DPP4 in Cardiometabolic Disease
Recent Insights From the Laboratory and Clinical Trials of DPP4 Inhibition

Jixin Zhong, Andrei Maiseyeu, Stephen N. Davis, Sanjay Rajagopalan

Abstract: The discovery of incretin-based medications represents a major therapeutic advance in the pharmacological management of type 2 diabetes mellitus (T2DM), as these agents avoid hypoglycemia, weight gain, and simplify the treatment of T2DM globally. DPP4 inhibitors are modestly effective in reducing HbA1c (glycated hemoglobin) (≈0.5%) and while these agents were synthesized with the understanding of the role that DPP4 plays in prolonging the half-life of incretins such as glucagon-like peptide-1 and gastric inhibitory peptide, it is now recognized that incretins are only one of many targets of DPP4. The widespread expression of DPP4 on blood vessels, myocardium, and myeloid cells and the nonenzymatic function of CD26 as a signaling and binding protein, across a wide range of species, suggest a teleological role in cardiovascular regulation and inflammation. Indeed, DPP4 is upregulated in proinflammatory states including obesity, T2DM, and atherosclerosis. Consistent with this maladaptive role, the effects of DPP4 inhibition seem to exert a protective role in cardiovascular disease at least in preclinical animal models. Although 2 large clinical trials suggest a neutral effect on cardiovascular end points, current limitations of performing trials in T2DM over a limited time horizon on top of maximal medical therapy must be acknowledged before rendering judgment on the cardiovascular efficacy of these agents. This review will critically review the science of DPP4 and the effects of DPP4 inhibitors on the cardiovascular system. (Circ Res. 2015;116:1491-1504. DOI: 10.1161/CIRCRESAHA.116.305665.)

Key Words: cardiovascular diseases ■ diabetes mellitus ■ DPP4 protein, mouse ■ glucagon-like peptide-1 ■ incretins

The growing burden of type 2 diabetes mellitus (T2DM) worldwide represents one of the most important challenges for global health. More than 50% of the risk of mortality from T2DM is attributable to cardiovascular causes, with T2DM contributing significantly to death and disability-adjusted life years.1 Although diet and lifestyle approaches are fundamental to the treatment of risk in T2DM, these treatments often fail in many patients necessitating pharmacological approaches. Dipeptidyl peptidase-4 (DPP4, also known as CD26) is a widely expressed glycoprotein that has gained attention owing to its role in the catalytic degradation of incretins such as glucagon-like peptide-1 (GLP-1) and as a receptor for the Middle Eastern respiratory syndrome (MERS) virus. The development of DPP4 inhibitors (DPP4i) as a class of antidiabetic medications was predicated on the simple notion that these drugs would raise GLP-1/gastric inhibitory peptide levels resulting in enhancement of insulinotropic effects of glucose. This rather simple construct is now replaced with a much more nuanced understanding of this protein. In this review, we will summarize the structure and function of DPP4 and its known role in physiology. We will review its importance in the pathophysiology of cardiometabolic disorders and provide the evidence to date, on the effects of DPP4 inhibition, both from the context of experimental models, mechanistic human studies, and recent clinical trial evidence on cardiovascular outcomes.

Overview of DPP4 Biology and Regulation
Human DPP4 is a 766 amino acid single-pass type II integral transmembrane glycoprotein that belongs to S9b DPP family, which also include quiescent cell proline dipeptidase (also called DPP2), fibroblast activation protein, DPP8, and DPP9. Monomeric DPP4 has a short N-terminal cytoplasmic portion (6 residues, AA 1–6), a 22-residue transmembrane domain (AA7–29) and an extracellular domain, comprised an 8-blade β-propeller (Arg54–Asn497) and a large α/β-hydrolase domain (Gln508-Pro766) responsible for binding to adenosine deaminase (ADA) and matrix proteins such as fibronectin and collagen.2,3 Residues 630, 708, and 740 in the α/β-hydrolase domain are critical for catalytic function of DPP4. Although the C-terminal α/β-hydrolase domain is relatively conserved, the N-terminal 8-blade β-propeller domain demonstrates sequence...
variability. The catalytic pocket responsible for cleavage of several protein substrates is 8 Å and contained within a 15 Å wide opening at the interface between its hydrolyase and propeller domains. 6 Residue 294 and residues 340 to 343 within the cysteine-rich segment of DPP4 is essential for ADA binding. 4 DPP4 exists as a monomer, homodimer, or homotetramer on the cell surface, with the homodimer representing the predominant catalytically active form. 5 DPP4 is subject to post-translational modification via glycosylation and N-terminal sialylation, both of which have been suggested to regulate catalytic activity. 6, 7

Current understanding of DPP4 molecular regulation is incomplete. The promoter of DPP4 contains a consensus GAS (interferon γ activated sequence) sequence at -35 to -27, which has a binding motif for STAT1α. Administration of both interferons and retinoic acid results in the tyrosine phosphorylation of STAT1α and subsequent nuclear translocation and binding to the GAS motif resulting in DPP4 transcription. 5 In addition to interferon (IL)-12 and tumor necrosis factor (TNF)-α, IL-1α has also been shown to regulate the expression of DPP4. 4 The promoter for DPP4 also contains consensus sites for nuclear factor (NF)-κB, SP-1 (specificity protein 1), EGFR (epidermal growth factor receptor), AP-1 factor (activator protein 1), and hepatocyte NF-1. IL-12 enhances the translation but not transcription of DPP4 in activated lymphocytes, whereas TNFα decreases cell surface expression of DPP4, suggesting a regulatory role of IL-12 and TNFα in the translation and translocation of DPP4. 9

DPP4 also circulates as a soluble form in the plasma. Soluble DPP4 (sDPP4) lacks the cytoplasmic and transmembrane domain with preserved catalytic activity. Whether sDPP4 is cleaved from the membrane or is secreted is unclear. For instance, studies investigating viral liver infection suggest that sDPP4 is cleaved from membrane-bound DPP4. 10 sDPP4 is also detected in the lumen of secretory granules in pancreatic A cells and in the exocytic secretory lysosomes of natural killer cells, suggesting that it may also be processed intracellularly. 11, 12

