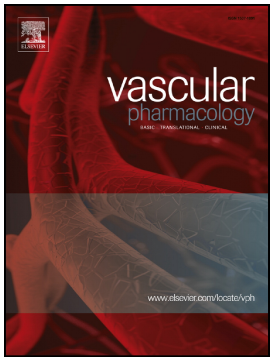

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EDITORIAL

Dipeptidyl peptidase IV inhibitors as novel regulators of vascular disease

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Abstract

Dipeptidyl peptidase IV (DPP-IV) has been revealed as an adipokine with potential relevance in cardiovascular disease (CVD), while clinically used DPP-IV inhibitors have demonstrated beneficial cardiovascular effects in several experimental studies. Perivascular adipose tissue (PVAT) is a unique adipose tissue depot in close anatomical proximity and bidirectional functional interaction with the vascular wall, which is a source of DPP-IV and its biology may be influenced by DPP-IV inhibition. Recently, DPP-IV inhibition has been associated with decreased local inflammation and oxidative stress both in the vascular wall and the PVAT, potentially regulating atherogenesis progression *in vivo*. DPP-IV inhibition may thus be a promising target in cardiovascular disease. However, the exact pleiotropic mechanisms that underlie the cardiovascular effects of DPP-IV inhibition need to be clarified, while the *in vivo* benefit of DPP-IV inhibition in humans remains unclear.

Key words: atherosclerosis; oxidative stress; perivascular adipose tissue; DPP-IV inhibitors

Type 2 Diabetes Mellitus (T2DM) is a metabolic disease that is closely associated with an increased rate of cardiovascular morbidity and mortality [1, 2]. Over the past years, research has identified novel regulators of hyperglycaemia, allowing for efficient glycaemic control in diabetic patients [3]. However, cardiovascular complications are still prevalent in diabetic patients, whereas successful glycaemic control is often not adequate to prevent these complications [4]. As such, there is an unmet need to identify novel agents able to regulate blood glucose while also conveying protective cardiovascular effects in diabetic patients.

Dipeptidyl peptidase IV (DPP-IV) is an enzyme cleaving dipeptides from the N-terminal end of a variety of peptides containing proline or alanine residues in the penultimate position, which may affect the activity of the latter in either positive or negative ways [5]. DPP-IV has a small cytoplasmic region, a transmembrane part as well as a large C-terminal portion which harbours its catalytic domain [6]. DPP-IV exists both as a circulating isoform (lacking its small transmembrane portion) and as a transmembrane surface enzyme in various cell types including endothelial cells, adipocytes and immune cells in humans [7, 8]. The integrated regulation of DPP-IV activity in individual cell types versus the systemic circulation is unknown, although it has been shown that activation of particular cell types (e.g., inflammatory activation of immune cells) is able to upregulate DPP-IV activity in these cells [6].

DPP-IV exerts multiple physiological roles that mainly depend upon its enzymatic activity but also on its non-enzymatic co-interaction with extracellular matrix proteins [6]. For example, DPP-IV is able to modify the activity of various chemokines and cytokines such as RANTES, stromal cell-derived factor 1 (SDF-1) and interleukin 10 (IL-10), eventually regulating leukocyte migration and activation of immune and endothelial cells [6, 9, 10]. Considering the integral role of systemic inflammation in diseases such as central obesity [2, 11], T2DM and cardiovascular disease (CVD), it is plausible to hypothesise that DPP-IV is able, on the basis of its aforementioned properties, to modulate multiple disease states [6, 12].

The ability of DPP-IV to regulate the systemic activity of glucagon-like peptide-1 (GLP-1) is perhaps its most clinically relevant role at present [13]. GLP-1 is an endogenous incretin secreted mainly by the intestine that increases pancreatic insulin secretion, decreases glucagon secretion and may improve peripheral insulin sensitivity, thus attracting interest as a potential target in the treatment of T2DM [14]. Importantly, DPP-IV enzymatically modifies GLP-1, facilitating its degradation and reducing their bioavailability [15]. Inhibition of DPP-IV activity via DPP-IV inhibitors has been proposed as a strategy to control systemic glucose levels in diabetic patients [5]. Indeed, DPP-IV has been suggested as a pathophysiological link between obesity and the metabolic syndrome [12]. Furthermore, dendritic DPP-IV expression has been implicated in obesity associated visceral adipose tissue inflammation [16].

