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Review Article

CARDIOVASCULAR EFFICACY OF DIPEPTIDYL PEPTIDASE INHIBITOR-4: RECENT AFFIRMATION ON HEART FAILURE

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ABSTRACT

Diabetes Mellitus contributes to significant morbidity and mortality, with its prevalence rising day by day. Although there are various therapeutic agents to manage this devastating condition, varying efficacy, along with significant adverse effects, limit the use of many of them in the long run. Thus, there is an emerging need for newer therapeutic options that can maintain an optimal balance between drug efficacy and safety. Various anti diabetic agents include insulin, oral hypoglycemic agents, etc. In this review, we aim to focus on Dipeptidyl peptidase inhibitor-4 (Gliptins), which show promise in the fight against diabetes. Major gliptins include saxagliptin, alogliptin, linagliptin, anagliptin, teneligliptin and vildagliptin. Although the mechanism of action of DPP-4 inhibitors is somewhat unclear, they are known to inhibit the remote GLP-1 breakdown, thus ameliorating GLP-1 levels. DPP-4 inhibitors also upgrade the half-life of GLP-1, owing to the former's property of inhibiting DPP-4 enzyme (which contributes to GLP-1 breakdown). This review focuses on their impact on cardiovascular events, since insight into their effects in the cardiovascular system is also important to justify their use in diabetics in a health-care setting. In experimental models, gliptins have shown to provide favorable effects, chiefly improved endothelial function, reduction of inflammatory markers, etc. Gliptins have created a stir in the pharmaceutical company, owing to their pleotropic and multisystemic effects. A number of randomized controlled trials, meta-analyses, observational studies and pharmacovigilance reports have been conducted to establish the efficacy of gliptins, along with their underlying risks of cardiovascular problems, hypoglycemia, pancreatitis, bone fracture, arthralgia, etc. According to the results from three randomized controlled trials (SAVOR-TIMI 53, EXAMINE, TECOS), gliptins were shown to confer neither protective nor detrimental effects to the cardiovascular system. A high propensity for heart failure was observed in the SAVOR-TIMI 53 trial. At the same time, increased adinopectin levels and moderate decrease in lipid levels and blood pressure were observed. Available cardiovascular safety data from the non-clinical safety and clinical pharmacology details for saxagliptin, with respect to potentiality for non-clinical or early clinical sign of myocardial injury has been under controversy, demanding further investigation into the same. More studies are required in future to assess the cardiovascular safety profile of DPP-4 inhibitors.

KEYWORDS: *Dipeptidyl peptidase inhibitor-4, Cardiovascular efficacy, Diabetes mellitus, GLP-1 and Antidiabetic drugs.*

INTRODUCTION

The world, especially South Asia, is witnessing an increased pervasiveness of Diabetes Mellitus Type 2, with India having the largest number of diabetics. It is estimated by the International Diabetes Federation (IDF) that the number of diabetics will shoot up to 80 million by 2025. The rise in prevalence of Diabetes Mellitus Type 2 over the next 20 years will lead to a significant clinical and financial oppression in the healthcare system [1].

The standard agents used to treat Type 2 Diabetes Mellitus often exhibit reduced efficacy with time, leading to insufficient glycemic control accompanied with numerous adverse effects. Therefore, in order to overcome the limitations associated with the conventional antidiabetic agents, there is a requirement for alternative therapies.

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Biguanides (metformin) and sulphonylureas have been the anchors of therapy for diabetes for several years. Lately, thiazolidinediones have found a significant role in supplementing the reformation of insulin resistance, whilst lately there have been concerns over its safety. Meglitinide analogues and alpha-glucosidase inhibitors have some role in treatment of diabetes, although their roles have got their share of limitations. Insulin therapy is routinely required in several individuals with prolonged Type 2 diabetes, due to relentless decline of beta-cell [2].