Physiological Role of Catalytic Function of DPP4

DPP4 exerts its peptidase function by removing N-terminal dipeptides displaying proline, alanine, or serine as the penultimate (P1) amino acid residue. Inactivation of GIP and GLP-1 is responsible for the antihyperglycemic effect of DPP4 inhibition. Mice lacking the gene encoding DPP4 are refractory to the development of obesity and hyperinsulinemia and demonstrate improved postprandial glucose control. 12, 13 GLP-1 and GIP suppress glucagon release, decrease gastric emptying, promote β-cell proliferation, and suppress β-cell death. 14–16 Pharmacological inhibition of DPP4 enzymatic activity improves glucose tolerance in wild-type, but not in Dpp4−/− mice. Interestingly, DPP4 inhibition improves glucose tolerance in Glp1r−/− mice, indicating that DPP4 contributes to blood glucose regulation by additional substrates such as GIP or through GLP-1R-independent mechanisms. 13 In addition to gut-derived peptides GLP-1 and GIP, the other substrates include a variety of neuropeptides and chemokines. A recent study suggests in addition to chemokines other cytokines such as GM-CSF, G-CSF, IL-3, and erythropoietin could also be cleaved by DPP4. 14 The catalytic activity of DPP4 and its substrates (Figure 1) have been extensively reviewed elsewhere 7, 15 and we will not go into detail here.

Physiology of Noncatalytic Function of DPP4

In addition to its well-known peptidase activity, DPP4 also possesses noncatalytic functions through its interaction with a ligands including ADA, caveolin-1, fibronectin, and CXCR4 (CXC chemokine receptor 4).

Interaction With ADA and Mediation of T-Cell Costimulation

The best known noncatalytic function of DPP4 is to provide costimulation for T cells by interacting with ADA. 16 Activation of DPP4 induced tyrosine phosphorylation of molecules downstream of T cell receptor (TCR)/CD3, such as p56ck,
DPP4 Expression and Diabetes Mellitus

DPP4 is an important regulator of postprandial glucose via degradation of GLP-1 and GIP. Both GLP-1 and GIP are rapidly inactivated by DPP4, resulting in a short half-life (<2 minutes for GLP-1 and <2 minutes in rodents or 7 minutes in human for GIP). In contrast to early reports suggesting that GLP-1 levels are decreased in T2DM, recent studies suggest that, in general, patients with T2DM do not exhibit reduced GLP-1 secretion in response to an oral glucose tolerance test or euglycemic–hyperinsulinemic clamp. DPP4 expression increases with functional maturation of DCs and macrophages from monocytes with a role for upregulation of CD86 expression and activation of the NF-κB.

Noncatalytic Interactions of DPP4 and Inflammation

The mechanism by which DPP4 may potentiate inflammation in T2DM likely involves both its catalytic and noncatalytic function. There is good evidence suggesting a role for DPP4 noncatalytic function in the regulation of T-cell activation. DPP4 expression increases with functional maturation of DCs and macrophages from monocytes with a role for upregulation of CD86 expression and activation of the NF-κB.

Catalytic Inhibition of DPP4 Function in Diabetes Mellitus

There are currently 4 DPP4i approved by the Food and Drug Administration (FDA) and 1 DPP4i approved by the European Medicines Agency: sitagliptin (FDA approved in 2006), saxagliptin (FDA approved in 2009), linagliptin (FDA approved in 2011), alogliptin (FDA approved in 2013), and vildaglaptin (European Medicines Agency approved in 2007). They can be broadly divided into 2 classes based on structure: DPP4 dipeptide structure mimetics and nonpeptidomimetics. The first class includes sitagliptin (β-amino acid based), vildaglaptin, and saxagliptin (nitrite containing), whereas the nonpeptidomimetics include alogliptin (modified pyrimidinedione) and linagliptin (xanthine-based). There are several others in advanced clinical trials including dutaglaptin and gemigliptin and at least 2 once weekly DPP4i are in advanced clinical trials. DPP4i demonstrate a 0.4% to 0.8% lowering of HbA1c, with the degree of lowering depending on the baseline HbA1c, concomitant therapy, and patient population.

In general, the glyceremia lowering efficacy with DPP4i is lower than that with sulfonloyureas, insulin, and thiazolidinediones, but they are significantly better tolerated and devoid of weight gain. The most frequently reported side effects of DPP4i include nasopharyngitis, upper respiratory tract infection, urinary tract infection, and headache. In contrast to other members of the class, linagliptin has a primarily nonrenal route of excretion and does not need dose adjustment in renal impairment. Several studies corroborate improvement in β-cell function indices including homeostasis model assessment β-cell function index, fasting proinsulin:insulin ratio, and insulin secretion rates in response to mixed meal challenge.

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pathway. The interaction between DPP4 and ADA may also facilitate T-cell activation through regulation of pericellular adenosine levels. Jurkat cell (a T-cell line) with a DPP4 mutant devoid of ADA binding activity is sensitive to adenosine-mediated inhibition of T-cell proliferation, indicating that DPP4 on immune cells facilitates adenosine clearance by binding to ADA (Figure 2). In assays using T-cell/DC cocultures, adenosine dose-dependently suppresses T-cell proliferation, whereas preincubation of DCs with ADA relieved the inhibitory effect of adenosine in a dose-dependent manner. Small interfering RNA knockdown of DPP4 on DC suppresses proliferation of both CD4+ and CD8+ T cells while sitagliptin did not. Both T-cell receptor signaling and Signal transducer and activator of transcription 3 (STAT3), an important signaling molecule that regulates T-cell proliferation and activation, are regulated by DPP4-expressing DCs. STAT3 phosphorylation increases on T-cell activation, an effect suppressed by adenosine. Lymphocyte-specific protein tyrosine kinase (Lck), a Src family tyrosine kinase that is activated with TCR activation and allows binding and phosphorylation of ZAP-70 to mediate downstream signaling events, is prevented from being activated in T cells cocultured with DPP4 small interfering RNA-transfected DC (as suggested by an increase in phospho-Lck [Tyr505], the inactive form of Lck). These results suggest that DPP4 on antigen presenting and T cells may promote adipose inflammation and insulin resistance through its noncatalytic function. However, the precise extent to which noncatalytic function regulates inflammation independent of the catalytic function in T2DM will require experiments in animals expressing human DPP4 that additionally have mutations in enzymatic function as murine DPP4 lacks the ADA binding site.

