Mechanism of cardiovascular disease benefit of glucagon-like peptide 1 agonists

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Glucagon-like peptide 1 (GLP-1)-based therapies reduce hyperglycaemia in type 2 diabetes. Diabetes cardiovascular comorbidity remains prevalent, although current treatments are effective at reducing hyperglycaemia. GLP-1 exerts specific actions on the cardiovascular system in both healthy individuals and patients with cardiovascular pathology, and GLP-1 therapies have improved the cardiovascular profile of diabetic patients. GLP-1 exerts its action by binding to its receptor (GLP-1 receptor) at the cell surface. Mechanistically, it is not clear how GLP-1 therapies exert beneficial effects on the cardiovascular system. It is difficult to arrive at any conclusions on the ability of GLP-1 receptor agonism to reduce cardiovascular disease from animal/human studies because of varying experimental designs. This review highlights recent findings from long-term human GLP-1 therapy studies, and summarizes postulated mechanisms as to how GLP-1 receptor agonism may alleviate cardiovascular disease. *Cardiovasc Endocrinol Metab* **7:18–23**

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Type 2 diabetes (T2D) is a chronic complex multifactorial disease with an incompletely understood aetiology and pathogenesis [1,2]. The majority of T2D patients are overweight (60–90% in western countries), implying that diets involving excessive nutrient consumption cause disease pathogenesis [3]. However, this does not explain how individuals with a BMI of less than or equal to 25 develop T2D and the majority of overweight individuals remain disease free [2,4]. Interestingly, ~50% of T2D patients are not overweight in Japan [5]. It is also noteworthy that overweight patients have been reported to have a lower mortality rate because of cardiovascular disease (CVD) than normal-weight patients, termed 'the obesity paradox' [6]. The obesity paradox implies that the diabetic phenotype promotes CVD independent of patient BMI. Despite current treatments being effective at reducing hyperglycaemia, diabetes cardiovascular (CV) comorbidity remains prevalent, and therefore novel therapies are desirable: ~75% of diabetic patients die from CVD [7]. Evidence suggests that glucagon-like peptide 1 (GLP-1) exerts specific actions on the cardiovascular system (CVS) in both healthy individuals and patients with CV pathology, and GLP-1 therapies have improved the CV profile of diabetic patients [8,9].

The best-characterized function of GLP-1 is its promotion of the incretin effect [9]. The incretin effect is reduced in T2D – incretin hormones account for less than 20% of the insulin release after glucose ingestion in T2D patients compared with 70% in nondiabetic individuals [10]. The current consensus is that GLP-1 levels are normal in T2D, but its action is reduced [11]. GLP-1 has a very short half-life (~1.5 min) because of its rapid proteolytic degradation in the plasma by dipeptidyl peptidase IV (DPP-IV) enzymes [11]. The DPP-IV resistant GLP-1 analogues are effective at reducing hyperglycaemia in T2D patients as they prolong the GLP-1 response because of their extended half-lives [8]. However, GLP-1 also has extrapancreatic functions (Fig. 1) [9]. Importantly, GLP-1 therapies induce weight loss, which is associated with reducing CVD in diabetic and nondiabetic patients [8,9]. GLP-1-based therapies also appear to exert other specific actions in diabetes [9].

GLP-1 induces its effects by acting as an agonist to the glucagon-like peptide 1 receptor (GLP-1R). The effects induced by GLP-1 vary in different tissues as GLP-1R is coupled to a range of intracellular signalling pathways in different tissues, each of which promotes the desired physiological response elicited by receptor activation [12,17]. GLP-1 also indirectly affects organs through the insulin secretion that it promotes – ~28% of the postprandial insulin released into circulation is because of the action of this hormone [13,18]. GLP-1R knockout and knockdown studies in mice have shown that the ability of GLP-1 to act as an incretin hormone is dependent on the presence of its receptor in islet β-cells [19,20]. GLP-1R is a class B G-protein-coupled receptor, consisting of a large hydrophilic N-terminal extracellular domain, seven hydrophobic transmembrane α-helices (TM1-7) joined by three hydrophilic extracellular loops (ECL1-3) and three intracellular loops (ICL1-3), and an intracellular

