Cardiovascular Actions and Clinical Outcomes With Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors

ABSTRACT: Potentiation of glucagon-like peptide-1 (GLP-1) action through selective GLP-1 receptor (GLP-1R) agonism or by prevention of enzymatic degradation by inhibition of dipeptidyl peptidase-4 (DPP-4) promotes glycemic reduction for the treatment of type 2 diabetes mellitus by glucose-dependent control of insulin and glucagon secretion. GLP-1R agonists also decelerate gastric emptying, reduce body weight by reduction of food intake and lower circulating lipoproteins, inflammation, and systolic blood pressure. Preclinical studies demonstrate that both GLP-1R agonists and DPP-4 inhibitors exhibit cardioprotective actions in animal models of myocardial ischemia and ventricular dysfunction through incompletely characterized mechanisms. The results of cardiovascular outcome trials in human subjects with type 2 diabetes mellitus and increased cardiovascular risk have demonstrated a cardiovascular benefit (significant reduction in time to first major adverse cardiovascular event) with the GLP-1R agonists liraglutide (LEADER trial [Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Ourcome Results], −13%) and semaglutide (SUSTAIN-6 trial [Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide], −24%). In contrast, cardiovascular outcome trials examining the safety of the shorter-acting GLP-1R agonist lixisenatide (ELIXA trial [Evaluation of Lixisenatide in Acute Coronary Syndrom]) and the DPP-4 inhibitors saxagliptin (SAVOR-TIMI 53 trial [Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53]), alogliptin (EXAMINE trial [Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome]), and sitagliptin (TECOS [Trial Evaluating Cardiovascular Outcomes With Sitagliptin]) found that these agents neither increased nor decreased cardiovascular events. Here we review the cardiovascular actions of GLP-1R agonists and DPP-4 inhibitors, with a focus on the translation of mechanisms derived from preclinical studies to complementary findings in clinical studies. We highlight areas of uncertainty requiring more careful scrutiny in ongoing basic science and clinical studies. As newer more potent GLP-1R agonists and coagonists are being developed for the treatment of type 2 diabetes mellitus, obesity, and nonalcoholic steatohepatitis, the delineation of the potential mechanisms that underlie the cardiovascular benefit and safety of these agents have immediate relevance for the prevention and treatment of cardiovascular disease.

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Glucagon-like peptide-1 (GLP-1) was initially discovered as an insulinotropic hormone produced in and secreted from the gut after food intake.[1] It has received attention because of its role in the physiology of glucose metabolism (ie, its function as an incretin[2]) but more so as a parent compound mediating the actions of 2 classes of glucose-lowering medications used in the treatment of type 2 diabetes mellitus (T2D), GLP-1 receptor (GLP-1R) agonists, and dipeptidyl peptidase-4 inhibitors (DPP-4Is).[1] GLP-1R agonists, either small peptides or much larger peptidomimetics, mediate their glucoregulatory actions by a single GLP-1R. In contrast, inhibitors of the protease DPP-4 prevent the degradation and inactivation of both GLP-1 and the incretin hormone glucose-dependent insulinotropic polypeptide.[1]

GLP-1R agonists and DPP-4Is are approved for the treatment of hyperglycemia in patients with T2D.[2] Although glycemic control reduces the microvascular complications of diabetes mellitus (neuropathy, nephropathy, and retinopathy), the relationship between glucose control and reduction of macrovascular events is more challenging.[3] It is notable that incretin-based therapies (GLP-1R agonists [GLP-1RAs] and DPP-4Is) exert multiple nonglycemic actions in the cardiovascular system, heightening the interest in their potential for cardiovascular benefit.[4–6] The recent findings that 2 GLP-1RAs, liraglutide[7] and semaglutide,[8] significantly reduced the combined primary outcome of 3 point major adverse cardiovascular events in large cardiovascular outcome trials elevates the importance of understanding how activation of the GLP-1R translates into clinical cardiovascular benefit. The purpose of the present review is to summarize the literature on indirect (through lowering glucose and modifying known cardiovascular risk factors) and direct (through stimulating GLP-1Rs and inhibition of DPP-4) effects of (1) GLP-1, (2) GLP-1RAs, and (3) DPP-4Is on the heart and blood vessels. Herein we discuss concepts of incretin action in the context of results of cardiovascular outcomes trials with DPP-4Is and GLP-1RAs and, wherever possible, link underlying mechanisms to observed clinical benefits.

