Review Article

# The Role of DPP-4 Inhibitors in Cardiovascular Protection among Type-2 Diabetic Patients; Literature Review

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## Abstract

A combination of metabolic disorders manifested by increased blood glucose levels causes Diabetes mellitus. Patients with diabetes are more prone to morbidity and increased rate of mortality compared to the general population, with a substantial contribution to healthcare costs. One of the significant risk factors for cardiovascular problems is Diabetes Mellitus. Hence, the additional cardiovascular beneficial effect has been reported in various new antidiabetic agents, including DPP-4 inhibitors. This literature aims to evaluate the cardiovascular efficacy and safety of DPP-4 inhibitors. We used PubMed search engine to search for relevant studies. We used different Mesh words, including "DPP-4, Diabetes mellitus, cardiovascular risk, heart failure". DPP-4 inhibitors may provide cardiovascular benefit amount type-2 diabetic patients. There is still debate about the increased risk of heart failure hospitalization. Generally, DPP-4 inhibitors are secure, and endure and accepted by the patients. It should be noted that a beneficial atherosclerotic effect was reported with inhibitors of DPP-4. However, the HF hospitalization risk remains an area of debate. Further multi-national trials are recommended to establish DPP-4 inhibitors' cardiovascular efficacy safety.

**Keywords:** DPP-4 inhibitors, Diabetes mellitus type-2, Cardiovascular risk, Oral antidiabetic agent, Heart failure, Diabetes mellitus

## Introduction

A combination of metabolic disorders manifested by increased blood glucose levels causes Diabetes mellitus [1]. Patients with diabetes are more prone to morbidity and increased rate of mortality compared to the general population, with a substantial contribution to healthcare costs [1, 2]. It is one of the prevalent diseases in the latter few decades, especially in the era of the increasing obesity pandemic [2]. Furthermore, currently, diabetes accounts for the seventeenth major reasons of death in the United States and worldwide, with a projected value of 5.2 million deaths worldwide related to diabetes, with a mortality rate of 82.4 per 100,000, and 252,806 deaths in the United States alone in 2015 [2]. In 2017, diabetes accounted for 4125 million cases, and its prevalence will increase to 629 million by 2040 [3].

The most predominant type of diabetes is Type-2 Diabetes Mellitus (T2DM), which is the leading cause of up to 90-95% of all presented cases, and continues to be quickly progressing globally and in the United States of America [2, 3]. Indeed, the global rise of unhealthy lifestyles, population aging, socioeconomic development, urbanization, poor physical activity, and increasing incidence of obesity among adults and children may probably explain the diabetic pandemic [2, 3]. The risk factors for T2DM include genetic and metabolic factors, which contribute to its prevalence [2]. Also, non-modifiable risk factors include ethnicity, family history, previous gestational diabetes, and older age [2]. Additionally, modifiable risk factors, including obesity, unhealthy diet, poor physical activities, and smoking, can predispose to the evolution of T2DM [2].

Moreover, patients with T2DM are more prone to develop diabetic kidney disease (DKD) and cardiovascular disease (CVD), both result in increased mortality [4]. Common initial presentation of CVD-related diabetes is a peripheral arterial disease (16.2% or three times greater) and heart failure (HF) (14.7%), followed by angina and nonfatal myocardial

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infarction (MI) [2]. Hence, timely screening of non-detectable peripheral arterial disease and HF is highly suggested [2]. According to the study of San Antonio on Heart, a recall of 4875 patients for 7-8 years was found that diabetes mellitus profoundly leads to increased all-cause mortality [2]. Additionally, increased risk of HF up to 40% was seen in diabetic patients than was seen in non-diabetic with a 2-3 times increased risk of developing it [2]. Also, 26% of stroke cases were attributed to diabetes according to the National and Nutrition Examination Survey cohort (NHANES), with a two-fold higher risk in diabetic people for ischemic strokes and a 50% increase for hemorrhagic strokes [2]. The rate of mortality after MI is also greater in diabetic compared to a patient without diabetes, and the rate of CV death was 4.4-fold higher in diabetes alone without other typical cardiovascular risk factors than non-diabetic with the same group of age [2].