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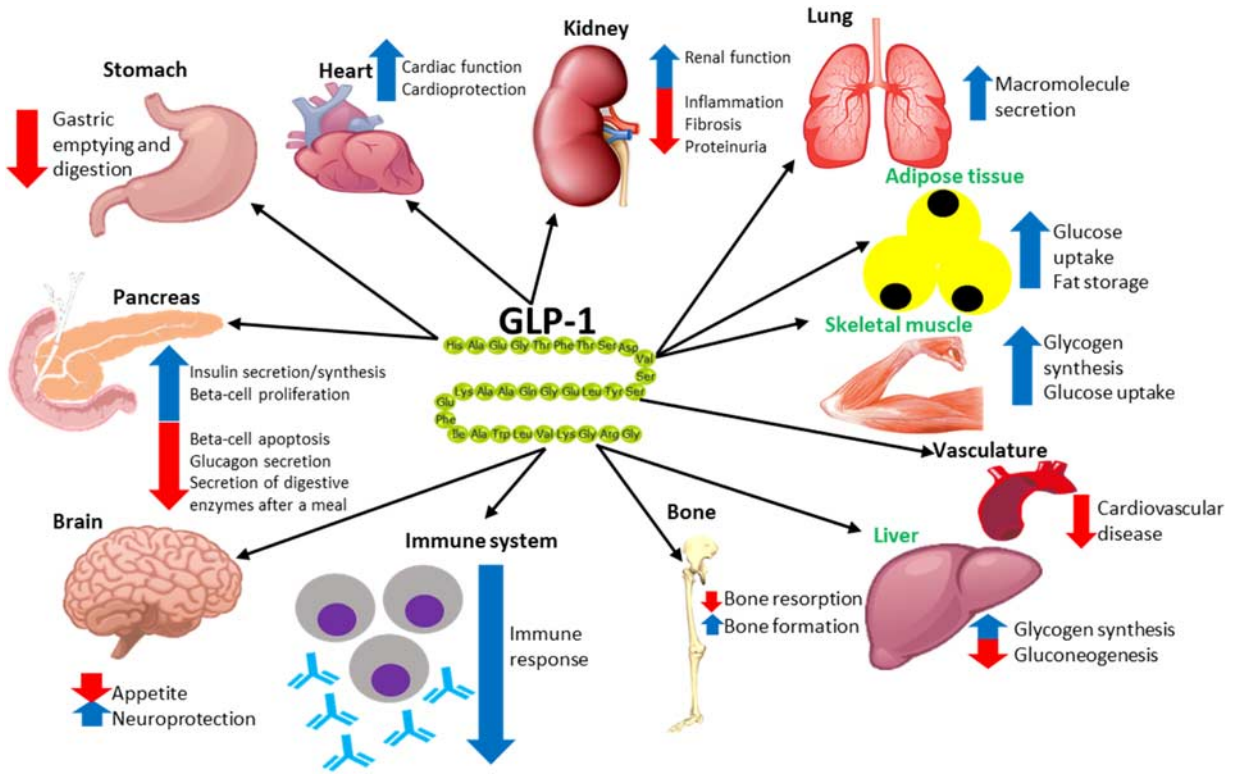
Fig. 1



