

Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action

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Abstract

Type 2 diabetes mellitus (T2DM) and obesity are metabolic disorders characterized by excess cardiovascular risk. Glucagon-like peptide 1 (GLP1) receptor (GLP1R) agonists reduce body weight, glycaemia, blood pressure, postprandial lipaemia and inflammation – actions that could contribute to the reduction of cardiovascular events. Cardiovascular outcome trials (CVOTs) have demonstrated that GLP1R agonists reduce the rates of major adverse cardiovascular events in patients with T2DM. Separate phase III CVOTs of GLP1R agonists are currently being conducted in people living with heart failure with preserved ejection fraction and in those with obesity. Mechanistically, GLP1R is expressed at low levels in the heart and vasculature, raising the possibility that GLP1 might have both direct and indirect actions on the cardiovascular system. In this Review, we summarize the data from CVOTs of GLP1R agonists in patients with T2DM and describe the actions of GLP1R agonists on the heart and blood vessels. We also assess the potential mechanisms that contribute to the reduction in major adverse cardiovascular events in individuals treated with GLP1R agonists and highlight the emerging cardiovascular biology of novel GLP1-based multi-agonists currently in development. Understanding how GLP1R signalling protects the heart and blood vessels will optimize the therapeutic use and development of next-generation GLP1-based therapies with improved cardiovascular safety.

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Key points

- Cardiovascular outcome trials in individuals with type 2 diabetes mellitus demonstrate that glucagon-like peptide 1 (GLP1) receptor (GLP1R) agonists reduce the rates of non-fatal myocardial infarction, fatal stroke and cardiovascular death.
- A single, canonical GLP1R, expressed at low levels in the heart and blood vessels, mediates the major cardiovascular actions of GLP1R agonists.
- GLP1R activation might reduce cardiovascular morbidity indirectly through reductions in glycaemia, blood pressure, inflammation, postprandial lipaemia and body weight.
- GLP1R agonists increase heart rate and might not be beneficial in individuals with severe left ventricular dysfunction, reduced ejection fraction and/or a history of repeated hospitalization for heart failure.
- New GLP1-based multi-agonist therapies seem to be substantially more effective than older GLP1R agonists in reducing body weight but their safety requires ongoing scrutiny in trials assessing outcomes in individuals with obesity.

Introduction

Incretin hormones – glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP1) – are released from gut endocrine cells and potentiate meal-stimulated insulin secretion^{1,2}. GLP1 has become the most extensively studied gut hormone, with multiple agents that act on the GLP1 receptor (GLP1R) now approved for the treatment of type 2 diabetes mellitus (T2DM). Intact, biologically active GLP1 refers to both GLP1 (7–36) amide and GLP1 (7–37), which act on a single identified GLP1R on pancreatic islet β -cells, δ -cells and α -cells to increase insulin and somatostatin secretion and decrease glucagon secretion, respectively³ (Fig. 1). In addition, GLP1 and GLP1R agonists have multiple extrapancreatic actions that also contribute to glucose lowering and weight loss (Fig. 1), while reducing chylomicron secretion and blood pressure (BP). The most common adverse events reported with the use of GLP1R agonists are nausea, diarrhoea, vomiting and gallbladder disorders, including cholelithiasis and cholecystitis (Fig. 1), with gastrointestinal adverse events waning over time. The rapid inactivation of gut-secreted GLP1 by dipeptidyl peptidase 4 (DPP4) provided the rationale for the development of DPP4 inhibitors for the treatment of T2DM⁴. Given that the complex biology and metabolic actions of GLP1 and DPP4 have been previously extensively described^{1,2,5,6}, they will not be discussed further in this Review.

The incidence of cardiovascular events among individuals with T2DM is approximately threefold greater than that observed in individuals without diabetes⁷, with diabetes now being considered a “cardio-vascular risk equivalent”⁸. Furthermore, observations from clinical studies have raised the question of whether some glucose-lowering agents might worsen cardiovascular outcomes⁹. Therefore, new agents developed for the management of T2DM, including GLP1R agonists, are studied in cardiovascular outcome trials (CVOTs) to scrutinize their cardiovascular safety. The primary composite outcome used in these trials comprises death from cardiovascular causes, non-fatal myocardial infarction (MI) and non-fatal stroke – otherwise known as three-point major adverse cardiovascular events (MACE).

In this Review, we provide an overview of the data from CVOTs of GLP1R agonists in patients with T2DM, which have been largely positive. We then consider the possible mechanisms of action for GLP1R agonist-mediated cardioprotection, which could have therapeutic potential in a range of cardiovascular conditions. The emergence of new GLP1-based medicines highlights the importance of understanding and preserving the beneficial cardiovascular actions of structurally distinct GLP1R agonists. For each indication (hypertension, coronary heart disease, stroke and heart failure (HF)), we first describe the clinical data and then discuss the potential mechanisms from preclinical studies that link GLP1R agonists to a reduction in cardiovascular events and help to elucidate the clinical observations. We end with a summary of emerging GLP1R agonist-based therapies.

GLP1R agonists in CVOTs

The first GLP1R agonist approved for clinical use (in April 2005) was twice-daily exenatide. Subsequently, the GLP1R agonist portfolio was expanded to include once-weekly exenatide, once-daily liraglutide, once-daily lixisenatide, and two other medicines taken once weekly – dulaglutide and semaglutide¹⁰. Albiglutide, a once-weekly GLP1R agonist, was marketed for several years and reduced the rates of MACE but was withdrawn from the market due to a lack of widespread uptake.