GLP-1RS IN THE CARDIOVASCULAR SYSTEM AND EFFECTS ELICITED BY STIMULATING WITH GLP-1, GLP-1RAS, OR DPP-4IS (PRECLINICAL STUDIES)

GLP-1Rs in the Cardiovascular System

GLP-1R expression has been detected in various cardiovascular tissues and cell types at the mRNA and protein levels. Although native GLP-1 improves endothelial function, augments ventricular contractility, enhances myocardial glucose uptake, and exerts cytoprotective and metabolic actions on blood vessels and cardiomyocytes, the endogenous canonical GLP-1R is not highly expressed in many of the cell types responsive to GLP-1 or GLP-1RAs. Hence, some of the well-described actions of GLP-1 in preclinical studies may reflect indirect mechanisms or the actions of ≥1 GLP-1 degradation products acting through GLP-1R-independent mechanisms. Details are summarized in Table I in the online-only Data Supplement, which highlights well-documented effects on the heart (contractile function, substrate supply, coronary and myocardial blood flow, rate control), blood pressure, and platelet aggregation. Because the present review is focused on human studies, we refer to Table I and accompanying text in the online-only Data Supplement and several recent reviews for details of preclinical studies.[4–6,9,10]

Potential Mechanisms Explaining Biological Effects of N-Terminal GLP-1 Fragments GLP-1 [9–36] Amide, GLP-1 [9–37], or GLP-1 [28–36] Amide

Considerable evidence supports biological activity for N-terminally truncated GLP-1 peptides, principally GLP-1 [9–36] amide[10,11] and GLP-1 [28–36] amide[12] in the cardiovascular system. Although a distinct receptor for these peptides has not been identified, they successfully target cytoplasmic and mitochondria-linked pathways, leading to a reduction of reactive oxygen species in hepatocytes, endothelial cells, and cardiomyocytes.[10,11] Moreover, GLP-1 [28–36] directly activates prosurvival kinases in the ischemic mouse heart or vascular cells through mechanisms linked to soluble adenylate cyclase and cAMP generation in isolated cardiomyocytes ex vivo.[12] Hence, studies using native GLP-1 may be associated with activation of dual cardiovascular pathways mediated through the classical GLP-1R and nonclassical cAMP-mediated pathways activated by truncated peptides converging on cardiomyocyte and vascular protection.[10]

DPP-4 in the Cardiovascular System

DPP-4 is widely expressed in most cells and tissues and exhibits enzymatic activity against dozens of chemokines and peptide hormones with roles in inflammation, vascular function, stem cell homing, and cell survival.[13] DPP-4 exhibits exopeptidase activity through its 2 principal molecular forms, a membrane-tethered 766 amino acid protein with a small intracellular tail and a soluble form that is 39 amino acids smaller, devoid of the short membrane spanning domain and intracellular tail, and yet otherwise structurally identical.[13] Although soluble DPP-4 exerts vascular, immune, and proinflammatory actions independent of its catalytic activity, the

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majority of the experimental literature has studied the importance of DPP-4-mediated peptide cleavage in the pathophysiology and treatment of cardiovascular disease.

Attribution of mechanism(s) linking reduction of DPP-4 activity to attenuation of cardiovascular injury or preservation of cardiovascular function is difficult for several reasons. First, DPP-4 cleaves dozens of substrates simultaneously, initiating complex changes in multiple signaling pathways.[4,5] Second, the majority of DPP-4 substrates circulate at low levels and are difficult to quantitate. Third, highly sensitive and specific assays distinguishing full length from DPP-4-cleaved peptides are generally not commercially available. Hence, measurements of total immunoreactive peptide detect a mixture of cleaved versus intact substrates. Fourth, many of the DPP-4-cleaved peptide metabolites retain biological activity in the cardiovascular system, albeit through different receptors and signaling pathways. Hence, DPP-4 simultaneously inactivates and potentiates the activity of numerous cardioactive substrates.[5,13] Last, only a few highly selective antagonists for DPP-4 peptide substrates are available, and these reagents have not been widely used in cardiovascular studies.