CVD was found to be the major reason for mortality and many conditions in the diabetic population, who are prone to MI and stroke [5, 6]. Because the risk of CVD is two to four times higher in people with diabetes which is not the same case in people without diabetes, preventing CVD is an essential aspect of treatment, besides glycemic control [6], since the vascular complications might be early present before the diagnosis of diabetes or in the pre-diabetes status [3]. Nevertheless, CVD risk factors in diabetic patients are suboptimally controlled in the USA [6]. Lifestyle modifications followed by metformin as the drug of choice for treatment of type 2 Diabetes Mellitus were suggested by The American Diabetes Association and European Association for the Study of Diabetes recommended [6]. Additional oral antidiabetic agents are not guided if metformin failed to achieve glycemic control [6]. Most current guidelines recommended the addition of sulphonylurea, thiazolidinediones (TZDs), DPP-4 inhibitors GLP-1 Receptor Agonists, and SGLT-2 inhibitors [6].

Antidiabetic agents may contribute to reducing cardiovascular risk, besides controlling blood glucose [6]. However, which antidiabetic agent may contribute to additional cardiovascular protection, remains an area of controversy. It is reported that some antidiabetic agents may potentiate CVD risk, particularly rosiglitazone, which was understood to be linked with an increased risk of MI and death [6]. Therefore, the US Food and Drug Administration and the European Medicine Agency started to demand all the new antidiabetic agents to demonstrate a safe cardiovascular risk profile [6]. In this literature review, we will focus on the evidence-based provided to the DPP-4i in terms of cardiovascular protection and safety.

## Results and Discussion

### *Dipeptidyl Peptidase-4 Inhibitors; Overview and Mechanism of Action*

DPP-4i is a ubiquitous enzyme in the thin membrane which line the blood vessels and heart and can be found in the various body part and quantifiable as circulating plasma activity of an enzyme [7]. Incretins are the only substrates of DPP-4 that have been well proved in humans are GLP-1 and glucose-dependent insulinotropic peptide (GIP) [7, 8]. In normal physiology, within a few minutes, DPP-4 cleaves and inactivates GLP-1 with the amino acid alanine or proline in position 2 of the N-terminus of the peptide chain [7]. Hence, DPP-4i works by blocking the effect of DPP-4 that rapidly breaks down GLP-1, which is normally released by the small intestinal endocrine cells after the ingestion of meals, resulting in prolongation of the incretins half-life [8, 9]. In T2DM, the GLP-1 is found less produced in many patients and has impaired response to GIP [9].

DPP-4i received FDA approval as early as 2006 and has shown promising outcomes since then [10]. Sitagliptin and vildagliptin are extensively studied in clinical trials, and it found that the concentration of the active endogenous GLP-1 increased twice or thrice after a standard meal [7]. As a result, GLP-1 levels, which are low in diabetic patients, become elevated and stimulate pancreatic glucose-dependent insulin release by beta-cell and achieve satiety by the direct effect of the hypothalamus satiety center [8, 10]. Hence, DPP-4 inhibitors effectively lower blood glucose and HbA1c when given orally in people with T2DM [8]. Also, DPP-4i promotes islet survival and function by maintaining beta-cell mass [8].

Moreover, DPP-4 is not only expressed in the circulation but also on endothelial cells, liver, gut, kidneys, lungs, and T-lymphocytes cell membrane as CD26 [7, 10]. Nevertheless, there is no clear evidence that enzyme catalytic activity plays a role in immune function [7]. Notably, no serious adverse outcomes were reported in the clinical trials of DPP-4i in terms of immunological regulatory mechanisms [7]. DPP-4 is a family member of endopeptidase, and evidence suggests that selective DPP-4 inhibitors may play a significant role in the safety profile for this new antidiabetic agent [7]. Sitagliptin, saxagliptin, vildagliptin, and alogliptin are competitive DPP-4 inhibitors with a high affinity [7]. Both sitagliptin and vildagliptin demonstrated acceptable clinical efficacy for T2DM management in both monotherapy or combination with established oral antidiabetic agents, such as metformin (7). Besides glycemic control, DPP-4i demonstrated additional glycemic control by reducing gastrointestinal motility and slowing gastric emptying [10].

To date, clinical trials demonstrated well safety profile for DPP-4i, with an incidence of hypoglycemia similar to placebo and a neutral impact on body weight [7]. In thirteen trials investigating the effect of DPP-4i on weight, there was a slight increase in weight with DPP-4i compared to a placebo of 0.5kg [8]. Nevertheless, In non-inferiority trials, sitagliptin had a favorable weight profile compared to glipizide, and vildagliptin also had a favorable weight profile compared to TZDs [8]. A long-term clinical trial has shown that sitagliptin use resulted in no difference between sitagliptin and placebo

groups in terms of serious adverse effects [7]. Nevertheless, DPP4i were associated with a greater risk of acute pancreatitis in a network meta-analysis of 236 randomized clinical trials [11]. Moreover, sitagliptin and vildagliptin have demonstrated low drug-drug interactions, particularly with other oral antidiabetic agents [7].