Amongst their plethora of pleiotropic effects, DPP-IV inhibitors have revealed direct cardiovascular roles that are, at least partially, independent of their glucose-lowering abilities [7, 13]. Indeed, DPP-IV inhibitors have revealed direct cardiovascular effects including attenuation of vascular inflammation, blood pressure lowering, endothelial function improvement and oxidative stress reduction [6, 7, 17]. Although GLP-1 and related analogues have displayed similar effects in *in vitro* and *ex vivo* models [18-20], evidence suggests that some of the effects of DPP-IV inhibition appear to be independent of GLP-1 regulation [7]. Interestingly, DPP-IV also inactivates brain natriuretic peptide (BNP), a peptide with vaso- and cardio-protective properties, thus providing another potential mechanistic link with CVD [6]. The clinical implications of the aforementioned findings are still uncertain, while more mechanistic details are required regarding the cardiovascular effects of DPP-IV; nevertheless, this molecule appears to be a promising target for future research in the combat against vascular disease, especially in the context of T2DM.

Perivascular adipose tissue (PVAT) is unique adipose tissue (AT) depot that is in continuous paracrine mutual interactions with the vascular wall due to its anatomical location [21-23].

Recent literature has identified PVAT as a dynamic source of secreted adipokines and cytokines which directly influence vascular biology [24]. Crucially, the secretome of PVAT is dysregulated in obesity and vascular disease, producing excess amounts of pro-inflammatory and pro-atherogenic molecules[25]. This shift in the secretory profile of PVAT is presumably initiated by local perivascular inflammation resulting from endothelial injury [25, 26]. Although much remains to be elucidated regarding the secretome of PVAT and its complex regulation, further investigation of the dynamic role of PVAT in vascular disease may reveal novel diagnostic, prognostic or therapeutic options against vascular disease.

PVAT secretes DPP-IV which can then directly exert its previously described effects on the vasculature [24]. In addition, PVAT itself is subject to the effects of and DPP-IV activity [24]. A variety of DPP-IV inhibitors have been shown to reduce AT inflammation in response to high carbohydrate and fatty acid diet as well as in chronic obesity in mouse models [27-29]. Furthermore, DPP-IV may have lipolytic effects on AT, which could be involved in the secretion of free fatty acids that promote systemic insulin resistance [30]. Interestingly, AT also secretes low levels of GLP-1, which reduces lipid accumulation [31], increases the expression of the vasoprotective hormone adiponectin [32] and promotes M2 macrophage polarisation in AT [33]. The detrimental effects of DPP-IV in AT may thus be GLP-1-dependent, although it is possible that pleiotropic, non-GLP-1-dependent mechanisms are involved [12, 30].

In their recent study, HM Salim *et al* [34] have investigated the effects of teneligliptin (a DPP-IV inhibitor) on the phenotype of PVAT and ultimately on atherogenesis in a model of normoglycaemic apolipoprotein-E-deficient mice (ApoE-/- mice). In detail, oral administration of teneligliptin (60 mg/kg/day) resulted in decreased atherosclerotic lesion burden in the aortic arch without influencing systemic parameters such as blood glucose and blood pressure. Furthermore, teneligliptin also reduced lipid accumulation and monocyte chemoattractant

protein 1 (MCP-1) expression in the atherosclerotic lesions and decreased tumour necrosis factor alpha (TNFα) and MCP-1 in the abdominal aorta. Moreover, teneligliptin improved endothelium-dependent vasorelaxation *ex vivo* and decreased systemic oxidative stress evaluated by urinary 8-hydroxy-2'-deoxyguanosine. Finally, teneligliptin reduced the expression of the Nox4 isoform of NADPH-oxidases in PVAT. Exendin-4, a GLP-1 analogue, reduced the expression of inflammatory markers and Nox4 in *in vitro* cell culture models, suggesting that the *in vivo* effects of teneligliptin could be, at least partially, explained by its regulating GLP-1 activity. In summary, the findings by Salim *et al* [34] propose novel anti-inflammatory and anti-oxidant roles for teneligliptin in the vasculature and PVAT, with promising translational potential (fig. 1).