Preclinical Effects in Myocardial Infarction Models and Cardiovascular Function

When myocardial infarction is experimentally induced by occluding (ligating) a coronary artery, the myocardial area receiving blood supply through the vessel to be occluded can be defined as an area at risk, and the resulting area of necrosis can be identified by specific staining methods.[14] Administration of GLP-1, GLP-1RAs (eg, exenatide, liraglutide), and DPP-4Is (eg, sitagliptin, vildagliptin, alogliptin) reduces the resulting necrosis (relative to the area at risk), as summarized in Figure I in the online-only Data Supplement. Examples encompass in vivo and ex vivo (isolated perfused heart) studies, studies in rodents and larger mammals, and with various pharmacological agents (GLP-1 [7–36 amide], DPP-4Is, and GLP-1RAs) (Figure I in the online-only Data Supplement). Additional studies examining effects of the GLP-1RAs exenatide,[15] lixisenatide,[16] and albiglutide[17] and the DPP-4Is sitagliptin[18] and linagliptin[19] have been published. Although occasional reports do not replicate these findings (eg, with liraglutide in a porcine model[20]), the majority of studies found a significant reduction in the necrotic area in hearts of animals treated with GLP-1 or GLP-1RAs (Figure I in the online-only Data Supplement). The cardioprotective effects of GLP-1 can be inhibited by the specific GLP-1RA exendin [9–39]. Thus, these effects seem to be mediated by an interaction with the canonical GLP-1R.[14] More details are described in the online-only Data Supplement.

CARDIOVASCULAR ACTIONS IN HUMANS

Table 1 summarizes human studies examining cardiovascular function or changes in renal function, lipoprotein metabolism, and hepatic fat accumulation.

GLP-1R in Human Cardiovascular Tissues

The atrial expression of the GLP-1R protein was identified in nonhuman primate and human hearts using a highly specific monoclonal antibody, localizing an immunoreactive GLP-1R protein to cells within the sinoatrial node.[21] Nevertheless, some studies have detected partial *GLP-1R* mRNA transcripts by reverse transcription polymerase chain reaction techniques using RNA isolated from human ventricles, although GLP-1RAs such as exenatide failed to augment contractility in the majority of isolated strips from human ventricles in the same experiments.[27] RNASeq analyses have detected the presence of *GLP-1R* mRNA transcripts in RNA from human left ventricles (http://www.gtexportal.org/home/gene/GLP1R). Hence, these findings imply that under some circumstances, transcriptional or translational control may dictate whether a ventricular *GLP-1R* mRNA transcript is expressed and gives rise to functional GLP-1R protein in the human heart (including the working myocardium in atria and ventricles). The presence or absence of a functional GLP-1R in human coronary arteries is not clearly established.[6]

Cardiac Output

Intravenous GLP-1 at a pharmacological dose improved left ventricular function, maximum oxygen uptake, and physical performance in subjects with congestive heart failure.[25] Likewise, intravenous exenatide (GLP-1RA) improved cardiac index and pulmonary capillary wedge pressure and reduced atrial natriuretic peptide.[28] However, in vitro, exenatide increased contractility in human atrial but not ventricular myocardium.[27] Larger randomized controlled clinical trials with albiglutide or liraglutide failed to demonstrate any beneficial effect of sustained GLP-1RA treatment in human subjects with moderate to severe heart failure and reduced ejection fraction,[29,30] independent of the presence or absence of diabetes mellitus. In patients with advanced heart failure, liraglutide did not improve a composite end point of cardiovascular events that included changes in N-terminal pro-brain natriuretic peptide. A numeric but statistically nonsignificant increase in mortality and hospitalization for heart failure was detected (hazard ratio [HR], 1.30; 95% confidence interval [CI], 0.92–1.83; *P*=0.14), indicating a potential for harm in patients with reduced ejection fraction and a prior history of hospitalization for heart failure. It is possible that this may be related to

Table 1. Effects of Stimulating GLP-1 Receptors With GLP-1, GLP-1 Receptor Agonists, or DPP-4 Inhibitors in Human Studies, Which Lead to a Modified Cardiovascular Function (Directly or Indirectly)

