The regulatory role of DPP4 in atherosclerotic disease

Lihua Duan1,2, Xiaoquan Rao2, Chang Xia23, Sanjay Rajagopalan2 and Jixin Zhong2*

Abstract
The increasing prevalence of atherosclerosis has become a worldwide health concern. Although significant progress has been made in the understanding of atherosclerosis pathogenesis, the underlying mechanisms are not fully understood. Recent studies suggest dipeptidyl peptidase-4 (DPP4), a regulator of inflammation and metabolism, may be involved in the development of atherosclerotic diseases. There has been increasing clinical and pre-clinical evidence showing DPP4-incretin axis is involved in cardiovascular disease. Although the cardiovascular outcome of DPP4 inhibition or incretin analogues has been or being evaluated by several large scale clinical trials, the exact role of DPP4 in atherosclerotic diseases is not completely understood. In the current review, we will summarize the recent advances in direct and indirect regulatory role of DPP4 in atherosclerosis.

Keywords: Dipeptidyl peptidase, Gliptins, Atherosclerosis, Incretin, DPP4 inhibitor

Background
Atherosclerosis, the primary cause of cardiovascular disease, is a chronic progressive condition with lipids and fibrous elements accumulated in the vessel wall of large arteries [1–3]. It accounts for 50% of all deaths in the Western countries [4]. The increasing prevalence of atherosclerosis has become a worldwide health concern [5]. Despite of rapid progress in atherosclerosis research in the recent years, the underlying mechanisms remain elusive. Dipeptidyl peptidase-4 (DPP4) inhibitors are a novel class of glucose-lowering drugs [6]. Various studies suggest DPP4 inhibitors may also possess cardioprotective effect [7–12], including atherosclerosis [13–15]. In the current review, we will summarize the recent advances in direct and indirect regulatory role of DPP4 in cardiovascular disease, especially in atherosclerosis.

Experimental evidence of the beneficial effects of DPP4 inhibition on cardiovascular disease
Dipeptidyl peptidase-4 is a membrane-bound enzyme that cleaves N-terminal dipeptide from its substrates. It belongs to the S9b dipeptidyl peptidases family [16]. There are over a dozen proteins identified as the substrates of DPP4. These include glucagon-like peptide (GLP) -1 and -2, glucose-dependent insulinotropic peptide (GIP) [17], stromal-cell-derived factor-1 (SDF-1) [18], GM-CSF [19], regulated on activation normal T-cell expressed and presumably secreted (RANTES) [20], eotaxin [21], neuroptide Y (NPY) [22], etc. The molecular basis of catalytic activity of DPP4 has been reviewed elsewhere and we will only discuss the recent advances in DPP4 biology [23–25].

DPP4 inhibitors are being increasingly used in clinical for the treatment of type 2 diabetes as they are safe and weight neutral [26–32]. They preserve incretin hormones such as GLP-1 and GIP by inhibiting DPP4-mediated degradation, and thus could promote postprandial insulin secretion and reduce pancreatic β cell apoptosis [33–36]. Furthermore, antiapoptotic effects of DPP-4 inhibitor were observed in human umbilical vein endothelial cells (HUVECs) cultured under hypoxic condition. Besides, the CXCR4 antagonist or Stat3 inhibitor can abolish this effect. These results suggested that
DPP-4 inhibitor has a potential for protecting vessels where CXCR4/Stat3 pathways might be involved [37]. In animal experiments, Salim HM et al. demonstrated that linagliptin ameliorated atherogenesis in non-diabetic ApoE−/− mice by inhibiting the oxidative stress [38], and it also showed that linagliptin prevents the development of aortic and endothelial stiffness in female mice resulting from western diet-induced vascular abnormalities [39]. We have previously also shown long-term enzymatic inhibition of DPP4 by sitagliptin or alogliptin reduced atherosclerotic plaque burden in Ldlr−/− and ApoE−/− mice, accompanied by reduced monocyte activation and migration [40]. In consistency with that, a recent study demonstrated 12-week anagliptin treatment suppressed atherosclerosis progression and macrophage infiltration in the plaque in cholesterol-fed rabbits [41], and 20-week teneligliptin administration inhibited the development of atherosclerosis in the aortic arch in ApoE−/− mice through restraining macrophage infiltration, downregulating lipid deposition and MCP-1 expression, and in vitro experiment GLP-1 analogue treatment suppressed the pro-inflammatory cytokines production [42]. Not only by reducing monocyte activation and migration, DPP4 inhibitor sitagliptin can attenuate atherosclerosis by promoting M2 macrophages polarization [43]. Acute in vitro DPP4 inhibition also relaxed pre-constricted aorta segments by activating Src-Akt-eNOS pathway in a GLP-1-independent manner [44]. In addition, combination therapy with DPP4 inhibitor and sodium-glucose cotransporter 2 inhibitor showed the greatest suppression of plaque volume in the aortic root of diabetic ApoE−/− mice [45].