**Effects of DPP4 Inhibition on Cardiovacular System**

**Effects of DPP4i on Endothelial Cells, NO, and Blood Pressure**

DPP4 is expressed on endothelial cells and seems to play a physiological role in the regulation of vascular tone and angiogenesis. Studies have suggested that DPP4/Incretin axis has substantial implication in cardiovascular system (Figure 3). Incubation of human umbilical vein endothelial cells with DPP4i such as alogliptin and vildagliptin has been shown to result in endothelial nitric oxide synthase (eNOS) and Akt phosphorylation paralleled by a rapid increase in NO. DPP4 inhibition relaxes preconstricted aortic segments in a dose-dependent manner, responses unaffected by the GLP-1R antagonist, exendin 9–39. In 1 study, vascular relaxation was reduced by endothelial denudation, L-NG-nomemethyl-arginine citrate, and by the soluble guanylate cyclase inhibitor ODQ, whereas a combination of L-NG-nomemethyl-arginine citrate and blockers of calcium activated potassium channels completely obviated relaxation in response to DPP4 inhibition, suggesting that both eNOS and potassium channels mediated effects on vascular function. Inhibition of Src kinase decreased eNOS and Akt phosphorylation in response to DPP4 inhibition NO. DPP4 inhibition–mediated GLP-1R activation may also represent a mechanism for the blood pressure–lowering effect of DPP4i. However, the locus of GLP-1R activation is controversial. Although endothelial cells have been shown to express GLP-1R at least in some studies, at least in 1 study the antihypertensive effects of GLP-1R activation by liraglutide did not directly relax preconstricted aortic rings or increase cGMP. However, conditioned medium from liraglutide-treated hearts relaxed aortic rings in an endothelium-independent, GLP-1R–dependent manner. The decrease in BP involved an indirect natriuretic effect dependent on ANP release from the atria in a GLP-1R–dependent manner. Several other studies in animal models support a favorable effect of DPP4 inhibition in improving endothelial function and blood pressure. In contrast to the positive effects in animals, the effects of DPP4i on endothelial function in humans have been inconsistent. Although some of the inconsistency may relate to differences...
in end points, methodology, and patient characteristics, it is possible that these conflicting results may reflect differential alteration in the levels of substrates and their metabolites by DPP4i, which may vary depending on the study participants. In a double-blind study in T2DM, treatment with vildagliptin for 4 weeks improved forearm blood flow in response to intra-arterially delivered aceytylcholine.60 In contrast, 2 studies using flow-mediated dilation of the brachial artery have shown opposite results with 1 study showing that both sitagliptin and alogliptin worsen flow-mediated dilation, whereas in another study sitagliptin improved flow-mediated dilation in association with an increase in CD34+ cells in another study.61,62 Although earlier studies in small cohorts seem to suggest a favorable effect of DPP4i in reducing BP, these effects have not been consistently observed.63,64 An obvious explanation is that the magnitude of effect which is typically small (1–3 mm Hg) may not be easily observed in studies using clinic systolic blood pressure, particularly as a secondary end point. Indeed a large meta-analysis of published data on DPP4i using clinic BP does not support an effect on blood pressure.65 An alternate hypothesis that has been proffered relates to differential alteration of substrates of DPP4 such as NPY, which shifts the receptor affinity from Y1 to non-Y1 receptors.66 DPP4 inhibition has been demonstrated to enhance sodium excretion through interaction with the renal sodium hydrogen exchanger type 3 exchange protein and does so in both wild-type and Glp1r−/− mice.67 The mechanisms may relate to the physical association of the sodium hydrogen exchanger type 3 with DPP4 with inhibition of DPP4 catalytic activity, suppressing sodium hydrogen exchanger type 3–mediated NaHCO3 reabsorption in rat renal proximal tubule, resulting in increased Na+ excretion.68 Further the redistribution of the complex of DPP4–sodium hydrogen exchanger type 3 is thought to represent an adaptive mechanism in chronic hypertension.69 It has also been suggested that catalytic inactivation of natriuretic peptides such as brain natriuretic peptide by DPP4 may regulate blood pressure through natriuretic and vasodilatory effects. DPP4 converts brain natriuretic peptide (BNP) to produce BNP(3–32),70 which has reduced vasodilatation and natriuretic effects.71 In humans, however, inhibition of DPP4 with sitagliptin acutely, does not potentiate BNP levels or its effects on forearm blood flow.72 In a post hoc analysis of SAVOR-TIMI, NT-proBNP level was not increased with Saxagliptin treatment and was lower when compared with placebo.73