Type 2 diabetes mellitus

Dedicated CVOTs for eight GLP1R agonists in patients with T2DM have been completed to date, of which five have demonstrated a reduction in three-point MACE (Fig. 2). The first positive GLP1R agonist CVOT to be reported was the LEADER trial¹¹ in 2016. In this study, 9,340 patients with T2DM and at least one coexisting cardiovascular condition were randomly assigned to liraglutide (1.8 mg once daily) or placebo. The median duration of follow-up was 3.8 years. The primary outcome (first occurrence of three-point MACE) occurred in 608 out of 4,668 patients (13.0%) in the liraglutide group compared with 694 out of 4,672 patients (14.9%) in the placebo group¹¹. The reductions in three-point MACE in the LEADER trial included a significant reduction in death from cardiovascular causes and a trend towards a reduction in non-fatal MI with liraglutide¹¹. In SUSTAIN-6 (ref. 12), 3,297 patients with T2DM were randomly assigned to semaglutide (0.5 mg or 1.0 mg once weekly) or placebo for 2 years. The rate of three-point MACE was 6.6% with semaglutide compared with 8.9% with placebo¹². Semaglutide did not significantly decrease the rate of death from cardiovascular causes but significantly decreased the rate of non-fatal stroke, and there was a trend towards a reduced rate of non-fatal MI. In the Harmony Outcomes trial¹³, 9,463 patients with T2DM and established coronary disease were randomly assigned to albiglutide (30 mg or 50 mg once weekly) or placebo. During follow-up (median 1.5 years), albiglutide significantly reduced the incidence of three-point MACE compared with placebo (338 events (7%) versus 428 events (9%)), which included a significant reduction in the rate of non-fatal MI¹³. In the REWIND trial¹⁴, 9,901 patients with T2DM and either a previous cardiovascular event or cardiovascular risk factors were randomly assigned to once-weekly treatment with dulaglutide (1.5 mg) or placebo. During follow-up (median 5.4 years), three-point MACE occurred in 594 patients in the dulaglutide group (12.0%) and 663 patients (13.4%) in the placebo group, primarily reflecting a significant reduction in the rate of non-fatal stroke¹⁴. In 2021, the AMPLITUDE-O trial¹⁵ investigators reported on 4,076 patients with T2DM (~90% with previous cardiovascular disease (CVD)) who were randomly assigned to receive either 4 mg or 6 mg of efglenatide once weekly or placebo. The median duration of follow-up was 1.81 years. Intriguingly, during this

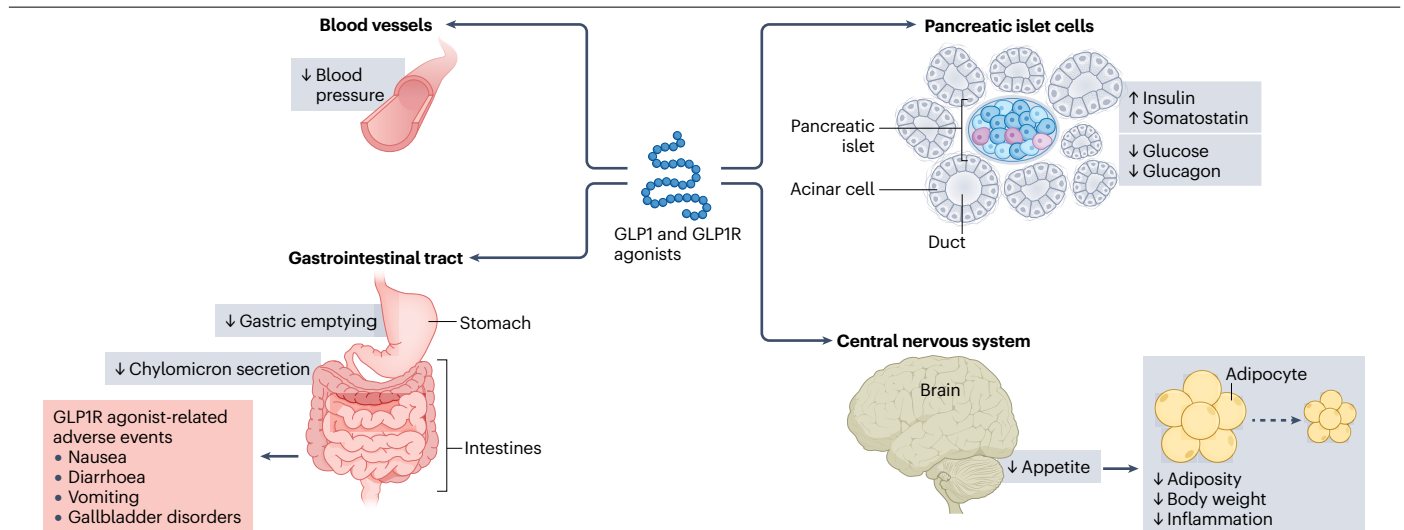


Fig. 1 Major cardiometabolic actions of GLP1. Glucagon-like peptide 1 (GLP1) and GLP1 receptor (GLP1R) agonists act on pancreatic islet cells, gastric emptying and the central nervous system to improve glucose homeostasis

while reducing appetite and body weight, resulting in reduced blood pressure, adiposity and inflammation^{1,2,5,6}. The principal adverse events associated with GLP1R agonists are shown.

short period of time, efglenatide treatment significantly reduced the rate of three-point MACE (3.9 events versus 5.3 events per 100 person-years) and significantly decreased the incidence of an expanded MACE composite end point¹⁵. The AMPLITUDE-O trial¹⁶ included a substantial proportion (~15%) of patients who were also receiving a sodium–glucose cotransporter 2 inhibitor, and efglenatide reduced the rate of MACE irrespective of whether patients were also receiving this drug.

Although the findings of the LEADER, SUSTAIN-6, Harmony Outcomes, REWIND and AMPLITUDE-O CVOTs^{11–15} support the use of optimized, long-acting GLP1R agonists in the management of diabetic CVD, some clear differences in benefits have been observed. Reductions in non-fatal stroke were observed in the SUSTAIN-6 (ref. 12) and REWIND¹⁴ trials, whereas reductions in non-fatal MI were observed in the LEADER¹¹ and Harmony Outcomes¹³ trials. In the AMPLITUDE-O trial¹⁵, reductions in non-fatal stroke and non-fatal MI were similar.

Although the reasons for the discrepancies between trials in the reduction of particular MACE component events (stroke versus MI) remain unclear, they could stem from differences in the duration of treatment, the extent of GLP1R engagement or trial design. In the majority of these CVOTs, ≥70% of enrolled patients had established CVD and 60–70% were men. However, in the REWIND trial¹⁴, only 31.5% of patients had CVD and 46.3% were women. Furthermore, except for the Harmony Outcomes trial¹³, these positive GLP1R agonist CVOTs included patients with severe impairment in kidney function (estimated glomerular filtration rate <30 ml/min/1.73 m²). There were also differences in exclusion criteria for other glucose-lowering medications. In the Harmony Outcomes¹³ and REWIND¹⁴ trials, patients receiving DPP4 inhibitors were not excluded, whereas they were excluded from both the LEADER¹¹ and SUSTAIN-6 (ref. 12) trials. In the AMPLITUDE-O study¹⁵, patients were excluded if they had used DPP4 inhibitors during the 3 months before screening.