Interestingly, DPP4 inhibitor but not GLP-1 or GIP reduced incidence of angiotensin II-induced abdominal aortic aneurysm in ApoE−/− mice (40% in DPP4 inhibition group vs. 70% in control group) [46]. Using an experimental myocardial infarction model, Sauvé et al. examined the effects of DPP4 enzymatic inhibition or genetic deletion of DPP4 on cardiovascular function in normoglycemic and diabetic mice [47]. Dpp4−/− mice displayed normal cardiac structure and function, with increased levels of phosphorylated AKT (pAKT), pGSK3β, and atrial natriuretic peptide (ANP) in the heart. After left anterior descending (LAD) coronary artery ligation, Dpp4−/− mice showed a modestly improved survival and functional recovery from ischemia–reperfusion injury as measured by left ventricle developed pressure. Treatment of DPP4 enzymatic inhibitor sitagliptin also reduced mortality and enhanced functional recovery from ischemia–reperfusion injury in wild-type diabetic mice after myocardial infarction [47]. Consistently, treatment with DPP-4 inhibitor vildagliptin markedly improved the survival rate after myocardial infarction in type 2 diabetic rats, and the protective effect was linked with restoration of autophagic response resulting from increased both LC3-II protein level and autophagosomes after vildagliptin treatment [48]. Furthermore, Ma et al. also DPP4 inhibition exerted a potential strategy for treating cerebral vascular complications in T2DM through reducing oxidative stress and suppressing blood–brain barrier disruption [49]. Although a number of animal studies suggest DPP4 inhibition may have cardiovascular beneficial effects in addition to its glycemic lowering effect [8, 50, 51], while there was no study uncover the precise cells and tissues which is critical for incretin degradation. Recently, a study clearly showed that levels of soluble plasma DPP4 activity, incretin degradation, and glucose regulation rely heavily on endothelial cell-derived DPP4. Surprisingly, fasting GIP, but not GLP-1, was mainly degraded by bone marrow-derived DPP4 [52], and a study also demonstrated that active GIP levels were increased more than GLP-1 after DPP-4 inhibitor treatment [53]. Shigeta and colleagues also reported DPP4 expressed on the cardiac capillary endothelia is up-regulated by diabetes, resulting in a reduction in myocardial SDF-1 and increased interstitial fibrosis. Both genetic and pharmacological inhibition of DPP4 restored diabetes-induced SDF-1 and reversed pressure overload-induced diastolic left ventricular dysfunction by GLP-1-dependent mechanisms [54].

Clinical trials on the cardiovascular effects of DPP4 inhibition

In contrast to the consistent beneficial cardiovascular effects of DPP4 inhibition on experimental animal models, the cardiovascular effects of DPP4 in human studies on seem more complicated and inconsistent (Table 1) [55–63]. Three months of vildagliptin (50 mg twice daily) or sitagliptin (100 mg once daily) also significantly reduced carotid intima-media thickness (IMT), a surrogate marker of atherosclerosis, in patients with type 2 diabetes [64]. Further analysis indicated this maybe relates to the reduction in daily acute glucose fluctuation and plasma LDL level [64]. A randomized controlled trial, the sitagliptin preventive study of IMT evaluation (SPIKE), demonstrated that sitagliptin 104-week treatment had a greater changes in the mean and left maximum IMT of the common carotid arteries, which measured by echography [65]. Besides, a study of preventive effects of alogliptin on diabetic atherosclerosis (SPEAD-A), which includes T2DM patients with alogliptin treatment (n = 172) or conventional treatment (n = 169), showed that 20 months of alogliptin treatment significantly changed the mean common and the right and left maximum IMT of the carotid arteries (P = 0.022, P = 0.025,
Regarding the different conclusion reported by different carotid IMT as a marker of atherosclerosis, which however, PROLOGUE randomized controlled trial in T2DM patients with 26 weeks of linagliptin administration in a small study with a limited number of participants (RELEASE) when compared with placebo (P = 0.035) [69]. Kutoh et al. [70] recently reported that 12.5–25 mg/day alogliptin monotherapy for 3 months significantly improved insulin resistance and beta cell function and reduced athogenic lipids in type 2 diabetic patients with a better glycemic response to alogliptin. In another study, however, DPP4 inhibitor sitagliptin as an add-on in type 2 diabetic patients for 6 months did not improve athogenic lipids including total cholesterol, LDL cholesterol, and malondialdehyde-modified LDL (an oxidized LDL increased in diabetes) [71]. In addition to previous study, a multicenter Randomized Controlled Trial (prospective, randomized, open label, blinded endpoint, PROLOGUE design) also revealed that sitagliptin treatment had no effect on the progression of carotid IMT in T2DM patients [72]. A further sub-analysis of the PROLOGUE study also showed that no significant effect of sitagliptin on the arterial stiffness and endothelial function in T2DM patients which are thought to contribute to the occurrence of atherosclerosis [73, 74]. However, PROLOGUE randomized controlled trial used carotid IMT as a marker of atherosclerosis, which can not entirely represent the status of atherosclerosis. Regarding the different conclusion reported by different clinical trials, Nozue et al. [75] design a prospective, non-randomized, multicenter trial performed in Japan, where T2DM patients who have intermediate coronary artery stenosis will be recruited. The diameter stenosis will be evaluated by coronary computed tomography angiography (CCTA) at the starting point and ending point (48 weeks alogliptin treatment). This clinical trial will provide a strong evidence for the effect of alogliptin in the anti-atherosclerosis.

It is reported that treatment with vildagliptin for 4 weeks in patients with type 2 diabetes improved forearm blood vasodilator responses to intra-arterially administered acetylcholine, but not to sodium nitroprusside [76]. Nakamura et al. [77] also reported that sitagliptin treatment for 12 weeks significantly improved flow-mediated dilatation in diabetic patients uncontrolled on sulfonylurea, metformin or pioglitazone treatment. In contrast, another study demonstrated that the flow-mediated dilation was suppressed by both sitagliptin and alogliptin [78].

