Science Letters
2016 | Volume 4 | Issue 3 | Pages 170-178

DATA ANALYSIS OPEN ACCESS

Cardiovascular Effect of Dipeptidyl Peptidase-4 Inhibitor in Diabetic Patients: A Review

Sharvan Rampersad, Manna Zhang, Hong Li, Shen Qu*

Department of Endocrinology and Metabolism, Shanghai Tenth People's Hospital, Tongji University School of Medicine, 301 Yanchang Road, Shanghai 200072, China

Abstract
Diabetes mellitus has taken pandemic proportions, with an increased morbidity and associated mortality, prompting the development of new drugs for better glycemic control. Dipeptidyl peptidase-4 inhibitor (DPP4-i) is a relatively new drug. However, following the incident with rosiglitazone, it has become mandatory for any new anti-diabetic drug to be thoroughly tested for adverse cardiovascular effects. We conducted this review to better understand the cardiovascular effects of this drug. Studies selected for the review using different search tools were mainly randomized controlled trials. Most of the trials concluded in either a non-inferior or neutral cardiovascular effects when compared against a comparator. Moreover, beneficial effects on markers affecting the cardiovascular health have also been reported. However, two studies reported adverse effect; one on the flow-mediated vasodilatation and one on the frequency of hospitalization for heart failure. Although these two studies reported adverse effects, other studies examining the same parameters reported either neutral or beneficial effects. Moreover, the increased hospitalization for heart failure may be due to a single drug and not a drug class effect. Hence, we can conclude that use of DPP4-i, except for one, has a neutral cardiovascular effect.
Keywords Cardiovascular health, dipeptidyl peptidase-4 inhibitor, heart failure hospitalization, major adverse cardiac event, saxagliptin, type 2 diabetes mellitus.

Received July 02, 2016 **Accepted** November 04, 2016 **Published** December 15, 2016
***Corresponding author** Shen Qu **E-mail** qushencn@hotmail.com

To cite this manuscript: Rampersad S, Zhang M, Li H, Qu S. Cardiovascular effect of dipeptidyl peptidase-4 inhibitor in diabetic patients: a review. Sci Lett 2016; 4(3):170-178.

Introduction

Diabetes mellitus (DM) is a non-communicable disease with pandemic proportions. It is a major metabolic disorder. Though not always life-threatening, it has a high prevalence of morbidity in those with longstanding disease. Aggressive and early glycemic control has been linked to a delay in the appearance and progress of the associated complications and these have led to the development of new drugs in order to achieve adequate glycemic control. A relatively new addition, used since 2006, is the incretins [1]. They are based on the body's indigenous incretin system. They are of 2 types: (1) the incretin mimetic, i.e., the glucagon-like peptide-1 (GLP-1) analogs, administered subcutaneously; (2) the dipeptidyl peptidase-4 inhibitor (DPP4-i), taken orally. The GLP-1 is released in response to the presence of food in the intestines, causing satiety, an increase in insulin secretion by the pancreatic β-cells, decrease gastric emptying, affect gut motility, inhibit gastric acid secretion and inhibit glucagon secretion [2]. Once the GLP-1 is released, it is actively metabolized by the dipeptidyl peptidase-4 enzyme (DPP4). DPP-4 preferentially cleaves peptides with the amino acid alanine or proline in position 2 of the N-terminus of the peptide chain. Active GLP-1(7–36) amide is cleaved by DPP-4 to yield a dipeptide (His-Ala) and GLP-1 (9–36) amide [3, 4]. The mean duration of action of the GLP-1 is a mere 2 minutes. The DPP4-i is a member of a family of endopeptidases that competitively inhibit the action of the DPP4 enzymes [5], hence prolonging the duration of action of the secreted GLP-1. This aids in maintaining appropriate control over the post-prandial hyperglycemia.

Since the incretin's effect is glucose dependent, the incidence of hypoglycemia is minimal. Based on its relative safety in regards to hypoglycemia, mechanism of action targeting postprandial glycemic surge, ease of administration, and weight neutrality, DPP4-i has become a widely used drug, either in combination or as monotherapy. However, following the incident with rosiglitazone and its adverse effect on the cardiovascular (CV) system [6], governing bodies such as the American Diabetes Association and European Diabetes Association, have stated that prior to public use, any new anti-diabetic drug should first be appropriately tested, especially in regards to its CV effects [7]. Many studies about the effect of DPP4-i on the CV system have been carried out, and we have conducted this review to summarize a few of

these results, in terms of CV health markers and major adverse cardiac events.

Data collection and analysis

Using PubMed's, the Cochrane Library's and Medline's database from inception till 30th June 2015, relevant articles were selected. Only articles published in English were considered. Data from PubMed was restricted to randomized control trials while those from the other two databases were not. A total of 155 articles were thus obtained from all three databases. All the articles were then reviewed as per both their title and abstract. Among those, 53 articles were kept for further reviewing based on the following selection criteria:

Selection criteria

Articles fulfilling the following criteria were included in the review:

1. Based on human trials only.
2. Based on patients 18 years and above.
3. Patients suffering from type 2 diabetes mellitus.
4. The selected patients should be taking a DPP4-i for glycemic control.
5. Combination therapy with any other anti-diabetic drug class is acceptable.