Several GLP1R agonist CVOTs have demonstrated neutral findings for three-point MACE. The ELIXA trial¹⁷ showed that, among 6,068 patients with T2DM and a recent history of acute coronary syndrome, treatment with lixisenatide (maximum dose 20 µg once daily) was non-inferior to placebo (median follow-up 25 months). Similarly, the incidence of

three-point MACE with exenatide treatment (2 mg once weekly) was not significantly different from that with placebo (median follow-up 3.2 years) in 14,752 patients with T2DM in the EXSCCEL trial¹⁸. However, the discontinuation rate of >40% in both groups (patient decision) should be noted¹⁸. In the FREEDOM trial¹⁹, 4,156 patients with T2DM were randomly assigned to receive placebo or the subcutaneous device ITCA 650, which delivers a constant infusion of exenatide (20 µg daily for 3 months followed by 60 µg daily) through an osmotic minipump. During follow-up (median 16 months), use of the ITCA 650 was found to be non-inferior to placebo¹⁹.

Understanding why improved cardiovascular outcomes with GLP1R agonists were not observed in the ELIXA¹⁷, EXSCCEL¹⁸ and FREEDOM¹⁹ CVOTs is challenging. These findings might reflect differences in trial design, high variability in sample sizes and duration of follow-up, and limitations in achieving optimal sustained pharmacokinetics during drug development. Consistent with less robust GLP1R target engagement, exenatide and lixisenatide are less effective than dulaglutide, liraglutide and semaglutide for glucose control and weight loss^{20,21}. Nevertheless, in the EXSCCEL trial¹⁸, once-weekly exenatide led to a 12% reduction in all-cause mortality and reductions in three-point MACE that almost reached statistical significance.

One comparative efficacy study of glucose-lowering agents that included a single GLP1R agonist in patients with T2DM has been conducted. The GRADE Study Research Group investigated the metabolic and cardiovascular actions of gliclazide, sitagliptin, insulin glargine and liraglutide in 5,047 patients over ~5 years²². Most patients had additional risk factors for CVD²². The risk of developing any CVD was lower with liraglutide than in the other randomized treatment groups (HR 0.7, 95% CI 0.6–0.9), although the incidence of cardiovascular events was low. No significant differences were found in cardiovascular or all-cause mortality between groups²².

Weight loss and obesity

Most of the data on cardiovascular outcomes for GLP1R agonists has been obtained from studies of patients with T2DM. The body mass index (BMI) of most of these participants exceeded 28 kg/m² and, therefore,

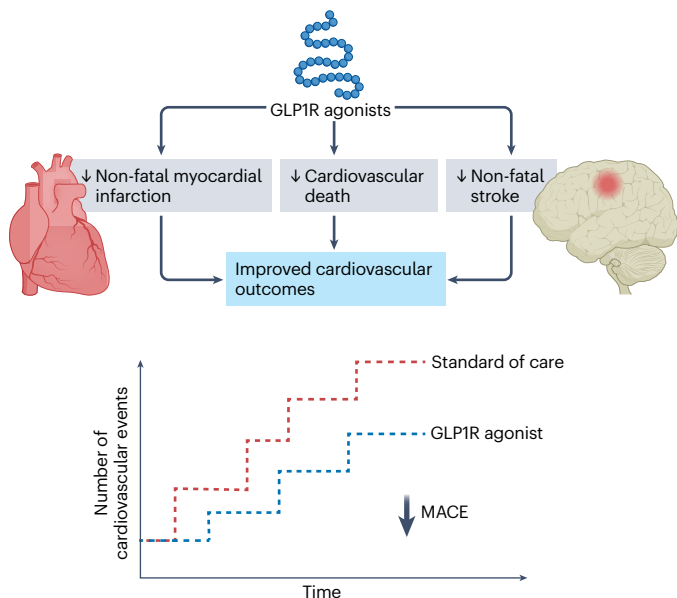


Fig. 2 | GLP1R agonists reduce MACE. In cardiovascular outcomes trials, glucagon-like peptide 1 receptor (GLP1R) agonists have been shown to reduce the rates of major adverse cardiovascular events (MACE), comprising non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, in patients with type 2 diabetes mellitus.

they were also overweight or obese. Two GLP1R agonists – liraglutide (3 mg once daily) and semaglutide (2.4 mg once weekly) – have been approved for weight loss in people who are overweight and have comorbidities, or those with obesity (BMI >30 kg/m²)²³.

Participants in the SCALE weight-loss programme had reductions in BP and plasma lipid levels with liraglutide treatment²⁴. However, these patients were generally younger (mean age 45 years) with lower cardiovascular risk than those enrolled in other CVOTs, and cardiovascular event rates were too low across the five randomized, controlled SCALE trials²⁴ to form clear conclusions about cardiovascular safety. Improvements in cardiovascular risk factors, such as BP and lipid levels, were also seen with semaglutide treatment in the STEP 1 and STEP 4 trials²⁵, which included patients with either a BMI ≥30 kg/m² or a BMI ≥27 kg/m² and one or more weight-related comorbidities.

The cardiovascular safety of semaglutide 2.4 mg once weekly in 17,605 patients aged >45 years who are overweight or obese but without T2DM is being studied in the ongoing SELECT CVOT²⁶. The mean age of participants is 61.6 years, and 72.5% are men. The mean BMI is 33.34 kg/m², and the mean glycated haemoglobin (HbA_{1c}) level is 5.78%. Other baseline characteristics include a history of MI (76.3%), stroke (23.0%), peripheral artery disease (8.6%), HF (24.0%) and prediabetes (64.5%). The primary end point of the SELECT trial is the incidence of three-point MACE²⁶. However, observational evidence from other studies indicates a more rapid improvement in HF than in MACE end points following weight loss secondary to dietary intervention or bariatric surgery²⁷.

Although weight loss in individuals who are overweight or obese might partially contribute to GLP1R agonist-mediated improvement in cardiovascular outcomes, there is undoubtedly a contributory component of GLP1R agonist action that is independent of weight loss. For example, in the Harmony Outcomes trial¹³, the action of albiglutide on

glucose lowering and weight loss was modest in patients with T2DM (0.52% reduction in HbA_{1c}, 0.83 kg decrease in body weight) but albiglutide treatment was associated with a 22% reduction in cardiovascular events over 1.6 years. Similarly, preclinical studies of GLP1R agonists have demonstrated cardioprotection in the absence of weight loss^{28,29}. Accordingly, in the remainder of this Review, we focus on delineating the mechanisms of action for GLP1R agonist-mediated cardioprotection (Fig. 3) and consider the major cell types in the cardiovascular system that express GLP1R (Fig. 4) in an attempt to differentiate between direct and indirect actions.

