Incretin-based therapies: can we achieve glycemic control and cardioprotection?

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Abstract

Glucagon-like (GLP-1) is a peptide hormone secreted from the small intestine in response to nutrient ingestion. GLP-1 stimulates insulin secretion in a glucose-dependent manner, inhibits glucagon secretion and gastric emptying, and reduces appetite. Because of the short circulating half-life of the native GLP-1, novel GLP-1 receptor (GLP-1R) agonists and analogs and dipeptidyl peptidase 4 (DPP-4) inhibitors have been developed to facilitate clinical use. Emerging evidence indicates that GLP-1-based therapies are safe and may provide cardiovascular (CV) benefits beyond glycemic control. Preclinical and clinical studies are providing increasing evidence that GLP-1 therapies may positively affect CV function and metabolism by salutary effects on CV risk factors as well as via direct cardioprotective actions. However, the mechanisms whereby the various classes of incretin-based therapies exert CV effects may be mechanistically distinct and may not necessarily lead to similar CV outcomes. In this review, we will discuss the potential mechanisms and current understanding of CV benefits of native GLP-1, GLP-1R agonists and analogs, and of DPP-4 inhibitor therapies as a means to compare their putative CV benefits.

Introduction

Despite significant advances in anti-glycemic therapies, cardiovascular disease (CVD) remains the major cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) (Fox *et al.* 2004, Booth *et al.* 2006, Perk *et al.* 2012). Moreover, certain classes of potent anti-diabetic agents reduce microvascular complications but carry a increased risk of cardiovascular (CV) events (Nissen & Wolski 2007, Tzoulaki *et al.* 2009). At a time when T2DM constitutes a worldwide epidemic, there is a growing demand for new treatments that not only control plasma glucose but also reduce macrovascular complications.

Glucagon-like peptide 1 (GLP-1) is a peptide hormone synthesized in and secreted by enteroendocrine L cells in the gut and by the brainstem in the CNS. GLP-1 is secreted from the gut at low basal levels in the fasted state, peaking in response to nutrient ingestion, and leading to enhancement of glucose-stimulated insulin secretion, inhibition of glucagon secretion and gastric emptying, and reduction of appetite (Drucker 2006, Ussher & Drucker 2012). The native peptide (GLP-1 (7–36) amide) is rapidly cleavage by the dipeptidyl peptidase 4 (DPP-4) enzyme (Deacon *et al.* 1995), limiting circulating half-life and subsequent biological effects on pancreatic β cells. This pharmacokinetic response has led to the development of novel GLP-1 receptor (GLP-1R) agonists and analogs that are DPP-4-resistant and thus have a longer half-life. Similarly, DPP-4 inhibitors have also been developed that prolong the half-life of circulating native

GLP-1 (Fakhoury *et al.* 2010, Cernea & Raz 2011). All classes of agents share the same insulinotropic properties and have been shown to have similar glucose-lowering properties (Fineman *et al.* 2012). However, they vary with respect to extra-pancreatic effects, including weight loss and blood pressure (BP) control. Emerging evidence indicates that GLP-1-based therapies are safe and may provide CV benefits (Monami *et al.* 2011, Sun *et al.* 2012), making this class of agents a particularly attractive option for treating T2DM (Addison & Aguilar 2011).

Interestingly, the CV benefits of GLP-1 therapies seems to be only partially mediated by their positive action on glucose control in T2DM (Ussher & Drucker 2012). The mechanisms whereby this class of agents mediates CV effects may be distinct, not necessarily leading to similar outcomes. This review discusses the potential mechanisms and current understanding of the associated CV benefits of native GLP-1 (Barragan *et al.* 1994, 1996) and its metabolites, GLP-1R agonists and analogs, and of DPP-4 inhibitor therapies (Table 1).

Improving glucose control: effect on CV outcomes

GLP-1R activation stimulates adenylate cyclase, which increases cAMP, leading to activation of protein kinase A (PKA) and insulin biosyntheses by the β cells (Li *et al.* 2003).

GLP-1 stimulates insulin release in a K_{ATP}-mediated, glucose-dependent fashion. GLP-1 also inhibits glucagon secretion from pancreatic α cells, reducing hepatic glucose production, further facilitating improvement in glycemic control. Thus, the metabolic profile of GLP-1-based therapies is broad and not restricted to its role as an insulin secretagogue. Although results of studies examining the association between glycemic control with alternative anti-diabetic agents and CV outcomes in patients with T2DM have been inconsistent (Barragan *et al.* 1996, Control *et al.* 2009, Ray *et al.* 2009), the broader metabolic profile of GLP-1 may lead to beneficial effects on CV outcomes not seen with the other anti-diabetic agents (Ceriello 2006, Ussher & Drucker 2012, Herzlinger & Horton 2013). As presented in Table 2, over 90 000 patients are currently enrolled in clinical studies designed to assess the CV safety and efficacy of incretin-based therapies and hopefully these will provide a better understanding of the influence of GLP-1 in CVD (Scirica *et al.* 2011, White *et al.* 2011, Sivertsen *et al.* 2012). Most of new trials enrolled thousands of patients and are adequately powered for safety and to show superiority rather than non-inferiority. Recently, preliminary results from the non-inferiority Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) trial were presented at the Heart Failure Congress in Lisbon (McMurray 2013). In this study, 254 patients with T2DM and New York Heart

Table 1 GLP-1-based therapies: current knowledge of differences between native GLP-1, GLP-1 analogs and agonists, and DPP-4 inhibitors