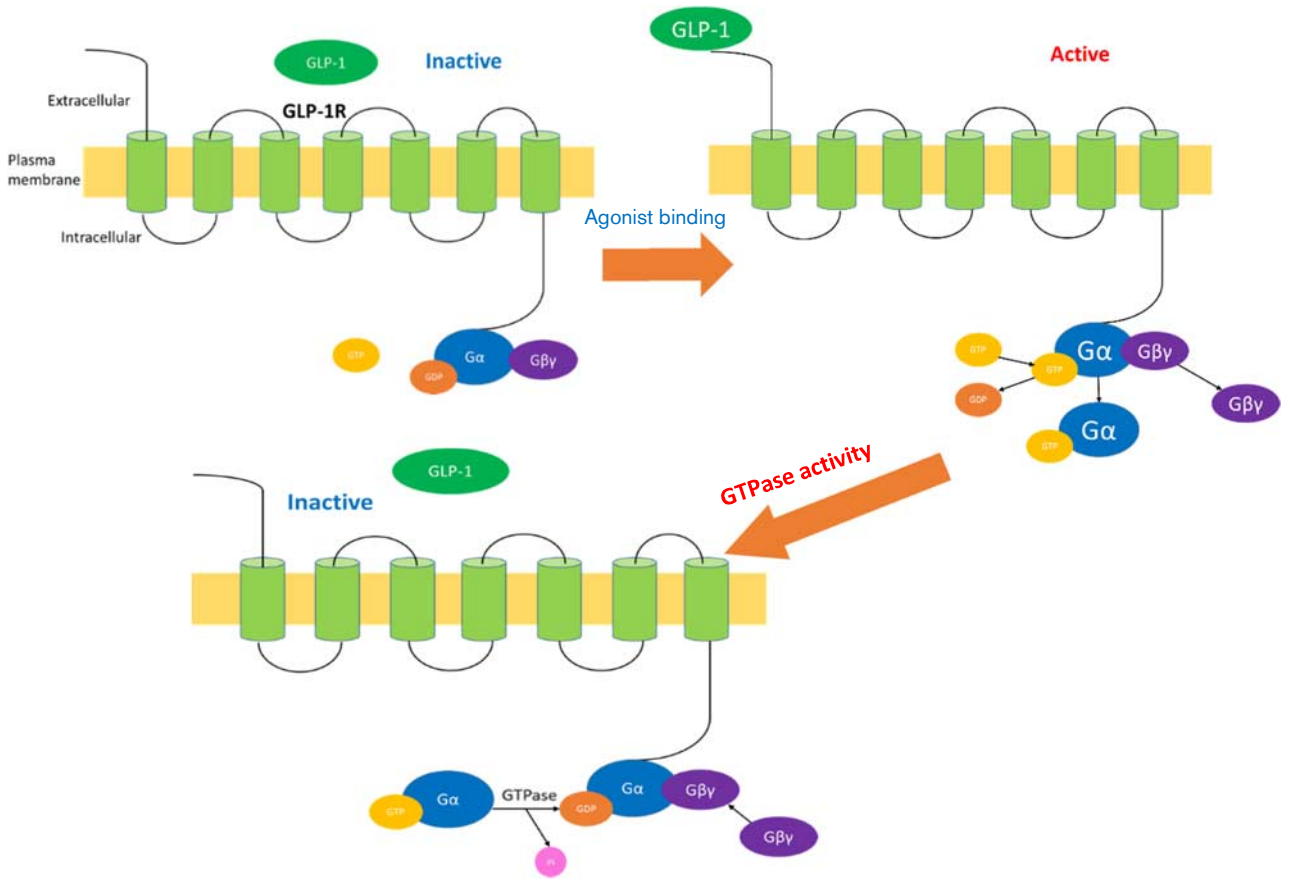
Summary of the effects that glucagon-like peptide 1 (GLP-1) has on various organs. Organs highlighted in green do not express GLP-1 receptor, but GLP-1 has mediated direct insulin-like effects during experimental settings. This figure is adapted from de Graaf and colleagues [8,12–16].

C-terminal domain. The GLP-1R C-terminal domain interacts with heterotrimeric G-proteins that consist of α, β and γ subunits that activate downstream signalling pathways upon agonist (GLP-1) binding (Fig. 2) [17,21–24].

There are currently five licenced GLP-1-based therapies, one of which has two modes of delivery (exenatide as twice-daily Byetta or once-weekly Bydureon) [25], and semaglutide is being considered by regulatory authorities [26]. These have differing levels of efficacy on glycaemic control and weight loss, perhaps because of differing GLP-1R activation of these drugs – for example, because of different penetration of the central nervous system [27]. Both animal and human studies generally suggest that GLP-1 therapies exert beneficial CV actions [9].

Chronic GLP-1R agonism in rodents was reported to reduce blood pressure (BP) and prevent hypertension [28–31]. However, acute GLP-1 infusion in rodents increases heart rate and BP [9,32]. Human short-term clinical trials have reported conflicting findings as acute GLP-1 therapy has had no effect on BP and heart rate, or increased both [9]. GLP-1 analogue-based and DPP-IV inhibition-based therapies reduced plasma lipid levels in healthy and diabetic rodents, and the same therapies also had similar effects on T2D patients [9,33,34]. However, one study found that exenatide treatment for 24 weeks had no effect on lipid profiles [35]. Rodent in-vitro studies have reported vasorelaxant actions of GLP-1, and different studies postulated different mechanisms as to how this was achieved [9]. In-vivo rodent studies have reported that GLP-1 induces vasodilation of certain blood vessels and promotes vasoconstriction of others, as well as improving endothelial function [9,36,37]. Similarly, improved blood flow and endothelial function has been reported in diabetic individuals in response to acute GLP-1 therapies [9,38,39]. Interestingly, exendin-4 treatment did not affect short-term triglyceride exposure-induced endothelial dysfunction in rat femoral artery, which suggests that the reported in-vivo beneficial actions of GLP-1 therapies on the endothelium likely occur by extracardiovascular GLP-1 signalling [40]. Rodent and human studies have provided evidence that GLP-1 therapies have antiatherosclerotic actions and angiogenic effects [9,41,42]. GLP-1 therapies have been reported to reduce levels of proinflammatory molecules (associated with atherosclerotic development) in patients [9], and one study reported that anti-inflammatory benefits persisted for 12 weeks in obese T2D patients after a single exenatide injection [43]. Finally, GLP-1 treatments during rodent and human in-vitro/in-vivo studies