DPP4 Inhibition in Angiogenesis and Stem Cell Homing

Expression of DPP4 on Sca-1+lin– donor hematopoietic cells negatively regulates homing and engraftment vasculogenesis.74 By inhibiting DPP4 catalytic function or deleting DPP4, the transplantation and engraftment efficacy of hematopoietic stem cells was greatly enhanced.74 Stromal-cell–derived factor-1 (SDF-1) is a substrate for DPP4 and has been implicated in the mobilization and homing of hematopoietic cells in response to G-CSF treatment in experimental ischemia/infarction.75,76 DPP4-truncated SDF-1 not only loses its chemotactic activity but also blocks chemotactic effects of full-length SDF-1.77 Sitagliptin treatment in patients with T2DM results in a 2-fold increase of circulating EPC (endothelial progenitor cell) with concomitant increase in plasma SDF-1.78 Short-term treatment with DPP4i has also been demonstrated to increase SDF-1 levels and CD34+ cells.78,79 The increase in CD34+ cells corresponded to increased homing and deposition to an ischemic hindlimb preparation79 and infarcted myocardium.80 DPP4 may also regulate HSCs (hematopoietic stem cells) and HPCs (hematopoietic progenitor cells) by truncating multiple CSFs (other than SDF-1) with consequent loss of their activity. DPP4 knockout or pretreatment of HPCs from human cord blood or mouse bone marrow with DPP4i enhances the proliferative action of GM-CSF, G-CSF, IL-3, and erythropoietin.81 DPP4 deficiency or catalytic inhibition promotes hematopoiesis and bone marrow engraftment in mice after radiation or chemotherapy.82 Interestingly, DPP4-truncated CSFs blunt the activity...
of their respective full-length CSF, both in vitro and in vivo with the truncated GM-CSF, demonstrating a higher affinity to GM-CSF receptor. However, there were also studies showing that DPP4 inhibition reduces angiogenesis through inactivation of NPY(1–36). Truncation of NPY by DPP4 leads to a shift of receptor subtype specificity with cleaved NPY(3–36) binding to non-Y1 (Y2, Y3, and Y5) receptors. Production of NPY(3–36) is required for angiogenic activity as DPP4 inhibition by neutralizing antibody suppresses NPY-mediated endothelial cell migration in an endothelial wound assay.

Pharmacological inhibition of DPP4 catalytic function stimulates angiogenesis, enhances endothelial cell migration, aortic sprouting, and angiogenesis in in vivo assays. Src kinase-mediated eNOS-Akt activation in response to DPP4 inhibition seems to play an important role in the angiogenic response to DPP4 inhibition. The effects of DPP4 inhibition in enhancing angiogenesis in vitro are paralleled by an improvement in hindlimb blood flow in a hindlimb ischemia model. DPP4 inhibition has also been shown to improve healing of chronic foot ulcer in patients with T2DM, in parallel with increased HIF-1α (hypoxia-inducible factor) and VEGF (vascular endothelial growth factor) in the periphery of the ulcer and ulcer capillary density. Similarly, the angiogenic capacity of circulating proangiogenic cells in patients with T2DM has been shown to be increased in vivo in response to DPP4 inhibitors.

Effects on Lipid Metabolism
Administration of DPP4i to hyperlipidemic mice reduces postprandial lipoprotein levels. The effects of DPP4i on lipoprotein metabolism have been reviewed extensively. A single dose of sitagliptin after a high-fat liquid formula administered under pancreatic clamp conditions decreased triglyceride-rich lipoproteins apoB48 concentration by reducing production rates in healthy subjects. The magnitude of lipid lowering seen with different DPP4i seems to be comparable and of a similar magnitude with that seen with the GLP-1R agonist exenatide.

In a 4-week single center, randomized double-blind study in T2DM, vildagliptin (n=31; 50 mg bid) reduced postprandial plasma triglyceride, chylomicron apoB48 after mixed meal challenge, without changes in apoB100. Vildagliptin also increased intact GLP-1, suppressed inappropriate glucagon secretion. In a randomized cross-over study, alogliptin (25 mg/d, for 7 days) suppressed postprandial elevation of triglyceride, apoB48, and remnant lipoproteins. In a double-blind crossover study, sitagliptin >6 weeks (100 mg/d) significantly decreased postprandial area plasma apoB48 triglyceride, and very-low-density lipoprotein-cholesterol. In a randomized cross-over study >7 days of vildagliptin versus placebo, with microdialysis catheter-based analysis of metabolites, vildagliptin treatment was associated with a reduction in postprandial lactate and pyruvate production in the skeletal muscle with evidence of enhanced lipolysis. These effects may reflect improvement in hepatic glucose production by the liver because of obviation of insulin resistance by DPP4i and was supported by calorimetry suggesting increased energy expenditure and lipid oxidation rates.

Effects on Atherosclerosis
Several DPP4i have been shown to reduce atherosclerosis in experimental models (Online Table I). These studies have all consistently noted a reduction in foam cell formation and inflammatory content. In at least 2 of these studies a reduction in migratory capacity of monocytes has been implicated. Pretreatment with DPP4i for 2 weeks in ApoE−/− mice markedly reduced the migration of labeled bone marrow–derived monocytes to atherosclerotic plaque in response to exogenous administered TNFα and sDPP4. In vitro Boyden chamber assays using alogliptin and sitagliptin performed in the presence of nanomolar concentration of TNFα confirmed reduced monocyte migration in response to a CC chemokine ligand (CCL)-2 gradient, which was not inhibited by GLP-1 9–39. The effects of DPP4i include reduction in inflammatory gene expression and a reduction in monocytes and T cells. Given the effects of DPP4 in costimulation and regulation of adenosine, it may suggest a role for DPP4, independent of its effects on substrates such as GLP-1. GLP-1 has been shown to decrease monocyte migration in response to CCL-2 and regulated on activation, normal T-cell expressed and secreted in a concentration-dependent manner. GLP-1 may also exert anti-inflammatory effects via cAMP-dependent mechanisms, which may reduce NF-κB and Erk activation. Infusion of exendin-4 for 4 weeks reduces neointimal formation, foam cells, and atherosclerotic lesion size. In support of a role for GLP-1 in DPP4-mediated effects, administration of antagonists to GLP-1 and GIP (exendin(9–39) and Pro(3) GIP) attenuated antiatherosclerotic effects of vildagliptin on atherosclerosis (Online Table I). In humans, 1 study noted a reduction in carotid intima media thickness progression with sitagliptin compared with placebo >12 months in newly diagnosed patients with T2DM with coronary artery disease.

