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Dipeptidyl Peptidase-4 Inhibitors and Cardiovascular Outcome

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A B S T R A C T

WHO projects that diabetes will be the seventh leading cause of death in 2030. One of the macrovascular of diabetes is cardiovascular (CV) diseases, reported incidence of heart failure in diabetic patients is twice greater than control subjects and intensive use of antidiabetic drugs in diabetic patients increase CV mortality. This review will discusses the effect of DPP4 inhibitors (DPP-4i) on CV outcomes.Data sources: PubMed 32 journals, Google Scholar 17 journals, BioMed Central 5 journals and others 1 journal. Method: A systemic search of all English-language articles from 2000 up to 2020 was conducted using the following terms: dipeptidyl peptidase-4 inhibitors, sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, omarigliptin, cardiovascular, and mechanism on cardiovascular diseases.The cardiac effect parameters assessed were the cardioprotective effect and the incidence rate of MACE (Major Adverse Cardiac Events) namely the death rate from cardiovascular disease, non-fatal myocardial infarction, non-fatal stroke, and hospitalization due to unstable angina.Results: Positive effect on CV of DPP-4i mediated by activate *phosphatidyl inositol 3-kinase* (PI3K),*cyclic adenosine monophosphate* (cAMP), *endothelial NO-synthase* (eNOS) and*protein kinase A* (pKA, and negative effect because their effects in modulate SP, peptide YY, and neuropeptide Y. CV outcomes of DPP-4i versus placebo are variated for MACEs, which are reported on sitagliptin HR 0.98, 95% CI 0.89 to 1.08; Vildagliptin RR 0.82, 95% CI 0.61 to 1.11; Saxagliptin HR 1.00, 95% CI, 0.89 to 1.12; Linagliptin HR 0.78, 95% CI, 0.55 to 1.12; Alogliptin HR 0.85, CI 95%, 0.66 to 1.10; and Omarigliptin HR=0.85, CI 95%, 0.66-1.10.Conclusion: Based on the mechanism DPP-4i inhibitors have either cardioprotective actions or poorer outcomes on CV because their activities are connected with the inhibition of various substrates. DPP-4i sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, and omarigliptin did not significantly increase of MACE (major adverse cardiac events).

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1. INTRODUCTION

Diabetes mellitus is a serious public health problem which the cases are significantly increase over the years. In 2014, around 422 million people worldwide were living with diabetes and caused 1.5 million deaths in 2012 and estimated 1.6 million in 2015. The morbidity and mortality of diabetes mellitus are related with its cardiovascular complications such as atherosclerosis, myocardial infarction, stroke, and increased rate of heart failure. Almost half of patients with type 2 diabetes in risk to have heart failure, and those with both diabetes and history of heart failure have more severe prognosis (1).

It is well-established that heart failure is a major comorbid of diabetes mellitus. The incidence of heart failure in diabetic patients is twice greater per decade of life than in control subjects (2). Additionally, in 2008 there was a large clinical trial explained that the intensive use of antidiabetic drugs increase cardiovascular mortality in diabetic patients (HR 1.35; 95% CI 1.04-1.76; p = 0.02) (1). Thus make FDA suggests the manufacturers to assess cardiovascular safety for all novel class of oral antidiabetic agents including DPP4 inhibitor, especially in regards to heart failure. A previous meta analyses suggested that DPP4 inhibitor offer cardiovascular benefit but there are lack of long term data about the cardiovascular safety (3). This review aims to assess the cardiovascular safety of DPP4 inhibitor.

2. METHOD

This review use data sources from PubMed 32 journals, Google Scholar 17 journals, BioMed Central 5 journals and others 1 journal. A systemic search of all English-language articles from 2000 up to 2020 was conducted using the following terms: dipeptidyl peptidase-4 inhibitors, sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, omarigliptin, cardiovascular, and mechanism on cardiovascular diseases.

3. RESULT AND DISCUSSIONS

Pharmacokinetics/ pharmacodynamics properties of DPP-4 inhibitors shown in table 1.

