Incretin-based therapies for the failing heart

John R. Ussher[a,b,c] and Jonathan E. Campbell[d,e,f]

The gut incretin hormone, glucagon-like peptide 1 (GLP-1), regulates islet hormone secretion, circulating glucose levels, and body weight, making it an attractive agent for the treatment of type 2 diabetes. As cardiovascular disease represents the leading cause of death in patients with diabetes, it is important to understand how GLP-1-based drugs impact the cardiovascular system. Here, we review recent advances in our understanding of two incretin-based drug classes, GLP-1 receptor agonists and dipeptidyl peptidase 4 inhibitors, specifically in the context of heart failure. In addition to illustrating how these therapies influence cardiac signaling processes, we describe the cardioprotective mechanisms identified in preclinical studies, while reviewing the clinical data from studies in patients with type 2 diabetes. We end by speculating why observations made in preclinical studies are not necessarily reflected in a clinically relevant patient population. *Cardiovasc Endocrinol* **5:86–92 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.**

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[a]Faculty of Pharmacy and Pharmaceutical Sciences, [b]Alberta Diabetes Institute, [c]Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada, [d]Duke Molecular Physiology Institute, Departments of [e]Medicine and [f]Pharmacology and Cancer Biology, Duke University, Durham, North Carolina, USA

Correspondence to Jonathan E. Campbell, PhD, 300 N Duke Street, Duke University, Durham, NC 27701, USA
Tel: +1 919 684 4865; fax: +1 919 684 0905;
e-mail: jonathan.campbell@duke.edu

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Introduction

The incretin hormone glucagon-like peptide 1 (GLP-1) is a gut-derived peptide released from intestinal enteroendocrine cells in response to the ingestion of nutrients. Significant attention has been focused on understanding the biology of the GLP-1 action as this hormone exerts robust effects on β-cell function, highlighted by its ability to potentiate glucose-stimulated insulin secretion [1]. Two agents that enhance GLP-1 action have been approved for use in the clinic: (a) GLP-1 receptor (GLP-1R) agonists and (b) inhibitors of dipeptidyl peptidase 4 (DPP-4), an enzyme that inactivates GLP-1. As such, a need to understand the extrapancreatic actions of this hormone has arisen. In particular, the actions of GLP-1-based drugs on cardiovascular biology in clinically relevant populations have drawn remarkable interest in recent years since cardiovascular disease represents the leading cause of death in diabetic patients [2,3].

As we have described in extensive detail previously, the cardiovascular biology of GLP-1 and DPP-4 [4,5], the aim of this review is to focus specifically on the role of GLP-1 and DPP-4 in the failing heart. Heart failure (HF) is defined as 'a complex clinical syndrome that can arise from any structural and/or functional cardiac disorder that diminishes the ability of the ventricle to fill with or eject blood,' which has adverse consequences on human health, affecting more than five million individuals in North America alone [6]. The comorbidity of HF is of particular relevance to type 2 diabetes (T2D) patients as it is associated with a significant increase in the risk of death in these individuals [7,8]. In addition, we will focus on recent developments showing that GLP-1R agonists and DPP-4 inhibitors (DPP4i) cannot be considered equivalent with respect to cardioprotective effects as they produce divergent actions on ventricular function in both preclinical and clinical studies. Finally, we will discuss observations from recent cardiovascular outcomes, suggesting that some DPP4i may increase the risk of hospitalization for HF in T2D patients, and the potential for this to be a drug class-specific effect.

GLP-1 and DPP-4

GLP-1 is synthesized and secreted by L-cells found throughout the small and large intestine and exerts its biological actions through a specific G-protein-coupled receptor (GLP-1R) found in select tissues throughout the body.

DPP-4 is a multifunctional protein belonging to the serine peptidase/prolyl oligopeptidase family. GLP-1 is one of several biological substrates for DPP-4 and is cleaved at the N-terminus to yield GLP-1(9–36). Truncation of GLP-1 renders this peptide biologically inactive in terms of eliciting a functional receptor response, and consequently, DPP4i have been developed as a therapeutic strategy to increase endogenous levels of intact GLP-1 to improve glycemia in patients with T2D [9].