This review emphasizes on Gliptins, which offer an unorthodox therapeutic strategy for Type 2 diabetes patients. Dipeptidylpeptidase-4 inhibitors depict a prototype shift in the management of Type 2 Diabetes Mellitus. Upregulation of the expression of glucose transport protein (GLUT- 2 and 4) by GLP-1 has been shown by invitro studies, which in turn ameliorates insulin resistance. There has been a marked reduction of GLUT-4 expression. GLP-1 mediates GLUT-4 translocation to the cardiac myocyte surface to increase glucose uptake. DPP-4 inhibitors are beneficial for diabetics, in that they have a correlative mechanism of action with other antidiabetic medications, side-effects are considerably agreeable and show a nonaligned effect on weight [3]. Although the mechanism of action of DPP-4 inhibitors is somewhat uncertain, they are known to inhibit the remote GLP-1 breakdown, thus augmenting GLP-1 levels. DPP-4 inhibitors also

upgrade the half-life of GLP-1, owing to the former's property of inhibiting DPP-4 enzyme (which contributes to GLP-1 breakdown) [4].

The review is based on the standing of the gliptins with emphasis on their abilities to positively or negatively influence the cardiovascular system, and their possible involvement in major adverse cardiovascular events (MACE). Alogliptin, anagliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin and vildagliptin are the contemporary compounds in clinical use. Improved endothelial function, oxidative stress/ischemia, reduction of inflammatory markers and atherogenesis are some of the favorable changes in chemical structures and metabolic pathways exerted by gliptins on experimental models. In addition, increased adiponectin levels and moderate decrease in lipemia and blood pressure were reported. In clinical settings, several trials that were employed on sitagliptin with 3 years of mean follow-up did not show an increased risk for ischemic events. Clinically, improvements in several risk factors of Diabetes Mellitus Type 2 have been found with DPP-4 inhibitors. Cardioprotective effects, with a trend for a lower incidence of major cardiovascular events with gliptins than with placebo has been suggested in the post-hoc analyses of phase II-III and control [5].

Ever since its discovery in 1967, serine protease DPP-4 has been a favored subject of research [6]. In the late 1980-90s, the first DPP-4 inhibitors were distinguished .It was indispensable for each inhibitor to establish an early structure activity relationship (SAR) for successive investigations [7]. A sequence of β-aminoacyl-containing cyclic hydrazine derivatives were amalgamated and assessed as DPP-IV inhibitors. They selectively bind to substrates that contain proline at the P1-position, thus many DPP-4 inhibitors have 5-membered heterocyclic rings that mimic proline, e.g. pyrrolidine, cyanopyrrolidine, thiazolidine and cyanothiazolidine [8, 9]. Researchers from Zeria Pharmaceuticals in 1994 revealed cyanopyrrolidines with a nitrile functional group that was conjectured to form an imidate with the catalytic serine. Simultaneously, other DPP-4 inhibitors without a nitrile group were published but they contained other serine-interacting motifs, e.g. boronic acid, phosphonates or diacyl hydroxylamine. These compounds were not as potent because of the similarity of DPP-4 and prolyl oligopeptidase (PEP), as well as chemical instability. Ferring Pharmaceuticals filed for patent on two cyanopyrrolidine DPP-4 inhibitors, which they published in 1995. These compounds had excellent potency and improved chemical stability [10].

In 1995, Edwin B. Villhauer at Novartis started to explore N-substituted glycinyl-cyanopyrrolidines built on the certainty that DPP-4 identifies N-methylglycine as a N-terminal amino acid. Vasopeptidase inhibition is believed to enhance the antidiabetic effect of DPP-4 inhibition by stimulating insulin secretion. DPP-4 inhibitor and vasopeptidase-inhibiting motif are connected to each other at the N-substituent [10].

To conclude, the available cardiovascular safety data from the nonclinical safety and clinical pharmacology development program for saxagliptin, with discrete heed to potential findings that may have been symptomatic of a nonclinical or early clinical signal of myocardial injury has been interrogated.