	Native GLP-1 (7–36)	GLP-1 analogs and agonists	DPP-4 inhibitors
Administration	Infusion/injection	Injection	Oral
GLP-1 level	Pharmacological	Pharmacological	Physiological
DPP-4-resistant	No	Yes	NA
Mechanism of action	GLP-1 receptor and metabolites	GLP-1 receptor	GLP-1 receptor, SDF1α, BNP, decrease cytokines
Metabolic actions			
FPG	Improved	Improved	Improved
PPG	Improved	Improved	Improved
HbA1c	Improved	Improved	Improved
Glucagon	Reduced	Reduced	Reduced
Insulin sensitivity	Enhanced/neutral	Improved	Unknown
Lipid profile	Improved	Improved	Improved
Weight effects	Loss	Loss	Neutral
Cardiovascular actions			
Heart rate[a]	Unmodified	Unmodified/increased	?
Blood pressure[a]	Reduced	Reduced	Reduced
Cardioprotection	Present	Present	Present
Cardiac function	Improved	Improved	Improved

FPG, fasting plasma glucose; PPG, postprandial plasma glucose; BNP, brain natriuretic peptide; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; NA, not applicable; SDF1α, stromal cell-derived factor-1α ; ?, Uncertain/not known or definite.
[a]Clinical studies.

Table 2 Ongoing cardiovascular outcome studies in patients with type 2 diabetes mellitus

Agent (clinical study)	Identification number (ClinicalTrials.gov)	Estimated primary completion date	Primary outcome measures	Time frame	Study design	Intervention	Estimated enrollment	Eligibility criteria			
								HbA1c (%)	Treatment regimens	Age (years)	CV history
GLP-1R agonists and analogs											
Exenatide (EXSCEL) (Gaebler et al. 2012)	NCT01144338	03/2017	Composite (CV death, MI, or stroke)	5.5 years	R, S/E, PA, DB, phase 3	2 mg s.c. weekly	9500	6.6–10.0	OAD mono or combination therapy[a] ±Insulin	≥18	
Dulaglutide (REWIND)	NCT01394952	04/2019	Composite (CV death, MI, or stroke)	6.5 years	R, S/E, PA, DB, phase 3	1.5 mg s.c. weekly	9622	≤9.5	Treatment naïve, or OAD mono or combination therapy[b] ±Insulin	≥50	CV, cerebrovascular or peripheral vascular disease or CRF or CHF or ≥60 years with ≥2 CV risk factors
Liraglutide (LEADER)	NCT01179048	01/2016	Composite (CV death, MI, or stroke)	60 months	R, S/E, PA, DB, phase 3	Maximum dose of 1.8 mg s.c. daily	9340	≥7	Treatment naïve, or OAD mono or combination therapy[b] ±Insulin	≥50	CV, cerebrovascular or peripheral vascular disease or CRF or CHF or ≥60 years with CV risk factors
Lixisenatide (ELIXA)	NCT01147250	09/2014	Composite (CV death, MI, stroke, or unstable angina)	203 weeks	R, E, PA, DB, phase 3	20 µg s.c. daily	6000	5.5–11	Treatment naïve, or OAD mono or combination therapy[b]	≥30	ACS last 180 days
DPP-4 inhibitors											
Alogliptin (EXAMINE) (White et al. 2011)	NCT00968708	05/2013	Composite (CV death, MI, stroke, or unstable angina)	4.75 years	R, S, PA, DB, phase 3	12.5 mg oral daily	5389	6.5–11	OAD mono or combination therapy[b] ±Insulin	≥18	ACS before 15–90 days
Linagliptin (CAROLINA)	NCT01243424	09/2018	Composite (CV death, MI, stroke, or unstable angina)	400 weeks	R, S/E, PA, DB, phase 3	5 mg OAD	6000	6.5–8.5	Treatment naïve, or mono/dual therapy with metformin and/or an α-glucosidase inhibitor[b]	40–85	CV or diabetes end-organ damage or ≥70 with ≥2 CV risk factors
Saxagliptin (SAVOR-TIMI53) (Scirica et al. 2011)	NCT01107886	07/2013	Composite (CV death, MI, stroke, or unstable angina)	4 years	R, E, PA, DB, phase 4	5 mg or 2.5 g oral daily	16 500	≥6.5	Treatment naïve, or antidiabetic treatment/insulin[b]	≥40	CV disease and/or multiple risk factors

Table 2 *Continued*

Agent (clinical study)	Identification number (Clinical-Trials.gov)	Estimated primary completion date	Primary outcome measures	Time frame	Study design	Intervention	Estimated enrollment	HbA1c (%)	Treatment regimens	Eligibility criteria	
										Age (years)	CV history
Sitagliptin (TECOS)	NCT00790205	12/2014	Composite (CV death, MI, stroke, or unstable angina)	5 years	R, S, PA, DB, phase 3	50 or 100 mg oral daily	14 000	6.6–8	Anti-diabetic treatment/insulin	≥50	CV disease

CV, cardiovascular; EXSCEL, Exenatide Study of Cardiovascular Event Lowering Trial; MI, nonfatal myocardial infarction; R, randomized; S/E, safety/efficacy; PA, parallel assignment; DB, double blind; OAD, oral anti-diabetic drug; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ELIXA, Evaluation of Cardiovascular Outcomes in patients with Type 2 Diabetes After Acute Coronary Syndrome During Treatment with AVE0010; CRF, chronic renal failure; CHF,chronic heart failure; ACS, acute coronary syndrome; EXAMINE, Cardiovascular Outcomes Study of Alogliptin in Subjects with Type 2 Diabetes and Acute Coronary Syndrome; CAROLINA, Cardiovascular Outcome Study of Linagliptin Bersus Glimepiride in Patients With Type 2 Diabetes; SAVOR-TIMI53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.
[a]Excluding other GLP-1 receptor agonist.
[b]Excluding other incretin-based therapy.