Effect on Myocardial Function and Ischemia–Reperfusion
Genetic disruption of the Dpp4 in mice is not associated with baseline abnormalities in cardiac structure or function. Table 1 reviews the effects of DPP4i on models of ischemia reperfusion. In response to experimental infarction, Dpp4−/− mice exhibit improved survival with a trend toward reduction in infarct size. Hearts from Dpp4−/− mice contained higher levels of phosphorylated AKT, pGSK3, and ANP, well-known prosurvival pathways. In a postinfarction model, sitagliptin treatment led to an improvement in passive left ventricular compliance, increased endothelial cell density, reduced myocyte hypertrophy, and reduced collagen. Treatment with sitagliptin resulted in improved postinfarction survival without change in infarct size, an effect associated with up-regulation of prosurvival pathways HO-1 and Akt, pathways activated by GLP-1. Whether the results in response to DPP4 inhibition are because of an increase of DPP4 target proteins such as GLP-1 cannot be definitively inferred from studies to date. Recent studies seem to contest the role of direct effects of GLP-1 on myocardial cells and invoke a role for GLP-1–dependent atrial natriuretic peptide synthesis from atrial cells, because myocytes do not seem to express GLP-1 receptors.

DPP4 and Heart Failure
DPP4 levels correlate with heart failure with plasma DPP4 activity being significantly higher in patients with more advanced
Table 1. Studies That Evaluate Cardiovascular Effect of DPP4 Inhibitors