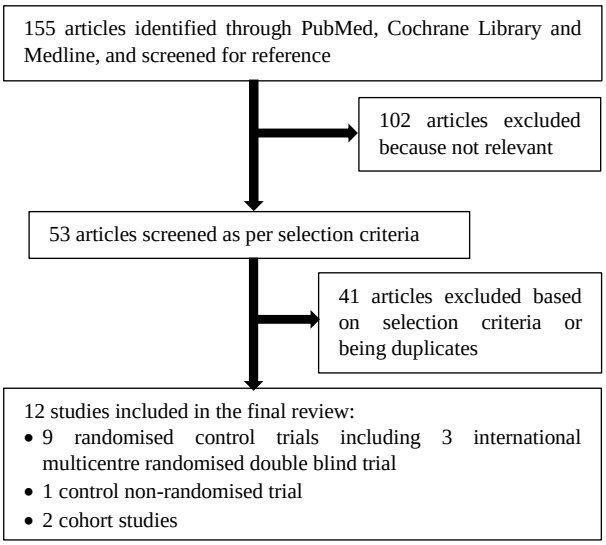

Fig. 1 Flow chart for article selection of different studies.

Exclusion criteria

The exclusion criteria were as follows:

1. Patients suffering from type 1 diabetes mellitus.
2. Patients suffering from unstable cardiovascular disease, for example, those having a New York Heart Association Type IV heart failure (HF).
3. Patients suffering from refractory angina, uncontrolled arrhythmias, etc. (Fig. 1).
4. Pregnant female patients

Based on the above-cited criteria, the articles were streamlined down from 53 studies to 12 studies. Table 1 shows the selected studies after article screening and selection process [8-19].

DPP4-i and weight, BMI, HbA1c and postprandial hyperglycaemia (PPH)

The DM is a major "non-communicable disease" that is affecting more and more people. It causes an imbalance in the glucose metabolism causing elevated blood glucose levels and abnormal glucose fluctuations. The deranged glucose homeostasis can be shown by an elevated HbA1c, a 3-month glycaemic control indicator. It has been shown that higher HbA1c levels are associated with an increased risk of developing CV disease [20]. However, HbA1c does not assess the glycaemic fluctuations. Studies have shown that abnormal glycaemic fluctuations are a major contributor to the CV complications that arise in diabetic patients [21, 22]. Glucose fluctuations are mainly a post-prandial response. Deranged fluctuations eventually lead to an increase HbA1c, thus the latter is important for homeostasis assessment, though an OGTT provides a better understanding of the fluctuations. Therefore, as DM patients will over time develops vascular complications, both micro- and macro-vessels are involved. The presence of accelerated atherosclerosis process in DM can also explain the presence of complications [23]. Hence, DM patients are at a higher risk of developing some CV disease in their lifetime [24, 25]. DM has been shown to be a major CV risk factor [24], causing an increased incidence of coronary artery disease and stroke [26]. Also, the main cause of death in diabetics is of CV cause [27]. All the complications result in a decrease in life expectancy of 5-6 years [28]. Although no definite treatment is available at present, tight glycaemic control and decrease in glycaemic fluctuations decrease the vascular complications [29]. Hence, anti-diabetic drugs are being developed in order to target the different mechanisms of the glucose metabolism. The incretins are a relatively new addition to the anti-diabetic drugs [30-32]. Having a glucose-dependent action, they mainly target post-prandial glycaemic response with less risk of hypoglycaemia. Also, as compared to another secretagogue, mainly sulfonylurea, they do not appear to cause secondary failure of the pancreatic βcells [33].

In some of the studies, improvement in HbA1c and post prandial hyperglycaemia (PPH) has been noted. Barbieri et al. [9] reported a decrease in the

Table 1 Details of the studies used in this review.