The study by Salim *et al* highlights the anti-oxidant and anti-inflammatory roles for DPP-IV inhibitors, which could be of clinical benefit by affecting vascular disease pathogenesis. Indeed, a number of DPP-IV inhibitors have demonstrated direct antioxidant effects in tissues such as the kidney, heart and vessels [35, 36]. In particular, DPP-IV inhibition is able to improve endothelium-dependent vasorelaxations in animal *ex vivo* models [36, 37], while reducing vascular NADPH-oxidase activity and expression [38, 39] and overall oxidative stress as suggested by vascular malondialdehyde levels [40]. Through modulation of cytokine and chemokine activity and T cell activation [7, 16], DPP-IV inhibitors are also able to modulate vascular and AT inflammation [7, 8, 28, 41]. In an *in vivo* mouse model of atherosclerosis, sitagliptin has displayed the ability to downregulate aortic inflammation (suggested by the reduced aortic expression of MCP-1 and interleukin 6 (IL-6)) and atherosclerosis burden [42]. Moreover, DPP-IV inhibition has been shown to inhibit the proliferation of vascular smooth muscle cells, further protecting against atherosclerosis [43]. Interestingly, GLP-1 and its analogues have demonstrated vascular effects that resemble those of DPP-IV, namely the ability to decrease vascular inflammation and production of reactive oxygen species while

improving endothelial function [13, 20]. Consequently, although it seems evident that modulation of the incretin system has direct vascular implications, the existing literature regarding the vascular effects of DPP-IV inhibitions fails to clearly separate the contribution of GLP-1 versus other substrates of DPP-IV such as brain natriuretic peptide, neuropeptides and cytokines [7].

The clinical relevance of the incretin system, in terms of cardiovascular outcomes, comprises another major issue under investigation. On the basis of pre-clinical and small-scale clinical studies [17, 44], large clinical trials have been performed to test the use of various DPP-IV inhibitors [45, 46]. Unfortunately, most of these trials have failed to reveal a significant benefit of DPP-IV inhibitors for cardiovascular risk [45, 46]. On the contrary, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial has demonstrated that the GLP-1 analogue liraglutide is able to significantly reduce cardiovascular risk [47]. Therefore, it can be presumed that modulation of the incretin system may indeed be useful in cardiovascular disease [48]; however, direct stimulation of the GLP-1 pathway seems more effective than upstream regulation of DPP-IV in reducing the incidence of adverse cardiovascular outcomes [48]. However, considering that the majority of the aforementioned trials were basically safety trials primarily designed to show non-inferiority versus placebo, it is possible that statistical parameters of individual studies may underestimate the clinical effect of DPP-IV inhibition [48]. On the other hand, the variety of substrates cleaved by DPP-IV challenges our understanding of the integrated effects of DPP-IV inhibition, adding a strong element of inherent biological variability in the cited clinical studies [7, 48]. The wide spectrum of the biological effects of DPP-IV inhibitors may also increase the risk for non-specific side-effects [49], while it could also be responsible for the possibly increased heart failure risk observed with some DPP-IV inhibitors [50].

In summary, this study by Salim *et al* [34] have investigated the *in vivo* cardiovascular effects of DPP-IV inhibition, topic that is both highly promising and controversial. Using an ApoE-/- mouse model, Salim *et al* have demonstrated that administration of teneligliptin results in a variety of beneficial effects including inhibition of inflammation and oxidative stress in both the vasculature and PVAT, ultimately reducing atherosclerosis progression. Conversely, a lot remains to be elucidated regarding the differential cardiovascular effects of individual DPP-IV inhibitors versus GLP-1 analogues as well as with regards to the potential clinical implications of such effects. Nevertheless, the study by Salim *et al* is an important addition to the growing body of evidence supporting a beneficial cardiovascular role for DPP-IV inhibitors that warrants further investigation.