Several large scale clinical trials were carried out to evaluate the cardiovascular effects of DPP4 inhibitors and GLP-1R agonists [79–83]. The cardiovascular safety of DPP4 inhibitors, especially in heart failure, has been questioned since 2013 when the first 2 large clinical trials assessing the cardiovascular safety of DPP4 inhibitors (EXAMINE and SAVOR-TIMI 53) were completed [84, 85]. Both of these trials demonstrated that DPP4 inhibitors do not increase overall cardiovascular risks. However, there was also no beneficial effect on primary cardiovascular outcomes in both trials. Interestingly, the SAVOR-TIMI 53 trial reported a 27% increase in hospitalization for heart failure in saxagliptin group, although no increased heart failure-related death was observed (3.5% vs. 2.8%; hazard ratio, 95% CI 1.27, 1.07–1.51; P = 0.007) [85]. In the EXAMINE trial, there were no heart failure-related outcomes reported in their first report although there were 28% of subjects having congestive heart failure at baseline [84]. After re-analysis, the heart failure hospitalization data of the EXAMINE trial was published in 2015, reporting a negative effect of alogliptin on the occurrences of heart failure hospitalization (3.1% in alogliptin vs. 2.9% in placebo group; HR 1.07, 0.79–1.46; P = 0.68) [86]. The 3rd large scale trial assessing the cardiovascular effect of DPP4 inhibitor, TECOS, finished in 2015. In consistency with the first two trials, sitagliptin neither increases nor reduces cardiovascular events (primary outcome incidence, 11.4% vs. 11.6%; HR 0.98, 95% CI 0.88–1.09) [87]. More importantly, the hospitalization rate for heart failure was identical in sitagliptin and placebo (3.1% vs. 3.1%; HR 1.00, 0.83–1.20; P = 0.98). Furthermore, a pre-specified patient-level pooled analysis of all available double-blind, randomized, controlled trials, ≥12 weeks’ duration (19 trials, 9459 subjects) also demonstrated that linagliptin was not associated with increased cardiovascular risk in T2DM patients [88]. Based on the three trials currently available, it seems the excessive heart failure effect may not be a class effect of DPP4 inhibitors. This will be further tested by the ongoing trials on linagliptin (CAROLINA and CARMELINA), both of which are expected to be completed in 2018.

There were two large trials examining the cardiovascular safety of GLP-1R agonists recently completed, one on lixisenatide (ELIXA) and one on liraglutide (LEADER). The ELIXA trial indicates lixisenatide is neither inferior nor superior to placebo in terms of cardiovascular safety. In addition, there were similar hospitalization rates for heart failure compared with placebo (HR 0.96; 95% CI 0.75–1.23) [89]. Surprisingly, the LEADER trial indicates...
a beneficial effect of liraglutide on cardiovascular outcomes. Liraglutide significantly reduced the risk of major adverse cardiovascular events [90]. These data suggest the heart failure effect of saxagliptin is independent of preservation of incretins.

Mechanisms by which DDP4 participates in cardiovascular disease

Chronic inflammation is key process in the pathogenesis of atherosclerosis. DPP4 inhibition may reduce monocyte migration to atherosclerotic plaque in response to TNFα and soluble DPP4 [40], it also up-regulates the adiponectin expression which exerts anti-inflammation [91]. Recent study also showed that T2DM patients with GLP-1 analogues or DPP4 inhibitors treatment had a significant smaller portion of plaque area occupied by macrophages and T-cells compared with the patients who never used GLP-1 analogues or DPP4 inhibitors, and the difference was closely associated with adiponectin and adaptor protein PH domain and leucine zipper containing 1 (APPL1) which can be induced by GLP-1 in ex vivo cell culture system [92]. Inhibition of DPP4 also results in elevation of SDF-1, a chemoattractant for many types of hematopoietic stem cells and progenitor cells such as cardiac stem cells, endothelial progenitor cells, and mesenchymal stem cells [18, 93–96]. Enhancement of SDF-1-mediated hematopoietic stem cell and progenitor cell chemotaxis and repopulation may then promote neovascularization and recovery of tissue injury [18]. Nevertheless, the enhancement of angiogenesis through SDF-1-mediated epithelial progenitor cell migration and repopulation may contribute to plaque instability [97].

Many groups have shown that DPP4 inhibition is able to lower lipid levels [98–103]. DPP4 inhibitors treatment following a high-fat liquid formula significantly reduced triglyceride-rich lipoproteins apoB48 in healthy individuals [103–105]. Three-month alogliptin monotherapy has been shown to reduce atherogenic lipids in type 2 diabetic patients who had a better glycemic response to alogliptin [70]. In consistency, diabetic patients treated with vildagliptin (50 mg bid for 4 weeks) [106] or sitagliptin (100 mg/day for >6 weeks) [107] or alogliptin (25 mg/day for 7 days) [108] also displayed decreased postprandial plasma triglyceride, chylomicron apoB48 after mixed meal challenge.

In a follow-up study of SAVOR-TIMI 53, the authors suggest the increased heart failure hospitalization rate in saxagliptin group might be related to previous history of heart failure, low glomerular filtrate rate (eGFR < 60 ml/m), highbrain natriuretic peptide (BNP) and high albumin/creatinine ratio. In addition, Zhou et al. [109] presented results that DPP4 inhibitor can evoke significant diuretic and natriuretic responses and increased GFR by potentially affecting on renal sodium and water handling, which might be benefit to heart failure. BNP is able to promote vasodilation and natriuresis and it can be degraded by DPP4 to a less potent metabolite BNP(3–32) [110]. BNP also promotes norepinephrine release, which may counteract the beneficial effects of BNP-mediated vasodilation and natriuresis on heart failure [111]. Treatment of sitagliptin 200 mg/day increased forearm blood flow and decreased forearm vascular resistance in healthy humans, while BNP infusion also caused vasodilation in a dose-dependent manner [112, 113]. However, the authors did not observe an effect of sitagliptin on BNP-mediated vasodilation [112]. In addition, DPP4 inhibition has also been shown to induce vasodilation by promoting endothelial nitric oxide synthase (eNOS)-mediated NO release independent of GLP-1R signaling [44, 114]. DPP4 inhibition-mediated GLP-1R signaling may also activate Epac2 and induce atrial natriuretic peptide (ANP) release from the atrium, and thus dilate vessels [115]. DPP4 inhibition has been shown to increase sympathetic activation by preserving substance P [113] and thus may increase systolic blood pressure [112]. GLP-1R agonist may also activate sympathetic nervous system and increase heart rate [116]. A recent study reported that genetic deficiency of DPP4 improve cardiac function, whereas chemical inhibition of DPP4 by MK-0626 induced cardiac hypertrophy and impaired cardiac function, indicating drug related unspecific effects might negatively impact cardiac function [117].