Association (NYHA) class I–III were randomized to vildagliptin ($n=128$) or placebo ($n=126$). By 52 weeks, the mean increase in the ejection fraction (EF) did not differ between groups while the mean HbA1c difference between vildagliptin and placebo at 16 weeks was 0.62% ($P<0.001$). Unexpectedly, treatment was associated with increases in left ventricular (LV) end-diastolic volume ($P=0.007$), end-systolic volume ($P=0.06$), stroke volume ($P=0.002$), and mortality (8.6 vs 3.2%), raising concerns regarding the safety of vildagliptin in heart failure patients. Unfortunately, the study was underpowered to properly evaluate safety, leaving open questions to be answered by the ongoing trials.

Incretins and CV effects of weight loss

GLP-1R activation in the hypothalamus reduces appetite and promotes satiety by inhibition of gastric emptying, leading to weight loss (Flint *et al.* 1998, Larsen *et al.* 2001). In patients with T2DM, the use of exenatide (Amori *et al.* 2007) and liraglutide (Vilsboll 2007) has been associated with significant weight loss. Similar results were confirmed in a study with non-diabetic, obese patients treated with liraglutide (Astrup *et al.* 2012). The weight-reducing effect of GLP-1 contributes to beneficial effect on CV risk factors such as lipid profile and BP (Flint *et al.* 1998, Larsen *et al.* 2001, Kenchaiah *et al.* 2002, Shibata *et al.* 2005, Horton *et al.* 2010) in addition to glycemic control. In experimental animal models, reduction of body weight in spontaneously hypertensive and heart failure-prone rats treated with native GLP-1 was seen in association with improvement of LV function, systemic metabolic parameters, and survival (Poornima *et al.* 2008). Similarly, a 5-week infusion of native GLP1 was associated with ∼5 kg weight reduction in patients with class III/IV NYHA heart failure (Sokos *et al.* 2006). Clinical trials with GLP-1R agonists and analogs in patients with T2DM have demonstrated reductions in BP in parallel with reductions in body weight (Varanasi *et al.* 2012). The extent to which weight reduction leads to BP reduction is difficult to discriminate in these clinical trials but underscores the fact that GLP-1 may have several and perhaps synergistic mechanisms of action to favorably influence the metabolic profile.

CV effects of GLP-1 and GLP-1R agonists and analogs

The human GLP-1R is a class B G-protein-coupled receptor expressed not only on pancreatic islet α and β cells but also in the heart (Fig. 1A and B), kidney, brain, blood vessels,
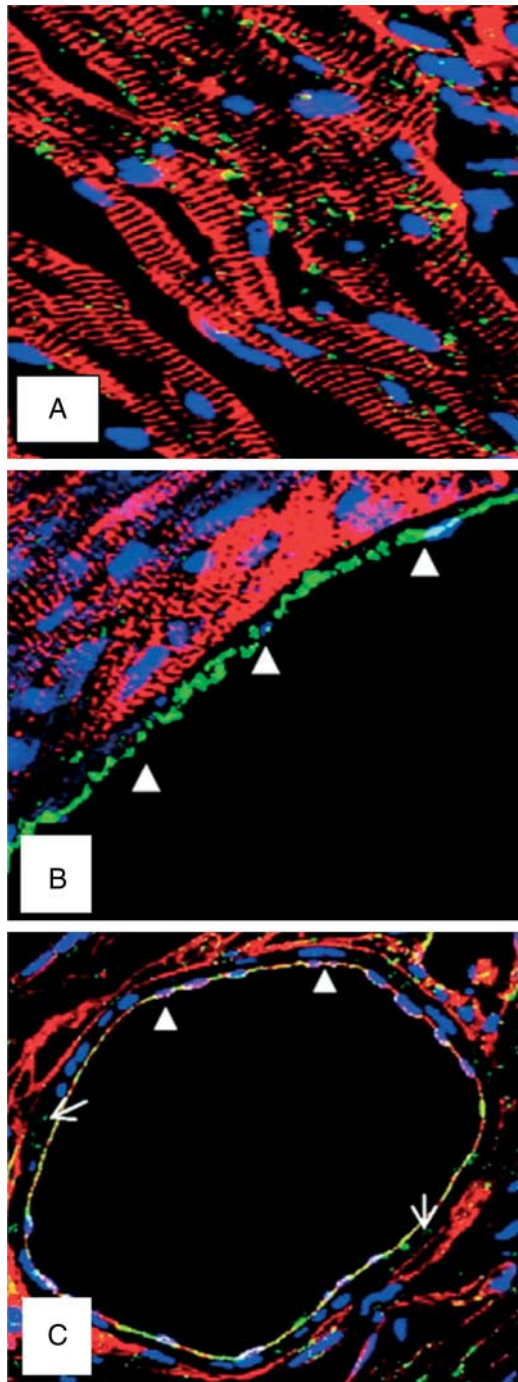
Figure 1

GLP-1R expression in mouse hearts. (A) Hearts labeled with anti-sarcomeric α-actinin (red), anti-GLP-1R (green), and Hoechst nuclear stain (blue) revealed GLP-1R expression on cardiomyocytes, (B) endocardium (arrowheads), (C) vascular endothelium, and smooth muscle cells (SMCs) (arrowheads and arrows respectively). (C) and 30 μmol/l (A and B). Modified, with permission, from Ban K, Noyan-Ashraf MH, Hoefer J, Bolz SS, Drucker DJ & Husain M 2008 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** 2340–2350.

endothelial cells, and gastrointestinal tract (Bullock *et al.* 1996, Ban *et al.* 2008). Preclinical and clinical studies have elucidated some of the biological actions of the GLP-1R system on the heart and blood vessels independent of its actions on pancreatic islets and the subsequent improvement in glycemic control (Barragan *et al.* 1994, Zhao *et al.* 2006, Green *et al.* 2008).