Patients	Intervention	Control	Major outcome	Ethnicity	Reference
48 patients with HbA1c>6.5%	Sitagliptin 50 mg daily for 3 months	Placebo	↓ FBG, HbA1c, inflammatory markers ↑ Anti-inflammatory markers, GLP-1	Japanese	[8]
90 T2DM patients on metformin with inadequate glycemic control	Sitagliptin 10 0mg daily or vildagliptin 50mg twice daily for 12 weeks		↓ FBG, HbA1c, PPH, inflammatory cytokines ↓ IMT	Italians	[9]
A. 24 T2DM pts with HbA1c >6.2%	Sitagliptin 50 mg daily for 6 weeks	Voglibose 0.9 mg daily	↓ FMD, ↓NMD, ↓ body weight, FBG, HbA1c ↑ HDL	Japanese	[10]
B. 45 T2DM pts	Sitagliptin 50 mg daily or alogliptin 25 mg daily for 6 weeks		↓ FMD ↓ NMD	Japanese	
66 T2DM patients with poor glycemic control on metformin/ sulfonylurea/ lifestyle changes	Sitagliptin 50 mg daily for 12 weeks	Voglibose 0.6 mg daily	↑ FMD, ↑ CD34 ↑ Oxidative stress marker (MDA-LDH, 8-OHdG) ↓ Inflammatory markers (hs-CRP, PTX-3)	Japanese	[11]
36 T2DM patients on metformin, no lipid lowering medications	Sitagliptin 100 mg daily for 6 weeks	Placebo	↓Inflammatory cytokines (IL-6, IL-18, CRP) ↓ $sPLA_2$, ICAM-1 E-selectin	Canadians	[12]
80 IGT or T2DM patients	Sitagliptin 100 mg daily for 12 months	Placebo	↓ Weight, BMI, SBP, FBG, HbA1c ↓ 2 hours postprandial, ↓ LDL, ↓ IMT	Japanese	[13]
32 T2DM pts on metformin	Sitagliptin 100 mg daily for 4 weeks	No additional treatment	↑ $CD34^{+}KDR^{+}$, ↑ SDF-1α, ↓ MCP-1	Italians	[14]
84756 patients	Sitagliptin	Metformin	No significant difference in all-cause mortality and risk of composite endpoints	Danish	[15]
5380 patients	Alogliptin	Placebo	↓ HbA1c no significant difference in risk of composite endpoints	49 countries	[16]
14,671 patients	Sitagliptin	Placebo	no significant difference in risk of composite endpoints	38 countries	[17]
16,492 patients	Saxagliptin	Placebo	no significant difference in risk of composite endpoints ↑rate of hospitalization for heart failure	26 countries	[18]
3,282 patients	Sitagliptin	Other diabetic drugs excluding a DPP4-i	no significant difference in risk of composite endpoints	Taiwan	[19]

All abbreviated terms are explained in the abbreviations section.

HbA1c values (values not shown). In Ishikawa et al. [13] work, greater reduction in body weight, 2-hour postprandial glucose level, and HbA1c levels were noted. When sitagliptin was compared to Voglibose, body weight decreased by 2.2% from 65.8 to 64.3 kg vs 0.3% (61.6 to 61.4kg). Two hours, post 75 g OGTT glucose level changed by 17.3% from 181.7mg/dl (10.1mmol/l) to 156.3mg/dl (8.7 mmol/l), vs 0.3% (from 177 mg/dl [9.83 mmol/l] to 182 mg/dl [10.1 mmol/l]). The Hba1c level was decreased by 4.7%, from 5.77% to 5.49%, vs a change of 1.3%, from 5.76 to 5.68%. Similarly, Satoh-Asahara et al. [8] reported a decrease in HbA1c level from 8.2 to 7.5%, for the first 1.5 months, and in the second 1.5 month, HbA1c was decreased from 7.5% to 7.2%, while no significant difference was noted in the control group (8.2% to 7.9%). Similarly, a decrease in HbA1c level was also noted in both the TECOS and EXAMINES trials.

Decrease in HbA1c by 0.27% [13] and 1% [8] are expected following the use of DPP4-I and the expected decrease was being 0.28%-0.80% following 12-52 week treatment [34-36]. Also, the

post-prandial response was shown to improve, a decrease by 17.3% noted in 2-hour post 75g OGTT [13]. As stated earlier, the degree of glycaemic fluctuation is the main contributor to the development of vascular complications in diabetic patients [21, 22]. Improving the 2-hour OGTT results indicated an improvement in PPH relating to decreasing glycaemic fluctuation. Thus, as already discussed above, less glycaemic fluctuation correlates with a decrease in the development and progression of vasculopathy, which is directly related to CV health. Hence amelioration of these parameters, such as HbA1C and PPH indicates an improvement of CV health.

DPP4-i and pro- and anti-inflammatory cytokines, and cell adhesion molecules

Satoh-Asahara et al. [8] reported that the use of 50 mg of sitagliptin per day for 3 months causes a marked decrease in the serum pro-inflammatory cytokine levels, as compared to placebo. Serum amyloid A-LDL (SAA-LDL) was decreased from 15.6 to 10.3 µg/ml vs an increase from 18.4 to 20.1 µg/ml on placebo. C-reactive protein (CRP) (µg/ml) had a more marked decrease compared to placebo, from 0.8 to 0.5 vs 0.8 to 0.7, respectively. Further, tumor necrosis factor-α (TNF-α) (pg/ml) was decreased from 10.2 to 6.6 vs an increase from 8.8 to 9.2, respectively. There was no significant change in serum interleukin-6 (IL-6) level. Furthermore, an increase in the anti-inflammatory cytokines was noted. Interleukin-10 (IL-10) (pg/ml) significantly increased from 9.8 to 12.8 with sitagliptin vs a decrease from 8.7 to 8.2 in the control group. A similar trend was noticed in the monocytes. IL-10 expression was increased from 0.9 to 1.1 vs a decrease from 0.8 to 0.7, while IL-6 and TNF-α were decreased from 4.3 to 3.8 with sitagliptin vs an increase from 4.3 to 5.1 with placebo and from 3.3 to 1.9 vs 3.9 to 4.5, respectively.