Direct and indirect actions of GLP1R

Localization of GLP1R in the heart

GLP1R expression (RNA and, to a lesser extent, protein) has been reported in the human atria and ventricles^{30,31}, including in cardiomyocytes^{32,33}. Commercially available antisera against GLP1R often have suboptimal sensitivity and specificity^{31,34}, contributing to challenges in the interpretation of mechanistic data linking cardiovascular protection to GLP1R⁺ cell types in the myocardium.

In cultures of atrial and ventricular cardiomyocytes from adult mice, full-length *Glp1r* mRNA transcripts were detected by reverse transcription PCR, predominantly in atrial cardiomyocytes³⁵. Similarly, transgenic expression of a yellow fluorescent reporter protein under the control of endogenous mouse *Glp1r* regulatory sequences did not generate reporter expression in the ventricular myocardium of mice, although cells positive for yellow fluorescence were scattered throughout the atria³⁶. Furthermore, a GLP1R-selective mouse monoclonal antibody localized GLP1R expression via immunohistochemistry to the atria, predominantly in the sinoatrial node, in monkey and human heart tissue³⁷. These findings are consistent with an earlier report in which *Glp1r* expression was detected in the right and left atria but not in the ventricles of the mouse heart³⁸. However, low levels of *Glp1r* expression in non-cardiomyocyte cell types in the ventricles, including blood vessels³³, cannot be excluded. Indeed, *Glp1r*-directed reporter expression was observed in ventricular coronary vessels that co-expressed smooth muscle actin, suggesting that GLP1R is expressed in vascular smooth muscle cells³⁶. Nevertheless, GLP1R transcriptional regulatory sequences driving reporter expression might be first activated in endocardial cells during development, which could subsequently serve as progenitor precursors for multiple cardiac cell lineages in mice³⁹, highlighting the need for caution in interpreting GLP1R localization studies based solely on reporter gene expression.

Indeed, PCR analysis of RNA isolated from cell fractions of mouse heart identified full-length *Glp1r* mRNA transcripts, predominantly in endocardial endothelial cells³³. Consistent with these findings, cardiac *Glp1r* expression was completely lost in mice with targeted inactivation of *Glp1r* in endothelial and haematopoietic cell lineages using Cre recombinase under control of the TEK receptor tyrosine kinase promoter (*Glp1r*^{EC-/-} mice)³³. By contrast, independent RNA-sequencing analyses of normal and ischaemic hearts from humans have localized *GLP1R* mRNA transcripts predominantly to a subset of atrial and ventricular cardiomyocytes³³. Analysis of RNA from 15 hearts obtained from patients with HF undergoing heart transplantation or from deceased organ donors revealed full-length *GLP1R* expression in all four cardiac chambers, at levels similar to those in the human pancreas; levels were highest in the left atrium³¹. The very low levels of *GLP1R* expression in the heart, coupled with a paucity of reports detecting cellular localization of GLP1R protein or GLP1 binding sites in the heart, and clear differences in mouse versus human GLP1 physiology,

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imply that our understanding of cardiac GLP1R expression and function is incomplete and requires further careful interrogation.

Effects of GLP1R on inflammation and lipids

GLP1R agonists produce anti-inflammatory effects in the cardiovascular system²⁸. In the immune system, GLP1R is expressed predominantly in gut intraepithelial lymphocytes; *Glp1r*^{-/-} mice have altered gut microbiota profiles and increased sensitivity to colonic inflammation⁴⁰. Whether GLP1R⁺ immune cells are recruited to the myocardium in response to cardiac injury remains to be determined. GLP1R agonists also reduce hepatic steatosis as well as circulating triacylglycerol and LDL cholesterol levels, which requires the presence of a functional GLP1R^{28,41}. These actions have been recapitulated in humans. For example, patients with either T2DM, obesity or non-alcoholic steato-hepatitis (NASH) treated with semaglutide had decreased circulating levels of triacylglycerol, LDL cholesterol and non-HDL cholesterol^{25,42,43}. Similarly, several GLP1R agonists reduce postprandial plasma levels of triacylglycerol, with more modest effects on fasting plasma levels of LDL cholesterol, even in the presence of statins⁴⁴.

Enterocytes and hepatocytes do not express GLP1R; however, a subset of GLP1R⁺ endothelial and intrahepatic $\gamma\delta$ T cells mediates a component of the anti-inflammatory effect of GLP1R agonists in mouse liver⁴⁵. A reduction in fasting plasma levels of cholesterol and triacylglycerol could indirectly reflect the extent of weight loss achieved²⁷ because GLP1R agonists have little direct effect on hepatocyte lipid metabolism⁴⁶. Although the hepatic actions of GLP1R agonists might indirectly contribute to GLP1R agonist-mediated cardioprotection in humans with T2DM, this topic has been reviewed previously⁴⁶ and will not be discussed further in this Review.

GLP1R agonists and hypertension

Clinical studies

GLP1R agonists increase heart rate and reduce BP, the latter effect being most notable in individuals with hypertension^{28,29,47}. The addition of

GLP1R agonists to the standard of care (which includes BP-lowering agents) in patients with T2DM in CVOTs often results in additional BP lowering of approximately 2–3 mmHg (ref. 48). Importantly, this reduction in BP could be independent of both glucose lowering and weight loss also observed with these agents⁴⁹.

In the DURATION-1 trial⁵⁰, exenatide 2 mg once weekly was shown to decrease BP by as much as 6 mmHg after 1 year in patients with T2DM. Almost half of participants in this trial achieved normal systolic BP (SBP) at study completion. Similarly, patients treated with exenatide once weekly in the EXSCEL trial¹⁸ also had reductions in SBP (-1.57 mmHg) and, in another study, liraglutide (up to 3.0 mg once daily for 20 weeks) decreased SBP (-4.6 mmHg) in patients with obesity but without T2DM⁵¹.