Effects on heart rate and BP

The mechanisms leading to reduced BP and changes in heart rate (HR) are not fully understood, but GLP-1's effects on BP and HR appear to be both species- (rodents vs other mammals) and preparation-specific (anesthetized vs conscious, isolated vs intact cardiac preparations) with differing effects depending on the duration of the GLP-1R activation and preexistence of comorbidities. Preclinical studies with GLP-1 analogs indicate that reduction in BP could be dependent on the autonomic nervous system (Bharucha *et al.* 2008), while a recent study indicates that GLP-1R activation promotes the secretion of atrial natriuretic peptide (ANP) and that a GLP-1R-dependent and ANP-dependent axis regulates BP (Kim *et al.* 2013). Similarly, both autonomic nervous system-dependent and -independent mechanisms have been suggested to lead to rises in HR (Gardiner *et al.* 2008).

Acute administration of GLP-1 and exendin-4 in rats increased BP and HR (Barragan *et al.* 1996), while a 7-day infusion of exendin-4 resulted in reduction of BP in a rat model (Laugero *et al.* 2009). In healthy human subjects, infusion of native GLP-1 for 65 min had no effect on BP or on HR variability (Bharucha *et al.* 2008), while 48-h infusion in 15 non-diabetic patients with heart failure (NYHA class II/III) resulted in small increase in HR and diastolic BP (Halbirk *et al.* 2010). In contrast, in a 5-week infusion of native GLP-1 in 12 heart failure patients (NYHA class III/IV), there were no significant changes in the HR or BP, although the systemic vascular resistance was significantly lower in the treated group (Sokos *et al.* 2006). Thus, even in humans with heart failure, the effects of native GLP-1 on HR and BP vary with respect to severity of heart failure and duration of GLP-1 exposure.

The body of evidence examining the effects of GLP-1 agonists and analogs is more robust in patients with T2DM. A significant reduction in systolic BP was demonstrated after a 52-week treatment with exenatide in a randomized trial with T2DM patients (Buse *et al.* 2010). Similar results confirm the reduction in BP with exenatide therapy in a large retrospective analysis of patients with T2DM (Horton *et al.* 2010). Moreover, a

meta-analysis including 31 trials evaluating the effects of exenatide and liraglutide on BP confirmed a reduction in systolic pressure by -1.79 mmHg (-2.94 to -0.64) and -2.39 mmHg (-3.35 to -1.42) compared with placebo and active anti-diabetic drug therapy respectively (Robinson *et al.* 2013). Whether changes in BP were a consequence of the concomitant reduction in body weight remains to be determined definitively. In keeping with a direct anti-hypertensive effects is the finding that liraglutide significantly reduced systolic in T2DM (Gallwitz *et al.* 2010, Varanasi *et al.* 2012), before the significant weight loss was observed (Gallwitz *et al.* 2010).

In addition, small increases in HR have been reported in several clinical studies and recently compiled in a meta-analysis including 22 trials (Marre *et al.* 2009, Pratley *et al.* 2010, Buse *et al.* 2011, Nathanson *et al.* 2012, Robinson *et al.* 2013). GLP-1 agonists lead to an increase in HR of 1.86 beats/min (bpm; 0.85–2.87) and 1.9 bpm (1.30–2.50) compared with placebo and active control respectively. HR rises were more evident for liraglutide than exenatide, and for exenatide long-acting release than exenatide twice daily (Robinson *et al.* 2013). The clinical relevance of those findings is still not fully understood and may be clarified by the ongoing CV safety trials (Table 2).

Cardioprotective effects

The cardioprotective effects of GLP-1 and GLP-1R agonists and analogs in ischemic heart disease have been supported by extensive studies of rodent models of ischemia–reperfusion using isolated heart preparations (Bose *et al.* 2005a,b, Nikolaidis *et al.* 2005a, Zhao *et al.* 2006, Noyan-Ashraf *et al.* 2009, Timmers *et al.* 2009). The cardioprotective effects seem to be related to the elevation of intracellular calcium by a cAMP-activated PKA pathway (Xiao *et al.* 2011) and with the anti-apoptotic signaling and inhibition of mitochondrial permeability transition pore opening by the activation of the pro-survival reperfusion injury salvage kinase pathway (Hausenloy & Yellon 2004, 2007). Indeed, GLP-1 (Nikolaidis *et al.* 2005a, Xiao *et al.* 2011), exendin-4 (Fineman *et al.* 2012), exenatide (Timmers *et al.* 2009), albiglutide (Bao *et al.* 2011), GLP-1-transferrin (Matsubara *et al.* 2011), and liraglutide (Noyan-Ashraf *et al.* 2009) improved post-ischemic contractile dysfunction and decreased infarct size in different *in vivo* animal models of ischemia and reperfusion. In a porcine model of ischemia–reperfusion, exenatide reduced infarct size by 40% and prevented further deterioration of systolic and diastolic function (Timmers *et al.* 2009). These findings were associated with

reduced apoptosis and nuclear oxidative stress and improvement in myocardial glucose metabolism (Timmers *et al.* 2009). Moreover, GLP-1 administered to conscious dogs undergoing a 10-min coronary occlusion followed by 24 h of reperfusion enhanced recovery from myocardium stunning as demonstrated by the earlier and complete recovery of the regional wall motion in the treated animals (Fig. 2; Nikolaidis *et al.* 2005a). In addition, GLP-1 was associated with improvement in myocardium glucose uptake and isovolumic LV relaxation (Barragan *et al.* 1994).