Fig. 2



The canonical model of glucagon-like peptide 1 (GLP-1) receptor activation. Upon GLP-1 binding, the Gα subunit is activated by exchanging GDP for GTP, and then the G-protein subunits dissociate. Both the active Gα and the Gβγ subunits activate downstream effectors to propagate G-protein-coupled receptor signalling. The intrinsic GTPase activity converts the Gα subunit bound GTP to GDP, and the G-protein subunits then reassociate, ready for the arrival of a new agonist. This figure is adapted from Thompson and colleagues [11,17].

have been reported to exert beneficial effects on the myocardium such as protection against diabetic cardiomyopathy [9].

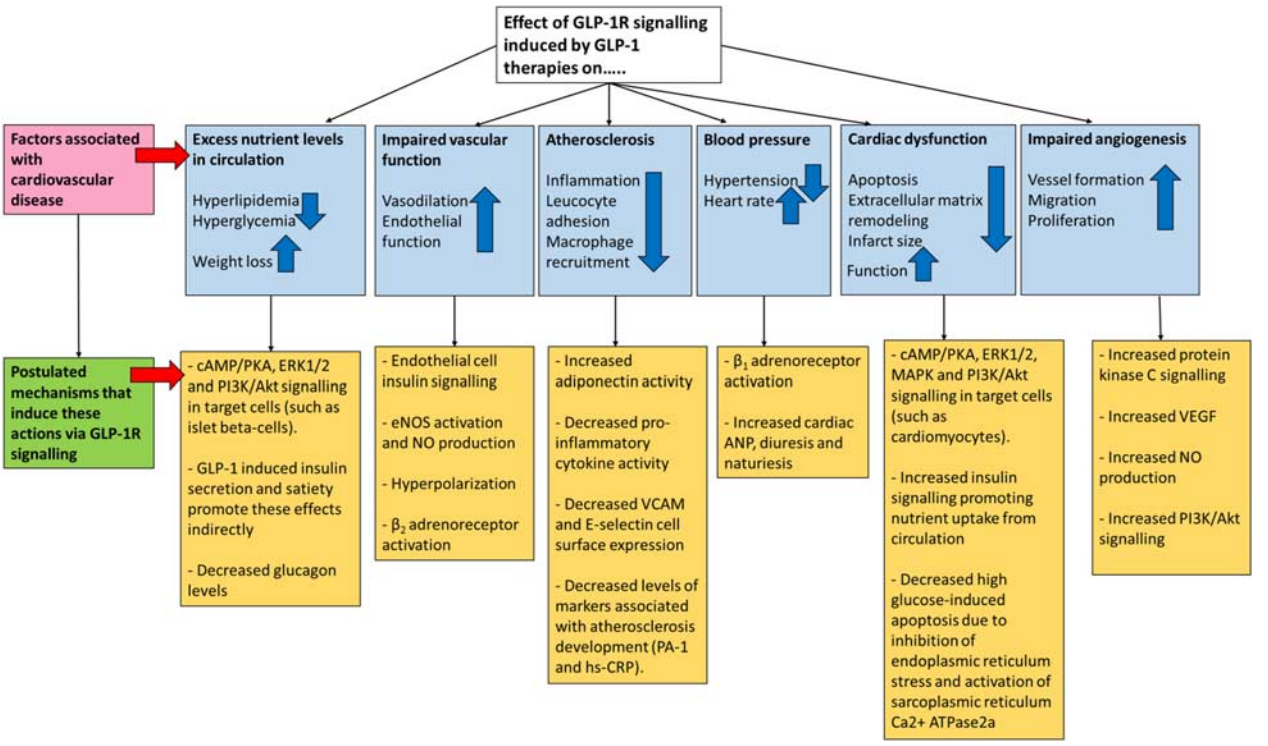
Long-term human studies have shown that chronic DPP-IV inhibition did not significantly confer any CV benefits [44,45]. In contrast, chronic GLP-1-based treatments showed multiple CV benefits in diabetic patients [9]. Four cardiovascular outcome trials have been reported for GLP-1 analogues: ELIXA [46], LEADER [47], SUSTAIN 6 [26] and EXSCEL [48] trials have tested lixisenatide, liraglutide, semaglutide and exenatide, respectively. ELIXA showed no advantage over placebo in terms of influencing the primary outcome of a four-point major adverse cardiac event, which included CV mortality, nonfatal myocardial infarction, nonfatal stroke and hospital admission for unstable angina [46]. The other cardiovascular outcome trials all used a three-point major adverse cardiac event primary end-point (excluding unstable angina); superiority was found for liraglutide and semaglutide (*albeit* not a prespecified analysis for semaglutide), but not for exenatide. All-cause mortality benefit was shown for liraglutide and exenatide, but not for semaglutide, although the latter agent was tested in a smaller study. The ELIXA population all had a CV event within 180 days of the study start, and it is reasonable to assume that the stability of their coronary lesions would have made any drug effect difficult to determine. Conversely, the EXSCEL study included 27% of patients at a much lower CV risk, which may have resulted in the marginal lack of statistical superiority. Examination of components of the primary end-point showed heterogeneity between the two trials that reported reduced CVD with GLP-1 analogues, with the LEADER superiority being driven by a significant reduction in CV mortality, whereas SUSTAIN 6 superiority was largely because of a reduction in nonfatal stroke. In both of these studies, the mechanisms by which these drugs reduced CV outcomes are elusive. A moderator analysis of the LEADER study suggests that the reductions in glycated haemoglobin, weight and