GLP1 and GLP1R agonists have been shown to improve several parameters of endothelial and vascular function (Fig. 3) in small studies of humans. These improvements include increases in acetylcholine-induced forearm blood flow and flow-mediated vasodilatation of the brachial artery^{52,53}. Mechanistic interpretation of these findings is often complicated by the failure to control for simultaneous GLP1R agonist-mediated increases in insulin levels and reductions in glycaemia.

Lowering of BP might contribute to the improvements in cardiovascular outcomes observed in some patients with T2DM treated with GLP1R agonists. Nevertheless, BP reductions have been modest in several CVOTs (1.2 mmHg with liraglutide in LEADER¹¹, 1.7 mmHg with dulaglutide in REWIND¹⁴ and a negligible (0.67 mmHg) change in systolic BP with albiglutide at 16 months in Harmony Outcomes¹³). Furthermore, both Cox and Vansteelandt analyses indicated that BP reductions did not mediate the cardiovascular benefit in LEADER⁴⁸. Therefore, BP reductions alone are highly unlikely to mediate the reductions in MACE in these CVOTs^{11,13,14}.

Preclinical studies

GLP1 and GLP1R agonists reduce BP in experimental mouse and rat studies of hypertension. For example, treatment with exenatide (20 nmol/kg)

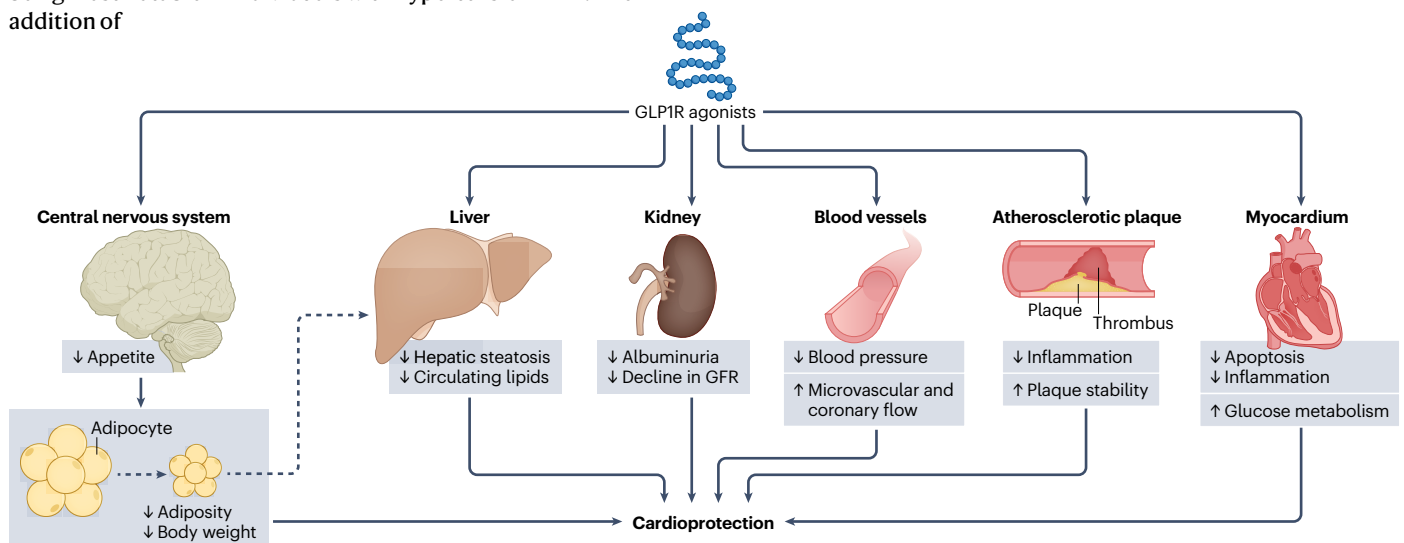


Fig. 3 | Direct and indirect actions of GLP1R agonist-mediated cardioprotection. Glucagon-like peptide 1 receptor (GLP1R) agonists might improve cardiovascular outcomes by acting on the central nervous system to reduce appetite and body weight, while indirectly improving circulating lipid

profiles via a reduction in hepatic steatosis. GLP1R agonists might also have direct and indirect effects on blood vessels to improve blood flow and reduce atherosclerosis, on the kidney to preserve renal function, and on the heart to help to prevent myocardial infarction or limit infarct size. GFR, glomerular filtration rate.

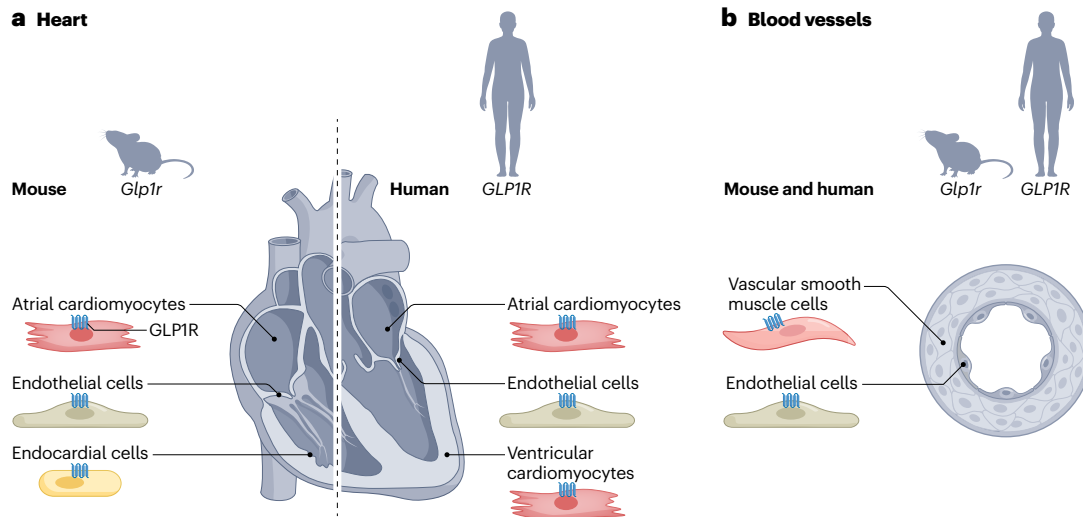


Fig. 4 | Distribution of mouse *Glp1r* and human *GLP1R* mRNA expression. **a**, In the heart, *Glp1r* or *GLP1R* expression in major cardiac cell types differs between mice and humans. Insufficient information is available on the

localization of glucagon-like peptide 1 receptor (GLP1R) protein expression in the heart. **b**, In blood vessels, *Glp1r* or *GLP1R* expression is detected in endothelial and vascular smooth muscle cells of both mice and humans.