Barbieri et al. [9] also showed improvement of circulating inflammatory cytokines (IL-6, IL-18, TNF-α) and in nitrotyrosine levels, an oxidative stress marker. A decrease was noted in both fasting and interprandial serum levels of these markers. Prandial nitroprusine (µmol/h/L) was decreased from 115 to 94.8, in the sitagliptin group and from 114 to 73 in the vildagliptin group. Interprandial nitroprusine (µmol/L) was also decreased from 0.76 to 0.62 in the sitagliptin group and from 0.75 to 0.50 in the vildagliptin group. Similarly, prandial and interprandial IL-6, IL-18 and TNF-α levels were also decreased.

Nakamura et al. [11] also showed a decrease in the circulating high sensitive CRP (hsCRP) (from 2194.4 to 1202.0) and pentraxin-3 (PTX-3) (from 1.606 to 1.491), both inflammatory markers. Moreover, a significant increase in $CD3^{4+}$ level, a marker for positive endothelial progenitor cell (EPC) from 0.956 to 1.134 was noted. However, they also noticed an increase in the oxidative stress markers: malonaldehyde-modified LDL (MDA-LDLD) and 8-hydroxy-21-deoxyguanosine (8-OHDG), though no significant difference as compared to those on voglibose.

Fadini et al. [37] also observed the change in progenitor cells, assessed by the change in CD34+KDR+ levels, believed to be a more accurate assessment of the EPC. They reported an increase by twofold of the CD34+KDR+ level. The Stromal Derived Factor-1α (SDF-1α) required for bone marrow release of EPC, was increased by 50%. Monocyte chemo-attractant Protein-1 (MCP-1), which plays an important role in attracting monocytes to the arterial sub endothelium was decreased by 25% [38]. Tremblay et al. [12] also reported a decreased in the levels of some adhesion molecules, namely inter-cellular adhesion molecule-1 (ICAM-1) by 5.3% and E-selectin by 5.9%. However, Vascular Cell Adhesion Molecule-1 (VCAM-1) level had no significant change. Moreover, IL-6, IL-18, CRP and secreted phospholipase A2 (sPLA2) levels, all pro-inflammatory markers were decreased by 44.9%, 24.7%, 7.3% and 12.9%, respectively. These studies were all conducted using sitagliptin in a dose of either 50 mg or 100 mg per day for varying duration. All reported improvement in both pro- and anti-inflammatory cytokine levels. A reduction in the systemic vascular inflammatory markers and oxidative stress markers were important as they are associated with a decrease in the Mean Amplitude of Glycaemic Excursion (MAGE). MAGE is a method to assess the glycaemic fluctuation, which has been shown to be more relevant to the progression of atherosclerosis than sustained hyperglycaemia itself [39]. Atherosclerosis is a direct indicator of the CV health and improving the factors that positively affect its progression is definitely beneficial to the CV health.

In another study, a significant increase in the CD34+ levels, a marker of positive EPC was reported [11]. EPC is known to provide protection to the vessels by promoting neo-angiogenesis and endothelial repair [40]. EPC are mobilized from the bone marrow and their mobilization has been shown

to be dependent or affected by the circulating levels of SDF-1α. SDF-1α being a substrate of the DPP4 enzymes [41], the use of DPP4-i will increase its circulating levels. An increase in SDF-1α and thus EPC will result in better neo-angiogenesis and endothelial repair. This increases vessel health status and resistance to damage. Also, improvement in the MCP-1 levels by 25% was reported, which is important in decreasing the rate of atherosclerosis formation in the DM patients [14]. Leucocyte adhesion to the endothelial cells plays an important role in atherosclerosis [42] and MCP-1 has been shown to play an important role in attracting monocytes to the arterial sub endothelium [38]. Thus a decrease in the MCP-1 level decrease rate of monocyte infiltration resulting in decreased atheroma formation.

An increased cellular adhesion, caused by an increase in the adhesion molecules, usually seen in diabetic patients and the associated endothelial dysfunction "sets the stage" for the recruitment of inflammatory cells, the release of cytokines and recruitment of lipid into the atherosclerotic plaque [43]. Furthermore, the use of a DPP4-i causes a decrease in inter-cellular adhesion molecule 1 (ICAM-1) by 5.3% and in E-selectin by 5.9% [12], which again hinders the atherosclerotic process. Amelioration of all above cytokines delays the formation and progression of atheromatous plaque, which is an accelerated process in diabetic patients. Hence, DPP4-i improves vascular health.

DPP4-i, and endothelial function and intima-media thickness (IMT)

The ideal cardiovascular health score (ICHS) is inversely related to the carotid IMT [44]. Thus a decrease in IMT will increase the ICHS. Barbierie et al. [9] studied the possible change in IMT of the common carotid, its bifurcation and the internal carotid arteries that may be brought about by the usage of a DPP4-i for 3 months. However, the effect of sitagliptin was assessed against that of vildagliptin. No significant difference noted at baseline, but after 3 months treatment with DPP4-i, a significant decline in IMT was noted, more in those on vildagliptin. Changes in IMT were significantly correlated with changes in Mean Amplitude of Glycaemic Excursion (MAGE), but not with change in HbA1c. Ishikawa et al. [13] also demonstrated similar effects of DPP4-i in diabetic patients with stable angina (diagnosed with more than 50% stenosis by quantitative coronary angiography). After a 12 month treatment with DPP4-i, carotid IMT was significantly decreased from 1.11 mm to 1.09 mm vs a marked increase from 1.02 mm to 1.07 mm in the control group. Statistically, a significant decrease in IMT is strongly correlated to MAGE [9], and this decrease in IMT is attributed to the DPP4-i's effects.