Conclusions

The cardiovascular side effect is a big concern of oral anti-diabetic drugs. The cardiovascular safety of DPP4 inhibitors, as a new class of oral anti-diabetic drugs, has drawn much attention. The three large trials recently completed indicate DPP4 inhibitors as a class are safe from cardiovascular perspective. Many preclinical and clinical studies have shown DPP4 inhibitors may modulate atherosclerotic disease by reducing plasma lipids, suppressing inflammation, and promoting vascular relaxation (Fig. 1). However, inhibition of DPP4 may also exacerbate cardiovascular disease by enhancing
sympathetic activation and angiogenesis. Ongoing trials assessing the cardiovascular effects of DPP4 inhibitors and GLP-1R agonists will provide further insights into the cardiovascular actions of DPP4 inhibitors.

Abbreviations
DPP4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; GIP: glucose-dependent insulinotropic peptide; SDF-1: stromal-cell-derived factor-1; RANTES: regulated on activation normal T cell expressed and presumably secreted; NPY: neuropeptide.

Authors’ contributions
LD, XR, CX reviewed the literature and wrote the first draft. SR, JZ reviewed the literature and finalized the manuscript. All authors read and approved the final manuscript.

Author details
1 Department of Rheumatology and Clinical Immunology, The First Affiliated Hospital of Xiamen University, Xiamen 361003, Fujian, China. 2 Cardiovascular Research Institute, School of Medicine, Case Western Reserve University, 2103 Cornell Rd, Wolstein Research Building 4525, Cleveland, OH 44106, USA. 3 Department of Microbiology and Immunology, Wuhan Polytechnic University, Wuhan 430023, Hubei, China.

Acknowledgements
Not applicable.

Competing interests
JZ is currently receiving a Grant (IIS2015-10485) from BoehringerIngelheim. The remaining authors declare that they have no competing interests.

Funding
This work was supported by Grants from NIH (K01 DK105108), AHA (17GRNT33670485, 15SDG25700381 and 13POST17200033), Mid-Atlantic Nutrition Obesity Research Center (NORC) under NIH Award Number P30DK022488, BoehringerIngelheim (IIS2015-10485), and National Natural Science Foundation of China (81671544).

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Table 1 Dipeptidyl peptidase 4 inhibitors and atherosclerosis outcome trials

| Study     | Study design         | Drug      | Duration   | Result                                                                 |
|-----------|----------------------|-----------|------------|------------------------------------------------------------------------|
| SPIKE     | Randomized/blinded-endpoint | Sitagliptin | 104-week | The mean IMT and left maximum IMT of common carotid arteries were reduced |
| SPEAD-A   | Randomized/blinded-end point | Alogliptin | 24-month | The progression of carotid IMT was attenuated                          |
| RELEASE   | Randomized/double-blind | Linagliptin | 26 weeks  | Aortic PWV was decreased                                                |
| PROLOGUE  | Randomized/blinded-end point | Sitagliptin | 24-month | No additional effect on the progression of carotid IMT                 |
| TRACT     | Non-randomized       | Alogliptin | 48-week   | Not end. Intermediate coronary artery stenosis of T2DM patients will be evaluated by CCTA |

CCTA, coronary computed tomography angiography; IMT, intima-media thickness; PWV, pulse wave velocity; T2DM, type 2 diabetes mellitus

Fig. 1 Mechanisms underlying the cardiovascular action of DPP4 inhibition: ATH, atherosclerosis; ANP, atrial natriuretic peptide; CM, chylomicron; EC, endothelial cell; HR, heart rate; NO, nitric oxide; SDF-1, stromal-cell-derived factor-1
References

1. Raikob GE, Agchosuksri P, Blanco AN, Buller H, Gallus A, Hunt BJ, Hylek EM, Kakkar A, Konstantinides SV, McCumber M, et al. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol. 2014;34(11):2363–71.

2. Fark E, Nakano M, Benzton JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists’ view. Eur Heart J. 2013;34(10):719–28.

3. Palombo C, Kozakova M. Arterial stiffness, atherosclerosis and cardiovascular risk: pathophysiologic mechanisms and emerging clinical indications. Vasc Pharmacol. 2016;77:1–7.

4. Luis AJ. Atherosclerosis. Nature. 2000;407(6801):233–41.

5. Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiologic aspects of atherosclerosis: the role of low-density lipoprotein cholesterol. J Am Coll Cardiol. 2015;65(23):2555–67.

6. Inzucchi SE, McGuire DK. New drugs for the treatment of diabetes: part II. Incretin-based therapy and beyond. Circulation. 2008;117(4):574–84.

7. Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycemic drug therapy. Lancet. 2015;385(9982):2107–17.

8. Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. Eur Heart J. 2013;34(22):2388–96.

9. Zhong J, Gong Q, Goud A, Srinivasamaharaj S, Jagapalagapalan S. Recent advances in dipeptidyl-peptidase-4 Inhibition therapy: lessons from the bench and clinical trials. J Diabetes Res. 2015;2015:60931.

10. Hausenloy DJ, Whittington HJ, Wynne AM, Begum SS, Theodorou L, Rikkers LL, Kumar S, McTernan PG. DPP-IV inhibition enhances the antilipolytic action of NPY in human adipose tissue. Diabetes Obes Metab. 2009;11(4):285–92.