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Conflict of interest

None

References

[1] J.A. Beckman, M.A. Creager, Vascular Complications of Diabetes, Circulation research 118(11) (2016) 1771-85.
[2] A.S. Antonopoulos, E.K. Oikonomou, C. Antoniades, D. Tousoulis, From the BMI paradox to the obesity paradox: the obesity-mortality association in coronary heart disease, Obes Rev 17(10) (2016) 989-1000.
[3] p.-d. Task Force on diabetes, C. cardiovascular diseases of the European Society of, D. European Association for the Study of, L. Ryden, P.J. Grant, S.D. Anker, C. Berne, F. Cosentino, N. Danchin, C. Deaton, J. Escaned, H.P. Hammes, H. Huikuri, M. Marre, N. Marx, L. Mellbin, J. Ostergren, C. Patrono, P. Seferovic, M.S. Uva, M.R. Taskinen, M. Tendera, J. Tuomilehto, P. Valensi, J.L. Zamorano, ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD - summary, Diab Vasc Dis Res 11(3) (2014) 133-73.
[4] E. Mannucci, S. Giannini, I. Dicembrini, Cardiovascular effects of basal insulins, Drug Healthc Patient Saf 7 (2015) 113-20.
[5] D. Dicker, DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors, Diabetes care 34 Suppl 2 (2011) S276-8.
[6] J. Zhong, X. Rao, S. Rajagopalan, An emerging role of dipeptidyl peptidase 4 (DPP4) beyond glucose control: potential implications in cardiovascular disease, Atherosclerosis 226(2) (2013) 305-14.
[7] G.P. Fadini, A. Avogaro, Cardiovascular effects of DPP-4 inhibition: beyond GLP-1, Vascul Pharmacol 55(1-3) (2011) 10-6.
[8] L. Badimon, J. Cubedo, Adipose tissue depots and inflammation: effects on plasticity and resident mesenchymal stem cell function, Cardiovasc Res (2017).
[9] G. Vilahur, S. Ben-Aicha, L. Badimon, New insights into the role of adipose tissue in thrombosis, Cardiovasc Res (2017).
[10] O. Sorop, T.D. Olver, J. van de Wouw, I. Heinonen, R.W. van Duin, D.J. Duncker, D. Merkus, The microcirculation: a key player in obesity-associated cardiovascular disease, Cardiovasc Res (2017).
[11] A.S. Antonopoulos, C. Antoniades, The role of epicardial adipose tissue in cardiac biology: classic concepts and emerging roles, J Physiol (2017).
[12] D. Lamers, S. Famulla, N. Wronkowitz, S. Hartwig, S. Lehr, D.M. Ouwens, K. Eckardt, J.M. Kaufman, M. Ryden, S. Muller, F.G. Hanisch, J. Ruige, P. Arner, H. Sell, J. Eckel, Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic syndrome, Diabetes 60(7) (2011) 1917-25.
[13] J.R. Ussher, D.J. Drucker, Cardiovascular biology of the incretin system, Endocr Rev 33(2) (2012) 187-215.
[14] J.M. Trujillo, W. Nuffer, S.L. Ellis, GLP-1 receptor agonists: a review of head-to-head clinical studies, Ther Adv Endocrinol Metab 6(1) (2015) 19-28.
[15] A.M. Lambeir, C. Durinx, S. Scharpe, I. De Meester, Dipeptidyl-peptidase IV from bench to bedside: an update on structural properties, functions, and clinical aspects of the enzyme DPP IV, Crit Rev Clin Lab Sci 40(3) (2003) 209-94.
[16] J. Zhong, X. Rao, J. Deiuliis, Z. Braunstein, V. Narula, J. Hazey, D. Mikami, B. Needleman, A.R. Satoskar, S. Rajagopalan, A potential role for dendritic cell/macrophage-expressing DPP4 in obesity-induced visceral inflammation, Diabetes 62(1) (2013) 149-57.
[17] A. Solini, C. Rossi, E. Duranti, S. Taddei, A. Natali, A. Virdis, Saxagliptin prevents vascular remodeling and oxidative stress in db/db mice. Role of endothelial nitric oxide synthase uncoupling and cyclooxygenase, Vascul Pharmacol 76 (2016) 62-71.
[18] A. Shiraki, J. Oyama, H. Komoda, M. Asaka, A. Komatsu, M. Sakuma, K. Kodama, Y. Sakamoto, N. Kotooka, T. Hirase, K. Node, The glucagon-like peptide 1 analog liraglutide reduces TNF-alpha-induced oxidative stress and inflammation in endothelial cells, Atherosclerosis 221(2) (2012) 375-82.

