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REVIEW

DPP4 as a Potential Candidate in Cardiovascular Disease

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Abstract: The rising prevalence of cardiovascular disease has become a global health concern. The occurrence of cardiovascular disease is the result of long-term interaction of many risk factors, one of which is diabetes. As a novel anti-diabetic drug, DPP4 inhibitor has been proven to be cardiovascular safe in five recently completed cardiovascular outcome trials. Accumulating studies suggest that DPP4 inhibitor has potential benefits in a variety of cardiovascular diseases, including hypertension, calcified aortic valve disease, coronary atherosclerosis, and heart failure. On the one hand, in addition to improving blood glucose control, DPP4 inhibitor is involved in controlling cardiovascular risk factors. On the other hand, DPP4 inhibitor directly regulates the occurrence and progression of cardiovascular diseases through a variety of mechanisms. In this review, we summarize the recent advances of DPP4 in cardiovascular disease, aiming to discuss DPP4 inhibitor as a potential option for cardiovascular therapy.

Keywords: DPP4, DDP4 inhibitor, GLP-1, inflammation, cardiovascular disease

Introduction

Cardiovascular disease is a major cause of human death worldwide, claiming estimated 17.9 million lives each year. It mostly occurs in the middle-aged and old people over 50 years old, with high morbidity, high disability rate and high mortality rate. Cardiovascular disease is often caused by a combination of risk factors, such as smoking, unhealthy diet, obesity, alcohol consumption, diabetes, hyperlipidemia, and hypertension. According to studies, improving diet, exercising, quitting smoking, and limiting alcohol consumption could prevent up to 90% of cardiovascular disease. Furthermore, targeted drug therapy to relieve symptoms in patients with hypertension, hyperlipidemia, and diabetes may also improve the progression and prognosis of cardiovascular disease.[1–3]

Dipeptidyl peptidase 4, an enzyme in human body, is essential for glucose metabolism. However, recent studies found that DPP4 is widely expressed in the vascular system, including endothelial cells, macrophages, cardiomyocytes, smooth muscle cells, valve interstitial cells and other cell types, indicating that it may participate in the occurrence and progression of cardiovascular diseases. At present, DPP4 inhibitor, as a new hypoglycemic drug, is mainly used in the treatment of patients with diabetes.[4] Five recently completed large clinical trials have demonstrated the cardiovascular safety of DPP4 inhibitor, without showing benefits on major cardiovascular adverse events (MACE).[5–9] Surprisingly, more and more studies found that DPP4 inhibitor also shows protective effects on a variety of cardiovascular diseases, such as hypertension, calcified aortic valve disease, coronary atherosclerosis and heart failure.[10–12]

In this review, we discuss the clinical trials of DPP4 inhibitors and elucidate the potential mechanisms by which it may improve cardiovascular disease.

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DPP4: Structure and Functions

Dipeptidyl peptidase 4 (DPP4), also known as T cell surface antigen CD26, is a ubiquitous enzyme in human. It is widely expressed in a variety of tissues (lung, brain, pancreas, kidney, blood vessels, prostate, uterus, thymus, lymph nodes and spleen) and many cells (epithelial cells, inner skin cells, immune cells), especially highly expressed in kidney and small intestine.[13] DPP4 is a serine membrane anchored exopeptidase, belonging to DPP (dipeptidyl peptidase) family. It is a transmembrane glycoprotein composed of 766 amino acids with a relative molecular weight of 110kDa. Its basic structure mainly includes: intracellular N-terminal region, transmembrane region and extracellular region. The extracellular part consists of a flexible rod, a glycosylation rich region (binding region with anti-CD26 antibody, adenosine deaminase (ADA) and caveolin-1), a cysteine rich region (binding region with collagen and fibronectin) and a catalytic region composed of the catalytic triad Ser^{630}, Asp^{708} and His^{740}.[14,15]

DPP4 contains nine potential glycosylation sites for glycosylation modification. Among them, co-translational core N-glycosylation was significantly associated with DPP4 folding and stability, whereas N-terminal sialylation appeared to regulate more pathophysiological processes.[16] For example, hypersialylated DDP4 is responsible for the development of HIV and rheumatoid arthritis, while undersialylated DPP4 is shown to be linked with lung cancer.[17,18]

The dimerization of DPP4 determines its catalytic activity. The main ability of DPP4 is to degrade proteins and make them inactive, such as some incretin hormones. It is worth mentioning that two incretin hormones degraded by DPP4, called glucagon like peptide-1 (GLP-1) and Glucose dependent insulinotropic polypeptide (GIP), are involved in regulating glucose metabolism.[19] In addition to incretins, a variety of other peptides are also proved to be cleaved by DPP4, including substrate derived factor-1α (SDF-1α), chemokines, neuropeptides, and vasoactive peptides, thereby altering their biological activity. DPP4 normally cleaves the amino-terminal dipeptide with L-proline or L-alanine at the penultimate position. This peptidase transmits intracellular signals through a small intracellular tail.[20] In addition to peptidase activity, another important function of DPP4 is to exert immunomodulatory functions by binding to a series of ligands. Studies demonstrated that DPP4 on the surface of T cells directly provides co-stimulatory signals by binding to ADA to enhance T cell activation. Meanwhile, the ADA-independent nonenzymatic activity of DPP4 also contributes to T cell activation. In addition, caveolin 1 on antigen-presenting cells also binds to DPP4 on T cells to initiate a signaling cascade, leading to its activation.[21] These all indicate that the function of DDP4 is very complex.