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Dose</th>
<th>Duration</th>
<th>Subject</th>
<th>Disease</th>
<th>Major Findings</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Angiogenesis</td>
<td></td>
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<tr>
<td>Diprotin A or</td>
<td>5 mmol/L diprotin A or Val-Pyr</td>
<td>15 min in vitro treatment</td>
<td>Mouse, Bone marrow transplantation</td>
<td>DPP4 inhibition or deletion improved hematopoietic stem cell homing and engraftment</td>
<td>Christophers et al74</td>
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<tr>
<td>Val-Pyr</td>
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<tr>
<td>Diprotinin-A or</td>
<td>10 μmol/L diprotinin-A or P32/98</td>
<td>3–4 d</td>
<td>Mouse, HMVEC</td>
<td>Angiogenesis</td>
<td>Pharmacological inhibition of CD26/DPP4 enhanced endothelial growth both in vitro and in vivo</td>
<td>Takasawa83</td>
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<td>P32/98</td>
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<tr>
<td>Sitagliptin</td>
<td>10 or 20 mg/kg per day (oral gavage)</td>
<td>7 wk</td>
<td>Mouse, Hindlimb ischemia</td>
<td>Sitagliptin treatment augmented ischemia-induced increases in SDF-1 and improved blood flow in ischemic limb. In addition, sitagliptin promoted EPC mobilization and homing to ischemic tissue</td>
<td>Huang et al79</td>
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<tr>
<td>Linagliptin</td>
<td>10 nmol/L or 0.5 μmol/L</td>
<td>4 h in vitro treatment</td>
<td>HUVEC, Endothelial cell damage</td>
<td>Linagliptin inhibition inhibits AGE-induced ROS production in HUVEC</td>
<td>Ishibashi et al105</td>
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<tr>
<td>Vildagliptin</td>
<td>1 5, or 10 nmol/L</td>
<td>6 h</td>
<td>Mouse, HUVEC</td>
<td>Hindlimb ischemia</td>
<td>Vildagliptin stimulated ischemia-induced revascularization through an eNOS signaling</td>
<td>Ishii et al86</td>
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<td>Myocardial infarction</td>
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<td>Sitagliptin</td>
<td>250 mg/kg per day (in vivo) or 5 μmol/L (in vitro infusion)</td>
<td>8-wk feeding or 20 min in vitro infusion</td>
<td>Mouse, MI</td>
<td>Sitagliptin improved functional recovery after I/R injury via increasing cardiac pAKT, pGSK3β, and atrial natriuretic peptide</td>
<td>Sauvé et al106</td>
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<tr>
<td>Diprotin A</td>
<td>10 mmol/L</td>
<td>6 h</td>
<td>Mouse, HUVEC</td>
<td>Thrombosis</td>
<td>Diprotin A enhanced the amount of tissue factor encountered and induced the adherence of platelets under flow conditions</td>
<td>Krijnen et al107</td>
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<tr>
<td>Sitagliptin</td>
<td>300 mg/kg per day</td>
<td>2 wk</td>
<td>Fischer F344 rat</td>
<td>MI</td>
<td>Sitagliptin improved passive left ventricular compliance, increased endothelial cell density, reduced myocyte hypertrophy, and decreased the abundance of collagen 1</td>
<td>Connelly et al108</td>
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<td>Kidney disease</td>
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<td>Sitagliptin</td>
<td>1 μmol/L</td>
<td>In vitro treatment</td>
<td>Rat, Renovascular response</td>
<td>Sitagliptin enhanced angiotensin II–induced increase of perfusion pressure in isolated kidneys from both lean and obese ZSF1 rats</td>
<td>Tofovic et al109</td>
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<tr>
<td>Vildagliptin</td>
<td>1 or 10 mg/kg (IV)</td>
<td>One dose</td>
<td>Rat, Renal I/R injury</td>
<td>Vildagliptin reduced tubular necrosis, Bax/Bcl-2 and CXCL10 mRNA expression, and serum creatinine level after renal I/R</td>
<td>Glorie et al110</td>
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<tr>
<td>Vildagliptin</td>
<td>4 or 8 mg/kg per day</td>
<td>24 wk</td>
<td>Rat, Kidney injury</td>
<td>Vildagliptin decreased proteinuria, albuminuria, and urinary albumin/creatinine ratio, improved creatinine clearance, and inhibited interstitial expansion, glomerulosclerosis, and the thickening of the glomerular basement membrane in diabetic rats</td>
<td>Liu et al111</td>
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<tr>
<td>Sitagliptin</td>
<td>200 mg/kg per day</td>
<td>8 wk</td>
<td>Rat, Kidney injury</td>
<td>Sitagliptin suppressed nephrectomy-induced activation of P38K-Akt and FoxO3a. Sitagliptin treatment also reduced apoptosis by decreasing cleaved caspase-3 and caspase-9 and Bax levels</td>
<td>Joo et al112</td>
<td></td>
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<tr>
<td>MK0626</td>
<td>33 mg/kg chow (=10 mg/kg per day)</td>
<td>16 wk</td>
<td>Mouse, Obesity-induced renal injury</td>
<td>MK0626 prevented high-fructose/high-fat diet–induced glomerular and tubular injury independent of blood pressure/insulin sensitivity</td>
<td>Nistala et al113</td>
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<tr>
<td>Linagliptin</td>
<td>83 mg/kg rat chow</td>
<td>8 wk</td>
<td>Zucker obese rat</td>
<td>Obesity-related glomerulopathy</td>
<td>Linagliptin enhanced filtration barrier remodeling, improved proteinuria, increased active GLP-1 and SDF-1α, and improved oxidant markers</td>
<td>Nistala et al114</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>5 mg/kg per day in drinking water</td>
<td>4 wk</td>
<td>Mouse, kidney fibrosis</td>
<td>Linagliptin ameliorated kidney fibrosis in diabetic mice without altering the blood glucose levels associated with the inhibition of EndMT and the restoration of microRNA 29s</td>
<td>Kanasaki et al115</td>
<td></td>
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<tr>
<td>Blood pressure</td>
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<tr>
<td>Alogliptin</td>
<td>Various doses (in vitro)</td>
<td>In vitro treatment</td>
<td>Mouse aorta, HUVEC</td>
<td>Vascular function</td>
<td>Alogliptin relaxed preconstricted aortic segments in a dose dependent manner. Alogliptin induced eNOS and Akt activation in HUVEC cells is independent of GLP-1</td>
<td>Shah et al116</td>
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<tr>
<td>Sitagliptin</td>
<td>40 mg/kg twice daily</td>
<td>8 d</td>
<td>SHR rat, Hypertension</td>
<td>Sitagliptin decreased blood pressure in young SHR rats but not adult SHRs</td>
<td>Pacheco et al117</td>
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<tr>
<td>Sitagliptin</td>
<td>10 mg/kg per day</td>
<td>2 wk</td>
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<td>Sitagliptin treatment improved endothelium-dependent relaxation in renal arteries, restored renal blood flow, and reduced systolic blood pressure in SHR rats</td>
<td>Liu et al118</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Dose</td>
<td>Duration</td>
<td>Subject</td>
<td>Disease</td>
<td>Major Findings</td>
<td>Reference</td>
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<tr>
<td>Saxagliptin</td>
<td>10 mg/kg per day</td>
<td>8 wk</td>
<td>SHR rat</td>
<td>Hypertension and endothelial dysfunction</td>
<td>Saxagliptin treatment reduced blood pressure in SHRs, an effect that was accompanied an increase in aortic and glomerular N0 release with reductions in peroxynitrite levels</td>
<td>Mason et al(^{118})</td>
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<tr>
<td>Linagliptin</td>
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<td>ZO rat</td>
<td>Hypertension</td>
<td>Linagliptin blunted elevated blood pressure progression in ZO rats without reducing left ventricular hypertrophy, fibrosis, or oxidative stress</td>
<td>Aroor et al(^{79})</td>
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<tr>
<td>Atherosclerosis</td>
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<tr>
<td>Alogliptin</td>
<td>15 mg/kg per day gavage</td>
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<td>Mouse</td>
<td>Diabetic atherosclerosis</td>
<td>Alogliptin reduced atherosclerotic lesions and TLR4-mediated upregulation of IL-6 and IL-1β in diabetic ApoE(^{-/-}) mice</td>
<td>Ta et al(^{113})</td>
</tr>
<tr>
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<td>Mouse</td>
<td>Atherosclerosis</td>
<td>Alogliptin reduced atherosclerotic plaque and vascular inflammation in atherosclerosis-prone Ldlr(^{-/-}) and ApoE(^{-/-}) mice</td>
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<tr>
<td>PKF275-055 (vildagliptin analogue)</td>
<td>100 μm/kg per day in drinking water</td>
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<td>Atherosclerosis</td>
<td>PKF275-055 reduced foam cell formation, atherosclerotic plaque, and macrophage accumulation in the aortic wall</td>
<td>Terasaki et al(^{96})</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>1.1% in diet</td>
<td>12 wk</td>
<td>Mouse</td>
<td>Atherosclerosis</td>
<td>Sitagliptin reduced plaque macrophage infiltration and plaque MMP-9 levels, increased plaque collagen content but did not change overall lesion size</td>
<td>Vittone et al(^{85})</td>
</tr>
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<td>Anagliptin</td>
<td>0.3% in diet</td>
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<td>DPP4 inhibition reduced accumulation of monocytes and macrophages in the vascular wall and SMC content in plaque areas</td>
<td>Ervinna et al(^{100})</td>
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<tr>
<td>Vildagliptin</td>
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<td>4 wk</td>
<td>Mouse</td>
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<td>Vildagliptin confers a substantial antiatherosclerotic effect in both nondiabetic and diabetic mice, which was abolished by incretin blockers exendin(9–39) or (Pro(3))GIP</td>
<td>Terasaki et al(^{97})</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>0.3% in diet</td>
<td>16 wk</td>
<td>Mouse</td>
<td>Atherosclerosis</td>
<td>Sitagliptin treatment reduced atherosclerotic plaque size, collagen fiber, MCP-1, and IL-6 in plaques, serum levels of soluble vascular cell adhesion molecule-1 and P-selectin, and increased activation of AMPK and Akt in aortas</td>
<td>Zeng et al(^{98})</td>
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<tr>
<td>Heart failure</td>
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<tr>
<td>Vildagliptin</td>
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<td>Heart failure</td>
<td>Vildagliptin reversed diabetic diastolic left ventricular dysfunction and pressure overload-induced left ventricular dysfunction</td>
<td>Shigeta et al(^{122})</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>30 mg/kg per day</td>
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<td>Pig</td>
<td>Overpacing-induced heart failure</td>
<td>Sitagliptin increased stroke volume and preserved glomerular filtration rate in pigs with pacing-induced heart failure</td>
<td>Gomez et al(^{121})</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>10 mg/kg per day</td>
<td>Up to 7 wk</td>
<td>Mouse</td>
<td>Dilated cardiomyopathy</td>
<td>Saxagliptin treatment improved glucose tolerance but not survival in a transgenic murine model of dilated cardiomyopathy</td>
<td>Vyas et al(^{122})</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>10 mg/kg per day</td>
<td>4 wk</td>
<td>Mouse</td>
<td>Heart failure</td>
<td>Vildagliptin ameliorated TAC-induced left ventricular enlargement and dysfunction, and improved survival rate on day 28</td>
<td>Takahashi et al(^{122})</td>
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<tr>
<td>Vildagliptin</td>
<td>30 mg/kg per day</td>
<td>7 days</td>
<td>Rat</td>
<td>Cardiac hypertrophy</td>
<td>Vildagliptin attenuated the (\beta)-adrenergic stimulation-induced cardiac hypertrophy as well as cardiomyocyte hypertrophy and perivascular fibrosis</td>
<td>Miyoshi et al(^{124})</td>
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<tr>
<td>MK0626</td>
<td>33 mg/kg in diet (=10 mg/kg per day)</td>
<td>16 wk</td>
<td>Mouse</td>
<td>Diastolic dysfunction</td>
<td>MK0626 improved Western diet–induced insulin resistance and diastolic relaxation, accompanied by reduced myocardial oxidant stress and fibrosis</td>
<td>Bostick et al(^{125})</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>1.5 mg/kg per day</td>
<td>7 wk</td>
<td>Rat</td>
<td>Heart failure with preserved ejection fraction (sitagliptin)</td>
<td>DPP4 inhibition prevented the development of cardiac diastolic dysfunction induced by subtotal nephrectomy, without change in renal function or structure improvement</td>
<td>Connelly et al(^{126})</td>
</tr>
</tbody>
</table>