Furthermore, DPP4i plays a significantly beneficial role in the CV risks, including hypertension and dyslipidemia [12]. DPP4i offers anti-inflammatory and antioxidant actions, improved endothelial function, and reduced urinary albumin excretion [12]. A beneficial effect was found on non-alcoholic fatty liver disease, which is an independent CV risk in T2DM patients treated with DRPP4i [12]. Indeed, DPP4i improves left ventricular function and reduces post-ischemic stunning in T2DM patients and coronary artery disease [12]. It offers neutral and beneficial control on body weight, blood pressure (without reflux tachycardia), and postprandial lipemia [13]. DPP4i started to replace sulfonylurea in various countries due to a lower risk of hypoglycemia and weight gain [13].

### *The Effect of DPP-4 Inhibitors on Cardiovascular Disease*

Sean *et al*. study had concluded that the use of DPP4i was not linked with decreased mortality compared with placebo or without management [11]. This result remains an area of controversy. An increased risk for SAVOR-TIMI 53 trial in HF hospitalization is seen as the result of Saxagliptin use, the TECOS trial showed no increased risk of HF hospitalization in sitagliptin [14]. Furthermore, Alogliptin had shown in the EXAMINE trial a trend toward an increased HF hospitalization risk [14]. In the latest CARMELINA trial, linagliptin was not linked with higher chances of HF hospitalization and adverse renal outcome [14]. Nevertheless, it revealed a reduction in microvascular events through the reduction of albuminuria progression [14]. In a population-based cohort study, a similar outcome to the CARMELINA trial was found; a higher risk of HF or cardiovascular outcomes was not seen in DPP4i use as was seen in sulfonylurea [15].

Moreover, in a network meta-analysis of nine large cardiovascular outcomes of the new antidiabetic agents, Osama *et al*. had concluded that the use of DPP4i did not profoundly lessen the risk of the primary endpoint (cardiovascular death, nonfatal MI, stroke, nonfatal MI, nonfatal stroke and demise from any cause) [16]. Importantly, the use of DPP4i was associated with a non-significant increase in HF hospitalization (13%) [16]. Besides, based on a nationwide cohort study comparing the cardiovascular effect of adding antidiabetic agents (GLP-1 RA or SGLT-2i) vs DPP-4 inhibitors to metformin [17]. Interestingly, the study revealed there was no major difference in the risk of HF hospitalization and death between the two groups [17]. Nevertheless, a lower risk of MI, strokes, and CV deaths were relatively found in GLP-1 RA and SGLT2i compared to DPP4i [17]. Although Ghadeer *et al*. in a study assessed the risk of hospitalization with GLP-1 RA compared to DPP-4 inhibitors in a retrospective cohort study [18]. The result showed that 14% risk reduction resulted in the DPP4i group compared to the GLP-1 RA group [18]. Also, Zheng *et al*.'s meta-analysis showed that the use of GLP-1 RA decreases the risk concerning HF hospitalization compared to DPP4i use [18].

### *The Effect of DPP-4 Inhibitors on Atherosclerotic Lesions*

Numerous human trials had shown that DDP4i slows the progression in thickness of carotid intima-media among T2DM people suffering from the disease of the coronary artery [19]. Also, Sitagliptin can inhibit the expression of plaque MMP9 and also reduces circulatory metalloproteases MMP2 and MMP9 [19]. Besides, plaque collagen volumes in ApoE knockout mice can be also increased by sitagliptin, resulting in stable atherosclerotic plaque [19]. DPP4i improves endothelial cell dysfunction, which is the early indicator of atherosclerosis [19]. On the other hand, linagliptin increases the polarization of M2 macrophages through inhibition of expression DPP-4 and its activity [20]. This result may explain the beneficial effect of DPP4i in diabetic macrovascular progression [20]. Additionally, in an experimental animal study, the use of DPP4i was found effective as disease-modifying agents in aortic stenosis progression [21]. Their favorable effect though to be related to better tissue distribution profile and anti-calcification effects [21].

## Conclusion

New antidiabetic agents may provide additional cardiovascular protection, which is the leading cause of death among diabetic people. DDP-4 inhibitors have shown a beneficial and safe cardiovascular profile. Further, a beneficial atherosclerotic effect was reported with inhibitors of DPP-4. However, the HF hospitalization risk remains an area of debate. Further multi-national trials are recommended to establish DPP-4 inhibitors' cardiovascular efficacy safety.

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