With the in-depth understanding of DPP4, it is generally believed that the protein is also crucial in cell signaling and cell-cell interaction.[22] Unusually, there was no correlation between DPP4 expression and activity, with higher expression leading to higher signal transduction but no increase in enzymatic activity.[23]

At the same time, a soluble form of DPP4 (sDPP4) is also found in body fluids. Serum sDPP4 lacks the transmembrane and intracellular domains, starting at residue 39 (serine). sDPP4 is directly involved in the regulation of some physiological functions, including endothelial dysfunction or immune regulation.[24,25] However, the source and release mechanism of sDPP4 have not been clarified. Limited known sources include bone marrow-derived cells, lymphocytes, skeletal muscle cells, vascular smooth muscle cells and adipocytes.[26] Fortunately, the concentration and activity of this soluble form is usually easily detected in serum or plasma, indicating that it has the potential to become a biomarker for some diseases in the future.

DPP4 Inhibitor

DPP4 inhibitor (dipeptidyl peptidase 4 inhibitor) is a novel hypoglycemic drug for the management of type 2 diabetes.[27] The main mechanisms of DPP4 inhibitor are as follows. On the one hand, DPP4 inhibitor increases the concentration of DPP4 substrates, including GLP-1, GIP, through suppressing DPP4 enzymatic activity. They are polypeptide hormones produced in the intestine. They promote the release of insulin from pancreatic β cells and inhibit the secretion of glucagon from pancreatic α cells, thereby lowering blood glucose.[28] At the same time, DPP4 inhibitor effectively controls postprandial blood glucose by delaying gastric emptying. DPP4 inhibitor also increases the content of substrate SDF-1α, which plays other beneficial effects together with GLP-1. On the other hand, DPP4 inhibitor reduces circulating sDPP4 and ultimately attenuates the harmful effects of sDPP4. At present, there are many kinds of DPP4 inhibitors on the market: alogliptin, saxagliptin, sitagliptin, linagliptin, vildagliptin, gemigliptin and teneligliptin. Among them,

gemigliptin and teneligliptin are mainly used in Asia. Compared with other hypoglycemic drugs, it has the advantage of lowering blood glucose without hypoglycemic tendency, obesity and cardiovascular hazards. Moreover, DPP4 inhibitors are only accompanied by mild adverse drug reactions, such as diarrhea and upper respiratory tract infection.[27] The successful clinical application of DPP4 inhibitors brings new hope to T2DM patients.

In recent years, five clinical trials have been conducted on the cardiovascular safety of DPP4 inhibitor, including EXAMINE, SAVOR-TIMI 53, TECOS, CARMELINA and CAROLINA. The primary endpoint of these clinical trials was major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, and the primary endpoint of TECOS also included hospitalization for unstable angina.[29] (Table 1) EXAMINE, SAVOR-TIMI 53 enrolled patients with type 2 diabetes and acute coronary syndrome within the last 15–90 days and randomly assigned them to receive DPP4 inhibitor or placebo. The risk of MACE was similar in patients in the DPP4 inhibitor and placebo group, demonstrating the cardiovascular safety of alogliptin and saxagliptin.[5,6] Similarly, the subsequent TECOS also confirmed the neutral effect of sitagliptin on MACE and hospitalization for unstable angina, which has become the most commonly used DPP4 inhibitor in the world.[7] In addition, the cardiovascular safety of linagliptin was also confirmed by two recently completed cardiovascular outcomes trials, named CARMELINA and CAROLINA. Compared with the 3 previous placebo-controlled CV outcome trials with other DPP4 inhibitors, CARMELINA targeted patients with type 2 diabetes and high cardiovascular risk and high renal risk to evaluate the cardiovascular safety and renal outcome of linagliptin in these patients. Compared with the placebo group, treatment with linagliptin slowed down the progression of albuminuria (including the change from normal albuminuria to microalbuminuria/macroalbuminuria or from microalbuminuria to macroalbuminuria).[8] Meanwhile, in CAROLINA, patients with type 2 diabetes and high cardiovascular risk were randomly assigned to receive the linagliptin or glimepiride instead of placebo. In view of this, CAROLINA is unique because it compares DPP4 inhibitor with sulfonylureas. Sulfonylureas are the second-line hypoglycemic drugs commonly used after metformin, and their cardiovascular safety has always been controversial.[9] Each of these trials demonstrated that the addition of DPP4 inhibitor to standard treatment did not increase the risk of MACE. However, in the SAVOR-TIMI 53, the application of saxagliptin increased the risk of hospitalization for heart failure, especially in T2DM patients with elevated natriuretic peptide levels, previous heart failure or chronic kidney disease, but this was not related to the increase in cardiovascular death or all-cause mortality.[30] Moreover, other DPP4 inhibitors were not found to increase the risk of hospitalization for heart failure in other CV outcome trials, indicating that this adverse event is not a common problem of DPP4 inhibitors. There are no cardiovascular outcome