AGE indicates advanced glycation end product; AKT, protein kinase B, also known as PKB; ApoE, apolipoprotein E; DPP4, dipeptidyl peptidase-4; EndMT, endothelial-to-mesenchymal transition; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; GIP, gastric inhibitory peptide; GLP, glucagon-like peptide-1; HMVEC, human microvascular endothelial cell; HUVEC, human umbilical vein endothelial cell; I/R, ischemia–reperfusion; IL, interleukin; MI, myocardial infarction; MMP, Matrix metalloproteinase; pAKT, phosphorylated AKT; P38K, phosphatidylinositol-3-kinases; ROS, reactive oxygen species; SHR, short-root; SMC, smooth muscle cell; TAC, transverse aortic constriction; and TLR, Toll-like receptor.
heart failure. Pharmacological DPP4 inhibition in models of diabetic cardiomyopathy, pressure overload model of heart failure has been consistently shown to improve ventricular remodeling and survival as well as ameliorating severity of heart failure. Similarly, both pharmacological and genetic DPP4 inhibition reversed diabetic diastolic left ventricular dysfunction and pressure-overload–induced left ventricular dysfunction. Diabetes mellitus is well known to impair angiogenic ability through SDF-1α–dependent pathways in cardiac tissue. DPP4 inhibition (both pharmacological and genetic) reversed SDF-1α–dependent microvasculopathy and diabetes mellitus–associated diastolic left ventricular dysfunction. Improved left ventricular function assessed by ejection fraction, mitral annular systolic velocity, and peak systolic velocity has also been observed in humans with DPP4 inhibition (Sitagliptin, single dose or 4 weeks of treatment). Although the effects of DPP4 inhibition on heart failure have been directly attributed to increase in GLP-1, the extent to which these effects are driven by GLP-1 is unclear. This is especially true given recent evidence contesting the presence of GLP-1 receptors in the myocytes and dependence of atrial synthesis of ANP for GLP-1 effects. The effects of GLP-1 itself are controversial. GLP-1 agonism has also been shown to increase left ventricular ejection fraction (all in short-term); however, reports on long-term cardiovascular effect of DPP4i and GLP-1 analogs are limited.

### Effects on Renal Injury and CKD Progression

DPP4 inhibition has been shown to exert renoprotective effects characterized by reduction in oxidative stress, podocyte injury, mesenchymal expansion, fibrosis, and proteinuria in experimental models (Table 1). These effects seem to occur without changes in blood pressure or insulin sensitivity. Treatment with sitagliptin and linagliptin has also been shown to reduce proteinuria. In a 6-month open label trial in 35 patients, albumin:creatinine ratio was reduced by at least 2-fold in patients with a range of albumin excretion from normal to macroalbuminuria (urinary albumin:creatinine ratio >300). A pooled analysis of 4 completed studies (n=217) of subjects with T2DM and prevalent albuminuria (defined as a urinary albumin:creatinine ratio of 30–3000 mg/g creatinine) receiving sitagliptin on top of stable doses of RAAS (renin–angiotensin–aldosterone system) inhibitors demonstrated a modest 28% placebo-adjusted reduction in albumin:creatinine ratio at 6 months independent of blood pressure.

Sitagliptin protects renal function in patients with T2DM as evidenced by reduced urinary albumin-to-creatinine ratio Renovascular response to angiotensin II may also be enhanced by DPP4 inhibition. Sitagliptin (1 μmol/L) significantly enhanced angiotensin II–induced increase of perfusion pressure in isolated kidneys from both lean (18.2±5.9 versus 3.4±1.3 mmHg) and obese (17.8±8.2 versus 5.5±1.3 mmHg) ZSF1 rats. Improvement in filtration barrier remodeling and suppression of fibrosis may also serve as alternative mechanisms of DPP4i in protecting renal function in chronic kidney disease.