11. Zhong J, Maiseyue A, Davis SN, Jagapalagapalan S. DPP4 in cardiometabolic disease: recent insights from the laboratory and clinical trials of DPP4 inhibition. Circ Res. 2015;116(9):1491–504.

12. Mulvihill EE, Drucker DJ. Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. Endor Rev. 2014;35(6):992–1019.

13. Ussher JR, Drucker DJ. Cardiovascular actions of incretin-based therapies. Circ Res. 2014;114(11):1788–803.

14. Lehmkreir M, Marx N, Patel S, Siek T, Crowe S, Cheng K, Von Eynatten M, Johansen OE. Safety and tolerability of linagliptin in patients with type 2 diabetes: a comprehensive pooled analysis of 22 placebo-controlled Studies. Clin Ther. 2014;36(8):130–46.

15. Lau DC, Teoh H. Impact of current and emerging glucose-lowering drugs on body weight in type 2 diabetes. Can J Diabetes. 2015;39(Suppl 5):S48–54.

16. Hansen HH, Hansen G, Paulsen S, Vrang N, Mark M, Jelsing J, Klein T. The DPP-IV inhibitor linagliptin and GLP-1 induce synergistic effects on body weight loss and appetite suppression in the diet-induced obese rat. Eur J Pharmacol. 2014;741:254–63.

17. Lind M. Incretin therapy and its effect on body weight in patients with diabetes. Prim Care Diabetes. 2012;6(3):187–91.

18. Maneghi IF, Orozco-Beltran D, Khunti K, Caputo S, Damcti T, Liebl A, Ross SA. Weight benefits for type 2 diabetes. J Clin Endocrinol Metab. 2011;96(11):3337–53.

19. Foley JE, Jordan J. Weight neutrality with the DPP-4 inhibitor, vildagliptin: mechanistic basis and clinical experience. Vasc Health Risk Manag. 2010;6:541–8.

20. Kalra S, Kalra B, Unnikrishnan A, Agrawal N, Kumar S. Optimizing weight control in diabetes: antidiabetic drug selection. Diabetes, Metab Syndr Obes. 2010;3:297–9.

21. Karaca M, Magnan C, Kargar C. Functional pancreatic beta-cell mass: involvement in type 2 diabetes and therapeutic intervention. Diabetes Metab. 2009;35(2):77–84.

22. Maida A, Hansota T, Longuet C, Seino Y, Drucker DJ. Differential importance of glucose-dependent insulinotropic polypeptide vs glucagon-like peptide 1 receptor signaling for beta cell survival in mice. Gastroenterology. 2009;137(6):2146–57.

23. Takeda Y, Fujita Y, Honjo J, Yanagimachi T, Sakagami H, Takayama Y, Makino Y, Abiko A, Kieffer TJ, Haneda M. Reduction of both beta cell death and alpha cell proliferation by dipeptidyl peptidase-4 inhibition in a streptozotocin-induced model of diabetes in mice. Diabetologia. 2012;55(2):404–12.

24. Shirakawa J, Arno K, Ohminami H, Orime K, Tozawa T, Tajima K, Koganei M, Sasaki H, Takeda E, et al. Protective effects of dipeptidyl peptidase-4 (DPP-4) inhibitor against increased beta cell apoptosis induced by dietary sucrose and fructose in mice. Diabetes. 2011;60(8):2547–76.

25. Naganine A, Hasegawa H, Hashimoto N, Yamada-Inagawa T, Hirose M, Kobara Y, Tadokoro K, Kobayashi Y, Takanob H. The effects of DPP-4 inhibitor on hypoxia-induced apoptosis in human umbilical vein endothelial cells. J Pharm Sci. 2017;106(1):42–8.

26. Salim HM, Fukuda D, Higashikuni Y, Tanaka K, Hirata Y, Yagi S, Soeki T, Shimabukuro M, Sata M. Dipeptidyl peptidase-4 inhibitor, linagliptin, ameliorates endothelial dysfunction and atherogenesis in normoglycemic apolipoprotein-E deficient mice. Vasc Pharmacol. 2016;79:16–23.

27. Manrique C, Habibi J, Acoror AR, Sowers JR, Jia G, Hayden MR, Garro M, Martinez-Lemus LA, Ramirez-Perez FI, Klein T, et al. Dipeptidyl peptidase-4 inhibition with linagliptin prevents western diet-induced vascular abnormalities in female mice. Cardiovasc Diabetol. 2016;15:94.

28. Shah Z, Kampfrath T, Deulius JA, Zhong L, Pineda C, Ying Z, Xu X, Lu Y, Moffatt-Bruce S, Durairaj R, et al. Long-term dipeptidyl-peptidase-4 inhibition reduces atherosclerosis and inflammation via effects on monocyte recruitment and chemotaxis. Circulation. 2011;124(21):2338–49.

29. Hirano T, Yamashita S, Takanashi M, Hashimoto H, Mori Y, Goto M. Anaglifip, a dipeptidyl peptidase-4 inhibitor, decreases macrophage infiltration and suppresses atherosclerosis in aortic and coronary arteries in cholesterol-fed rabbits. Metabolism. 2016;65(6):893–903.

30. Salim HM, Fukuda D, Higashikuni Y, Tanaka K, Hirata Y, Yagi S, Soeki T, Shimabukuro M, Sata M. Teneligliptin, a dipeptidyl peptidase-4
inhibitor, attenuated pro-inflammatory phenotype of perivascular adi- pose tissue and inhibited atherogenesis in normoglycemic apolipo- protein-E-deficient mice. Vasc Pharmacol. 2017.