[19] K. Ban, M.H. Noyan-Ashraf, J. Hoefer, S.S. Bolz, D.J. Drucker, M. Husain, Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways, Circulation 117(18) (2008) 2340-50.
[20] T. Okerson, R.J. Chilton, The cardiovascular effects of GLP-1 receptor agonists, Cardiovascular therapeutics 30(3) (2012) e146-55.
[21] A.S. Antonopoulos, M. Margaritis, P. Coutinho, J. Digby, R. Patel, C. Psarros, N. Ntusi, T.D. Karamitsos, R. Lee, R. De Silva, M. Petrou, R. Sayeed, M. Demosthenous, C. Bakogiannis, P.B. Wordsworth, D. Tousoulis, S. Neubauer, K.M. Channon, C. Antoniades, Reciprocal effects of systemic inflammation and brain natriuretic peptide on adiponectin biosynthesis in adipose tissue of patients with ischemic heart disease, Arteriosclerosis, thrombosis, and vascular biology 34(9) (2014) 2151-9.
[22] M. Margaritis, A.S. Antonopoulos, J. Digby, R. Lee, S. Reilly, P. Coutinho, C. Shirodaria, R. Sayeed, M. Petrou, R. De Silva, S. Jalilzadeh, M. Demosthenous, C. Bakogiannis, D. Tousoulis, C. Stefanadis, R.P. Choudhury, B. Casadei, K.M. Channon, C. Antoniades, Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels, Circulation 127(22) (2013) 2209-21.
[23] L. Woodward, I. Akoumianakis, C. Antoniades, Unravelling the adiponectin paradox: novel roles of adiponectin in the regulation of cardiovascular disease, British journal of pharmacology (2016).
[24] I. Akoumianakis, A. Tarun, C. Antoniades, Perivascular adipose tissue as a regulator of vascular disease pathogenesis: identifying novel therapeutic targets, Br J Pharmacol (2016).
[25] I. Akoumianakis, C. Antoniades, The interplay between adipose tissue and the cardiovascular system: is fat always bad?, Cardiovasc Res (2017).
[26] H. Abu Bakar, W.R. Dunn, C. Daly, V. Ralevic, Sensory innervation of perivascular adipose tissue: a crucial role in artery vasodilatation and leptin release, Cardiovasc Res (2017).
[27] J. Shirakawa, H. Fujii, K. Ohnuma, K. Sato, Y. Ito, M. Kaji, E. Sakamoto, M. Koganei, H. Sasaki, Y. Nagashima, K. Amo, K. Aoki, C. Morimoto, E. Takeda, Y. Terauchi, Diet-induced adipose tissue inflammation and liver steatosis are prevented by DPP-4 inhibition in diabetic mice, Diabetes 60(4) (2011) 1246-57.
[28] A.D. Dobrian, Q. Ma, J.W. Lindsay, K.A. Leone, K. Ma, J. Coben, E.V. Galkina, J.L. Nadler, Dipeptidyl peptidase IV inhibitor sitagliptin reduces local inflammation in adipose tissue and in pancreatic islets of obese mice, Am J Physiol Endocrinol Metab 300(2) (2011) E410-21.
[29] B. Icli, M.W. Feinberg, MicroRNAs in dysfunctional adipose tissue: Cardiovascular implications, Cardiovasc Res (2017).
[30] K. Kos, A.R. Baker, M. Jernas, A.L. Harte, J.C. Clapham, J.P. O'Hare, L. Carlsson, S. Kumar, P.G. McTernan, DPP-IV inhibition enhances the antilipolytic action of NPY in human adipose tissue, Diabetes Obes Metab 11(4) (2009) 285-92.
[31] J.J. Meier, GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus, Nat Rev Endocrinol 8(12) (2012) 728-42.
[32] T. Kim Chung le, T. Hosaka, M. Yoshida, N. Harada, H. Sakaue, T. Sakai, Y. Nakaya, Exendin-4, a GLP-1 receptor agonist, directly induces adiponectin expression through protein kinase A pathway and prevents inflammatory adipokine expression, Biochem Biophys Res Commun 390(3) (2009) 613-8.
[33] D. Shiraishi, Y. Fujiwara, Y. Komohara, H. Mizuta, M. Takeya, Glucagon-like peptide-1 (GLP-1) induces M2 polarization of human macrophages via STAT3 activation, Biochem Biophys Res Commun 425(2) (2012) 304-8.
[34] H.M. Salim, D. Fukuda, Y. Higashikuni, K. Tanaka, Y. Hirata, S. Yagi, T. Soeki, M. Shimabukuro, M. Sata, Teneligliptin, a dipeptidyl peptidase-4 inhibitor, attenuated pro-inflammatory phenotype of perivascular adipose tissue and inhibited atherogenesis in normoglycemic apolipoprotein-E-deficient mice, Vascul Pharmacol (2017).
[35] M.A. Alam, M.R. Chowdhury, P. Jain, M.A. Sagor, H.M. Reza, DPP-4 inhibitor sitagliptin prevents inflammation and oxidative stress of heart and kidney in two kidney and one clip (2K1C) rats, Diabetol Metab Syndr 7 (2015) 107.