Organ	Effect(s) on	GLP-1 [7–36 Amide] or [7–37]	GLP-1 Receptor Agonists	DPP-4 Inhibitors
Heart	Myocardial glucose uptake	• Intravenous GLP-1 (pharmacological dose): ≈[22]	• Exenatide (intravenous, pharmacological dose, type 2 diabetes mellitus, no CAD): ≈[23]	• Sitagliptin (subjects without diabetes mellitus, subjects with nonischemic cardiomyopathy): ↑[24]
	Left ventricular function	• Intravenous GLP-1 (pharmacological dose, 5 wk): LVEF ↑, VO_2 max. ↑, 6-min walk, distance ↑[25] • Improved LVEF not confirmed at lower dose of GLP-1[26]	• Exenatide: In vitro contractility of atrial, but not ventricular human myocardium ↑[27]; intravenous: cardiac index ↑, PCWP ↑, and ANP ↓[28] • Albiglutide: no significant effects[29] • Liraglutide: trend for reduced rate of hospitalization for congestive heart failure (LEADER)[7]; however, trends for worse outcomes (not significant) in dedicated heart failure trials[30,31]	• Sitagliptin (chronic congestive heart failure): left ventricular diastolic function ↑[32] • Rate of hospitalization for congestive heart failure ≈ (TECOS)[33] • Saxagliptin: rate of hospitalization for congestive heart failure ↑ (significant) SAVOR-TIMI 53[34,35] • Alogliptin: rate of hospitalization for congestive heart failure ↑ (nonsignificant) EXAMINE[36,37] • Vildagliptin: trend to reduced left venticular function (VIVIDD trial, unpublished)
	Cardioprotection against ischemia/ myocardial stunning	• Intravenous GLP-1 (pharmacological dose, dobutamine-induced stress) LVEF ↑, regional contractility ↑[38,39] • Coronary balloon occlusion: preserved left ventricular function[38,40] • 72 h after acute myocardial infarction: LVEF ↑, regional wall motility ↑[41]	• ST-segment elevation myocardial infarction: intravenous exenatide: salvage index (non-necrosed proportion of area at risk) ↑[42] • Subcutaneous exenatide: infarct size ↓[43] • Liraglutide preserved LVEF after PCI[44] • Non–ST-segment elevation myocardial infarction: liraglutide-preserved LVEF after PCI[45]	• Sitagliptin (dobutamine-induced stress): LVEF ↑, regional contractility ↑. Preferential effect in ischemic segments[46,47]
	Heart rate	• Intravenous GLP-1: ↑ (small), no decrease in vagal control[48]	• ↑ by 2–3 beats per min[49,50] • Sympathetic activation with exenatide?[51]	• Not reported in a study demonstrating lowering in systolic blood pressure by ≈ 2 mm Hg[52]
Peripheral arteries	Angiogenesis, endothelial cell proliferation	• New vessel formation from human endothelial cells improved by high doses of GLP-1[53]	• Exenatide-stimulated proliferation of human coronary artery endothelial cells[54]	• Not reported
	Endothelium-derived vasodilation (NO production)	• Endothelial nitric oxide synthase ↑ in HUVECs[55] • Intravenous GLP-1 (pharmacological dose): acetyl choline–induced vasodilation ↑ in healthy subjects[56] and in type 2 diabetes mellitus with stable CAD[57]	• Exenatide: endothelial nitric oxide synthase in HUVECs ↑[58]; postprandial endothelial function ↑[59] • Liraglutide: endoplasmic reticulum stress (induced by hyperglycemia) ↓[60] and TNF^{α}-induced oxidative stress ↓ and inflammation ↓ in HUVECs[61]; eNOS ↑, endothelin-1 expression ↓[62] • Liraglutide: Acetyl choline–mediated forearm blood flow (↑) (n.s.)[63]	• Sitagliptin: reactive hyperemia peripheral artery tonometry index ↑[64], flow- mediated vasodilation (type 2 diabetes mellitus) ↑[65] • Effect of DPP-4 inhibition on endothelial function not confirmed by other studies[66,67]
	Endothelium-independent vasodilation	• Nitroprusside-induced forearm vasodilation not augmented by intravenous GLP-1 (pharmacological dose)[56]	• Not reported	• Nitroglycerin-mediated dilatation not changed by sitagliptin[65]
	Anti-atherosclerotic effects	• No immediate effects	• Liraglutide: intimamedia thickness ↓ over 8 months[68]	• Sitagliptin,[69] linagliptin[70]: intimamedia thickness progression ↓
Blood pressure	Systolic	• Transient increase with GLP-1 (intravenous; pharmacological dose: transient ↑[71]; physiological dose: ≈[72])	• ↓ by 2–3 mmHg[49,50]	• Occasional reports of lowering systolic blood pressure in hypertensive subjects[52]
	Natriuretic peptides	• ANP ≈ (n.s.)[71,73]	• Liaglutide: pro-ANP ↓,[74] but ANP and pro-BNP ≈[75,76]; ANP ↑ and BNP ↑ also reported[77]	• Not reported

(*Continued*)