twice daily for 12 weeks reduced SBP in *db/db* mice supplied with 2% salt in their drinking water⁵⁴. Likewise, subcutaneous administration of liraglutide (30 µg/kg) twice daily decreased both SBP and diastolic BP in male C57BL/6J mice infused with angiotensin II^{35,55}. In another study of male C57BL/6J mice fed a low-fat diet (4.8% fat) or high-fat diet (43.0% fat) for 20 weeks, daily subcutaneous administration of liraglutide (100 µg/kg) for 21 days decreased both SBP and diastolic BP irrespective of diet⁵⁶. In mice, liraglutide increases the secretion of atrial natriuretic peptide (ANP) from atrial cardiomyocytes, and the BP-lowering actions of liraglutide are attenuated in angiotensin II-infused ANP-deficient mice³⁵. Liraglutide has been shown to increase circulating ANP levels in humans with T2DM in some but not all studies^{47,57}.

GLP1 intravenous infusion (30 pmol/kg/min) for 2 h in male Sprague–Dawley rats increased contrast-enhanced ultrasound-measured microvascular blood flow and volume⁵⁸, actions that were prevented by co-treatment with either N^G-nitro-L-arginine methyl ester⁵⁸ or the protein kinase A inhibitor H-89 (ref. 59). Similarly, treatment with liraglutide (30 µg/kg twice daily) increased acetylcholine-mediated relaxation of aortic rings in mice, whereas liraglutide did not decrease SBP or restore acetylcholine-mediated relaxation of aortic rings in hypertensive mice with selective *Glp1r* deletion in endothelial cells⁵⁵. Nevertheless, degradation-resistant GLP1R agonists often do not improve endothelial or vascular function in human studies^{29,59,60}. Resolution of these discrepancies requires a more comprehensive assessment of GLP1R expression and function in endothelial and vascular smooth muscle cells in various vascular beds *in vivo*³.

GLP1R agonists and coronary heart disease

Long-acting GLP1R agonists decrease the rate of MACE and, in some CVOTs (such as LEADER¹¹, SUSTAIN-6 (ref. 12) and Harmony Outcomes¹³), also reduce the rate of non-fatal MI. Pooled analyses of the eight CVOTs of GLP1R agonists indicate that these agents decrease rates of fatal and non-fatal MI by 10%⁶¹. This effect requires ≥12 months of exposure to GLP1R agonists in most CVOTs and might be attributable to the attenuation of atherosclerotic CVD progression or myocardial

actions resulting in decreased ischaemia–reperfusion injury and subsequent infarct size (Fig. 3).

Clinical studies of atherosclerosis

Participants enrolled in GLP1R agonist CVOTs ideally also receive optimal lipid-lowering and BP-lowering therapies. These trials have shown that the incidence of MACE does not differ between the GLP1R agonist and placebo groups until 12–18 months after initiation of therapy⁶², and this time frame is consistent with the possibility that GLP1R agonists are anti-atherogenic⁶³. A post hoc analysis of the LEADER trial revealed that patients with a history of MI, stroke or established CVD derived cardiovascular benefit from treatment with liraglutide, whereas the effect of this drug was neutral in those with elevated levels of cardiovascular risk factors alone⁶⁴. Nonetheless, a substantial proportion of patients with T2DM in the REWIND trial¹⁴ did not have established CVD but had reductions in MACE with dulaglutide treatment (HR 0.87 for those with or without prior CVD), albeit with a lower event rate. In a small, double-blind trial, 163 patients with T2DM were randomly assigned to once-weekly exenatide (for up to 18 months) or placebo⁶⁵. Exenatide treatment improved glycaemia but did not decrease the volume of carotid atherosclerotic plaque as assessed by MRI or plaque calcification⁶⁵. Conversely, in a prospective study, liraglutide added to metformin for 18 months in 121 patients with T2DM decreased carotid intima–media thickness assessed via colour Doppler ultrasonography, which was associated with reduced circulating levels of triacylglycerols⁶⁶.

GLP1R agonists also have anti-inflammatory effects that might contribute to reductions in atherosclerosis²⁸ (Fig. 3). For example, treatment with exenatide (10 µg twice daily) for 12 weeks decreased circulating levels of pro-inflammatory factors, including monocyte chemoattractant protein 1 (MCP1; also known as C-C motif chemokine 2), serum amyloid A and IL-6, in patients with T2DM and obesity⁶⁷. Lipopolysaccharide induces a fast inflammatory response that is acutely attenuated by GLP1R agonists in animals and healthy human volunteers⁶⁸ through mechanisms that are not completely understood.

Beyond acute administration, studies of sustained GLP1R agonism often do not account for the salutary actions of GLP1R agonists on systemic metabolism, including weight loss, improved glycaemia and favourable actions on pancreatic hormone profiles^{28,29}, which can indirectly contribute to reduced inflammation. Nevertheless, GLP1R agonists acutely reduce systemic inflammation within hours in humans^{67,68}, and semaglutide has been shown to exert greater anti-inflammatory effects than the sodium–glucose cotransporter 2 inhibitor empagliflozin in patients with T2DM despite achieving similar degrees of weight loss⁶⁹.

Preclinical studies of atherosclerosis

Preclinical studies in *ApoE*^{-/-} and *Ldlr*^{-/-} mice demonstrate suppression of atherosclerotic plaque progression in response to GLP1R agonists. Exenatide treatment (either 300 pmol/kg per day or 24 nmol/kg per day) for 28 days decreased Oil Red O staining of atherosclerotic lesions in male *ApoE*^{-/-} mice, whereas lixisenatide treatment (10 µg/kg per day) for 2 months decreased the extent of atherosclerotic lesions in male *ApoE*^{-/-}*Irs2*^{+/-} mice⁷⁰. Similarly, dulaglutide treatment (0.6 mg/kg twice weekly via subcutaneous injection) reduced the atherosclerotic plaque area in *ApoE*^{-/-} mice with streptozotocin-induced diabetes⁷¹. Likewise, subcutaneous semaglutide administration (up to 60 µg/kg once daily) for 12–14 weeks in *ApoE*^{-/-} mice and 17 weeks in *Ldlr*^{-/-} mice reduced atherosclerotic plaque area and carotid intima–media thickness, a surrogate marker of subclinical atherosclerosis⁷².