Table 1 Summary of Cardiovascular Outcome Trials of DPP4 Inhibitors

Clinical Trial	DPP4 Inhibitors Daily Dose	Year	Participants (n)	Proportion with Established CVD	Median Follow-Up Years	MACE HR (95% CI)	HF HR (95% CI)
EXAMINE	Alogliptin 25mg	2013	5380	100%	1.5	0.96 (≤ 1.16)	1.07 (0.79, 1.46)
SAVOR-TIMI 53	Saxagliptin 5mg	2013	16492	78%	2.1	1.00 (0.89, 1.12)	1.27 (1.07, 1.51)
TECOS	Sitagliptin 100mg	2015	14671	100%	3.0	0.98 (0.88, 1.09)	1.00 (0.83, 1.20)
CARMELINA	Linagliptin 5mg	2018	6991	57%	2.2	1.02 (0.89, 1.17)	0.90 (0.74, 1.08)
CAROLINA	Linagliptin 5mg	2019	6042	42%	6.3	0.98 (0.84, 1.14)	1.21 (0.92, 1.59)

Abbreviations: MACE, cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke; HF, heart failure; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes–Thrombolysis in Myocardial Infarction 53; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study with Linagliptin; CAROLINA, Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes.

trials for vildagliptin, but a non-interventive analysis cohort study showed the cardiovascular safety of vildagliptin compared with other hypoglycemic drugs, including the risk of heart failure.[31]

Since the efficacy of DPP4 inhibitor on cardiovascular terminal events is not completely satisfactory in these trials, there are several possible reasons. Firstly, the patients participating in these studies were all with diagnosed or high risk of cardiovascular disease, rather than general T2DM patients. Therefore, these CV outcome trials are not intended to evaluate the cardiovascular benefits of DPP4 inhibitor in general T2DM patients, but mainly to demonstrate the cardiovascular safety of DPP4 inhibitor by showing non inferiority compared with placebo. What's more, besides CAROLINA, the median follow-up time of these studies was short, all about 2 years, which may result in insufficient observation of the prognosis of cardiovascular diseases. Furthermore, in these COVTs, the patients were added with DPP4 inhibitor or placebo on the basis of standard anti-diabetic and anti-cardiovascular disease therapy to control blood glucose to the optimal level, leading to small difference in HbA1c between the two groups, which may weaken the potential benefits of DPP4 inhibitor via reducing HbA1c. It is worth mentioning that a meta-analysis of three major CVOTs (EXAMINE, SAVOR-TIMI 53, TECOS) showed that baseline metformin status may have regulatory effect on cardiovascular outcomes of DPP4 inhibitor.[32] Although this conclusion was overturned by a recent meta-analysis that included five CVOTs (EXAMINE, SAVOR-TIMI 53, TECOS, CARMELINA, CAROLINA), we still reasonably believe that the cardiovascular effects of DPP4 inhibitor may be affected by other types of hypoglycemic drugs.[33] Just as nationwide cohort study of T2DM patients found that metformin combined with DPP4 inhibitor treatment showed better cardioprotective effects than metformin combined with glimepiride. The risk of hospitalization for MACE, heart failure, acute myocardial infarction was significantly reduced, especially among patients receiving sitagliptin or vildagliptin.[34] Similarly, a previous large nationwide cohort study revealed that DPP4 inhibitor provides cardiovascular benefits to patients as second-line or third-line additional treatment without increasing the risk of heart failure, hypoglycemia or death.[35] In addition, the recently completed VERIFY study also showed that in newly diagnosed patients with type 2 diabetes, compared with metformin monotherapy, the early combined treatment of vildagliptin and metformin significantly and continuously improved the long-term blood glucose tolerance and could obtain long-term clinical benefits.[36] Of course, further clinical trials are necessary to verify this conclusion. All these indicate that there is still uncertainty about the cardiovascular benefits of DPP4 inhibitor, so further prospective trials or long-term observational studies are needed.

At the same time, DPP4 inhibitors also have their unique advantages, such as low incidence of hypoglycemia, few side effects, no weight gain and only need to be taken orally once a day without titration. Another favorable feature of DPP4 inhibitors is their efficacy and safety in patients with impaired renal function.[27] At present, on the one hand, more and more clinical studies found that DPP4 inhibitor has moderate beneficial effects on body weight, blood pressure (no increase in heart rate) and blood lipid of patients with type 2 diabetes.[37–39] On the other hand, massive basic studies also found that DPP4 inhibitor plays a beneficial role in hypertension, calcified aortic valve disease and coronary atherosclerosis models by effectively improving endothelial function and inhibiting inflammation and oxidative stress.[40–42] Although these beneficial effects appear to be weak individually, their combination may lead to positive CV results. In conclusion, despite these neutral results of clinical trials, we still believe that DPP4 is involved in the occurrence and progression of cardiovascular diseases. Therefore, we review the recently generated evidence supporting the potential use of DPP4 inhibitor in cardiovascular diseases (Tables 2–5).