43. Brenner C, Franz WM, Kuhlenthal S, Kuschnerus K, Remm F, Gross L, Theiss HD, Landresser U, Krankel N. DPP-4 inhibition ameliorates atherosclerosis by priming monocytes into M2 macrophages. Int J Cardiol. 2015;199:163–9.

44. Shah Z, Pineda C, Kampfrath T, Maiseyeu A, Ying Z, Racorna I, Deilis J, Xu X, Sun Q, Moffatt-Bruece S, et al. Acute DPP-4 inhibition modulates vascular tone through GLP-1 independent pathways. Vasc Pharmacol. 2011;55(1):2–9.

45. Terasaki M, Hiromura M, Mori Y, Kohashi K, Kusam M, Ohara M, Watanabe T, Andersson O, Hirano T. Combination therapy with a sodium-glucose cotransporter 2 inhibitor and a dipeptidyl peptidase-4 inhibitor additively suppresses macrophage foam cell formation and atherosclerosis in diabetic mice. Int J Endocrinol. 2017;2017:1365209.

46. Kohashi K, Hiromura M, Mori Y, Terasaki M, Watanabe T, Kusama H, Shimura K, Tomoyasu T, Nishimura M, Hirano T. A dipeptidyl peptidase-4 inhibitor but not incretins suppresses abdominal aortic aneurysms in angiotensin II-infused apolipoprotein E-null mice. J Atheroscler Thromb. 2016;23(4):441–54.

47. Sauve M, Ban K, Momen MA, Zhou YQ, Henkelman RM, Husain M, Drucker DJ. Genetic deletion or pharmacological inhibition of dipep- tidyl peptidase-4 improves cardiovascular outcomes after myocardial infarction in mice. Diabetes. 2010;59(4):1063–73.

48. Murae H, Kuno A, Miki T, Tanno M, Yano T, Kouzu H, Ishikawa S, Tosiwasa T, Ogasawara M, Nishizawa K, et al. Inhibition of DPP-4 reduces acute mortality after myocardial infarction with restoration of autophagic response in type 2 diabetic rats. Cardiovasc Diabetol. 2015;14:103.

49. Ma M, Hasegawa Y, Kobuchi N, Toyama K, Ueki K, Nakagawa T, Lin B, Kim-Mitsuji S. DPP-4 inhibition with linagliptin ameliorates cognitive impairment and brain atrophy induced by transient cerebral ischemia in type 2 diabetic mice. Cardiovasc Diabetol. 2015;14:54.

50. Avogaro A, Fadini GP. The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications. Diabetes Care. 2014;37(10):2884–94.

51. Paia L, Roteilla CM. The role of DPP4 activity in cardiovascular diseases: in vivo and in vitro evidence. J Diabetes Res. 2013;2013:590456.

52. Mulvihill EE, Varin EM, Gladanac B, Campbell JE, Ussher JR, Baggio LL, Yanagimachi T, Fujita Y, Takeda Y, Honjo J, Sakagami H, Kitsunai H, Takiyama H, Shigeta T, Aoyama M, Bando YK, Monji A, Mitsui T, Takatsu M, Cheng Mudaliar U, Zabetian A, Goodman M, Echouffo-Tcheugui JB, Albright Bae EJ. DPP-4 inhibitors in diabetic complications: role of DPP-4 beyond cardiovascular effects and outcomes. Cardiovasc Diabetol. 2015;14:129.

53. Barberi M, Rizzo MR, Marrella F, Boccardi V, Esposito A, Pansini A, Paolillo G. Decreased cardiac atherosclerotic process by control of daily acute glucose fluctuations in diabetic patients treated by DPP-4 inhibitors. Atherosclerosis. 2013;227(2):349–54.

54. Mita T, Katakami N, Shriawa T, Yoshii H, Onuma T, Kuriyagawa N, Osanoi T, Kaneto H, Kosugi K, Umayahara Y, et al. Sitagliptin attenuates the progression of carotid intima-media thickening in insulin-treated patients with type 2 diabetes: the sitagliptin preventive study of intima-media thickness evaluation (SPIKE), a randomized controlled trial. Diabetes Care. 2016;39(3):455–64.

55. Mita T, Katakami N, Yoshii H, Onuma T, Kaneto H, Osanoi T, Shriawa T, Kosugi K, Umayahara Y, Yamamoto T, et al. Alogliptin, a dipeptidyl peptide-4 inhibitor, prevents the progression of carotid atherosclerosis in patients with type 2 diabetes: the study of preventive effects of alogliptin on diabetic atherosclerosis (SPEAD-A). Diabetes Care. 2016;39(1):139–48.

56. Ohira M, Yusta B, Ayala J, Burmeister MA, Matthews D, et al. Cellular sites and mechanisms underlying atheroprotection of sitagliptin by dipeptidyl peptidase-4 inhibition with potential anti-atherogenic properties. Endocr Res. 2015;40(2):88–96.

57. Ohira M, Yamaguchi T, Saiki A, Ban N, Kawana H, Nagayama D, Nagumo A, Murano H, Shirai K, Tatsuno I. Metformin reduces circulating malondialdehyde-modified low-density lipoprotein in type 2 diabetes mellitus. Clin Invest Med. 2014;37(4):E243–51.

58. Oyama J, Murohara T, Kitakaze M, Ishizu T, Sato Y, Kitagawa K, Kamiya H, Ajioka M, Ishihara M, Dai K, et al. The effect of sitagliptin on carotid artery atherosclerosis in type 2 diabetes: the PROLOGUE randomized controlled trial. PLoS Med. 2016;13(6):e1002051.

59. Tomiyama H, Miwa T, Kan K, Matsuhashi M, Kamiya H, Nanasato M, Kitano T, Sano H, Ohno J, Iida M, et al. Impact of glyemic control with sitagliptin on the 2-year progression of arterial stiffness: a sub-analysis of the PROLOGUE study. Cardiovasc Diabetol. 2016;15(1):150.