It is worth of note that, positive findings are not universal as other animal studies were not able to demonstrate similar results (Kavianipour *et al.* 2003, Kristensen *et al.* 2009). In a porcine model of ischemia–reperfusion, recombinant GLP-1 infusion improved myocardial glucose utilization but had no beneficial effects on infarct size or cardiac function (Kavianipour *et al.* 2003). Similarly, despite being associated with higher HR, treatment with liraglutide had neutral effects on infarct size and hemodynamics in a porcine model of ischemia–reperfusion (Kristensen *et al.* 2009). These inconsistent results may be related to different doses, timing of administration, agents employed, and animal models
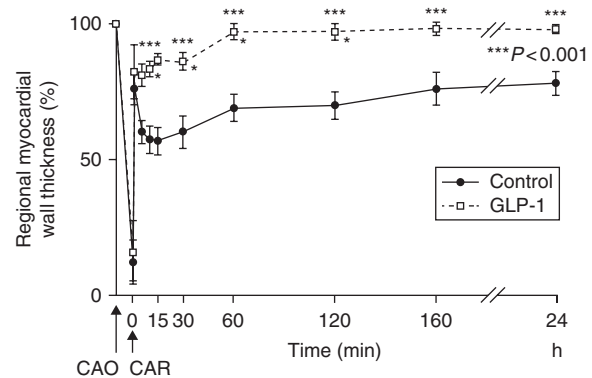
Figure 2

Regional post-ischemic contractile function recovery with GLP-1 in a canine model. Regional wall thickening responses to coronary artery occlusion and coronary artery reperfusion in a canine model. The differences in patterns of recovery of regional contractile function between the control (solid line) and GLP-1-treated animals (dotted lines) are illustrated by the significant dissociation between normalization of coronary flow and recovery of the respective posterior wall thickness, in the control group, consistent with myocardial stunning, even 24 h post-coronary artery reperfusion. In contrast, GLP-1-treated dogs demonstrated rapid and complete recovery of regional function in the ischemic zone over time. *$P<0.01$ vs baseline ***$P<0.001$ vs control by ANOVA. CAO, coronary artery occlusion; CAR, coronary artery reperfusion. Modified, with permission, from Nikolaidis LA, Doverspike A, Hentosz T, Zourelias L, Shen YT, Elahi D & Shannon RP 2005a Glucagon-like peptide-1 limits myocardial stunning following brief coronary occlusion and reperfusion in conscious canines. *Journal of Pharmacology and Experimental Therapeutics* **312** 303–308.

used, highlighting the need for further investigation, particularly in large-animal models.

Positive effects of native GLP-1 infusion in patients with acute myocardial infarction (MI) and LV dysfunction after successful reperfusion were demonstrated in a non-randomized pilot study ($n=21$; Nikolaidis et al. 2004b). In this study, 72-h infusion with GLP-1 significantly improved LVEF (29 ± 2–$39\pm2\%$; $P<0.01$), and wall motion score indices (1.94 ± 0.11–1.63 ± 0.09; $P<0.01$) compared with control (Fig. 3A and B respectively; Nikolaidis et al. 2004b). Furthermore, GLP-1 treatment was associated with significant reduction in hospital length-of-stay (6.1 ± 1.3 vs 9.8 ± 1.5 days; $P<0.02$) and in-hospital mortality (10 vs 27%; Nikolaidis et al. 2004b). Supporting those results, native GLP-1 infusion reduced ischemic LV dysfunction and mitigated stunning in

Figure 3
Effects of GLP-1 infusion on cardiac function in patients with acute myocardial infarction and left ventricular dysfunction. (A) Changes in LVEF after 72 h of rGLP-1 infusion (white bars) vs control subjects (black bars). (B) Changes in regional wall motion score at the per-infarct zone in rGLP-1-treated patients vs control subjects. Results indicate left ventricular function improvement in the GLP-1-treated patients compared with the control group. Modified, with permission, from Nikolaidis LA, Mankad S, Sokos GG, Miske G, Shah A, Elahi D & Shannon RP 2004b Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation* **109** 962–965.

20 non-diabetic patients with normal LV function and single-vessel coronary disease within the left anterior descending artery undergoing elective percutaneous coronary intervention (PCI; Read et al. 2011).

The cardioprotective effects of 6 h infusion of exenatide initiated 15 minutes before reperfusion was evaluated in 172 patients with ST-segment elevation MI treated with primary PCI. A significantly larger salvage index was found in the exenatide group compared with the control group (0.71 ± 0.13 vs 0.62 ± 0.16; $P=0.003$; Lonborg et al. 2012b). However, absolute infarct size was not different nor was residual left ventricle systolic function (LVEF). Interestingly, a *post-hoc* analysis of the study demonstrated that in patients with shorter durations of chest pain (≤132 min ($n=74$)), treatment with exenatide was associated with smaller infarct size (8% (Lonborg et al. 2012a) vs 11% (interquartile range 7–17), $P=0.015$) even after adjusting for myocardial area at risk ($P=0.006$). No difference was observed in infarct size in patients with longer durations of chest pain (>132 min; Lonborg et al. 2012a). Taken together, these data indicate that exenatide infusion at the time of reperfusion may reduce infarct size within a narrow clinical window of the first 2 h from the onset of chest pain.

Impact on cardiac function

Activation of GLP-1R has been associated with improvements in CV function in heart failure in preclinical (Nikolaidis et al. 2004a, Ceriello 2006, Bhashyam et al. 2010, Liu et al. 2010) and clinical settings (Sokos et al. 2006, Vilsboll 2007, Lonborg et al. 2012a). In a conscious, canine model of LV systolic dysfunction induced by rapid pacing, activation of p38 MAPK and nitric oxide (NO) synthase and an increase in GLUT1 expression led to an insulin-independent increase in myocardial glucose uptake, indicating a non-insulin-mediated mechanisms for CV benefits of GLP-1 (Bhashyam et al. 2010).