GLP-1R signaling and actions in the myocardium

Although initial studies had identified a ventricular GLP-1R in various mammalian species [10,11], demonstration that many of the widely used GLP-1R antibodies are nonspecific has questioned the accuracy of these findings

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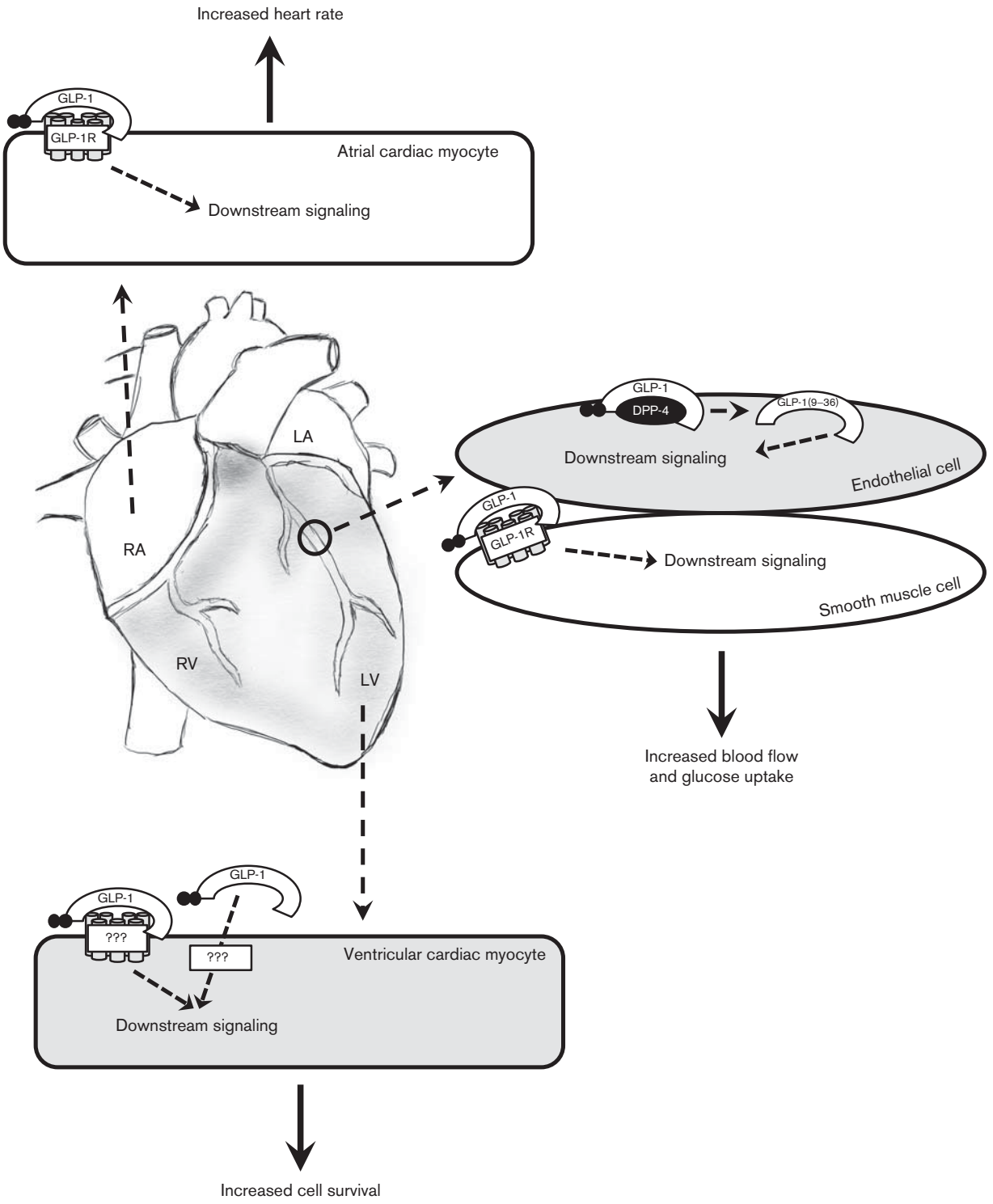
[12]. Furthermore, a number of recent studies combining sophisticated mouse genetics with PCR amplification of the full-length *Glp1r* coding region have shown that the cardiac GLP-1R is localized to atrial cardiac myocytes and vascular smooth muscle cells (VSMCs), but is not present in significant quantities within ventricular cardiac myocytes (Fig. 1) [13,14]. The use of a novel, validated mouse monoclonal antibody in monkey and human heart tissue confirmed these findings, and further localized the GLP-1R to specific regions within the sinoatrial node [15]. On the basis of these developments, the downstream signaling changes observed in the ventricular myocardium following systemic treatment with GLP-1R agonists are likely because of indirect actions following GLP-1R activation in peripheral tissues [5,16,17]. For example, GLP-1R activation in β-cells augments glucose-stimulated insulin secretion [1], and systemic treatment with GLP-1R agonists such as liraglutide is frequently associated with increased myocardial Akt phosphorylation [17,18], a critical downstream target of insulin receptor signaling [19]. Indeed, systemic liraglutide administration in mice fails to increase myocardial Akt phosphorylation in global *Glp1r*-deficient (*Glp1r*−/−) mice, but is restored in *Glp1r*−/− mice following restoration of β-cell expression of the human *GLP1R* [17], a mouse model that shows selective restitution of GLP-1R agonist-induced insulin secretion [20]. Accordingly, this β-cell/cardiac myocyte axis is likely responsible for the observation that systemic GLP-1R administration enhances myocardial glucose metabolism in preclinical studies [11,21,22]. Indirect GLP-1R-mediated actions on myocardial metabolism may also contribute toward the improvements in ventricular function observed in some HF patients treated with GLP-1R agonists (see the GLP-1R agonists and cardiovascular outcomes in HF section); a potentially important effect as optimization of cardiac energetics is a novel approach being pursued for the treatment of HF [23].