Another parameter of good CV health is arterial stiffness [45]. Change in Flow Mediated Vasodilatation (FMD) and Nitroglycerine Mediated Vasodilatation (NMD) has been used to assess the arterial stiffness. Both Ayaori et al. [10] and Nakamura et al. [11] studied changes in FMD of the brachial artery. Ayaori et al. [10 also assessed the NMD. Ayaori et al. [10], after a 6-week treatment with a DPP4-i, noted a significant decrease of 51.1% in the DPP4-i group vs an increase of 16.4% in the control group (who were on voglibose, a α1-glucosidase inhibitor, known to ameliorate the endothelial function [46]). No significant difference was noted in NMD. The study was repeated comparing sitagliptin to alogliptin, and after 6 weeks, the FMD was again decreased, by 39.6% and 31.7%, respectively. These findings point towards an adverse effect of the DPP4-i on the endothelial function, as assessed by the FMD. Nakamura et al. [11] did a similar study with a similar method to Ayaori's, with the DPP4-i being sitagliptin too, but for a longer duration, 12 weeks compared to 6 weeks. They noted an increase in the FMD from 5.41% to 6.17% in the DPP4-i group vs 4.96% to 5.94% in the voglibose group. There was no significant difference in change in FMD between the two groups.

Based on these two different studies, conflicting results were obtained for the FMD. Though both studies [10, 11] were similar, the results obtained were completely different, and the only reason could be because of the duration of DPP4-i use. This difference may be explained by the fact that both active (7-36) and inactive GLP-1 (9-36) have a vaso-relaxant property [47, 48]. However, the activeglp-1 (7-36) has a more potent effect, though the definite action is concentration dependent [49]. Normally, active GLP-1 (7-36) is within minutes degraded into the inactive form, and hence, the concentration of active GLP-1 is less than that of the inactive one [50], it can be assumed that the overall vaso-relaxant effect is mainly due to the inactive GLP-1 (9-36). With the use of a DPP4-i, the concentration of inactive glp-1 (9-36) decreases, together with its vaso-relaxant effect. Though the more potent GLP-1 (7-36)'s concentration increases, it is possible the GLP-1 (7-36) receptors responsible for the relaxing effect require more time to increase. This may

explain why there was a decrease in FMD after 6 weeks, but an increase after 12 weeks. However, these were not measured; hence further studies are required to confirm this hypothesis.

DPP4-i and major adverse cardiac events (MACE)

Scheller et al. [15] studied the possible effect of DPP4-i vs metformin on all-cause mortality and CV system. Metformin used as an active comparator as several studies have suggested that the latter may have a favorable effect on the all-cause mortality and CV effect vs. other hypoglycaemic agents [51-53]. In total, 84756 patients were studied with 1228 (1.4%) receiving sitagliptin and 83598 (98.6%) on metformin. Among those, 49 patients on sitagliptin (4.0%) died vs 3024 (3.6%). Based on a multivariate Cox Regression Model adjusted for age, sex, and duration of diabetes mellitus, use of sitagliptin was significantly correlated with the higher risk mortality due to any cause. However, when first adjusted for CV comorbidities and associated pharmacotherapy and then further adjusted for age, sex, DM duration, no statistically significant difference was noted. These results showed that sitagliptin monotherapy is as CV safe as metformin monotherapy.

Similarly, in the EXAMINE trial; the CV safety of a DPP4-i was assessed. In total, 5380 patients were followed for a mean period of 18 months and occurrence of primary, secondary and exploratory endpoints were observed. Patients eligible for this trial were T2DM patients who were on anti-diabetic drugs, except for an incretin, and who had suffered from an acute coronary syndrome within 15 to 90 days prior to randomization. At the end of the study, 11.3% of those on DPP4-i vs 11.8% on placebo had a primary endpoint event, being significant only for non-inferiority. A primary endpoint event is defined as a composite of death from CV causes, nonfatal MI or nonfatal stroke. Comparing principal secondary endpoint of death from CV cause, nonfatal MI or stroke, or urgent revascularization due to unstable angina revealed no significant difference between the 2 groups (12.7% and 13.4% respectively). From these results, rates of primary and secondary endpoints in T2DM patients with a recent acute coronary syndrome were similar to those on alogliptin as well as those on placebo.