DPP-4 Inhibitors and Cardiovascular Outcome Trials:

DPP-4 inhibitors are a novel class of oral anti-diabetic agents. EXAMINE and SAVOR TIMI-53 were the first two clinical trials which appraised the cardiovascular efficacy of DPP-4 inhibitors, suggesting that this novel class of anti-diabetics are safe from a cardiovascular perspective. Due to intermediate efficacy, lower incidence of hypoglycemia and weight neutrality, DPP-4 inhibitors have been increasingly used in clinics [11]. Nonetheless, concerns remain about their potential association with significant adverse reactions including heart failure, acute pancreatitis, pancreatic cancer. Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial, which randomized 16,492 patients with type 2 diabetes and either a history of cardiovascular disease (CVD) or multiple CVD risk factors to saxagliptin (Onglyza) or placebo reported the potential increased risk of heart failure with DPP-4 inhibitors. Unexpectedly, the patients randomly assigned to Saxagliptin had a higher risk of hospitalization by 27% for heart failure, a finding which hasn't been explained and requires further investigation. Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial was conducted, in which 5,380 patients with type 2 diabetes and had a recent hospitalization for acute coronary syndrome were randomly assigned to alogliptin (Nesina in the U.S. and Vipidia in Europe) or placebo. Overall, alogliptin wasn't analogous to increased rate of hospitalization for heart failure. Lately, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) randomized 14,671 patients to sitagliptin (Januvia) or placebo and observed no distinction in the risk of hospitalization for HF [12].

Clinical trials, as stated by The 2008 U.S. Food and Drug Administration (FDA) guidelines and the 2012 European Medicine Agency guidelines should include elderly patients, patients with renal impairment and patients with advanced diseases. An upper boundary of 1.3 was fixtured for the 95% confidence interval (CI) of the risk ratio for major CV events to exclude new type 2 diabetes therapies with unacceptable CV risk. Then, large, prospective trials involving >40,000 high-risk patients with type 2 diabetes were planned to test the non-inferiority or possible superiority of gliptins using pre-specified CV endpoints [5].

The Savor TIMI-53 Investigation:

By demonstrating, saxagliptin was non-inferior to placebo for the primary composite major adverse CV event (MACE) endpoints of CV death, non-fatal myocardial infarction, or non-fatal ischemic stroke (primary safety objective); hazard ratio (HR) 1.00, the objective of the 2008 US Food and Drug Administration (FDA) Guidance for industry on treatments for diabetes was met by the SAVOR study. Several attempts were made to discern any evidence of a potential cue that may foresee the unpredicted disparity in events of HF as observed with Saxagliptin in SAVOR [13].

The trial was designed to assess the safety and efficacy of saxagliptin concerning cardiovascular outcomes in patients with diabetes mellitus who are at risk for cardiovascular events.

Both clinical and non-clinical (in vitro, in vivo) studies were conducted to conclude the efficacy of saxagliptin. SAVOR-TIMI is a multicenter, double blind, randomized, phase-4, placebo-controlled trial. The trial, sponsored by AstraZeneca and Bristol-Myers Squibb and designed by the TIMI Study Group and Hadassah Medical Organization in association with the sponsors (who provided monitoring support and donated the drug), was conducted in 26 countries in 788 sites.

A post-hoc analysis was directed to appraise the safety, tolerability and efficacy of Saxagliptin in patients with type 2 Diabetes Mellitus and cardiovascular disease.16,492 patients were undertaken randomization from 1st May 2010 to 31st December 2011. A phase IV multicenter, randomized, double blind, placebo-controlled study was reinforced on the foundation of this analysis in order to assess the efficacy of saxagliptin in patients with a glycylated hemoglobin [HbA1c] of 6.5% - 12% with established cardiovascular disease. Patients in the age group 55- 60 years, median 10.3 years of diabetes, established atherosclerotic disease, hypertension, dyslipidemia, prior myocardial infarction, prior coronary revascularization and prior heart failure, estimated GFR of 72.5+/_ 22.6 and a median albumin creatinine ratio of 1.8 were considered as the baseline characters of the study population.

In a 1:1 ratio, patients who were eligible were assigned randomly to receive saxagliptin at a daily dose of 5mg, unlike in patients with an approximate GFR<=50ml per minute who received saxagliptin at a dose of 2.5mg daily. Patients were prohibited from collateral use of DPP-4 inhibitors or Glucagon Like Peptide-1 agonist [14].

A composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke was contemplated as the primary efficacy and safety end point. A concoction of the primary composite end point and hospitalization for heart failure, coronary revascularization, or unstable angina was considered as the secondary end point. The trial was designed as a superiority trial, with a closed testing echelon to preserve the alpha level that prespecified that a test for noninferiority with respect to the primary composite end point followed by a test for superiority [13].

Although the rate of hospitalization for heart failure was increased with saxagliptin, there was no increase or decrease in the rate of ischemic events [15]. In the nonclinical and clinical pharmacology studies, findings suggestive of myocyte injury or fluid overload that would prognosticate an increase in clinical risk for heart failure were absent.

In the nonclinical studies, changes reminiscing clinically significant CV findings weren't observed with saxagliptin when assessed in vitro or in vivo in animals. The absence of contractility change, heart weight increase or histopathology suggests no evidence of cardiac insufficiency in nonclinical species [13].

The Examine Investigation:

To demonstrate non-inferiority of alogliptin versus placebo concerning a composite of major adverse cardiac events (MACE) in high-risk patients with type 2 diabetes, The Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in patients with Type 2 Diabetes Mellitus and acute coronary syndrome (EXAMINE) study was carried out in which alogliptin (once daily) was compared with placebo (once daily) in combination with standard of care among individuals with Type 2 Diabetes Mellitus and acute coronary syndrome (ACS). EXAMINE was a phase 3, randomized, multi-center, double-blind, placebo-controlled trial conducted as part of the Canadian Network for Observational Drug Effect Studies (CNODES) June 18, 2013 was the eventual date for the assessment of the vital status [17].

All patients with an ordinal prescription for a noninsulin antidiabetic drug from the earliest to the last date of prescription drug information were gathered as a base cohort. A total of 8,033 patients were screened, and 5,380 patients were randomized to either alogliptin (N = 2,701) or placebo (N = 2,679). With a median study duration of 17.5 months [19], several exclusions were made in the study population. Patients who were less than 18 years of age, (except in Ontario, where patients with less than 66 years of age were excluded); patients who had in accordant dates, patients with less than 365 days of continuous coverage; patients with insulin treatment at any time before or on the date of base-cohort entry; with diagnosis of Type 1 Diabetes Mellitus [16], women diagnosed with gestational diabetes in the year before base-cohort entry ,women with a history of the polycystic ovary syndrome; pregnant women, or having a hemodynamically unstable cardiovascular disorder, or who received dialysis within 14 days before screening [5], were sequentially disbarred in a descending order [19].

The daily doses of alogliptin were 25 mg, 12.5 mg, or 6.25 mg, depending on estimated glomerular filtration rate. Modifying concomitant medications for type 2 diabetes and cardiovascular comorbidities throughout the duration of the study (except adding a DPP-4 inhibitor or a GLP-1 analogue) were allowed. The primary and secondary end points were time to an event within the primary and secondary MACE composites respectively. The primary MACE composite comprised of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, whereas the secondary MACE composite comprised of cardiovascular death, non-fatal stroke and dire revascularization due to unstable angina. Changes in A1C, fasting plasma glucose (FPG), and high sensitivity C-reactive protein levels, (angioedema, hypoglycemia, pancreatitis, cancer, and the results of laboratory testing) [17] were the additional efficacy end points [18]. Exploratory end points incorporated death from cardiovascular causes and death from any cause [19].

The prejudice associated with the suppositions of patients and investigators was minimized by the randomized, double-blind study design. Non-inferiority of alogliptin to placebo as shown in the results with respect to the primary end point appear to be sturdy, as the analyses accounted for regional differences in standard of care therapies and varying levels of renal function [16].

This trial manifested similar consequences of major cardiovascular events in treatment with the DPP-4 inhibitor alogliptin with placebo among patients with type 2 diabetes and substantial cardiovascular disease and cardiovascular risk, whereas no increase in cardiovascular risk with alogliptin in this population during this median follow-up period was observed. It has been conjectured that DPP-4 inhibitors may apply advantageous effects on the cardiovascular system. Whilst, recent clinical trial data's have shown a lower risk of major cardiovascular events with DPP-4 inhibitors than with other classes of anti-diabetic agents [17].