DPP4 and Cardiovascular Risk Factors

It is well known that the occurrence of cardiovascular disease is closely related to multiple risk factors, such as age, overweight and obesity, unreasonable diet, hyperlipidemia, diabetes, excessive alcohol consumption. Recent studies suggest that pharmacological inhibition of DPP4 helps control these risk factors. Firstly, as a hypoglycemic drug, DPP4 inhibitor mainly increases the concentration of GLP-1 and GIP in pancreatic β cells, thereby promoting insulin secretion and effectively controlling blood glucose.[27] At the same time, unlike insulin, sulfonylureas, and glinides, DPP4 inhibitors effectively control blood glucose without weight gain.[37] In addition, dyslipidemia, especially elevated triglycerides, elevated low-density lipoprotein, and reduced high-density lipoprotein are significant stimulatory factors for the development of various cardiovascular diseases, such as coronary atherosclerosis and calcified aortic valve disease.

Table 2 Major Mechanisms of DPP4 Inhibitor Inhibiting Hypertension

DPP4 inhibitor	Biological Mechanism	Protective Effect	Hypertension
	↑NO ↓ET1	Improving endothelial function	
	↓IL17A; IL18; IL6; TNFα ↑IL10	Inhibiting inflammation	
	↓AGE/RAGE induced ROS ↓$gp91^{phox}$, $p47^{phox}$, $p67^{phox}$ ↑UCP2	Inhibiting oxidative stress	
	↑BNP ↓NHE3	Reducing Blood volume	
	↑NO, AT2, Substance P ↓Ang II, AT1	Promoting vasodilation	
	↓Ang II, NHE1	Ameliorating Cardiac Remodeling	
	↑Nesfatin1, GLP1	Improving insulin resistance	

Notes: ↑: upregulation; ↓: downregulation.
Abbreviations: NO, nitric oxide; ET1, endothelin 1; IL, interleukin; TNFα, tumor necrosis factor α; AGE, advanced glycation end products; RAGE, receptor for advanced glycation end products; UCP2, uncoupling protein 2; BNP, B-type natriuretic peptide; NHE, sodium/hydrogen exchanger; Ang II, angiotensin II; AT, angiotensin receptor; GLP-1, glucagon-like peptide-1.

Table 3 Major Mechanisms of DPP4 Inhibitor Inhibiting Calcified Aortic Valve Disease

DPP4 inhibitor	Biological Mechanism	Protective Effect	Calcified aortic valve disease
	↓IL2; TNFα; IL1β; IL6	Inhibiting inflammation	
	↑IGF1 → ↓Runx2; OSX	Inhibiting osteoblastic differentiation	
	↓FN1; ITGβ; collagen I	Inhibiting myofibroblastic differentiation	

Notes: ↑: upregulation; ↓: downregulation.
Abbreviations: IL, interleukin; TNFα, tumor necrosis factor α; IGF1, insulin-like growth factor 1; Runx2, RUNX family transcription factor 2; OSX, osterix; FN1, fibronectin 1; ITGβ, integrin β.

Meaningfully, several studies demonstrated that DPP4 inhibitor is also able to regulate lipid metabolism and reduce triglycerides, low-density lipoprotein and free fatty acid, while its specific mechanism has not been fully elucidated.[39,43] The limited research to date found that DPP4 inhibitor affects the expression of liver enzymes responsible for lipid oxidation and lipid biosynthesis by modulating the GLP-1 receptor signaling pathway, leading to decreased intestinal lipid synthesis and secretion and inhibiting lipid absorption.[44] Meanwhile, DPP4 inhibitor increases plasma norepinephrine levels by activating the sympathetic nervous system, which in turn accelerates postprandial lipid mobilization and oxidation.[45] What's more, the European guidelines on cardiovascular disease prevention recognize that stress is a clinically significant risk factor for patients with high overall risk of cardiovascular disease or diagnosed cardiovascular disease.[46] On the one hand, stress alters people's lifestyle, including smoking, drinking, and unreasonable diet. On the other hand, stress induces imbalance of sympathetic parasympathetic nervous system, abnormal activation of HPA axis, inflammatory reaction, and coagulation dysfunction. Therefore, stress induces increased cardiac electrical instability, myocardial ischemia, plaque destruction and thrombosis, which ultimately lead to clinical events such as arrhythmia, myocardial infarction, cardiomyopathy and stroke.[47] In recent years, several studies found that chronic stress increases DPP4 activity in plasma and tissues of mice and rats. Vascular aging and cardiovascular disease under chronic stress conditions are effectively attenuated by inhibiting DPP4, which is at least partially attributed to the alleviation of plaque inflammation, oxidative stress and proteolysis associated with GLP-1-mediated APN production.[48,49]

Table 4 Major Mechanisms of DPP4 Inhibitor Inhibiting Coronary Atherosclerosis

DPP4 inhibitor	Biological Mechanism	Protective Effect	Coronary atherosclerosis
	↑NO ↓ET1	Improving endothelial function	
	↓ICAM; VCAM	Inhibiting adhesion of Inflammatory cells	
	↓MSRs	Inhibiting the formation of foam cells	
	↓CRP; MCP1; IL6; TNFα ↑IL10	Inhibiting inflammation	
	↓$gp91^{phox}$; $p22^{phox}$	Inhibiting oxidative stress	
	↑SDF-1α	Increasing endothelial progenitor cells	
	↓MMP2, MMP9	Improving plaque stability	
	↑NRF2, Caspase3	Inhibiting intimal hyperplasia and in-stent restenosis	
	↓PAI-1; vWF ↑ADAMTS13	Inhibiting thrombosis	

Notes: ↑: upregulation; ↓: downregulation.
Abbreviations: NO, nitric oxide; ET1, endothelin 1; ICAM, intercellular adhesion molecule; VCAM, vascular adhesion molecule; MSRs, macrophage scavenger receptors; CRP, C-reactive protein; MCP1, monocyte chemoattractant protein 1; IL, interleukin; TNFα, tumor necrosis factor α; SDF-1α, substrate derived factor-1α; MMP, matrix metalloproteinase; NRF2, nuclear factor erythroid 2-related factor 2; PAI-1, plasminogen activator inhibitor-1; vWF, von Willebrand factor; ADAMTS13, a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13.