In a population-based cohort study in Taiwan [19], the CV safety of a DPP4-i (sitagliptin) was compared against a control in a similar population as the one used in the EXAMINE trial. Here, T2DM patients admitted to a hospital for acute MI were included. A total of 3282 patients were followed up for an average of 1.15 years. There was no significant difference found in the incidence of primary CV outcome, recurrent myocardial infarction, and ischemic stroke or CV death. In a TECOS trial, sitagliptin was compared to a placebo for MACE. A total of 14671 patients followed for 3 years on an average were T2DM with known cardiovascular disorder. These included major coronary artery disease, ischemic stroke, a peripheral vascular disorder of atherosclerosis origin. A total of 839 patients on sitagliptin were compared to 851 on placebo. No significant difference was noted in both primary and secondary CV outcomes when checked for both non-inferiority and superiority. In another trial, the SAVOR-TIMI 53 trial, patients previously diagnosed as T2DM with either a history of established CV disease (a positive history of clinical event associated with atherosclerosis involving the coronary, cerebrovascular or peripheral vascular system) or with multiple risk factors for vascular disease (male ≥50 years or female≥ 60 years with either one of the following: dyslipidaemia, hypertension or active smoking). A total of 16492 patients were randomly assigned either saxagliptin or a placebo for a median follow-up period of 2.1 years. A total of 613 patients from the saxagliptin group vs 609 patients experienced a primary endpoint event, significant only for non-inferiority. In the modified intention to treat model, results were similar with 6.8% in the saxagliptin group vs 6.7%. A total of 1059 patients on saxagliptin vs 1034 had a major secondary endpoint.

Development and progress of vascular complications in diabetic patients is a major problem. By assessing the MACE in previously compromised patients is an adequate and rapid method to assess the safety of the drug. In the trials reviewed, all researchers reported neutral or non-inferior CV outcomes as compared to controls. These may be due to the beneficial changes brought about by the use of DPP4-i previously described in this article. By improving the CV status, this drug does not increase the MACE incidence. However, since no definite improvement was seen, and all concluded in the DPP4-i being non-inferior to control. This may be due to the exposure to the drug not being long enough to reverse years of pro-atherosclerotic process. Also, greater glycaemic differentiations (as greater HbA1C difference) between test and control groups have not shown definite macrovascular

benefit [29, 54, 55]. Moreover, a large proportion of patients in the trial received concomitant pharmacotherapy, such as statins, and these may have blunted the potential difference between study groups.

DPP4-i and heart failure hospitalization frequency (HF)

Together with assessing the MACE, the hospitalization incidence of HF was an outcome thoroughly assessed. The large multicentre trials have divergent conclusions concerning this outcome. In the population-based cohort study [19], the incidence of secondary outcomes, HF hospitalization, and percutaneous coronary revascularization was similar between the test and control groups. Subgroup analysis showed that patients with or without a previous history of HF had no higher risk for hospitalization as compared to the control. The risk of HF hospitalization did not increase in this study. Similarly, no significant difference in HF hospitalization rate was noted in the TECOS study. The incidence of the composite of hospitalization for HF or CV death as well as death from any cause was similar in both groups. Hence, the incidence of HF hospitalization in T2DM patients with the already established CV disorder was similar to the control group.

In the SAVOR-TIMI 53 trial, when an individual component of the major secondary endpoint was examined, significantly more patients receiving sitagliptin were hospitalized for HF (3.5% vs 2.8%). Although the risk of having a primary endpoint did not increase in this trial as compared to control, the incidence of hospitalization for HF was increased. To be noted, among all the trials reviewed, the SAVOR-TIMI 53 trial was the only one assessing saxagliptin. The reason for the increase in HF hospitalization is unclear. Since this trial assesses saxagliptin and no other trials assessing the same drug have reported an increase in HF hospitalization, the reason for this adverse effect may be due to saxagliptin only and not attributed to a drug-class effect.

Conclusions

From all the studies reviewed, it is shown that the use of DPP4-i has a beneficial effect on the CV health by positively affecting parameters in atheroma formation and improving vaso-relaxation. Also, it is non-inferior or neutral to other controls as per incidence of major adverse CV events. However, the unexplained increase in HF hospitalization in one study is the only adverse event encountered in these studies. This may be due to the use of saxagliptin, and may not be a drug-class effect. Apart from saxagliptin, which requires increased cautiousness when used, the other DPP4-i may be regarded as safe. For the effects to be properly appreciated, longer-term use of these drugs is required. Further studies assessing follow-up of patients on long-term DPP4-i use would help to better comprehend this drug.

Abbreviations

FBG = Fasting blood glucose
HbA1c = Glycated haemoglobin
GLP = Glucagon-like peptide 1
PPH = Post prandial hyperglycaemia
IMT = Intima media thickness
FMD = Flow mediated dilatation
NMD = Nitro-glycerine mediated dilatation
HDL = High density lipoprotein
LDH = Malonaldehyde-modified low density lipoprotein
OHdG = 8-hydroxy-21-deoxyguanosine
CRP = High sensitive c - reactive protein
PTX-3 = Pentraxin-3
IL-6 = Interleukin-6
IL-8 = Interleukin-8
CRP = C-reactive protein
$sPLA_2$ = Secreted phospholipase a2
ICAM-1 = Inter-cellular adhesion molecule-1
IGT = Impaired glucose tolerance
SBP = Systolic blood pressure
LDL = Low density lipoprotein
SDF-1 α = Stromal derived factor-1α
MCP-1 = Monocyte chemo-attractant protein-1