Despite the finding that the GLP-1R is not expressed within ventricular cardiac myocytes [13–15], a number of studies in the ex-vivo heart or in-vitro cultured cardiac myocytes show that GLP-1R agonists influence cardiac signaling [4,5]. This also includes direct activation of insulin signaling as observed by increases in Akt phosphorylation [24], as well as increases in cyclic AMP (cAMP) generation and cAMP response element-binding protein phosphorylation/activation [24,25], findings consistent with GLP-1R activation in islet β-cells [1]. The reasons why direct treatment of the ventricular myocardium or cardiac myocytes that do not express the canonical GLP-1R would produce these signal transduction-mediated events are unclear, but may involve the DPP-4-mediated GLP-1 cleavage product, GLP-1(9–36) (Fig. 1), which appears to harbor its own independent biological activity [10,24,26]. In support of this, a number of studies have shown that GLP-1(9–36) increases Akt phosphorylation in cultured neonatal ventricular cardiac myocytes [24], while increasing myocardial glucose uptake both *ex vivo* and *in vivo* [10,26]. In addition, the vast majority of studies that have shown direct effects of GLP-1R agonists in ventricular cardiac myocytes have utilized native GLP-1, which may be rapidly converted into GLP-1(9–36) in these paradigms [24,25,27]. In contrast, the relatively DPP-4 resistant GLP-1R agonist, liraglutide, and the highly DPP-4 resistant GLP-1R agonist, exendin-4, have both been reported to activate downstream signaling pathways in ventricular cardiac myocytes, including the stimulation of cAMP production [18,24]. Such observations suggest that ventricular cardiac myocytes may also express a second unidentified and yet to be characterized GLP-1R or that non-receptor-mediated mechanisms are involved (Fig. 1).