Table 5 Major Mechanisms of DPP4 Inhibitor Inhibiting Heart Failure

DPP4 inhibitor	Biological Mechanism	Protective Effect	Heart Failure
	↑GLP-1	Improving cardiac function	
	↑SDF-1	Improving cardiac function	
	↓Collagen type III	Improving myocardial fibrosis	
	RAAS imbalance	Affecting myocardial hypertrophy and fibrosis; sodium and water retention	

Notes: ↑, upregulation; ↓, downregulation.
Abbreviations: GLP-1, glucagon-like peptide-1; SDF-1, substrate derived factor-1; RASS, renin-angiotensin-aldosterone system.

DPP4 and Hypertension

It is common that most patients with diabetes are usually accompanied by hypertension. Endothelial dysfunction is a feature of hypertension, and decreased endothelium-dependent relaxation or enhancement of endothelium-dependent contraction play a key role in the pathogenesis of hypertension. DPP4 inhibitor exhibits beneficial effects in regulating blood pressure without increasing heart rate, independent of the reduction of blood glucose. This result was validated effectively in both clinical trials and animal models.[38,50] In clinical trial, compared with placebo, DPP4 inhibitor decreased mean systolic blood pressure by 3 mmHg and diastolic blood pressure by 1.5 mmHg in T2DM patients.[51] In a hypertensive rat model, the use of saxagliptin simultaneously reduced systolic, diastolic, and mean arterial pressures.[52] However, the specific mechanism has not yet been fully elucidated, and the results of current researches are as follows. (Table 2) First of all, DPP4 inhibitor improves endothelial cell function and enhances endothelial nitric oxide synthase (eNOS) activity, which in turn promotes nitric oxide (NO) release and improves the bioavailability of NO in aortic endothelial cells, resulting in vasodilation.[40] Secondly, DPP4 inhibitor also suppresses the expression of endothelin 1 by activating AMPK to inhibit the NF-κB/IκBα system, which improve the balance disorders between the vasodilation and vasoconstriction of endothelial cells, thereby lowering blood pressure.[53] Thirdly, DPP4 interferes with the function of the vascular endothelium by

regulating the activation and chemotaxis of monocytes/macrophages, T cells, and promoting the secretion of inflammatory mediators. T cells, especially Th17 cells with high levels of DPP4, secrete and transmit angiotensin II to elevate blood pressure, which is mainly initiated by interleukin-17. It has been previously demonstrated that saxagliptin can inhibit the activation of a series of cardiac proinflammatory mediators induced by angiotensin II (AngII), such as interleukin-17A (IL-17A) and interleukin-18 (IL-18).[54] Consistent with this, DDP4 inhibitor is also able to inhibit the activation and expression of other proinflammatory mediators associated with hypertension, including IL-6, TNF-α.[54] In contrast, interleukin 10 released by Treg cells exhibits beneficial effects in ameliorating inflammation, improving endothelial function and lowering blood pressure. Surprisingly, DPP4 inhibitor MK0626 is capable to upregulate IL-10 levels, leading to suppression of inflammatory injury responses.[55] Fourthly, the protective effect of DDP4 inhibitor in hypertension appears to be due to the reduction in oxidative stress partially. The interaction of advanced glycation end products (AGE) and receptor for advanced glycation end products (RAGE) stimulates the release of reactive oxygen, which upregulates DPP4 in endothelial cells. In turn, DPP4 further increases the adverse effects of AGE by interacting with mannose 6-phosphate/insulin-like growth factor II receptor (M6P/IGFIIR). DPP4 inhibitor linagliptin effectively prevents this detrimental feedback.[56] Besides, DPP4 inhibitor inhibits the expression of $gp91^{phox}$, $p47^{phox}$ and $p67^{phox}$ subunits of NADPH oxidase, thereby reducing NADPH-related oxidative stress.[57,58] Notably, DDP4 inhibitor also alleviates oxidative stress by activating the GLP-1R/AMPKa/UCP2 signaling cascade to reverse COX-2 overexpression, ultimately attenuating endothelium-dependent contractions.[59] Fifthly, B-type natriuretic peptide (BNP), another substrate of DPP4, has vasodilatory activity. Inhibition of DPP4 was shown to be able to maintain BNP hormone levels. It is well known that BNP also has the effects of diuretics and natriuretic peptides, which will reduce blood volume, resulting in decrease in blood pressure.[60] Sixthly, DPP4 inhibitor has the ability to downregulate the activity of sodium/hydrogen exchanger-3 (NHE-3), a Na^+/H^+ exchange isomer, to inhibit sodium ion reabsorption in the renal proximal tubules and increase water and sodium excretion, which also explains its beneficial antihypertensive effect.[61,62] Seventhly, DPP4 inhibitor interferes with the function of the RAAS system to exert anti-hypertensive effects as well. DPP4 inhibitor not only reduces circulating angiotensin II, but also affects the expression of angiotensin II receptor (AT), resulting in the downregulation of AT1 receptor and the upregulation of AT2 receptor. AT1 mainly causes arteriolar smooth muscle contraction, while AT2 generally promotes arteriolar smooth muscle relaxation.[63] Simultaneously, AngII directly enhances the expression and activity of cardiac sodium/hydrogen exchanger-1 (NHE-1), which is a regulator of intracellular acidity (pHi) and participates in cardiac remodeling of diseased myocardium. DPP4 inhibitor plays a protective role against hypertension and cardiac remodeling by regulating the AngII-NHE-1 axis.[64] Moreover, the antihypertensive effect of DPP4 inhibitor may also be related to the activation of sympathetic nerve centers. Substance P is an important neuropeptide, both a vasodilator and a sympathetic activator. For the reason that DPP4 is a potent substance P lyase, DPP4 inhibitor effectively inhibits the conversion of substance P to an inactive state.[65] However, it is worth noting that DDP4 inhibitor should be avoided in combination with high-dose ACEI. Both high-dose ACEI and DPP4 inhibitor can inhibit the degradation of substance P. At this circumstance, substance P may cause sympathetic nerve activation instead of vasodilation, eventually cause the elevation of blood pressure.[54,66] Finally, insulin resistance caused by diabetes may be significantly improved by DPP4 inhibitor as well. For example, administration of saxagliptin promotes nesfatin-1 secretion and ameliorates insulin resistance. A possible mechanism is that nesfatin-1 upregulates the secretion of GLP-1, which stimulates insulin release through cAMP-dependent pathway.[38,67] As a result, endothelial dysfunction is partially restored, accompanied by increased NO release, and insulin shows its vasodilatory effect. As the existing research is insufficient, the mechanism of DPP4 inhibitor regulating blood pressure has not been fully elucidated. Further studies are now needed to elucidate the specific regulatory role of DPP4 inhibitor on blood pressure.