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] MacDonald PE, El-Kholy W, Riedel MJ, Salapatek AM, Light PE, Wheeler MB. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. Diabetes 2002; 51 Suppl 3:S434-42.
[2] Mentlein R. Dipeptidyl-peptidase IV (CD26)--role in the inactivation of regulatory peptides. Regul Pept 1999; 85(1):9-24.
[3] Gault VA, Parker JC, Harriott P, Flatt PR, O'Harte FP. Evidence that the major degradation product of glucose-dependent insulinotropic polypeptide, GIP(3-42), is a GIP receptor antagonist in vivo. J Endocrinol 2002; 175(2):525-33.
[4] Knudsen LB, Pridal L. Glucagon-like peptide-1-(9-36) amide is a major metabolite of glucagon-like peptide-1-(7-36) amide after in vivo administration to dogs, and it acts as an antagonist on the pancreatic receptor. Eur J Pharmacol. 1996; 318(2-3):429-35.
[5] Weber AE. Dipeptidyl peptidase IV inhibitors for the treatment of diabetes. J Med Chem 2004; 47(17):4135-41.
[6] Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356(24):2457-71.

[7] Wood S. FDA Advisory panels acknowledge signal of risk with rosiglitazone, but stop short of recommending its withdrawal. Medscape, 2007 [updated Jul 31].
[8] Satoh-Asahara N, Sasaki Y, Wada H, Tochiya M, Iguchi A, Nakagawachi R, et al. A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism 2013; 62(3):347-51.
[9] Barbieri M, Rizzo MR, Marfella R, Boccardi V, Esposito A, Pansini A, et al. Decreased carotid atherosclerotic process by control of daily acute glucose fluctuations in diabetic patients treated by DPP-IV inhibitors. Atherosclerosis 2013; 227(2):349-54.
[10] Ayaori M, Iwakami N, Uto-Kondo H, Sato H, Sasaki M, Komatsu T, et al. Dipeptidyl peptidase-4 inhibitors attenuate endothelial function as evaluated by flow-mediated vasodilatation in type 2 diabetic patients. J Am Heart Assoc 2013; 2(1):e003277.
[11] Nakamura K, Oe H, Kihara H, Shimada K, Fukuda S, Watanabe K, et al. DPP-4 inhibitor and alpha-glucosidase inhibitor equally improve endothelial function in patients with type 2 diabetes: EDGE study. Cardiovasc Diabetol 2014; 13:110.
[12] Tremblay AJ, Lamarche B, Deacon CF, Weisnagel SJ, Couture P. Effects of sitagliptin therapy on markers of low-grade inflammation and cell adhesion molecules in patients with type 2 diabetes. Metabolism 2014; 63(9):1141-8.
[13] Ishikawa S, Shimano M, Watarai M, Koyasu M, Uchikawa T, Ishii H, et al. Impact of sitagliptin on carotid intima-media thickness in patients with coronary artery disease and impaired glucose tolerance or mild diabetes mellitus. Am J Cardiol 2014;114(3):384-8.
[14] Fadini GP, Boscaro E, Albiero M, Menegazzo L, Frison V, de Kreutzenberg S, et al. The oral dipeptidyl peptidase-4 inhibitor sitagliptin increases circulating endothelial progenitor cells in patients with type 2 diabetes: possible role of stromal-derived factor-1alpha. Diabetes care. 2010; 33(7):1607-9.
[15] Scheller NM, Mogensen UM, Andersson C, Vaag A, Torp-Pedersen C. All-cause mortality and cardiovascular effects associated with the DPP-IV inhibitor sitagliptin compared with metformin, a retrospective cohort study on the Danish population. Diabetes Obes Metab 2014; 16(3):231-6.
[16] White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013; 369(14):1327-35.
[17] Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2015; 373(3):232-42.
[18] Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013; 369(14):1317-26.
[19] Wang SH, Chen DY, Lin YS, Mao CT, Tsai ML, Hsieh MJ, et al. Cardiovascular Outcomes of Sitagliptin in Type 2 Diabetic Patients with Acute Myocardial Infarction, a Population-Based Cohort Study in Taiwan. PloS one 2015; 10(6):e0131122.
[20] Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic control and coronary heart disease risk in persons with and without diabetes - The atherosclerosis risk in communities study. Arch Intern Med2005;165(16):1910-6.
[21] Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. Diabetologia 1996; 39(12):1577-83.
[22] Group TDS. Is the Current Definition for Diabetes Relevant to Mortality Risk From All Causes and Cardiovascular and Noncardiovascular Diseases? Diabetes care. 2003; 26(3):688-96.
[23] Kanter JE, Johansson F, LeBoeuf RC, Bornfeldt KE. Do glucose and lipids exert independent effects on atherosclerotic lesion initiation or progression to advanced plaques? Circulation research. 2007; 100(6):769-81.
[24] Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes care. 1993; 16(2):434-44.
[25] Panzram G. Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1987; 30(3):123-31.
[26] Emerging Risk Factors C, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010; 375(9733):2215-22.
[27] Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001; 44 Suppl 2:S14-21.
[28] Emerging Risk Factors C, Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011; 364(9):829-41.
[29] Group AC, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358(24):2560-72.
[30] van Genugten RE, Moller-Goede DL, van Raalte DH, Diamant M. Extra-pancreatic effects of incretin-based therapies: potential benefit for cardiovascular-risk management in type 2 diabetes. Diabetes Obes Metab 2013; 15(7):593-606.
[31] Balakumar P, Dhanaraj SA. Cardiovascular pleiotropic actions of DPP-4 inhibitors: A step at the cutting edge in understanding their additional therapeutic potentials. Cell Signal 2013; 25(9):1799-803.
[32] Clifton P. Do Dipeptidyl Peptidase IV (DPP-IV) Inhibitors Cause Heart Failure? Clin Ther 2014;36(12):2072-9.
[33] Foley JE, Bunck MC, Moller-Goede DL, Poelma M, Nijpels G, Eekhoff EM, et al. Beta cell function following 1 year vildagliptin or placebo treatment and after 12 week washout in drug-naive patients with type 2 diabetes and mild hyperglycaemia: a randomised controlled trial. Diabetologia 2011;54(8):1985-91.
[34] Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA 2007; 298(2):194-206.
[35] McIntosh B, Cameron C, Singh SR, Yu C, Ahuja T, Welton NJ, et al. Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. Open Med 2011; 5(1):e35-48.
[36] Fakhoury WK, Lereun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. Pharmacology 2010; 86(1):44-57.
[37] Ceradini DJ, Kulkarni AR, Callaghan MJ, Tepper OM, Bastidas N, Kleinman ME, et al. Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1. Nat Med 2004; 10(8):858-64.
[38] Deshmane SL, Kremlev S, Amini S, Sawaya BE. Monocyte Chemoattractant Protein-1 (MCP-1): An Overview. J Interferon Cytokine Res 2009; 29(6):313-26.
[39] Su G, Mi S, Tao H, Li Z, Yang H, Zheng H, et al. Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes. Cardiovasc Diabetol 2011; 10:19.
[40] Fadini GP, Agostini C, Sartore S, Avogaro A. Endothelial progenitor cells in the natural history of atherosclerosis. Atherosclerosis 2007; 194(1):46-54.
[41] Jungraithmayr W, De Meester I, Matheeussen V, Baerts L, Arni S, Weder W. CD26/DPP-4 inhibition recruits regenerative stem cells via stromal cell-derived factor-1 and beneficially influences ischaemia-reperfusion injury in mouse lung transplantation. Eur J Cardiothorac Surg 2012; 41(5):1166-73.