Anti-inflammatory actions of GLP1R agonists are repeatedly detected in preclinical studies of atherosclerosis. These effects include reduced mRNA expression and secretion of tumour necrosis factor (TNF), MCP1 and IL-6 in mouse peritoneal macrophages^{70,73}, decreased macrophage infiltration into atherosclerotic plaque (measured by Mac-3 staining)⁷⁰, and development of an anti-inflammatory M2 phenotype by plaque macrophages (measured by increased arginase I and decreased inducible nitric oxide synthase staining)⁷⁰. GLP1R agonists can also increase plaque stability, as evidenced by decreased mRNA expression of matrix metalloproteinases (*Mmp2* and *Mmp3*) in the abdominal aortas of dulaglutide-treated *ApoE*^{-/-} mice with streptozotocin-induced diabetes⁷¹, and in semaglutide-treated *Ldlr*^{-/-} mice (*Mmp3* and *Mmp13*)⁷². In mice, endothelial cells are the major GLP1R⁺ cell type in the aorta⁴⁵. Nevertheless, deletion of *Glp1r* in endothelial and haematopoietic lineage cells did not affect atherosclerotic plaque progression in mice fed a high-fat and high-cholesterol diet combined with administration of an adeno-associated virus expressing pro-protein convertase subtilisin/kexin type 9 to induce dyslipidaemia⁴⁵. Furthermore, semaglutide treatment for 18 weeks (10 µg/kg subcutaneously) decreased aortic plaque area equally in *Glp1r*^{EC-/-} and control mice⁴⁵. Therefore, the anti-atherogenic actions of GLP1R agonists in mice might be indirect and independent of GLP1R expression in endothelial or haematopoietic cell lineages.

How GLP1R agonists reduce systemic or cardiovascular inflammation is not clear. Gut intraepithelial lymphocytes are the main cellular site of GLP1R expression in the immune system and are functionally important for the actions of GLP1R agonists to attenuate T cell-dependent systemic and gut inflammation⁷⁴. Nevertheless, the presence of a functional gut intraepithelial lymphocyte GLP1R is not required for GLP1R agonist-dependent attenuation of systemic inflammation induced by lipopolysaccharide⁷⁴, suggesting that inter-organ communication, perhaps via neural pathways, contributes to the indirect anti-inflammatory actions of GLP1R agonists.

Clinical studies of MI

In a randomized, placebo-controlled study, the effects of exenatide (10 µg subcutaneous injection and 10 µg intravenous bolus 5 min before angioplasty, followed by 10 µg subcutaneous injection twice daily for the next 2 days) were investigated in 58 individuals with ST-segment elevation MI (STEMI) and thrombolysis in MI flow grade 0. Exenatide treatment reduced the serum levels of creatine kinase-MB, decreased infarct size and increased left ventricular (LV) ejection fraction (LVEF) at 72 h, 1 month and 6 months after angioplasty, respectively⁷⁵. However, no clinically meaningful outcomes arising from exenatide therapy were reported. The effects of a 6-h infusion of placebo or exenatide (mean plasma concentration of 0.177 ± 0.069 nmol/l) initiated 15 min before the onset of reperfusion were investigated in 172 patients undergoing primary angioplasty for STEMI. Exenatide infusion reduced infarct size, provided that it took place <132 min from first medical contact to balloon treatment⁷⁶, while increasing the myocardial salvage index assessed via cardiac MRI at -90 days after infusion; however, no improvement in LVEF was observed⁷⁷. Importantly, these salutary actions ascribed to exenatide were independent of glycaemia because they were present in patients with or without T2DM⁷⁸. Conversely, 91 individuals with STEMI randomly assigned to placebo or intravenous exenatide infusion for 30 min before primary angioplasty and continued for 72 h at 0.84 µg/h had no reduction in infarct size or improvement in LVEF with exenatide, as assessed by cardiac MRI at 4 months after intervention⁷⁹. Likewise, in an open-label study of 92 patients undergoing coronary artery bypass graft surgery, postoperative infusion of exenatide (0.05-µg/min bolus for 1 h followed by a constant 0.025-µg/min infusion) neither decreased circulating troponin I levels nor improved LVEF when compared with intravenous insulin infusion in control individuals⁸⁰.

Consistent with the observed trend towards a reduced rate of non-fatal MI in the LEADER trial¹¹, a randomized, placebo-controlled study of 92 patients with acute STEMI scheduled to undergo primary angioplasty demonstrated favourable outcomes with liraglutide treatment⁸¹. Participants who received subcutaneous liraglutide (1.8 mg given 30 min before angioplasty in the ambulance, followed by 0.6 mg for 2 days, 1.2 mg for 2 days and, finally, 1.8 mg for 3 days) demonstrated a 4.1% increase in LVEF assessed via echocardiography at 3 months after angioplasty compared with patients who received placebo⁸¹. Similar findings were observed in 90 patients with non-STEMI, among whom treatment with liraglutide (0.6 mg for 2 days, 1.2 mg for 2 days and finally 1.8 mg for 3 days) produced a 4.7% increase in LVEF at 3 months after angioplasty versus placebo⁸². Although the MI-specific outcomes reported in these clinical studies align with the reduction in non-fatal MI events observed in several GLP1R agonist CVOTs, most of these patients did not have T2DM. Moreover, the magnitude of benefit in these acute-onset studies is small. Therefore, insufficient evidence exists to support the adjunctive use of GLP1R agonists at the time of acute myocardial ischaemia.

Preclinical studies of MI

GLP1R agonists protect against myocardial ischaemia–reperfusion injury in mice, rats, rabbits and pigs^{83–87}. For example, intravenous infusion of native GLP1 (4.8 pmol/kg/min) decreased infarct size in male Sprague–Dawley rats subjected to a 30-min temporary left anterior descending (LAD) coronary artery occlusion and 2-h reperfusion protocol⁸⁵, although concerns about underestimation of infarct size with short reperfusion times need to be considered. Nonetheless, these cardioprotective actions have been recapitulated with numerous GLP1R

agonists in the context of longer reperfusion periods, including exenatide (10 µg given 5 min before reperfusion followed by 10 µg twice daily for 3 days), which decreased infarct size in Dalland–Landrace pigs undergoing a 75-min temporary left circumflex coronary artery occlusion and 72-h reperfusion protocol⁸⁶. Furthermore, albiglutide treatment (maximum dose of 10 mg/kg) for 3 days also decreased infarct size in male Sprague–Dawley rats subjected to a 30-min temporary LAD coronary artery occlusion and 24-h reperfusion protocol⁸⁴.