DPP4 and Calcified Aortic Valve Disease

Calcific aortic valve disease is a chronic disease characterized by progressive fibrosis and calcific remodeling of the valve, ultimately leading to obstruction of blood flow. The pathological process of CAVD includes endothelial dysfunction, lipid deposition and inflammation in the initial stage, myofibroblast differentiation and osteogenic differentiation of valve interstitial cells in the propagation stage, fibrosis and calcification of leaflet in the end stage.[68] Due to the protective effects of DPP4 inhibitor in blood glucose, blood lipid, blood pressure, several recent studies focused on the potential link between DPP4 and CAVD.[69,70] A recent retrospective study on the relationship between DPP4 inhibitors and the

progression of aortic stenosis (AS) included patients with diabetes and mild to moderate AS. In this study, five DPP4 inhibitors were divided into favorable and unfavorable categories according to the anti-calcification ability and the Heart/Plasma (H/P) ratio. Among them, favorable DPP4 inhibitors with high anti-calcification ability and high H/P ratio are linagliptin and gemigliptin, while unfavorable DPP4 inhibitors include alogliptin, sitagliptin and vildagliptin. The result showed that, compared with patients receiving unfavorable DPP4 inhibitors or not receiving DPP4 inhibitors, patients receiving favorable DPP4 inhibitors had lower increase in Vmax as well as lower speed of AS progression and lower frequency of aortic valve intervention.[69] This experiment preliminarily proved the effect of two favorable DPP4 inhibitors on delaying the progression of AS, but the mechanism is still not completely clear. In animal models of CAVD, HFD+VitD feeding promoted a significant increase in trans-aortic maximal flow velocity and mean trans-aortic pressure gradient, as well as leaflet thickening, fibrosis and calcification, which were attenuated by DPP4 inhibitor.[41] According to the current research, the possible mechanism of DPP4 inhibitor inhibiting CAVD is as follows. (Table 3) First and foremost, DPP4 significantly increased the expression of inflammatory cytokines IL-2, TNF-α, IL-1β, and IL-6 to induce inflammation to promote the progression of CAVD. The application of DPP4 inhibitor is able to attenuate this pathological reaction.[41] In addition, NO depletion due to aortic valve endothelial dysfunction leads to increased NF-κB activity. NF-κB increases DPP4 expression by directly regulating DPP4 promoter activity, further inducing the degradation of insulin-like growth factor-1 (IGF-1). The subsequent osteogenic differentiation of VICs is accompanied by a marked increase in the expression of alkaline phosphatase and other osteogenic factors Runx2 and osterix (OSX), which can be alleviated by DPP4 inhibitor.[69,71] Last but not least, the use of DPP4 inhibitor also reduces the expression of fibrosis-related genes, fibronectin 1, integrin β and collagen 1, without affecting the expression of a-SMA in valve interstitial cells, suggesting that DPP4 may be involved in fibrin deposition in the aortic valve.[41] Taken together, these results demonstrate the beneficial effects of DPP4 inhibitor on anti-inflammation, anti-calcified nodule formation and anti-fibrosis in vitro and vivo. Currently, several DPP4 inhibitors shown considerable efficacy in blood glucose control due to their similar effect of inhibiting DPP4 activity. However, with regard to the anti-calcification efficacy, their effects are quite different. Therefore, in order to successfully apply DPP4 inhibitor to the management of CAVD, further studies are urgently needed to analyze and compare the anti-calcification ability of different DPP4 inhibitors.[69]