### Cardiovascular Clinical Trials With DPP4i

Online Table II lists completed and ongoing randomized controlled clinical trials with DPP4i. SAVOR-TIMI53 was designed as a superiority trial and failed to meet the prespecified superiority outcome of saxagliptin versus placebo in a high-risk patient population with established vascular disease and risk factors. In the EXAMINE (Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes Mellitus and Inadequate Glycemic Control) trial, designed as a safety trial in a high-risk postacute coronary syndrome population, the prespecified end point of noninferiority was met and alogliptin was noninferior to placebo with regards to cardiovascular outcomes. In both EXAMINE and SAVOR-TIMI53 trials, the primary outcome composed of cardiovascular death, myocardial infarction, and ischemic stroke was noninferior in DPP4i group when compared with placebo group. In both trials the median duration of follow-up was >4 years, the majority of whom were on evidence-based therapies. These factors are widely felt to have been responsible for lack of benefit with these

### Table 2. Dipeptidyl Peptidase-4 Inhibitors CV Outcome Trials

<table>
<thead>
<tr>
<th>Drug (Class)</th>
<th>Landmark Name</th>
<th>Study Population</th>
<th>Primary Outcome</th>
<th>Dosing</th>
<th>Estimated Enrollment</th>
<th>Duration, y</th>
<th>End Date</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>EXAMINE</td>
<td>T2DM with ACS (within &gt;15 to &lt;90 d)</td>
<td>MACE</td>
<td>6.25, 12.5, or 25 mg QD</td>
<td>5400</td>
<td>4.75</td>
<td>2013</td>
<td>NCT00968708</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>SAVOR-TIMI 53</td>
<td>T2DM with multiple CRF</td>
<td>Composite</td>
<td>2.5 or 5 mg QD</td>
<td>16500</td>
<td>4</td>
<td>2013</td>
<td>NCT01107886</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>TECOS</td>
<td>T2DM with pre-existing CVD</td>
<td>Composite</td>
<td>2.5 or 100 mg QD</td>
<td>14000</td>
<td>5</td>
<td>2014</td>
<td>NCT00792050</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>CAROLINA</td>
<td>T2DM with impaired renal function or CVD</td>
<td>Composite</td>
<td>5 mg QD</td>
<td>6000</td>
<td>7.5</td>
<td>2018</td>
<td>NCT01243424</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>CARMELINA</td>
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<td>Composite</td>
<td>5 mg QD</td>
<td>8300</td>
<td>4.5</td>
<td>2018</td>
<td>NCT01897532</td>
</tr>
<tr>
<td>Omariagliptin MK-3102-015 AM1</td>
<td>T2DM with inadequate glycemic control on diet/exercise therapy and oral antihyperglycemic agent monotherapy</td>
<td>Any adverse event</td>
<td>25 mg once weekly</td>
<td>585</td>
<td>1.5</td>
<td>2014</td>
<td>NCT01697592</td>
<td></td>
</tr>
<tr>
<td>Omariagliptin MK-3102-018 (MK3102)</td>
<td>T2DM with pre-existing CVD</td>
<td>Composite</td>
<td>25 mg once weekly</td>
<td>4000</td>
<td>5</td>
<td>2017</td>
<td>NCT01703208</td>
<td></td>
</tr>
</tbody>
</table>
agents. In SAVOR-TIMI 53, baseline NT-proBNP was measured in 12,301 patients. More patients treated with saxagliptin were hospitalized for heart failure when compared with placebo (hazard ratio, 1.27; 95% confidence interval, 1.07–1.51; P = 0.007). Differences in heart failure were seen in <6 months with rates at 12 months of 1.9% versus 1.3% (hazard ratio, 1.46, 95% confidence interval, 1.15–1.88; P = 0.002, with no difference thereafter). Subjects at greatest risk for heart failure had prior heart failure, eGFR (estimated glomerular filtration rate) ≤ 60 mL/min, and elevated baseline levels of NT-proBNP (risk in highest NT-proBNP quartile of 2.1%). Whether the association with heart failure applies to other DPP4i will need to be addressed in ongoing cardiovascular outcome trials of DPP4i.139

In consistence with this finding, a slight increase of heart failure hospitalization was observed in patients with alogliptin compared with those with placebo (3.9% versus 3.3%; hazard ratio, 1.19; 95% confidence interval, 0.90–1.58) in EXAMINE trial,2013 while the benefits of heart failure de novo thereafter). Subjects at greatest risk for heart failure had prior heart failure, eGFR (estimated glomerular filtration rate) ≤ 60 mL/min, and elevated baseline levels of NT-proBNP (risk in highest NT-proBNP quartile of 2.1%). Whether the association with heart failure applies to other DPP4i will need to be addressed in ongoing cardiovascular outcome trials of DPP4i.139

Conclusions
The development of DPP4i has evolved from the understanding of its role in regulation of incretin hormones. However, the widespread expression of this molecule in a variety of cell types clearly underscores a previously unrecognized role for this molecule in physiological processes. Despite the plethora of enzymatic substrates that serve as targets, the inhibition of enzymatic activity in animals and humans seems to be well tolerated and safe with modest reduction in HbA1c. The preponderance of evidence from inhibiting DPP4 enzymatic function in animal models of disease seems to suggest that salutary effects including in heart failure and in totality seem to suggest the possibility of beneficial cardiovascular effects in humans. At least 2 large randomized clinical trials focused on cardiovascular outcomes in high-risk patients with T2DM on best medical therapy seem to show no differences compared with placebo with regards to the composite end point of cardiovascular death, myocardial infarction, and stroke during a duration of <4 years of drug treatment. The noncatalytic function of DPP4, including its role as a costimulatory molecule and binding to several matrix proteins including ADA in humans, points to larger role for DPP4 outside of its catalytic function. Future mechanistic studies will need to focus on the relative contribution of the catalytic versus noncatalytic function in cardiometabolic disease, whereas clinical trials will need to address the heart failure safety signals and demonstrate a beneficial effect of this class in cardiovascular complications associated with T2DM.

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Jixin Zhong, Andrei Maiseyeu, Stephen N. Davis and Sanjay Rajagopalan

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