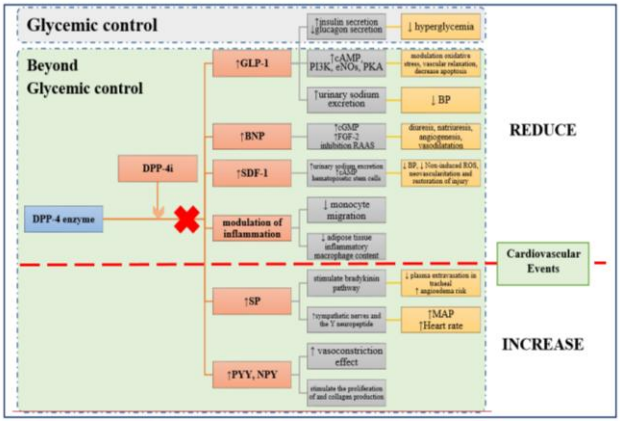
Tabel 1. Pharmacokinetics / Pharmacodynamics properties of dpp-4 inhibitors(4–6)

Pharmacokinetic Properties	
Absorption	Well and rapidly
Bioavailability	High (67-100%) ; except for linagliptin (30%)
Onset of action	5 minute after adminitration
T1/2	
Short half life	Saxagliptin, vildagliptin, teneligliptin, anagliptin
Moderately half life	Sitagliptin, alogliptin, gemigliptin,
Long half life	Linagliptin, trelagliptin, omarigliptin, and evoglptin
Protein bound	
Most gliptins	Poorly or almost negligibly
Linagliptin	Strongly bound >80%
Volume distribution	Widely in tissues (42 L)
Metabolism	The other DPP-4i are not metabolized through CYP substrates, except for saxagliptin
Elimination	Excretion: renal (for all DPP-4i with range between 75-87%), except linagliptin excretion by liver (85%)
Pharmacodynamic Properties	
Increase of GLP-1 levels	Ranging from 70-90% and 1,5-4 fold
Selectivity for DPP-4 versus DPP-8/DPP-9	Ranging from <100 fold to >14,000 fold

a. Mechanism of DPP-4 Inhibitors on Cardiovascular Diseases

DPP-4 enzyme is expressed by some tissues beside kidney, one of the strongly parts are the heart and blood vessels (7). Thus, the inhibition of this enzyme will affect their physiological mechanism that may cause either benefit or harmful effects. It has been reported that higher DPP-4 expression is correlated with poorer outcomes of heart failure rats (8). In the heart, DPP-4 cleaves multiple vasoactive peptides such as glucagon like peptide-1 (GLP-1), brain natriuretic peptide (BNP), stromal cell-derived factor-1 (SDF-1), substance P, peptide YY and neuropeptide Y (Fig. 1) that suggests a potential role in the pathophysiology of cardiovascular diseases (9). Hence administration of DPP-4i will significantly attenuate cardiac dysfunction through its cardio-protective effect, that are obtained from multiple factors including insulin resistance, oxidative stress, dyslipidemia, adipose tissue dysfunction, dysfunctional immunity and anti-apoptotic properties (8).

Figure 1. Effect of DPP-4i on cardiovascular system



In administration of DPP-4i, degradation of GLP-1 is declined and GLP-1 bioavailability is increased. Thus, the cardiac receptor for GLP-1 (GLP-1R) is stimulated and resulting in activation of cyclic adenosine monophosphate (cAMP) and phosphatidyl inositol 3-kinase (PI3K)(9,10). Increased cAMP concentration suggests the reduction of advanced glycation end products (RAGE) receptor,

reactive oxygen species (ROS) generation and inflammatory markers, whereas activation of PI3K pathway decreases apoptosis myocytes and contributes to ischemic preconditioning (11,12). PI3K pathway also mediate the insulin action in vascular cells through PI3K/insulin receptor substrate (IRS)-1, which stimulates the production of vascular dilator NO (13). Besides PI3K pathway, GLP-1 elevation also directly increase nitric oxide (NO), induce the vascular relaxation (14,15)and stimulate the proliferation of coronary artery endothelial cells by endothelial NO-synthase (eNOS) and protein kinase A (PKA) activation (16). Analog GLP-1 is also capable to reduce blood pressure and relaxing the vascular smooth muscle cells through increasing urinary sodium excretion and triggering atrial natriuretic peptide (ANP) released from the atrium (17–19).

Brain natriuretic peptide that plays a key factor in regulating blood fluid homeostasis and vascular tone, has been raised as well by DPP-4i. Enhancement of BNP leads to diuresis, natriuresis and vasodilatation through inhibition of renin angiotensin system and adrenergic activity, so that ventricular volume is increased and myocardial relaxation is improved (20). Beside those effect, BNP also modulates angiogenesis through the increased gene expression of fibroblast growth factor-2 (FGF-2) which is a potent cardioprotective and angiogenic mediator as well (21,22). In addition to BNP, increased SDF-1 on inhibition of DPP-4 enzymes also cause natriuresis effect. SDF-1 is a chemoattractant for hematopoietic stem cells and progenitor cells such as cardiac stem cells, endothelial progenitor cells, and mesenchymal stem cells. Up-regulation of this substrate enhances urinary sodium excretion via Na^+-Cl^- co-transporter or the epithelium sodium channel, so that blood pressure and GFR can be reduced (23,24). Furthermore, this up-regulation also increase the essential role of both SDF-1 receptors, CXCR7 on blood vessel protection and cardiac endothelial cell survival whereas CXCR4 on cAMP elevation and PKA activation (25,26). Elevation of the cAMP via CXCR4 pathway shows a direct cardio-protective effect in which the production of nicotinamide adenine dinucleotide phosphate oxidase dependent reactive oxygen species, including superoxide anion, is reduced and contribute to preventing fibrosis (27,28). Increased SDF-1 also mediated hematopoietic stem cells that may promote neovascularization and restoration of tissue injury (29).