DPP4 and Coronary Atherosclerosis

It is well known that coronary atherosclerosis is one of the major diseases threatening human life. Therefore, people focus their attention on the relationship between DPP4 and atherosclerosis. Fortunately, both animal and clinical studies have found a protective effect of DPP4 inhibitor on atherosclerosis. In animal models, DPP4 inhibitor reduced atherosclerotic plaque area in ApoE knockout mice and LDLR knockout mice, regardless of diabetes.[72] In clinical studies, DPP4 inhibitor effectively slowed down the progression of coronary atherosclerosis in patients with type 2 diabetes.[73] Coronary atherosclerosis is a chronic and complex process involving endothelial dysfunction, reduction of circulating progenitor cells, inflammation, lipid infiltration and oxidation.[74] Thus, the anti-atherosclerotic effect of DPP4 inhibitor includes multiple mechanisms. (Table 4) Firstly, the long-term stimulation of various harmful factors leads to endothelial dysfunction and impaired barrier function, which are the initial factors of atherosclerosis. On the one hand, DPP4 inhibitor increases NO production by activating eNOS enzyme. As a key endothelial regulatory factor with anti-atherosclerosis effect, NO regulates proliferation and apoptosis of endothelial cell, and inhibits adhesion and infiltration of leukocyte.[75] On the other hand, similar to the above, DPP4 inhibitor also inhibits the expression of ET-1, a potent vasoconstrictor and pro-inflammatory molecule secreted by the endothelium, via activating AMPK and inhibiting NF-κB signal pathway.[53] Secondly, injured endothelial cells release a series of adhesion molecules, including intercellular adhesion molecule (ICAM), vascular adhesion molecule (VCAM) and selectin, resulting in the adhesion of inflammatory cells and subsequent transdermal migration, thus promoting the formation of atherosclerotic plaque. As expected, the release of adhesion molecules is inhibited by DPP4 inhibitor.[76] Thirdly, monocytes migrate across the endothelium into the subendothelial and differentiate into macrophages, which in turn engulf oxidized low-density lipoprotein (oxLDL) to become foam cells. The formation of foam cells is a hallmark of early atherosclerosis.[77] DPP4 inhibitor participates in reducing the adhesion and infiltration of monocyte and regulating the differentiation of macrophage. Different types of macrophages have different functions in atherosclerosis: M1 macrophages generally play a proinflammatory role, whereas M2 macrophages generally

inhibit inflammation.[78] DPP4 inhibitor exerts anti-inflammatory effects by promoting the transformation of macrophages into M2 macrophages in the plaque area.[79] In addition, DPP4 inhibitor also inhibits the expression of macrophage surface scavenger receptors CD36 and LOX-1, the activation of NLRP3 inflammasome and the release of IL-1β by inhibiting PKC activity to restrain the formation of foam cells, which together repress the development of coronary atherosclerosis.[80,81] Fourthly, inflammation and oxidative stress are also indispensable key links in coronary atherosclerosis.[82] The atherosclerotic protective effect of DPP4 inhibitor is partly attributed to its anti-inflammatory and anti-oxidant stress effects. Treatment with DPP4 inhibitors not only reduces the levels of circulating inflammatory mediators CRP, MCP-1 and metalloproteinases, but also inhibits the expression of proinflammatory mediators IL-6 and TNF-α, along with the increased expression of anti-inflammatory mediator IL-10.[83,84] Similarly, DPP4 inhibitor ameliorates vascular oxidative stress via dramatically inhibiting the expression of NADPH oxidase subunits $gp91^{phox}$ and $p22^{phox}$ in the aorta.[42] Fifthly, endothelial progenitor cells have the potential to differentiate into mature endothelial cells and secrete various mediators to repair vascular endothelium and promote neovascularization. However, the study found that the number of circulating endothelial progenitor cells are decreased in patients with atherosclerosis. DPP4 inhibitor increases substrate derived factor-1α (SDF-1α), which has the ability to increase the number and activity of circulating bone marrow-derived endothelial progenitor cells in combination with the receptor CXCR4, thereby playing a protective role against atherosclerosis.[85,86] Sixthly, the increase in DPP4 activity activates proliferative capacity of hematopoietic stem cells through Adrβ3/CXCL12 axis signaling, increasing the output of neutrophils and monocytes as well. As we all known, activated inflammatory cells (macrophages and neutrophils) are the major sources of MMP2 and MMP9 in atherosclerotic lesions in humans and animals. Therefore, DPP4 inhibitor effectively inhibits the synthesis and secretion of MMP2 and MMP9 of inflammatory cells in plaques, thus increasing the collagen content in plaques to improve plaque stability and prevent plaque rupture.[87,88] Seventhly, in-stent restenosis in patients with coronary atherosclerosis is one of the common postoperative complications, mainly related to the migration, proliferation and phenotypic transformation of vascular smooth muscle cells.[89] According to studies, DPP4 inhibitor inhibits the proliferation of vascular smooth muscle by activating NRF2 and promotes the apoptosis of vascular smooth muscle cells by activating caspase3, thereby inhibiting the intimal hyperplasia and preventing the occurrence of in-stent restenosis.[90,91] Finally, patients after PCI need to take antiplatelet drugs for at least one year, which may greatly reduce the risk of stent thrombosis, the incidence of myocardial infarction and the risk of death. Recent studies revealed that DPP4 activity is a key factor in vascular thrombosis caused by chronic stress. Compared with the control mice, the levels of plasma DPP4, plasminogen activation inhibitor-1 (PAI-1) and von Willebrand factor (vWF) in mice treated with DPP4 inhibitor were significantly decreased, while the levels of ADAMTS13 were increased. Meanwhile, DPP4 inhibitor counteracted the increase in the number of leukocytes, neutrophils and platelets.[92] These all show the effective antithrombotic effect of DPP4 inhibitor, which may benefit patients after PCI. Therefore, the above evidence indicates that DPP4 is a potential target for the treatment of coronary atherosclerosis, but there is still a lack of sufficient long-term large-scale clinical trials to verify the role of DPP4 inhibitor in coronary atherosclerosis.