The TECOS Investigation:

Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) estimated the long-term cardiovascular safety of adding sitagliptin routinely, as compared with usual care alone, in patients with type 2 diabetes and established cardiovascular disease.

It was a randomized, double-blind, placebo-controlled, event-driven trial organized at 673 sites in 38 countries. The Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) in an academic collaboration with the sponsor, Merck Sharp & Dohme, designed and ran the study unconventionally [20]. In 2006 sitagliptin was the first agent approved in the class of antihyperglycemic agents [21].

Patients of minimum 50 years of age having type 2 diabetes with established cardiovascular disease, with a glycated hemoglobin level of 6.5 to 8.0% when treated with stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or insulin (with or without metformin) were entitled. Established cardiovascular disease included a history of major coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease. Patients who had taken a DPP-4 inhibitor, glucagon-like peptide-1 receptor agonist, or thiazolidinedione (except pioglitazone) during the anteceding 3 months; or had a history of two or more episodes of severe hypoglycemia during the anteceding 12 months; or if the estimated glomerular filtration rate (eGFR) was less than 30 ml per minute per 1.73 m^2 of body-surface area at baseline, were included in the study population [20]. Open-label glycemic rescue therapy was incorporated in several studies which, based upon progressively stricter, protocol-specified hyperglycemic criteria's, were encompassed. This was added to the ongoing, blinded study medication to which patients had been randomized [21].

Patients, randomly assigned in a 1:1 ratio, received either sitagliptin at a dose of 100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 ml per minute per 1.73 m^2) or matching placebo [20]. Analyses were executed in three cohorts: the intact 25-study cohort (sitagliptin vs. non-exposed), the cohort from placebo-controlled portions of studies (sitagliptin vs. placebo), and the cohort from studies comparing sitagliptin to a sulphonyl urea (sitagliptin vs. sulphonyl urea). Sulphonylureas have been found to be associated with an increased risk for cardiovascular events relative to metformin in some, but not in all observational studies, due to which the sitagliptin vs. sulphonyl urea analysis was executed by pooling the three double-blind studies (P010, P024, P803), which randomized patients at baseline to sitagliptin 100 mg/day (n = 1,226) or a sulphonyl urea (n = 1,225) for up to 2 years [21].

The primary composite cardiovascular outcome was defined as the first confirmed event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. The secondary composite cardiovascular outcome was primary outcome integrated with death from any cause, and hospitalization for heart failure. The primary composite cardiovascular outcome occurred in 839 patients in the sitagliptin group (11.4%, 4.06 per 100 person-years) and 851 in the placebo group (11.6%, 4.17 per 100 person-years). No significant difference between-group difference in the primary composite cardiovascular outcome (hazard ratio in the per-protocol analysis, 0.98; 95% CI, 0.88 to 1.09; P<0.001 for non-inferiority; hazard ratio in the intention-to-treat analysis, 0.98; 95% CI, 0.89 to 1.08; P=0.65 for superiority) or in the secondary composite cardiovascular outcome (hazard ratio in the per-protocol analysis, 0.99; 95% CI, 0.89 to 1.11; P<0.001 for noninferiority; hazard ratio in the intention-to-treat analysis, 0.99; 95% CI, 0.89 to 1.10; P=0.84 for superiority) [20].

MACE was analyzed in terms of exposure-adjusted incidence rates (i.e., the number of patients with ≥1 event divided by the total patient-years of exposure) in order to account for potential difference between groups in duration of subjection to treatment. Mantel-Haenszel method was used to conduct a sensitivity analysis, which included studies with no events by use of a continuity correction factor. A supplementary sensitivity analysis was conducted using Cox regression [21].

14,671 patients were encompassed in the intention-to-treat population. In this population, the primary composite cardiovascular outcome occurred in 839 patients in the sitagliptin group (11.4%, 4.06 per 100 person-years) and 851 in the placebo group (11.6%, 4.17 per 100 person-years). There was no significant difference in the rate of hospitalization for heart failure, which was reported in 228 patients in the sitagliptin group (3.1%; 1.07 per 100 person-years) and 229 in the placebo group. With respect to overall incidence of infections, cancer, site-reported renal failure or severe hypoglycemia there was no significant difference between the sitagliptin group and the placebo.