In order to diminish oxidative stress, DPP-4i also significantly inhibits the advanced glycation end products (AGE)-ROS generation in which suggests as a factor of endothelial cells (EC), vasculature remodeling and atherosclerosis (ATH) in the setting of diabetes (8). Inhibition of this pathway associate with modulation of insulin resistance and suppression of RAGE, ICAM-1 and plasminogen activator-1 gene expression in ECs (30), which may ameliorate the deleterious effect of AGE/RAGE in ECs and cardiac tissue. Besides oxidative stress, lipid parameters and chronic inflammation are also the key in the pathogenesis of ATH. Administration of DPP-4i significantly reduce intestinal secretion of TG, cholesterol and apolipoprotein B-48 via GLP-1 role in regulating lipoprotein assembly and secretion in enterocytes (31). In chronic inflammation, DPP4-i may reduce monocyte migration to atherosclerotic plaque in response to TNFα (32) and also regulate the expression of adiponectin containing anti-inflammation (33). DPP-4i will decrease the accumulation of M_1 macrophages and increase levels of M_2 macrophages in adipose tissue and in atherosclerotic lesion (32,34). Inflammation will be reduced as well by inhibiting monocyte activation and chemotaxis, reducing adipose tissue inflammatory macrophage content ($CD11b^+$, $CD11c^+$, $Ly6C^{hi}$) and up-regulating CD163 positive anti-inflammatory macrophages (8).

DPP-4i also decrease the degradation of vasoactive peptides that associate to the endothelial function, such as substance P (SP), peptide YY (PYY) receptor and neuropeptide Y (NPY). At this point, DPP-4i may be contraindicated in diabetic patients with taking angiotensin converting enzymes inhibitors (ACEi). The adverse effects of using both of these drugs simultaneously has been reported to be associated with increasing concentration of SP, which is a putative mediator of angioedema and stimulator of the sympathetic nerves and the Y neuropeptide (35,36). When ACE is inhibited, SP metabolism becomes strongly dependent on DPP-4 activity, so that used of DPP-4i will decrease inactivation of SP and elevate its concentration (37). This elevation will increase angioedema risk and sympathetic tonus that is shown through mean arterial blood pressure (MAP) (36). Furthermore, the risk of angioedema is also increased through bradykinin pathway on SP stimulation, which cause reduction of plasma extravasation in tracheal and other tissues (38).

The other mechanism of the DPP-4i on countering the blood pressure-lowering effect of ACEi is increasing of Y_1 receptors activity through NPY_{1-36} and PYY_{1-36} metabolism. NPY_{1-36} is a co-transmitter that is released with norepinephrine and activate Y_1 receptors to augment vasoconstrictor responses to norepinephrine, whereas PYY_{1-36} is an endogenous Y_1 receptor agonist that is released from the gut. DPP-4i will reduce metabolism of NPY_{1-36} and PYY_{1-36} to its inactive metabolite, which increase vasoconstriction effect (36).

b. Study of DPP-4 Inhibitors and Increased Risk of CVDs

1) Sitagliptin

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a randomized, double blind, prospective, and placebo-controlled trial that assessing the cardiovascular safety of sitagliptin versus placebo, which each of them added to standard diabetes and cardiovascular therapy. The subjects used in this study were patients with type 2 diabetes mellitus (T2DM) who had a history of cardiovascular disease and the HbA1c was between 6.5% to 8.0%. The TECOS cardiovascular (CV) safety trial had successfully shown that treatment with sitagliptin did not increase the risk of primary endpoint of MACEs and also did not increase the risk of heart failure hospitalization in

patients with type 2 diabetes. The primary composite cardiovascular outcome was 11.4% (*n*=839) of sitagliptin group and 11.6% (*n*=851) of placebo group (Hazard Ratio (HR), 0.98; 95% confidence interval (CI), 0.89 to 1.08), and identical in both the sitagliptin and placebo groups in the per-protocol analysis (9.6% (*n*=695) ; HR, 0.98; 95% CI, 0.88 to 1.09; p <0.001). There was also no increase in the heart failure hospitalization, and the mortality rates were similar in the both groups. All-cause mortality was also similar which were 7.5% (*n*=547) in sitagliptin group and 7.3% (*n*=537) in placebo group (HR, 1.01; 95% CI, 0.90 to 1.14) (39).