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Table 1. Continued

Organ	Effect(s) on	GLP-1 [7–36 Amide] or [7–37]	GLP-1 Receptor Agonists	DPP-4 Inhibitors
Renal function	Glomerular filtration	• Acutely ↑[78]	• Exenatide. ≈[79] • Lixisenatide: ≈[80] • Liraglutide: ≈[7]	• Generally no significant effect[36] • Sitagliptin: minor ↓ in the TECOS trial[33]
	Albumin excretion	• No immediate effects known	• Liraglutide: ↓[7,74] • Lixisenatide: ↓ (P=0.004)[80]	• Saxagliptin ↓,[34] linagliptin ↓[81]
Metabolic milieu	Hyperglycemia	• Plasma glucose ↓[82]	• See Figure 2	• See Figure 2
	Fasting lipoproteins/lipid concentrations	• No immediate effect, nonesterified fatty acids ↓ (transient)[82]	• See Figure 2	• See Figure 2
	Postprandial lipid concentrations	• Postprandial triglycerides ↓ (deceleration of gastric emptying)[83]	• Exenatide,[84] liraglutide[85]: triglycerides ↓, apolipoprotein B-48 ↓,[85] and in chylomicron remnant lipids ↓[84]	• Sitagliptin,[86] vildagliptin,[87] and alogliptin[88]: triglycerides ↓, apolipoprotein B-48 ↓
Liver	Hepatic fat deposition (hepatic steatosis, NAFLD)	• No effects reported	• Mechanistic study describes the role of exenatide and liraglutide in stimulating lipoautophagy (macroautophagy and chaperone-mediated autophagy) in preventing apoptiosis, fat-induced hepatocyte death, and progression to hepatic fibrosis and cirrhosis[89] • Exenatide: better reversal of fatty liver (ultrasonography) than with insulin[90] • Liraglutide: resolution of definite nonalcoholic steatohepatitis (histology) vs placebo ↑[91]	• Vildagliptin: hepatic triglyceride content ↓ vs placebo[92] • Sitagliptin: ≈ vs placebo[93]
Inflammatory responses	Reactive oxygen species/ oxidative stress	HUVECs: ROS ↓[94]	• Exenatide: ROS generation ↓[95], anti-oxidative potential in human monocytes/ macrophages ↑[96]	• No effects reported
	NF-κB binding/activation	No immediate effects reported	• Exenatide: nuclear factor-κB binding (mononuclear blood cells) ↓[95]	• Sitagliptin: nuclear factor-κB binding (mononuclear blood cells) ↓[97]
	Expression of inflammatory cytokines in mononuclear cells	IL-6 ↓[98]	• Exenatide: TNFα ↓, IL-1ß ↓, etc.[95] • Liraglutide: TNFα ↓, IL-1ß ↓, IL-6 ↓, etc.[99]	• Sitagliptin: significant reduction in IL-6, IL-18, sICAM-1, E-selectin[100]; significant reduction in TNFα, TLR-4, TLR-2, CCR-2[97]
	C-reactive protein	No immediate effects reported	• Exenatide: ↓ by 61%[101] • Liraglutide ↓ by 23%[102]	• Sitagliptin: ↓ by 44%[100]
	Adiponectin	• No immediate effects reported	• Exenatide: ↑ by 12%[101] • Liraglutide: ↑ by 40%[99]	• Increase more substantial with vildaglptin than with sitagliptin[103]
Platelet function	Platelet aggregation	• No immediate effects reported	• Exenatide: platelet aggregation ↓[104]	• Potential for reduced platelet aggregation(?)[105]
Stem cell homing	SDF-1 stabilization	• No immediate effects reported	• No immediate effects reported	• Circulating endothelial progenitor cells (reduced in subjects with type 2 diabetes) enhanced after 4 weeks of treatment with sitagliptin[106] • Benefits of improved stem cell homing not supported by results of the SITAGRAMI study (sitagliptin for 28 days and granulocyte-colony stimulating factor for 5 days after acute myocardial infarction)[107]

Ach indicates acetyl choline; ANP, atrial natriuretuc peptide; BNP, brain-type natriuretic peptide; CAD, coronary artery disease; CCR-2, chemokine receptor type 2; DPP-4, dipeptidyl peptidase-4; eNOS, endothelial nitric oxide synthase; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; GLP-1, glucagon-like peptide-1; HUVECs, human umbilical vein endothelial cells; IL-1ß, interleukin 1ß; IL-6, interleukin 6; IL-18, interleukin-18; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LVEF, left ventricular ejection fraction; NAFLD, nonalcoholic fatty liver disease; NF-κB, nuclear factor κB; n.s., not significant; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; ROS, reactive oxygen species; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction; SDF-1, stromal-derived factor-1; sICAM, soluble intercellular adhesion molecule; SITAGRAMI, Sitagliptin Plus Granulocyte-colony Stimulating Factor in Acute Myocardial Infarction; TECOS, Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin; TLR-2, toll-like receptor-2; TLR-4, toll-like receptor-4; TNFα, tumor necrosis factor α; VIVIDD, Vildagliptin in Ventricular Dysfunction Diabetes; VO_2, velocity of opxygen uptake; ↑, improved, enhanced; ↓, reduced, worsened; and ≈, no significant change.

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