SITAGRAMI (Safety and Efficacy of Sitagliptin plus Granulocyte Colony-Stimulating Factor in Patients Suffering from Acute Myocardial Infarction), a phase III multicenter trial piloting the myocardial regenerating effects after an acute MI which is the meld of sitagliptin and G-CSF, has encouraging results. But there is a need for provisional analysis of the results and confirmation with accomplishment of the long-term study [22].

FDA Analysis of CV Safety Trials with DPP 4 Inhibitors:

The U.S. Food and Drug Administration (FDA) published guidance inducing pooled analyses and meta-analyses of cardiovascular events (sometimes with post hoc arbitration) observed in trials with metabolic outcomes in December 2008. Although a reduction in the incidence of major CV events were suggested by the former trials, it was not confirmed by the specifically designed CV studies that followed.

Patients who encountered recent ACS were included in EXAMINE and ELIXA, although patients in TECOS had foregoing CV disease. On the contrary, 21.7% of enrolled patients with no prior CV events were discerned in SAVOR TIMI 53 trial, manifesting at least two risk factors. While selection of a higher risk population increases CV event rate, it reduces the sample size and/or the duration of the trial. However, the external validity of trial is the drawback of using a specific high-CV risk population. In patients with ACS, alogliptin manifested to be safe was during the last 90 days. Unexpectedly, in the SAVOR-TIMI 53 trial, saxagliptin was associated with an increased rate of hHF (3.5 vs. 2.8%; hazard ratio [HR] 1.27 [95% CI 1.07–1.51]; P = 0.007) during the first year, with no significant difference thereafter. In EXAMINE, hHF was a component of a pre-stated exploratory extended MACE end point with no statistically significant increase in the risk of first event of hHF with alogliptin versus placebo (3.1 vs. 2.9%; 1.07 [0.79– 1.46]. In TECOS, hHF was a secondary outcome where the rate of hHF in the sitagliptin arm (228 [3.1%]) did not differ statistically or numerically from that in the placebo arm (229 [3.1%]) (HR 1.00 [95% CI 0.83–1.2] P = 0.98) [23].

Unlike the trials conducted on the DPP-4 inhibitors where this class of antihyperglycemic drugs were compared to a placebo, linagliptin was compared to the active comparator glimepiride in the Cardiovascular Outcome Trial of Linagliptin versus Glimepiride in Type 2 Diabetes (CAROLINA) trial. It is an ongoing, randomized control trial since October 2010, with an approximate primary completion date of September 2018 in subjects with early type 2 diabetes and increased cardiovascular risk that will assess the long-term cardiovascular impact of linagliptin juxtaposed with sulphonyl urea glimepiride [24]. Whether CHF hospitalizations are increased with linagliptin or glimepiride and whether there were recurrent deaths due to CHF were addressed through independent arbitration by CAROLINA. The results of this trial are expected to illuminate insights beyond CV outcomes which includes renal outcomes, ambulatory beta cell functions, microvascular diabetes complications and cognitive functions.

Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) trial was conducted among patients with diabetes mellitus which was sought to assess the efficacy of vildagliptin which is a novel DPP-4 inhibitor. This trial showed that vildagliptin was non-inferior for change in LVEF among patients with DM2 and prior HF [25].

Plausible Cardiovascular Mechanisms of Dpp-4 Inhibitors in Heart Failure:

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretins, that are gut hormones secreted from the intestine in response to food intake, both of which augment glucose-induced insulin release, suppress glucagon secretion, and slow gastric emptying. Since GLP-1 and GIP are rapidly degraded and inactivated by dipeptidyl peptidase-4 (DPP-4), inhibition of DPP-4 and/or DPP-4-resistant GLP-1 analogues have been proposed as a potential target for the treatment of diabetes [26].