[36] L. Liu, J. Liu, X.Y. Tian, W.T. Wong, C.W. Lau, A. Xu, G. Xu, C.F. Ng, X. Yao, Y. Gao, Y. Huang, Uncoupling protein-2 mediates DPP-4 inhibitor-induced restoration of endothelial function in hypertension through reducing oxidative stress, Antioxid Redox Signal 21(11) (2014) 1571-81.
[37] S.M. Salheen, U. Panchapakesan, C.A. Pollock, O.L. Woodman, The Dipeptidyl Peptidase-4 Inhibitor Linagliptin Preserves Endothelial Function in Mesenteric Arteries from Type 1 Diabetic Rats without Decreasing Plasma Glucose, PloS one 10(11) (2015) e0143941.
[38] G. Pujadas, V. De Nigris, F. Prattichizzo, L. La Sala, R. Testa, A. Ceriello, The dipeptidyl peptidase-4 (DPP-4) inhibitor teneligliptin functions as antioxidant on human endothelial cells exposed to chronic hyperglycemia and metabolic high-glucose memory, Endocrine (2016).
[39] N. Koibuchi, Y. Hasegawa, T. Katayama, K. Toyama, K. Uekawa, D. Sueta, H. Kusaka, M. Ma, T. Nakagawa, B. Lin, S. Kim-Mitsuyama, DPP-4 inhibitor linagliptin ameliorates cardiovascular injury in salt-sensitive hypertensive rats independently of blood glucose and blood pressure, Cardiovasc Diabetol 13 (2014) 157.
[40] S. Takai, H. Sakonjo, D. Jin, Significance of vascular dipeptidyl peptidase-4 inhibition on vascular protection in Zucker diabetic fatty rats, J Pharmacol Sci 125(4) (2014) 386-93.
[41] A.S. Antonopoulos, D. Tousoulis, The molecular mechanisms of obesity paradox, Cardiovasc Res (2017).
[42] Y. Zeng, C. Li, M. Guan, Z. Zheng, J. Li, W. Xu, L. Wang, F. He, Y. Xue, The DPP-4 inhibitor sitagliptin attenuates the progress of atherosclerosis in apolipoprotein-E-knockout mice via AMPK- and MAPK-dependent mechanisms, Cardiovasc Diabetol 13 (2014) 32.
[43] N. Ervinna, T. Mita, E. Yasunari, K. Azuma, R. Tanaka, S. Fujimura, D. Sukmawati, T. Nomiyama, A. Kanazawa, R. Kawamori, Y. Fujitani, H. Watada, Anagliptin, a DPP-4 inhibitor, suppresses proliferation of vascular smooth muscles and monocyte inflammatory reaction and attenuates atherosclerosis in male apo E-deficient mice, Endocrinology 154(3) (2013) 1260-70.
[44] A.J. Scheen, Cardiovascular effects of gliptins, Nat Rev Cardiol 10(2) (2013) 73-84.
[45] J.B. Green, M.A. Bethel, P.W. Armstrong, J.B. Buse, S.S. Engel, J. Garg, R. Josse, K.D. Kaufman, J. Koglin, S. Korn, J.M. Lachin, D.K. McGuire, M.J. Pencina, E. Standl, P.P. Stein, S. Suryawanshi, F. Van de Werf, E.D. Peterson, R.R. Holman, T.S. Group, Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 373(3) (2015) 232-42.
[46] B.M. Scirica, D.L. Bhatt, E. Braunwald, P.G. Steg, J. Davidson, B. Hirshberg, P. Ohman, R. Frederich, S.D. Wiviott, E.B. Hoffman, M.A. Cavender, J.A. Udell, N.R. Desai, O. Mosenzon, D.K. McGuire, K.K. Ray, L.A. Leiter, I. Raz, S.-T.S. Committee, Investigators, Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus, N Engl J Med 369(14) (2013) 1317-26.
[47] S.P. Marso, G.H. Daniels, K. Brown-Frandsen, P. Kristensen, J.F. Mann, M.A. Nauck, S.E. Nissen, S. Pocock, N.R. Poulter, L.S. Ravn, W.M. Steinberg, M. Stockner, B. Zinman, R.M. Bergenstal, J.B. Buse, L.S. Committee, L.T. Investigators, Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 375(4) (2016) 311-22.
[48] E. Mannucci, O. Mosenzon, A. Avogaro, Analyses of Results From Cardiovascular Safety Trials With DPP-4 Inhibitors: Cardiovascular Outcomes, Predefined Safety Outcomes, and Pooled Analysis and Meta-analysis, Diabetes care 39 Suppl 2 (2016) S196-204.
[49] A.S. Abbas, H.M. Dehbi, K.K. Ray, Cardiovascular and non-cardiovascular safety of dipeptidyl peptidase-4 inhibition: a meta-analysis of randomized controlled cardiovascular outcome trials, Diabetes Obes Metab 18(3) (2016) 295-9.
[50] P. Clifton, Do dipeptidyl peptidase IV (DPP-IV) inhibitors cause heart failure?, Clin Ther 36(12) (2014) 2072-9.