The beneficial effects of GLP-1 in the failing heart were also demonstrated in clinical settings. GLP-1 infusion for 5 weeks added to standard therapy in patients with and without diabetes and NYHA class III/IV heart failure led to improvement in LV systolic function, and exercise tolerance, as well as the 6-min walk distance, and quality of life. No changes were observed in the control group (Table 3; Sokos et al. 2006). Indeed, GLP-1 was also demonstrated to have potential to improve myocardial glucose metabolism and cardiac function in patients with heart failure and DM (Thrainsdottir et al. 2004). Interestingly, in a randomized, double-blind, crossover trial of 20 non-diabetic patients with HF NYHA class II/III, short-
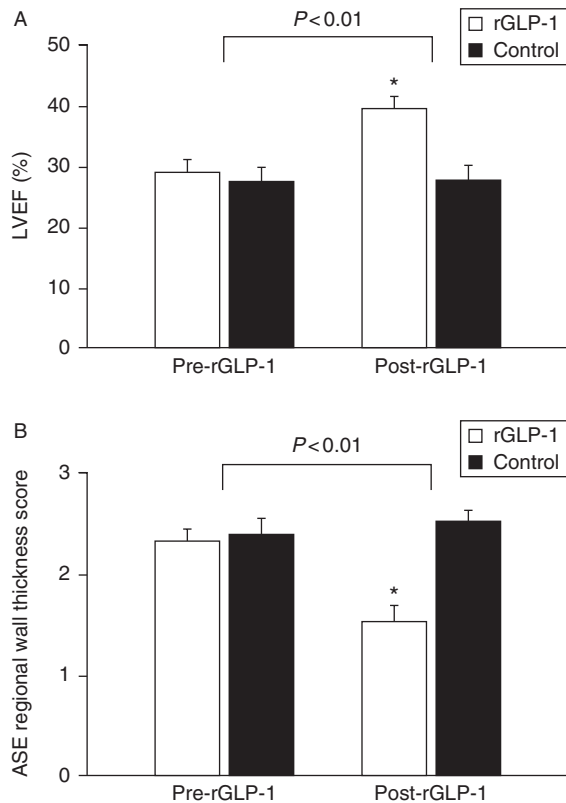
Table 3 Safety and efficacy of sustained GLP-1 infusion in with advanced heart failure. GLP-1 infusion in patients with advanced systolic hear failure (NYHA class III–IV), including both diabetics and non-diabetics, was associated with improvement in LVEF, exercise tolerance, and quality of life

	GLP-1 patients ($n=12$)		Control patients ($n=9$)	
	Baseline	5 weeks	Baseline	5 weeks
LVEF (%)	21±3	27±3*	21±4	21±4
VO2 max	10.8±0.9	13.9±0.6*	13.3±0.9	13.0±1.0
6-min walk (m)	232±15	286±12*	233±21	258±21
Minn QOL	64±4	44±5*	52±12	46±12
BNP (pg/ml)	289±90	218±102	296±129	285±152

*$P<0.001$ vs baseline. LVEF, left ventricle systolic function; VO2 max, maximal oxygen consumption; 6-min walk, 6-min walk distance test; Minn QOL, Minnesota Living with Heart Failure Quality of Life Score; BNP, brain natriuretic peptide. Reproduced, with permission, from Sokos GG, Nikolaidis LA, Mankad S, Elahi D & Shannon RP 2006 Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. *Journal of Cardiac Failure* 12 694–699.

term infusion of GLP-1 (over 48 h) increased circulating insulin levels and reduced plasma glucose concentration but had no cardiac function benefits compared with control. This indicates that incretin-based therapy may be most appropriate in advanced heart failure and long-term therapy may be required in order to see the benefits (Halbirk *et al.* 2010).

GLP-1R-independent CV effects of GLP-1

Although GLP-1R seems to transduce most of the known GLP-1 actions *in vivo*, several studies have demonstrated that cells and tissues that do not express GLP-1R can also be affected by GLP-1 (Bullock *et al.* 1996, Abu-Hamdah *et al.* 2009). Moreover, GLP-1 primary metabolite GLP-1 (9–36) and its secondary metabolites (e.g. GLP-1 (28–36); Ban *et al.* 2008, Elahi *et al.* 2008) also seem to have effects. GLP-1 (9–36) does not interact with known GLP-1R and seems to act as a weak competitive antagonist of GLP-1R located in the β-cells and in the gastrointestinal tract (Kieffer & Habener 1999). Although the literature indicates that most of the glucoregulatory effects of GLP-1 (9–36) are insulin-independent and occur in insulin resistance states (Elahi *et al.* 2008, Tomas *et al.* 2011), CV effects do not necessarily follow the same pattern. A school of thought is now emerging to suggest that the metabolites are not a product of degradation of the native peptide but rather a part of the full activation pathway of the incretin effect, resulting in additional CV benefits.

Ban et al. (2008) demonstrated that the vasodilatation and cardioprotection of GLP-1 (9–36) in a mouse model of ischemia–reperfusion injury was present even in the absence of functional GLP-1R. The authors proposed a NO/cGMP-dependent cardioprotective mechanism, supported by the finding of increased expression of cGMP and absence of effects upon NO synthase inhibition (Ban *et al.* 2008). In line with those results, a 48-h infusion of GLP-1 (9–36) in a model of pacing-induced heart failure in conscious dogs improved LV function, reduced systemic vascular resistance, and increased myocardial glucose uptake (Nikolaidis *et al.* 2005b) independent of the action of insulin. Functional improvements seen with continuous infusion of GLP-1 (9–36) paralleled the results using native GLP-1 in the same animal model, indicating that GLP-1 metabolites may play a key role in this setting (Nikolaidis *et al.* 2005b, Bhashyam *et al.* 2010; Fig. 4A, B, C and D). Although the data are promising, further studies are necessary to further elucidate the role of the GLP-1 metabolites as therapeutic agents in CVD. The work has considerable implications for use of these agents beyond glycemic control.