These new findings, especially considering that the cardiac GLP-1R appears to be localized to atrial cardiac myocytes and VSMCs [13–15], beg the question as to what is the physiological role for the cardiac GLP-1R. One possibility involves the regulation of heart rate (HR), which would be consistent with the atrial GLP-1R confined to myocytes within the sinoatrial node of human and monkey heart tissue (Fig. 1) [15], coupled with numerous findings that systemic treatment with GLP-1R agonists increases HR in animals and humans [17,28–32]. The GLP-1R-mediated increase in HR may arise from the direct activation of the atrial GLP-1R, as direct treatment of isolated working rat hearts that have intact atria with the GLP-1R agonist, ZP131, increases HR [28]. Conversely, the autonomic nervous system may also be involved as modulation of both sympathetic and parasympathetic activity has been implicated in the GLP-1R-mediated increase in HR in both animals and humans [29,33,34]. Nevertheless, as increases in HR are associated with an increased risk for cardiovascular mortality in hypertensive patients with left ventricular (LV) hypertrophy [35], understanding the precise mechanism (s) by which GLP-1R agonists increase HR is an area of growing importance. Another potential role for the atrial GLP-1R involves stimulating atrial natriuretic peptide (ANP) secretion, which may contribute toward the reductions in blood pressure frequently observed following the systemic administration of GLP-1R agonists in animals and humans [4,5]. However, the potential existence of a GLP-1R-ANP axis in humans has not been determined conclusively, with some studies supporting [36] and others challenging [31,37] the observations in animals. With respect to the VSMC GLP-1R, the expression of the GLP-1R in VSMCs may explain GLP-1-mediated increases in both microvascular and coronary blood flow in animals [38,39], and acetylcholine-induced forearm blood flow in humans [40]. Similarly, as endothelial cells appear to express DPP-4, but not the GLP-1-1R (Fig. 1) [5], GLP-1(9–36) may also contribute toward the vascular actions of GLP-1 as GLP-1(9–36) has been reported to increase human aortic endothelial cell viability

Fig. 1



GLP-1R in the cardiovascular system. The known actions of GLP-1R signaling in the myocardium are shown in the context of recent findings showing GLP-1R localization to vascular smooth muscle cells and atrial cardiac myocytes with the sinoatrial node of the right atria. Direct activation of the vascular smooth muscle cell GLP-1R, combined with DPP-4-mediated GLP-1(9–36) acting on endothelial cells likely explains how GLP-1R agonists increase microvascular blood flow in coronary vessels and enhance myocardial glucose uptake. However, atrial GLP-1R activity within the sinoatrial node of the right atria may be involved in GLP-1R agonist-mediated increases in heart rate. Although the GLP-1R appears to expressed negligibly in ventricular cardiac myocytes, the presence of a second and unidentified GLP-1R, or nonreceptor-mediated mechanisms, may explain the direct actions of GLP-1R agonists on ventricular cardiac myocyte survival that have been reported. DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; GLP-1R, glucagon-like peptide 1 receptor; LA, left atria; LV, left ventricle; RA, right atria; RV, right ventricle.

following exposure to hypoxia/reoxygenation [24] and to enhance vasodilation of mesenteric arteries isolated from both wild-type and *Glp1r*−/− mice [10].