Table 1: Representative targets of DPP-IV

Molecular target	Biological roles	Effect of DPP-IV
GLP-1	Improves insulin sensitivity; increases pancreatic insulin secretion; lowers blood glucose	Inactivates
GIP	Regulates gastrointestinal physiology; has insulinotropic properties; participates to lipid metabolism	Inactivates
PYY	Regulates appetite and food intake, thus being relevant in metabolic disease, e.g., T2DM	Both cleaved segments that are differentially active depending on tissue/receptor
RANTES	Chemokine involved in leukocyte recruitment and activation of various cells, e.g., NK cells, CD8+ T cells	Inactivates
SDF-1	Strong chemoattractant that also induces angiogenesis in adults	Inactivates
IL-10	Pleiotropic, immunoregulatory cytokine with anti-inflammatory roles	Inactivates
BNP	Insulin-sensitising, natriuretic, vasodilatory and blood pressure-lowering effects	May inactivate

DPP-IV: Dipeptidyl peptidase IV; GLP-1: Glucagon-like peptide 1; GIP: Gastric inhibitory polypeptide; PYY: Peptide YY; RANTES: Regulated on activation, normal T cell expressed and secreted; SDF-1: Stromal cell-derived factor 1; IL-10: Interleukin 10; BNP: Brain natriuretic peptide

Legend to Figure 1

Graphical abstract of the potential *in vivo* vascular effects of dipeptidyl peptidase IV (DPP-IV) inhibitors such as teneligliptin. DPP-IV inhibition has been associated with decreased lipid accumulation, monocyte/macrophage content and inflammatory molecule expression (such as monocyte chemoattractant protein 1 (MCP1 and tumour necrosis factor alpha (TNFα)) in the vasculature. DPP-IV inhibition also improves endothelial function as evidenced by assessment of vascular endothelium. In addition, DPP-IV inhibition decreases inflammation (evaluated by the expression of MCP1 and TNFα) and oxidative stress (indicated by the expression of the Nox4 isoform of the nicotinamide adenine dinucleotide phosphate (NADPH)-oxidases) in perivascular adipose tissue (PVAT), an adipose tissue depot that is in continuous mutual communication with the vascular wall and modulates vascular disease. These effects may partially be mediated via the modulation of local and systemic glucagon-like peptide 1 (GLP-1) activity. However, DPP-IV also modifies the function of various substrates such as the immune-modulatory stromal cell-derived factor 1 (SDF-1), the anti-inflammatory interleukin 10 (IL-10) and the vasoprotective brain natriuretic peptide (BNP). Therefore, regulation of DPP-IV activity may be able to influence vascular function in pleiotropic ways, which have not been elucidated yet.