CV effects of DPP-4 inhibitors

DPP-4 is the first step in the breakdown of native GLP-1 (7–36) amide. Inhibition of DPP-4 became an attractive therapeutic target as such agents would prolong the circulating half-life of native GLP-1 (7–36) and prolong its insulinotropic effects. However, DPP-4 cleaves multiple peptides, many of which have demonstrated to have CV actions (Fig. 5; Drucker & Nauck 2006, Ussher & Drucker 2012), although prolonged circulating GLP-1 levels may be important in many of those actions, the circulating concentrations achieved in the plasma are threefold to fourfold lower than those with pharmacological doses of GLP-1R agonist or analogs.

Thus, attention has focused on other DPP-4 substrates that have recognized CV benefits. B-type (brain) natriuretic peptide 1–32 (BNP 1–32) is a peptide secreted by the ventricle and a key factor in regulating body fluid homeostasis and vascular tone (Ogawa *et al.* 1996, Boerrigter *et al.* 2007). Therefore, cleavage by DPP-4 leads to a reduction of diuretic and natriuretic actions and inhibition of vasodilatation (Boerrigter *et al.* 2007). Additionally, BNP seems to reduce cardiac remodeling after acute myocardial infarction (Moilanen *et al.* 2011, Palazzuoli *et al.* 2011), which could be another potential benefit of using DPP-4 inhibitors (DPP-4i). Although cardioprotection of BNP via DPP-4 inhibition was demonstrated in a porcine model of heart failure (Gomez *et al.* 2012), further studies are needed to clarify those interactions.
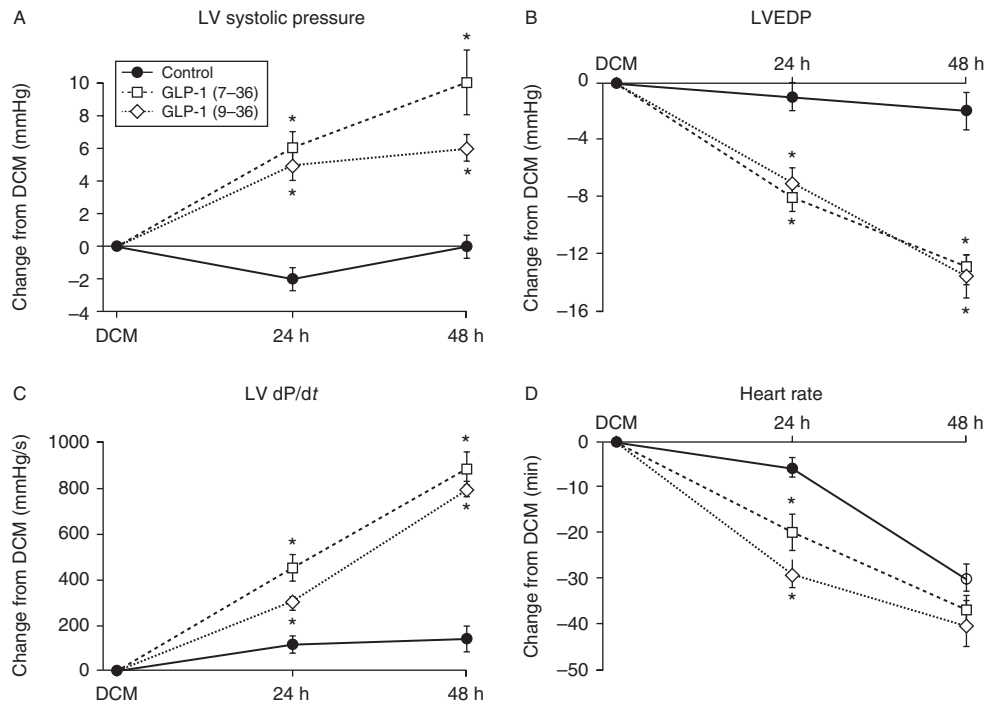
Figure 4

Positive effects of GLP-1 (7–36) and GLP-1 (9–36) on left ventricular function in conscious dogs with pacing-induced dilated cardiomyopathy. Effects of GLP-1 (7–36) ($n=9$ dogs) or GLP-1 (9–36) ($n=7$ dogs) on left ventricular pressures (A and B), contractility (C, LV dP/dt), and heart rate (D) in conscious dogs with pacing-induced dilated cardiomyopathy. Functional improvements were virtually identical with each form of the peptide compared with control (A, B and C), while there was no difference in the heart rate response, which decreased significantly in all three groups after 48 h (D). DCM, dilated cardiomyopathy; LVEDP, left ventricular end-diastolic pressure. *$P<0.05$ compared with response observed with saline control ($n=7$ dogs). Reproduced, with permission, from Nikolaidis LA, Elahi D, Shen YT & Shannon RP 2005*b* Active metabolite of GLP-1 mediates myocardial glucose uptake and improves left ventricular performance in conscious dogs with dilated cardiomyopathy. *American Journal of Physiology. Heart and Circulatory Physiology* **289** H2401–H2408.

Stromal cell-derived factor-1α (SDF1α) is a chemokine that promotes homing of endothelial progenitor cells to sites of injury and therefore promotes neoangiogenesis (Asahara *et al.* 1997). Because SDF1α is cleaved by DPP-4, DPP-4 inhibition increases levels of circulating SDF1α. As a result, sitagliptin increased levels of circulating endothelial progenitor cells in T2DM patients (Fadini *et al.* 2010), while diprotin A in association with granulocyte colony-stimulating factor decreased infarct size and enhanced neovascularization, LVEF, and survival in a rodent model of MI (Zaruba *et al.* 2009). Besides the potential beneficial actions of BNP and SDF1α, other DPP-4 substrates may also have CV affects. Thus, while DPP-4 inhibition and GLP-1 analogs may have similar CV profiles, they may be achieved through differing mechanisms.