DPP4 and Heart Failure

Heart failure refers to the failure of the systolic and/or diastolic function of the heart to fully discharge the venous blood back to the heart, resulting in blood stasis in the venous system and insufficient blood perfusion in the arterial system, leading to circulatory disorders. Heart failure is a terminal stage in the development of several heart diseases rather than an independent disease. Almost all cardiovascular diseases, such as myocardial infarction, cardiomyopathy, hemodynamic overload and other myocardial injury, may cause changes in myocardial structure and function, ultimately leading to heart failure.[93] The efficacy of DPP4 inhibitor in patients with heart failure remains controversial and the specific reasons need to be further explored.[94] European Heart Failure Societies explicitly state that saxagliptin increases the risk of hospitalization for heart failure,[6,12] especially in patients with elevated natriuretic peptide levels, previous heart failure or chronic kidney disease.[95] However, clinical trials have denied this adverse effect of other DPP4 inhibitors, indicating that this is not a common problem of DPP4 inhibitors. At present, with regard to the relationship between DPP4 and heart failure, researches are mainly limited to clinical trials and the understanding of its regulatory mechanism is very limited. (Table 5) Firstly, DPP4 inhibitor increases the concentration of GLP-1, a cardioprotective substrate, to improve cardiac function, but the specific mechanism still needs to be further explored.[96] Secondly, DPP4 inhibitor also increases the

content of the substrate stromal cell-derived factor-1 (SDF-1),[97] which acts as a chemical inducer of multiple cell types, including cardiac stem cells, endothelial progenitor cells, and mesenchymal cells. It plays an important and beneficial role in promoting hematopoiesis, angiogenesis, and stem cell homing, thus partially improving cardiac function in patients with chronic heart failure.[98,99] In addition, myocardial fibrosis caused by pressure overload is one of the detrimental factors to induce heart failure. Therefore, intervention in myocardial fibrosis may be an effective therapeutic strategy.[100] During pressure overload-induced left ventricular remodeling, cardiac fibroblasts differentiate into myofibroblasts, thereby promoting the synthesis and release of various cytokines and the deposition of extracellular matrix.[101] In the TAC mouse model, DPP4 activity was significantly increased in serum and myocardium, which may be mediated by increased expression of HIF-1a stimulated by pressure overload-induced cardiac ischemia. Early stage after TAC, DPP4 increased collagen III production, leading to the progression of myocardial fibrosis and heart failure.[102] At the same time, studies observed that DPP4 polymorphism is associated to RAAS activation.[63,103] The RAAS is involved in regulating vascular tension, left ventricular remodeling, and hydro-salinity balance.[104] Long-term activation of the RAAS leads to abnormal pathologies, such as progressive myocardial hypertrophy, fibrosis, increased systemic vascular resistance, and increased sodium and water retention. The polymorphism of DPP4 in T2DM patients may change the gene expression related to RAAS, thus causing abnormal prolonged activation of the RAAS in response to DPP4 inhibitor, which may partly explain the increased risk of hospitalization for heart failure caused by saxagliptin in SAVOR-TIMI 53.[105] Therefore, genetic testing or biomarkers related to gene polymorphism may be required to judge the application of DPP4 inhibitors in patients with heart failure. In summary, the current understanding of DPP4 regulating heart failure is still very limited, and further additional relevant studies are urgently needed to clarify the relationship between them.

Conclusion

In conclusion, DPP4 inhibitor is playing a more and more vital role in the treatment of diabetes, but its effects on cardiovascular diseases remain to be studied and may be underestimated. Based on the current research, the positive role of DPP4 inhibitor in hyperlipidemia, hypertension, calcified aortic valve disease and coronary atherosclerosis is encouraging, but its role in heart failure is still controversial. Existing studies show that DPP4 inhibitor exerts cardioprotective effects by regulating endothelial function, inflammation, oxidative stress and vasodilatation through GLP-1-dependent and non-dependent pathways. Further sufficient and long-term large-scale clinical trials and more in-depth basic researches are still needed to provide a basis for the successful application of DPP4 inhibitor in the treatment of cardiovascular diseases.

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Disclosure

The authors declare no conflict of interest.

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