The myocardial response following DPP-4 inhibition

Although the broad effects of DPP-4 inhibition are frequently assumed to be mediated by an increase in bioactive GLP-1, DPP-4 inhibition prevents the degradation of a number of substrates, some of which may also impact myocardial signaling (reviewed extensively elsewhere [4,9]). This includes stromal cell-derived factor-1, a key chemokine that promotes homing of endothelial progenitor cells to sites of tissue injury [4,9]. Indeed, treatment with DPP-4i to prevent stromal cell-derived factor-1 cleavage in conjunction with granulocyte-colony stimulating factor to promote stem cell mobilization enhances myocardial repair and LV function in experimental models of myocardial infarction [41,42]. Furthermore, brain natriuretic peptide (BNP) appears to be cleaved by DPP-4 in humans, and as both BNP(1–32) and the DPP-4-generated BNP(3–32) produce natriuresis and vasodilation, DPP-4-mediated changes in this peptide and its effects on ventricular function are areas that require further study in patients with T2D [4]. Of interest, the other incretin hormone, glucose-dependent insulinotropic peptide (GIP), is also a substrate for DPP-4 and as GIP receptor activation controls insulin and glucagon secretion [1,43], changes in bioactive GIP levels may also influence myocardial energy metabolism through a β-cell/cardiomyocyte axis. Furthermore, adipocyte GIP receptor activity has also been linked to obesity [44], which is a significant risk factor for cardiovascular disease. Other potential DPP-4 substrates that may regulate the cardiovascular system directly or indirectly include substance P, neuropeptide Y, and peptide YY, to name a few [4,9]. Collectively, it remains challenging to delineate whether DPP-4 inhibition leads to meaningful changes in cardioactive DPP-4 substrates and their breakdown products and to understand mechanistically how these changes, in unison, influence cardiac signaling and subsequent ventricular function.

GLP-1R agonists and cardiovascular outcomes in HF

A number of preclinical studies to date show that systemic treatment with GLP-1R agonists exerts beneficial actions on ventricular function during experimental HF. Key studies in dogs utilizing the rapid right ventricular pacing model of HF have shown that a 48 h GLP-1 infusion increases LV function, which is associated with increases in myocardial glucose uptake as a result of p38 mitogen-activated protein kinase-induced nitric oxide synthase activation and GLUT1 translocation to the sacrolemmal membrane [11,22]. Moreover, these investigators have also shown that a 3-month infusion of GLP-1 in the spontaneously hypertensive, HF-prone rat (SHHF) delays the progression of HF as indicated by a lack of deterioration in LV function and cardiac hypertrophy compared with SHHF rats infused with vehicle control [45]. Similarly, beneficial actions with the GLP-1R agonist, liraglutide, have been observed in experimental models of ischemic HF and obesity-induced cardiomyopathy [18]. A 1-week treatment with liraglutide before permanent left anterior descending (LAD) coronary artery ligation improves LV function at 4 weeks after LAD coronary artery ligation and is associated with a reduction in adverse LV remodeling and enhanced myocardial insulin signaling [18]. With respect to obesity-mediated cardiomyopathy, a 1-week treatment with liraglutide in mice fed a high-fat diet for 32 weeks restores LV function and reduces cardiac inflammation, findings dependent on the activation of 5′-AMP-activated protein kinase, as they are prevented in obese mice concurrently treated with the 5′-AMP-activated protein kinase inhibitor compound C [46].

The preclinical benefits attributed to systemic GLP-1R agonism on the failing heart may be translatable to humans, although the findings to date have not been as robust. In a small nonrandomized study in 21 patients with New York Heart Association (NYHA) class III or IV HF, a 5-week infusion with native GLP-1 was associated with significant improvements in LV ejection fraction, maximum myocardial ventilation oxygen consumption, and 6-min treadmill walking distances [47]. Moreover, improvements in the patients' overall quality of life were also observed as indicated by reductions in the Minnesota Living with HF quality-of-life scores. Conversely, a double-blind crossover study involving a 48 h infusion with native GLP-1 failed to improve LV function in 20 patients with NYHA class II and III HF, and actually resulted in mild increases in both diastolic blood pressure and HR [48]. The reasons for the discrepancies are not clear, but because of the small patient number in each study, definitive conclusions cannot be made. Results from the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial show that treatment with the GLP-1R agonist lixisenatide does not reduce rates for hospitalization because of HF (15.0 vs. 15.5% event rate) in T2D patients and was noninferior in terms of cardiovascular safety compared with placebo (standard of care) [49]. However, treatment with the GLP-1R agonist albiglutide in a randomized manner could not reproduce many of the findings obtained in animal models of ischemic heart disease [21] as a 3-month treatment with albiglutide failed to increase myocardial glucose metabolism, 6-min treadmill walking distances, or quality of life in 21 patients with NYHA class II and III HF [50]. However, similar to the findings in the study by Sokos *et al.* [47], these authors did observe an increase in peak myocardial ventilation oxygen consumption. Recent reports from the LEADER (Liraglutide Effect and Action in Diabetes [51]: Evaluation of Cardiovascular Outcome Results – A Long-Term Evaluation) trial indicate that liraglutide reduces major adverse cardiovascular events [51] in T2D patients with high cardiovascular risk and this was associated with a trend