60. Maruhashi T, Higashi Y, Kihara Y, Yamada H, Sato M, Ueda S, Odawara M, Terauchi Y, Dai K, Ohno J, et al. Long-term effect of sitagliptin on endothelial function in type 2 diabetes: a sub-analysis of the PRO-LOGUE study. Cardiovasc Diabetol. 2016;15(1):134.

61. Nozue T, Fukushima T, Takamura T, Sotou T, Hibi K, Kishi S, Michishita I. Effects of alogliptin on fractional flow reserve evaluated by coronary computed tomography angiography in patients with type 2 diabetes: rationale and design of the TRACT study. J Cardiol. 2017;69(3):518–22.

62. van Poppel PC, Netea MG, Smits P, Tack CJ. Vildagliptin improves cardiovascular effects and outcomes. Cardiovasc Diabetol. 2015;14:129.

63. Nakamura K, Oe H, Kihara H, Shimada K, Fukuda S, Watanabe K, Takagi H. The effect of sitagliptin on the regression of carotid intima-media thickness in patients with type 2 diabetes mellitus: a post hoc analysis of the sitagliptin preventive study of intima-media thickness evaluation. Int J Endocrinol. 2017;2017:1925305.

64. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation. 2002;106(16):2085–90.

65. de Boer SA, Heerspink HJ, Juarez Orozco LE, van Roon AM, Kamphuisen PW, Ait SJ, Starth RH, Lefrandt JD, Mulder DJ. Effect of linagliptin on pulse wave velocity in early type 2 diabetes: a randomized, double-blind, controlled 26-week trial (RELEASE). Diabetes, Obes Metab. 2017;19:295–301.

66. Kutoh E, Kanekita N, Hiram M. Alogliptin: a new dipeptidyl peptidase-4 inhibitor with potential anti-atherogenic properties. Endocr Res. 2015;40(2):88–96.

67. Ohira M, Yamaguchi T, Saiki A, Ban N, Kawana H, Nagayama D, Nagumo A, Murano H, Shirai K, Tatsuno I. Metformin reduces circulating malondialdehyde-modified low-density lipoprotein in type 2 diabetes mellitus. Clin Invest Med. 2014;37(4):E243–51.

68. Oyama J, Murohara T, Kitakaze M, Ishizu T, Sato Y, Kitagawa K, Kamiya H, Ajioka M, Ishihara M, Dai K, et al. The effect of sitagliptin on carotid artery atherosclerosis in type 2 diabetes: the PROLOGUE randomized controlled trial. PLoS Med. 2016;13(6):e1002051.

69. Tomiyama H, Miwa T, Kan K, Matsuhashi M, Kamiya H, Nanasato M, Kitano T, Sano H, Ohno J, Iida M, et al. Impact of glyemic control with sitagliptin on the 2-year progression of arterial stiffness: a sub-analysis of the PROLOGUE study. Cardiovasc Diabetol. 2016;15(1):150.

70. Maruhashi T, Higashi Y, Kihara Y, Yamada H, Sato M, Ueda S, Odawara M, Terauchi Y, Dai K, Ohno J, et al. Long-term effect of sitagliptin on endothelial function in type 2 diabetes: a sub-analysis of the PROLOGUE study. Cardiovasc Diabetol. 2016;15(1):134.

71. Nozue T, Fukushima T, Takamura T, Sotou T, Hibi K, Kishi S, Michishita I. Effects of alogliptin on fractional flow reserve evaluated by coronary computed tomography angiography in patients with type 2 diabetes: rationale and design of the TRACT study. J Cardiol. 2017;69(3):518–22.

72. van Poppel PC, Netea MG, Smits P, Tack CJ. Vildagliptin improves cardiovascular effects and outcomes. Cardiovasc Diabetol. 2015;14:129.
Kurose T, Hamamoto Y, Seino Y. Evaluation of large-scale clinical trials on cardiovascular disease risk in patients with type 2 diabetes mellitus treated with DPP-4 inhibitors and new class of drugs. J Diabetes Investig. 2017.

Rehman MB, Toudre BV, Soustre J, Buisson M, Arthambault P, Pouchain D, Vaillant-Rouset H, Gueyffier F, Faillie JL, Perault-Pochat MC, et al. Efficacy and safety of DPP-4 inhibitors in patients with type 2 diabetes: meta-analysis of placebo-controlled randomized clinical trials. Diabetes Metab. 2017;43(1):48–58.

Fitchett DH, Udel JA, Inzucchi SE. Heart failure outcomes in clinical trials of glucose-lowering agents in patients with diabetes. Eur J Heart Fail. 2017;19(1):43–53.

Mannucci E, Monami M. Cardiovascular safety of incretin-based therapies in type 2 diabetes: systematic review of integrated analyses and randomized controlled trials. Adv Ther. 2017;34(1):1–40.

Gupta P, White WB. Cardiovascular safety of therapies for type 2 diabetes. Expert Opin Drug Saf. 2017;16(1):13–25.

White WB, Cannon CP, Heller SR, Nissen SE, Bergenstald RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupper S, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327–35.

Scirica BM, Bhatt DL, Wiviott SD, Hoffman EB, et al. Saxagliptin and alogliptin, attenuates arterial inflammation and neointimal formation after injury in low-density lipoprotein (LDL) receptor-deficient mice. J Am Heart Assoc. 2015;4(3):e001469.

Lutz TA, Osto E. Glucagon-like peptide-1, glucagon-like peptide-2, and lipid metabolism. Curr Opin Lipidol. 2016;27(3):257–63.