[42] Rosenfeld ME. Leukocyte recruitment into developing atherosclerotic lesions - The complex interaction between multiple molecules keeps getting more complex. Arterioscler Thromb Vasc Biol 2002; 22(3):361-3.
[43] Li H, Cybulsky MI, Gimbrone MA, Libby P. An atherogenic diet rapidly induces VCAM-1, a cytokine-regulatable mononuclear leukocyte adhesion molecule, in rabbit aortic endothelium. Arterioscler Thromb 1993; 13(2):197-204.
[44] Huang W, Nie W, Li W, Li X, Zhang Y, Geng X, et al. The relationship between changes in ideal cardiovascular health score and the carotid intima-media thickness among the middle age and elderly population. honghua Xin Xue Guan Bing Za Zhi 2015; 43(12):1078-82.
[45] Gaye B, Mustafic H, Laurent S, Perier MC, Thomas F, Guibout C, et al. Ideal cardiovascular health and subclinical markers of carotid structure and function: The paris prospective study III. Arterioscler Thromb Vasc Biol 2016; 36(10):2115-24.
[46] Azuma K, Toyofuku Y, Iesaki T, Otsuka A, Tanaka A, Mita T, et al. Acarbose, an α-glucosidase inhibitor, improves endothelial dysfunction in Goto-Kakizaki rats exhibiting repetitive blood glucose fluctuation. Biochem Biophys Res Commun 2006; 345(2):688-93.
[47] Anagnostis P, Athyros VG, Adamidou F, Panagiotou A, Kita M, Karagiannis A, et al. Glucagon-like peptide-1-based therapies and cardiovascular disease: looking beyond glycaemic control. Diabetes Obes Metab 2011; 13(4):302-12.
[48] Ban K, Noyan-Ashraf MH, Hoefer J, Bolz S-S, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor–dependent and independent pathways. Circulation 2008; 117(18):2340-50.
[49] Green BD, Hand KV, Dougan JE, McDonnell BM, Cassidy RS, Grieve DJ. GLP-1 and related peptides cause concentration-dependent relaxation of rat aorta through a pathway involving KATP and cAMP. Arch Biochem Biophys 2008; 478(2):136-42.
[50] Knudsen LB, Pridal L. Glucagon-like peptide-1-(9-36) amide is a major metabolite of glucagon-like peptide-1-(7-36) amide after in vivo administration to dogs, and it acts as an antagonist on the pancreatic receptor. Eur J Pharmacol 1996; 318(2-3):429-35.
[51] Roussel R, Travert F, Pasquet B, Wilson PWF, Smith SC, Jr., Goto S, et al. Metformin use and mortality among patients with diabetes and atherothrombosis. Arch Intern Med 2010; 170(21):1892-9.
[52] Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ 2009; 339:b4731.
[53] Selvin E, Bolen S, Yeh H-C, Wiley C, Wilson LM, Marinopoulos SS, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. Arch Intern Med 2008; 168(19):2070-80.
[54] Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360(2):129-39.
[55] Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358(24):2545-59.