systolic BP were insufficient to account for all of the benefits. Recently, an analysis of severe hypoglycaemia has also been shown not to influence the outcome. The slow separation of the event curves in the Kaplan–Meier plots from both LEADER and SUSTAIN 6 suggests an impact on the atherosclerotic process, which is in contrast to that observed with the sodium-glucose cotransporter 2 inhibitors [49].

Mechanistically, it is not clear how GLP-1-based therapies exert beneficial effects on the CVS, but studies have suggested several pathways (Fig. 3). According to the postulated mechanisms, it appears that GLP-1 therapies mediate these effects directly and/or by promoting the incretin effect [2]. By promoting the incretin effect, GLP-1-based therapies alleviate the potential of the diabetic phenotype to promote CVD by reducing hyperglycaemia and hyperlipidaemia, as well as by improving blood flow systemically because of increasing vascular nitric oxide production [8,9]. These therapies also appear to promote the effects by direct mechanisms as well [9]. In addition, studies have found that GLP-1 therapies improve angiogenesis, reduce atherosclerosis progression, increase cardiac function and improve the prognosis of cardiac ischaemia by the incretin effect and extrapancreatic GLP-1R activity [8,9]. Chronic GLP-1 therapies have also been reported to prevent hypertension, and evidence suggests that this was achieved by CV GLP-1R activity [9].

Currently, several studies are testing the chronic effects of other GLP-1 analogues [9]. It is difficult to arrive at any conclusions on the conflicting findings on the ability of GLP-1-based therapies to reduce CVD from animal and human studies: animal species and trial design differed between animal studies, and trial design and cohorts varied between human studies. The notion that the 'inactive' forms of GLP-1 may have direct effects on the CVS warrants investigation [50]. The effect of allosteric GLP-1R agonists (discussed in the study by Thompson and Kanamarlapudi [11]) on the CVS is another area of future research. A better understanding of T2D aetiology/pathogenesis and how the disease phenotype promotes CVD, as well as further elucidation of GLP-1 activity/targets could provide better insight into

Fig. 3



Reported benefits of glucagon-like peptide 1 receptor (GLP-1R) agonism on cardiovascular disease. A summary of the reported benefits of glucagon-like peptide 1 (GLP-1)-based therapies on reducing cardiovascular disease burden in patients and in experimental settings, and the postulated mechanisms as to how this was achieved. This figure is adapted from Tate and colleagues [9,11]. ANP, atrial natriuretic peptide; eNOS, endothelial nitric oxide synthase; hs-CRP, high-sensitivity C-reactive protein; NO, nitric oxide; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

the therapeutic potential of GLP-1R agonism to reduce T2D-associated CVD.

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Conflicts of interest

There are no conflicts of interest.

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