Duvnjak L, Blaslov K. Dipeptidyl peptidase-4 inhibitors improve arterial stiffness, blood pressure, lipid profile and inflammation parameters in patients with type 2 diabetes mellitus. Diabetol Metab Syndr. 2016;8:26.

Furuhashi M, Hiramitsu S, Mita T, Fuyese T, Ishimura S, Omiro A, Matsuno M, Watanabe Y, Hoshina K, Tanaka M, et al. Reduction of serum FABP4 level by saxagliptin, a DPP-4 inhibitor, in patients with type 2 diabetes mellitus. J Lipid Res. 2015;56(12):2372–80.

Xiao C, Dash S, Morgantini C, Patterson BW, Lewis GF. Sitagliptin, a DPP-4 inhibitor, acutely inhibits intestinal lipoprotein particle secretion in healthy humans. Diabetes. 2014;63(7):2394–401.

Ahn CH, Kim EK, Min SH, Oh TJ, Cho YM. Effects of gemigliptin, a dipeptidyl peptidase-4 inhibitor, on lipid metabolism and endotoxemia after a high-fat meal in patients with type 2 diabetes. Diabetes Obes Metab. 2017;19(3):457–62.

Eliasson B, Moller-Goede D, Egg-Olofssson K, Wilson C, Cederholm J, Fleck P, Diamant M, Taskinen MR, Smith U. Lowering of postprandial lipids in individuals with type 2 diabetes treated with alogliptin and/or pioglitazone: a randomized double-blind placebo-controlled study. Diabetologia. 2012;55(4):915–25.

Matkainen N, Manttari S, Schwezer A, Ulvestad A, Mills D, Dunning BE, Foley JE, Taskinen MR. Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes. Diabetologia. 2006;49(9):2049–57.

Tremblay AJ, Lamarche B, Deacon CF, Weisnagel SJ, Couture P. Effect of sitagliptin therapy on postprandial lipoprotein levels in patients with type 2 diabetes. Diabetes Obes Metab. 2011;13(4):366–73.

Noda Y, Miyoshi T, Oh E, Ohno Y, Nakamura K, Toh N, Kohno K, Morita H, Kusano K, Ito H. Alogliptin ameliorates postprandial lipemia and postprandial endothelial dysfunction in non-diabetic subjects: a preliminary report. Cardiovasc Diabetol. 2013;12:8.

Zhou X, Huang GH, Lao J, Poca I, Forrest G, Price O, Roy S, Kelley DE, Sullivan KA, Forrest MJ. Acute hemodynamic and renal effects of glaglucon-like peptide 1 and analog and dipeptidyl peptidase-4 inhibitor in rats. Cardiovasc Diabetol. 2015;14:29.

Lutz TA, Osto E. Glucagon-like peptide-1, glucagon-like peptide-2, and lipid metabolism. Curr Opin Lipidol. 2016;27(3):257–63.

Noda Y, Miyoshi T, Oh E, Ohno Y, Nakamura K, Toh N, Kohno K, Morita H, Kusano K, Ito H. Alogliptin ameliorates postprandial lipemia and postprandial endothelial dysfunction in non-diabetic subjects: a preliminary report. Cardiovasc Diabetol. 2013;12:8.

Zhou X, Huang GH, Lao J, Poca I, Forrest G, Price O, Roy S, Kelley DE, Sullivan KA, Forrest MJ. Acute hemodynamic and renal effects of glaglucon-like peptide 1 and analog and dipeptidyl peptidase-4 inhibitor in rats. Cardiovasc Diabetol. 2015;14:29.

Musiket SM, Smits WM, Morsink LM, Diamant M. The gut-renal axis: do incretin-based agents confer renoprotection in diabetes? Nat Rev Nephrol. 2014;10(2):188–103.

Chan NY, Seyedi N, Takano K, Levi R. An unsuspected property of natriuretic peptides: promotion of calcium-dependent catecholamine release via protein kinase G-mediated phosphodiesterase type 3 inhibition. Circulation. 2012;125(2):298–307.

Devlin JK, Prentous M, Nian H, Yu C, Billings FTR, Brown NJ. Dipeptidylpeptidase-4 inhibition and the vascular effects of glaglucon-like peptide-1 and brain natriuretic peptide in the human forearm. J Am Heart Assoc. 2014;3(4):e001075.

Devlin JK, Prentous M, Nian H, Yu C, Billings FTR, Brown NJ. Substance P increases sympathetic activity during combined angiotensin-converting enzyme and dipeptidylpeptidase-4 inhibition. Hypertension. 2014;63(5):951–7.

Ishii M, Shibata R, Kondo K, Kambara T, Shimizu Y, Tanigawa T, Bando YK, Nishimura M, Ouchi N, Murohara T. Vildagliptin stimulates endothelial cell network formation and ischemia-induced vasorelaxation via an endothelial nitric-oxide synthase-dependent mechanism. J Biol Chem. 2014;289(39):27235–45.

Kim M, Platt MJ, Shibaba T, Quaggin SE, Backx PH, Seino S, Simpson JA, Drucker DJJ. GLP-1 receptor activation and Epac2 link atypical natriuretic peptide secretion to control of blood pressure. Nat Med. 2013;19(5):567–75.

Gardiner SM, March JE, Kemp PA, Bennett T. Mesenteric vasoconstriction and hindquarters vasoconstriction accompany the pressor actions of exendin-4 in conscious rats. J Pharmacol Exp Ther. 2006;316(2):852–9.

Mulgrew EE, Vann EM, Uszler JR, Campbell JE, Bang KW, Abdullah T, Baggio LL, Drucker DJ. Inhibition of dipeptidyl peptidase-4 impairs ventricular function and promotes cardiac fibrosis in high fat-fed diabetic mice. Diabetes. 2016;65(3):742–54.