Effects on BP

Sitagliptin reduced blood pleasure in a rodent model of metabolic syndrome (Ferreira *et al.* 2010). Discrepant results were found in a spontaneously hypertensive rat model, with benefit only observed in the young animals (5 vs 20 weeks old; Pacheco *et al.* 2011). Nevertheless, small clinical studies in non-diabetic (Mistry *et al.* 2008) and diabetic (Ogawa *et al.* 2011) hypertensive patients treated with sitagliptin identified an association with reduction of BP in the absence of weight loss. Similar results were also observed in larger studies in T2DM patients (Bergenstal *et al.* 2010, Russell-Jones *et al.* 2012). Notably, these effects on BP occur in the absence of significant weight loss.

DPP-4 inhibition in ischemic heart disease

DPP-4 inhibitors probably share some GLP-1R-dependent cardioprotective mechanisms previously described (Ogawa *et al.* 2011), although it should be noted that DPP-4 inhibitors yield physiological not pharmacological levels of circulating GLP-1. Indeed, preclinical studies demonstrate cardioprotection associated with DPP4-1 therapy in *in vivo* models (Ye *et al.* 2010, Huisamen *et al.* 2011,
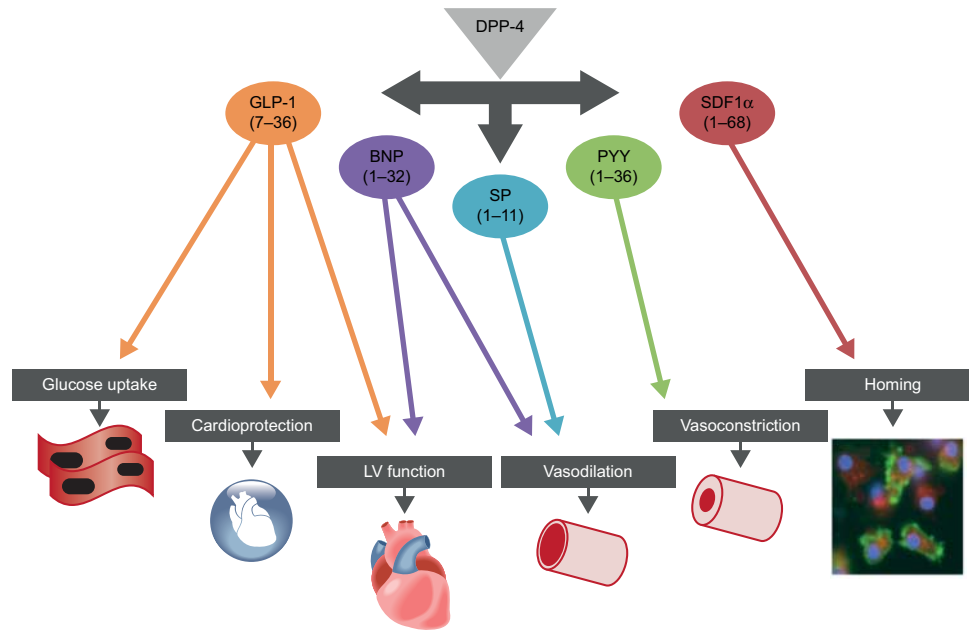
Figure 5

DPP-4 substrates that directly or indirectly regulate cardiovascular function. Multiple DPP-4 substrates have been identified that act on multiple peripheral tissues that influence the cardiovascular system.

Hocher *et al.* 2013). Moreover, data indicates that enhanced angiogenesis may also play a role in the cardioprotection as demonstrated by a study addressing the adjunctive affect of SDF1α (Zaruba *et al.* 2009). In clinical settings, the DPP-4i sitagliptin improved global cardiac performance and attenuated post-ischemic stunning in 14 patients with coronary artery disease during dobutamine stress echocardiography (Read *et al.* 2010). More recently, the preliminary results of the TIMI 53/Savor trial with saxagliptin indicate that while safe, this DPP-4i did not reduce composite CV events of CV death, MI, or stroke. The complete results of the study will be released shortly.

Role of DPP-4 inhibition in cardiac function

Few preclinical studies have directly addressed the role of DPP-4 inhibition in heart failure models. Sitagliptin increased stroke volume and reduced HR in a porcine model of pacing-induced heart failure (Gomez *et al.* 2012). On the other hand, vildagliptin had neutral effects on cardiac function in a rat model of ischemic cardiomyopathy (Yin *et al.* 2011). As previously described, the first clinical trial looking into CV effects of vildagliptin in patients with diabetes and NYHA class I–III ($n=254$) confirmed the neutral effects in cardiac function measured by the mean increase in EF in the treatment group

compared with the control group (4.1 vs 3.5% respectively, $P=0.67$) and raised safety concerns related to a potential negative effect on LV compliance and an increase in non-cardiac mortality (McMurray 2013). Taken together, these early data indicate that the CV profile of DPP-4 inhibitors may vary from the CV profile of the native GLP-1 peptide and GLP-1R agonists and analogs.

Summary

Incretin-based therapies have emerged as potent anti-diabetic agents of particular clinical interest due to the emerging evidence that they are associated with CV benefits. Currently, over 120 000 patients are enrolled in CV outcome trials with incretin-based therapies designed to demonstrate safety and efficacy. Specifically, most of these trials have primary major adverse cardiac event (MACE) outcomes of CV death, MI, or need for revascularization. As such, we stand on the verge of learning a great deal about the ability of incretin-based therapies to improve CV outcomes in T2DM. Nonetheless, much remains to be learned with respect to this promising class of agents. First, it is not certain whether this is a class effect or whether there are differences between types of incretin-based therapies (native peptide vs GLP-1 long-acting analogs vs DPP-4 inhibitors). A related question bears on whether the metabolites contribute

to CV benefits. Secondly, it is unclear whether incretin-based therapies have CV benefits that extend beyond T2DM. Finally, the use of incretin-based therapies as metabolic modulators in heart failure represents a new therapeutic approach in this important CV domain. Time and careful study will tell whether these agents will establish a new therapeutic paradigm.

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