] There is evidence to suggest that DPP-4 inhibitors may have beneficial effects on bone health while SGLT2 inhibitors may harm bone health.[59-61] This finding has significant clinical implications as many commonly prescribed second- and third-line glucose-lowering medications such as sulfonylureas, thiazolidinediones and insulin have been directly or indirectly linked with a higher risk of fracture. Hence, DPP-4 inhibitors may be considered as an alternative to those medications.[58]

Inflammatory Bowel Disease

Despite DPP-4 inhibitors being a popular second-line treatment for T2DM, there have been conflicting reports about their risk of developing inflammatory bowel disease. The results of a meta-analysis based on a conservative random-effect analysis showed that DPP-4 inhibitors do not appear to increase the risk of developing inflammatory bowel disease.[62]

Pancreatitis and Pancreatic Cancer

The results of a meta-analysis of randomized clinical trials indicated that no association between DPP-4 inhibitors with pancreatitis or pancreatic cancer was found. However, it has been stated that the risk of pancreatitis cannot be excluded in patients not at risk of pancreatic cancer. It has also been suggested that DPP-4 inhibitors could be capable of inducing pancreatitis in patients at elevated risk such as those with a history of pancreatitis, alcohol abuse, hypertriglyceridemia, but not in patients at low risk.[63]

A network meta-analysis conducted by Ling et al showed that there existed no significant variations in the incidence of diarrhea, renal and hepatic toxicity and hypersensitivity reaction between different DPP-4 inhibitors. However, it showed that the vildagliptin 100 QD, linagliptin 5 QD and linagliptin 0.5 QD had the least chances of reducing the incidence of diarrhea, renal and hepatic toxicity and hypersensitivity reactions, respectively. Amongst all the DPP-4 inhibitors, sitagliptin 100 QD had the lowest chance of reducing the incidence of URTI.[3]

CONCLUSION

DPP-4 inhibitors have been proven to be safe and efficacious in patients across different age groups and individuals with renal disorders. Early combination therapy with DPP-4 inhibitors and metformin has shown durable glycemic control in patients with T2DM. Through various clinical studies and meta-analyses, it has been shown that DPP-4 inhibitors have no causal association with the development of cardiovascular events. Additionally, the DPP-4 inhibitors are not reported to be associated with adverse events such as bone fracture, inflammatory bowel disease, pancreatitis and pancreatic cancer.

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