2) Vildagliptin

The CV safety profile of vildagliptin, primary endpoint MACEs (major adverse cardiovascular events) was assessed by a meta-analysis, total of 17446 patients, 9599 received vildagliptin and 7847 received comparators. The MACEs risk ratio (RR) was 0.82, 95% CI 0.61 to 1.11. RRs were also observed for each individual component of the composite endpoint, with the RR for myocardial infarction 0.87, 95% CI 0.56 to 1.38; stroke 0.84, 95% CI 0.47 to 1.50; and CV death 0.77, 95% CI 0.45 to 1.31, all RRs outcomes contain 1, indicated vildagliptin versus comparators was not different for MACEs (40).

Analytical cohort study assessed the CV safety of vildagliptin versus other non-insulin antidiabetic drugs (NIADs). The outcomes were myocardial infarction (MI), acute coronary syndrome (ACS), stroke, and congestive heart failure (CHF). of 738,054 patients was enrolled and used vildagliptin with an average follow-up time of 1.4 years. The adjusted Insidence Risk Rasios (IRRs) with 95% CI were 0.61–0.97 (MI), 0.55–1.60 (ACS), 0.02–0.77 (stroke), and 0.49–1.03 (CHF). The IRRs were close to 1, demonstrating no increased risk of adverse CV events (41).

3) Saxagliptin

One of the trial evaluated cardiovascular safety of saxagliptin was SAVOR-TIMI 53 trial, conducted the trial at 788 sites in 26 countries, the total 16,492 patients with type 2 diabetes, primary end point was MACEs. SAVOR-TIMI 53 trial reported with primary end point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group, HR 1.00; 95% CI, 0.89 to 1.12; p=0.99. Hospitalized for heart failure was one of the outcome of SAVOR-TIMI 53 trial, HR 1.27; 95% CI, 1.07 to 1.51; P = 0.007. Another outcomes such as hospitalization for unstable angina and coronary revascularization was similar between saxagliptin group and placebo group (42).

NT-proBNP was measured in 12,301 patients (74.6% of the overall SAVOR-TIMI 53 trial). There was a step-wise increased risk of hospitalization for heart failure with higher quartiles of baseline NT-proBNP (43). Analyses were performed of 20 randomized controlled studies (N = 9156) of saxagliptin as monotherapy or add-on therapy in patients with T2DM to evaluated MACEs. IRR for MACEs in the 20-study pool was 0.74; 95% CI , 0.45 to 1.25 (44). Saxagliptin is safe and not associated with an increased CV risk but the rate of hospitalization for heart failure was increased.

4) Linagliptin

Linagliptin was reported may have cardiovascular benefits inpatients with type 2 diabetes mellitus. Study mata-analysis was investigated the CV safety profile of linagliptin compared with comparators. Of 3319 received linagliptin once daily and 1920 received comparators. Risk estimates for primary composite CV endpoint with linagliptin versus total comparators were reported the HR showed significantly lower risk (HR 0.34, 95% CI; 0.16-0.70), Risk Reduction (RR) 0,34, 95% CI; 0.15-0.74 (45). Another meta-analysis who evaluated the CV safety of linagliptin vs comparators, the data from 9459 subjects with T2DM who participated in 19 clinical trials, outcome of this study was composite of prospectively adjudicated CV death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina (4P-MACE), reported that HR 0.78, 95% CI, 0.55–1.12. Hospitalization for congestive heart failure (CHF) was also evaluated, HR 1.04, 95% CI, 0.43–2.47 (46).

Crossover study randomised T2DM patients assessed the effects of linagliptin versus the glimepiride and placebo on measures of macro- and microvascular endothelial function reported that linagliptin significantly improved microvascular function as shown by a 34% increase in hyperaemia area (p = 0.045 vs glimepiride), a 34% increase in resting blow flow (p= 0.011 vs glimepiride, p = 0.003 vs placebo), and a 25% increase in peak blood flow (p= 0.009 vs glimepiride, p= 0.003 vs placebo), but Linagliptin had no effect on macrovascular function (40).