($P=0.14$) toward reduced hospitalization rates for HF. Similarly, the GLP-1R agonist semaglutide has also recently been reported to reduce the risk for major adverse cardiovascular events during the SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) trial [52]. In contrast, results from the FIGHT (A Randomized Trial of Liraglutide for High-Risk Heart Failure Patients with Reduced Ejection Fraction) trial showed in 300 advanced HF patients a clear trend toward an increased risk for the composite endpoint of death or HF rehospitalization in those treated with liraglutide [53,54]. The divergent findings between the LEADER and FIGHT trial are currently unknown and may be because of the fact that the patient populations in the FIGHT trial included advanced HF patients. It should also be noted that GLP-1R agonist cardiovascular outcomes trials are not designed to assess improvement or worsening of HF in their patient populations, and do not assess endpoints for HF assessment (i.e. 6-min treadmill test, maximum myocardial ventilation oxygen consumption, LV ejection fraction, etc.).

Taken together, GLP-1-mediated and GLP-1(9–36)-mediated increases in blood flow may certainly account for observed improvements in ventricular function during HF in rodents and humans following treatment with native GLP-1. Whether activation of the VSMC GLP-1R also contributes toward these improvements remains to be determined, as does indirect GLP-1R-mediated improvements in myocardial metabolism through changes in circulating factors such as increases in insulin levels. As already mentioned above, because increases in HR are associated with an increased risk for cardiovascular mortality in hypertensive patients with LV hypertrophy [35], it will be important to determine whether atrial GLP-1R activity may also influence cardiovascular outcomes in patients with both T2D and HF.

DPP-4i and cardiovascular outcomes in HF

Similar to GLP-1R agonists, the other incretin-based drug class, the DPP-4i, has also shown beneficial cardiovascular effects in preclinical studies [4,5,9]. In relation to the failing heart, numerous studies support that inhibition of DPP-4 can attenuate adverse LV remodeling and improve LV function in response to experimental HF. For example, DPP-4 deficient (*Dpp4*$-/-$) mice are protected against both ischemia-induced HF and pressure overload-induced HF, resulting from either permanent LAD coronary artery occlusion or transverse aortic constriction (TAC), respectively [55,56]. Similarly, DPP-4 deficient rats are also protected against abdominal aortic constriction-induced HF [57], as well as show a preservation of both systolic and diastolic function following TAC-induced HF [58]. Furthermore, treatment of T2D mice with sitagliptin for 8 weeks, by supplementation in the diet, before LAD coronary artery ligation improves survival rates and reduces rates of cardiac rupture [56]. Similarly, the treatment of C57BL/6J mice with vildagliptin in drinking water for 4 weeks, initiated the day after TAC surgery, improves survival, while mildly increasing LV function and decreasing adverse LV remodeling and cardiac myocyte apoptosis [59].