GLP-1 increases glucose-dependent insulin secretion in type 2 diabetics which makes it highly efficacious. On the contrary, GLP-1 has some potentially dangerous actions on other tissues, including the heart, vasculature, exocrine pancreas, liver, and central nervous system [27]. Among the pleiotropic actions described for GLP-1, cytoprotection in different cell types, including cardiomyocyte and cardioprotective action during myocardial ischemia is observed. The GLP-1 receptor (GLP1R), originally cloned from pancreatic β-cells, is coupled to cAMP production which enhances glucose-dependent insulin release from the pancreatic β-cells [28]. GLP-1R activation on endothelial cells manifests an increase in cAMP, with a subsequent activation of Protein kinase A (PKA) and endothelial nitric oxide synthase (eNOS). The activation of eNOS eventually leads to a consequence of release of nitric oxide (NO) and vessel relaxation [11]. There has been propositions from some literatures that DPP4-cleaved GLP-1 may also be a weak partial agonist or antagonist of GLP1R [29], engendering physiological responses such as vasodilation [30]. In addition to enhancing GLP-1 effect, DPP4 inhibitors also increase SDF-1, a chemoattractant for many types of hematopoietic cells including cardiac stem cells, endothelial progenitor cells, and mesenchymal stem cells. Enhancement of chemotaxis and repopulation ability of hematopoietic progenitor cells and stem cells is carried out by preservation of SDF-1, which in turn increases the neovascularization of injured tissues [28]. Sitagliptin therapy increased EPC levels and led to the upregulation of SDF-1α. The proinflammatory chemokine MCP-1 was decreased in the sitagliptin-treated patients. Functional EPCs represent a prerequisite for a healthy CV system in diabetic patients, and this ancillary effect of DPP-4 inhibition might have potential favorable CV implications [22].

There is a crosstalk between the AGEs-RAGE axis and DPP-4-incretin system in the pathogenesis of diabetes-associated disorders. Binding of AGEs to RAGE results in promotion of atherosclerosis/inflammation-related gene expression factors such as monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and plasminogen activator inhibitor-1 (PAI-1). MCP-1 plays an important role in the early phase of atherosclerosis by initiating monocyte recruitment to the vessel wall, and its expression is elevated in human atherosclerotic plaques. AGEs-RAGE axis plays a role in the pathogenesis of diabetic cardiomyopathy via inducing endothelial dysfunction, altering calcium handing/contractility, and evoking inflammatory, fibrotic and pro-apoptotic reactions in the myocardium [26].

It was manifested that genetic DPP-4 deficiency revamped cardiac function after transverse aortic constriction surgery, while it was evaluated that MK-0626(highly selective DPP4 inhibitor) manifested impairment of cardiac function, modest cardiac hypertrophy and cardiac fibrosis [31].

CONCLUSION

A relatively new class of oral hypoglycemics, the DPP-4 inhibitors have created a stir in the treatment of Diabetes mellitus type 2, owing to their pleiotropic and multisystemic effects. It has been proposed by a large body of experimental and clinical data that GLP-1 analogs exert a fortifying role in the cardiovascular system that includes declining blood pressure, atrial vasodilation, ameliorated endothelial and myocardial function and functional recovery of failing ischemic heart.

Several randomized controlled trials, meta-analyses, observational studies, pharmaco-vigilance reports with respect to saxagliptin, alogliptin, sitagliptin, linagliptin with an emphasis on cardiovascular risks, hypoglycemia, pancreatitis, bone fracture, arthralgia are being conducted to establish the efficacy of gliptins. Three established RCTs SAVOR-TIMI 53, EXAMINE, TECOS for saxagliptin, alogliptin and sitagliptin were designed as cardiovascular safety trials respectively. These trials yielded that gliptins neither increase nor decrease cardiovascular events. Unforeseenly, an increased risk of hospitalization was perceived in the SAVOR-TIMI 53 trial for HF. However, the CAROLINA trial has been conducted to address some of the uncertainties which came with the SAVOR-TIMI trial and to provide evidence on the CV effects of DPP-4 inhibitors. Advanced studies designed as superiority trails have to be conducted to assess the cardiovascular safety of DPP-4 inhibitors.

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