5) Alogliptin

The Examination of Cardiovascular Outcomes with Aloglitin versus Standard of Care (EXAMINE) study is a randomized, double-blind, placebo-controlled study that aims to evaluate the major cardiovascular event rates in alogliptin versus placebo in patients with T2DM who had an acute coronary syndrome recently (47).

In EXAMINE study, around 28% of patients had history of congestive heart failure at baseline. The first occurrence of heart failure hospitalization for alogliptin and placebo groups were 3.1% and 2.9% respectively (HR 1.07, 0.79-1.46, p = 0.657). For patients who were treated with alogliptin, 4.1% of them died as compared to 4.9% who were had placebo. That means there is no significant increase when treated with alogliptin (HR=0.85, CI 95%, 0.66-1.10). This goes to confirm an earlier study that there was no difference of between alogliptin and placebo group on the primary endpoint (48).

In this study, 3.9% of alogliptin-treated and 3.3% of placebo-treated patients had a hospitalization for heart failure (HR 1.19, 95% CI 0.89-1.58, *P* = 0.220). Based on the results, there was a statistically non significant increased risk for hospitalization due to heart failure between the two groups. However, in the group without history of heart failure, they more likely to be hospitalized for heart failure with the use of alogliptin (HR 1.76; 95% CI 1.07-2.90) (48).

6) Gemigliptin

Effects of gemigliptin, on postprandial lipoprotein

levels was evaluated by clinical research randomized, double-blind, placebo-controlled, crossover study. Fasting serum ApoB48 levels were significantly lower with gemigliptin than with placebo (p= 0.020). However, the plasma ApoB100 levels showed no significant difference (p= 0.734) (49). Study to evaluate cardiovascular outcomes of T2DM patientstreated with gemigliptin is still ongoing.

7) Anagliptin

The study about effect of anagliptin treatment was investigated on lipoprotein metabolism in fasting and postprandial to ten Japanese men with type 2 diabetes. It has been suggest that in men with type 2 diabetes, anagliptin improves hyperlipidemia. However, the sample size is small (50). The effects of cardiovascular safety have not been reported.

8) Teneligliptin

The safety of teneligliptin on cardiovascular detected slight prolongation of the QTc interval with dose 160 mg/day, but no QT prolongation were detected with 40 mg/day (51). Caution is needed if used of teneligliptin with drugs caused QT prolongation such as class IA or class III antiarrhythmic drugs (51). Teneligliptin was associated with improvements in LV ejection fraction ($p = 0.01$) and improvements endothelial functions ($p < 0.01$) (52). The spesific effects on MACE have not been reported.

9) Trelagliptin

The effects of trelagliptin treatment on vascular endothelial functions using FMD (flow-mediated dilatation), adiponectin and ADMA (asymmetric dimethylarginine) as indicators was evaluated. It showed no significant changes in FMD and ADMA with p value 0.785 and 0.402 respectively, serum adiponectin level was significantly increase ($p < 0.002$) (33). CV safety for trelagliptin has not been reported.

10) Omarigliptin

CV safety study of omarigliptin had been done in randomized, double-blind study, 4202 patients with T2DM and established CV disease with outcome to MACE and the analysis of first event of hospitalization for heart failure (hHF), reported that omarigliptin vs placebo did not increase the risk of MACE or hHF with HR 0.85, CI 95%, 0.66-1.10 and 0.60, 95% CI 0.35 to 1.05 respectively (53). In another study reporte omarigliptin did not affect the QT interval (54).

11) Evogliptin

CV safety for evogliptin has not been reported. One study reported evogliptin reduce progression of atherosclerosis by significantly suppressed the expression of adhesion molecules (ICAM-1, VCAM), activation of NFkB also inhibited with dose dependetly (55).

Based on the mechanism DPP4 inhibitors have cardioprotective actions because their effect to increase GLP-1 biovailability which can activate PI3K, CAMP, eNOS and PKA, to stimulate BNP, to increase SDF-1, to inhibit modulation of inflammation and to enhance urinary sodium excretion. Another mechanism for poorer outcomes on CV are the effects of DPP4 inhibitors in modulate SP, peptide YY, and Neuropeptide Y. DPP4 inhibitors are multitarget compounds, therefore their activities are connected with the inhibition of various substrates.

DPP4 inhibitors like sitagliptin, vildagliptin, linagliptin, and omarigliptin did not significantly increase of MACE or hHF. Saxagliptin and alogliptin are reported not significantly increase of MACE but they can increase hHF. The spesific effects on CV have not been reported for others gliptins like gemigliptin, anagliptin, teneligliptin, trelagliptin, and evogliptin. Co-administration DPP4 inhibitors with ACEi must be concerned because their potential interaction can induce heart rate and angioedema.

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