Despite these beneficial actions in preclinical studies, translational success in humans with T2D has been limited as the results of the cardiovascular outcomes trials such as EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) [60], SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53) [61], and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) [62] have not yielded positive signs for improving cardiovascular risk and reducing hospitalization rates for HF. In contrast, the recent observation from SAVOR-TIMI 53 that saxagliptin increases hospitalization rates for HF [61] has led to interest in determining whether this observation is a drug class-specific effect, and if so, how does DPP-4 inhibition adversely affect the myocardium and increase potential risk for HF? Moreover, a study in 254 patients with T2D and NYHA class I, II, or III HF treated with vildagliptin reported increases in LV end-diastolic and LV end-systolic volumes [63], further supporting a drug-class-specific effect of DPP-4i that may lead to mild deterioration in ventricular function in diabetic patients. It should also be noted that, in general, DPP4i appear to be cardiovascular safe (noninferior to standard of care/placebo), and that both TECOS and EXAMINE did not report increased hospitalization rates for HF. However, a recent meta-analysis pooled data from 43 randomized-controlled trials and 12 observational studies and concluded that current evidence suggests that DPP4i do lead to a small increase in the risk for hospitalization for HF in patients with existing cardiovascular diseases or multiple risk factors for vascular diseases [64]. Nevertheless, this meta-analysis also reported that the overall quality of the evidence formulating these conclusions was low, and thus additional randomized-controlled trials are needed before meaningful and definitive conclusions can be made in terms of DPP4i and HF.

The reasons for these divergent preclinical versus clinical observations remain elusive. However, the fact that the vast majority of DPP-4i studies in experimental models of HF utilize young and healthy animals devoid of any insulin resistance or T2D [57,59] or commence DPP-4i therapy at the onset of the insult that produces insulin resistance/T2D [56] may be implicated. Intriguingly, a recent study showed that the DPP-4 inhibitor MK-0626 leads to a decline in LV function and increase in cardiac fibrosis in older mice with established T2D [55]. Hence, DPP-4 inhibition yields a differential cardiovascular outcome response in diabetic versus lean and otherwise healthy animals. In addition, a separate group of older,

T2D mice treated with liraglutide showed improvements in LV function post-TAC compared with MK-0626 and vehicle control-treated animals. These findings indicate that GLP-1R agonists and DPP-4i have divergent actions on the cardiovascular system and cannot be considered equivalent, despite both drug classes improving glycemia by enhancing incretin hormone action. Conversely, obese and insulin-resistant rats subjected to permanent LAD ligation to induce myocardial infarction, followed by an 8-week treatment with vildagliptin showed a significant improvement in survival and ventricular function [65]. The reasons for the discrepancies between these two studies utilizing different DPP4i in models of established T2D are unknown, and emphasize the need for additional mechanistic studies before definitive conclusions on DPP4i and HF risk can be made.

Important considerations, future directions, and final summary

Taken together, the re-evaluation of the tools to detect tissues/cell types expressing the GLP-1R has led to a number of advancements that have improved our understanding of how GLP-1R agonists may directly and/or indirectly impact ventricular function in patients with T2D. Expression of the GLP-1R in VSMCs and a role for DPP-4-generated GLP-1(9–36) on endothelial cells may explain how GLP-1R agonists increase microvascular and coronary blood flow (Fig. 1), whereas indirect actions may explain how GLP-1R agonists potentially improve myocardial metabolism. Although atrial GLP-1R localization may explain why GLP-1R agonists are frequently associated with mild increases in HR in humans (Fig. 1), how the atrial GLP-1R controls HR remains to be determined and is an active area of ongoing investigation. Although GLP-1R agonists and DPP4i may be considered equivalent on the basis of the principle that they take advantage of incretin hormone action to improve glycemia in diabetic patients, recent findings from cardiovascular outcomes trials suggesting that DPP-4i may increase the risk for hospitalization for HF indicate divergent actions of these two drug classes. Thus, future studies should be aimed at improving our understanding of the cardiovascular biology of the numerous DPP-4 substrates and how they might contribute toward this potential HF signature associated with DPP-4i.

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Conflicts of interest

There are no conflicts of interest.

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