Mechanistically, GLP1R agonists reduce cardiomyocyte apoptosis, with reductions in the TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labelling) assay, cleaved caspase 3 levels and the expression of pro-apoptotic proteins^{84–86,88}. As GLP1R is not robustly expressed in mouse ventricular cardiomyocytes³⁵, these anti-apoptotic effects are likely to be indirect and mediated by other downstream actions of GLP1R. Another mechanism that might contribute to cardioprotection is the optimization of cardiac energetics. The cardioprotective actions of albiglutide in ischaemic heart disease due to temporary LAD coronary artery occlusion were associated with increases in myocardial glucose oxidation assessed by ¹³C-magnetic resonance spectroscopy (MRS)⁸⁴. Similarly, native GLP1 infusion increased myocardial glucose oxidation assessed by ¹³C-MRS in the non-ischaemic myocardium of male Sprague–Dawley rats, which was associated with reduced infarct size following a 30-min temporary LAD coronary artery occlusion and 24-h reperfusion protocol⁸³.

GLP1R agonist-mediated protection against ischaemic heart disease might require caveolins, which are integral membrane proteins involved in the formation of membrane invaginations (caveolae) that have an important role in the pathology of ischaemia–reperfusion injury⁸⁹. For example, a 30-ng/kg intravenous infusion of exendin 4 immediately before a 30-min temporary LAD coronary artery occlusion and 2-h reperfusion protocol decreased infarct size in male C57BL/6 mice, which was associated with increased migration of caveolin 3 to buoyant caveolar fractions⁹⁰. Importantly, the exendin 4-mediated reduction in infarct size was not seen in male caveolin 3-deficient mice⁸⁷. The capacity of GLP1R agonists to improve microvascular blood flow^{52,58,91} could, theoretically, contribute to the salutary actions of this drug class against ischaemia–reperfusion injury. Although native GLP1 acutely increases coronary artery blood flow in humans with coronary artery disease⁹², whether degradation-resistant GLP1R agonists consistently exert similar effects in humans is not clear^{93,94}.

Many preclinical studies are performed in male animals that are young, lean and otherwise healthy, whereas in CVOTs in general, participants of either sex are recruited and are usually older (mean age >60 years) and with T2DM, hypertension, dyslipidaemia and/or established coronary artery disease. Moreover, individuals enrolled in these CVOTs are often treated with β-blockers, calcium-channel blockers or antagonists of the renin–angiotensin–aldosterone system, which can mask the more robust cardiovascular phenotypes observed with GLP1R agonist treatment in animals with experimental CVD. Of note, not all preclinical studies demonstrate that GLP1R agonists produce cardioprotection, given that native GLP1 and liraglutide did not decrease infarct size in pigs^{95,96}. Furthermore, the species-specific differences in cellular myocardial GLP1R expression³³ complicate the extrapolation of insights from mechanistic preclinical studies to humans.

GLP1R agonists and stroke

Clinical studies

How GLP1R agonists reduce the rate of stroke remains unclear; however, reductions in blood pressure, lipid levels, inflammation and

hyperglycaemia could contribute indirectly to reduced stroke risk. In a placebo-controlled trial, acute exenatide administration had a minimal effect on cerebral or peripheral blood flow in healthy elderly volunteers (mean age 62 years)⁹⁷, and 26 weeks of once-daily administration of liraglutide did not reduce vascular (and carotid artery) inflammation in patients with T2DM as assessed by ¹⁸F-fluorodeoxyglucose (FDG) PET⁹⁸. A meta-analysis of eight CVOTs of GLP1R agonists in patients with T2DM revealed reductions in the rates of all stroke and ischaemic stroke but not of haemorrhagic stroke⁹⁹.

Preclinical studies

In preclinical studies, GLP1R agonists have been shown to have direct neuroprotective actions¹⁰⁰, but these acute vascular occlusion models are not likely to be reflective of the pathophysiology of stroke in humans. GLP1R agonists, such as liraglutide, directly inhibit thromboxane-induced platelet aggregation *ex vivo*, actions attenuated by the selective GLP1R antagonist exendin (9–39) and associated with the detection of GLP1R binding sites on human platelets¹⁰¹. Whether GLP1R agonists further inhibit platelet aggregation in patients with T2DM or obesity who are already being treated with platelet aggregation inhibitors remains uncertain.

GLP1R agonists and HF

Many GLP1R agonist CVOTs have demonstrated reduced rates of MI and stroke, but an important secondary outcome included in CVOTs is hospitalization for HF. GLP1R agonist-mediated reductions in hospitalization for HF have been heterogeneous across individual trials, although a meta-analysis of GLP1R agonist CVOTs (excluding the FREEDOM trial) encompassing >60,000 patients with T2DM demonstrated that GLP1R agonists decrease hospitalization for HF by 11%⁶¹.

Clinical studies

Several small studies seem to demonstrate the benefit of native GLP1 in patients with HF; however, these findings have not been widely reproduced with clinically used GLP1R agonists³⁹. A randomized, placebo-controlled study of albiglutide treatment for 12 weeks in 52 patients with NYHA class II–III HF demonstrated no improvement in LVEF or 6-min walking test scores¹⁰². Moreover, albiglutide did not increase myocardial glucose utilization assessed by FDG-PET¹⁰². In an expanded analysis of the LEADER CVOT, liraglutide treatment decreased the rates of cardiovascular death and hospitalization for HF among patients with pre-existing HF (NYHA class I–III; 18% of patients; HR 0.77) or without HF (82% of patients; HR 0.92)¹⁰³. Conversely, in patients with more severe HF in both the FIGHT¹⁰⁴ and LIVE¹⁰⁵ studies, liraglutide therapy was not beneficial. The FIGHT trial¹⁰⁴ included 300 patients with HF and LVEF ≤40% (~60% with T2DM) randomly assigned to either placebo or liraglutide treatment (1.8 mg) for 210 days. Liraglutide treatment produced a trend towards increased rates of death or re-hospitalization for HF in patients with T2DM (*P* = 0.07). The LIVE trial¹⁰⁵ included 241 patients with chronic HF and LVEF ≤45% (~30% with T2DM) randomly assigned to either placebo or liraglutide treatment (1.8 mg) for 24 weeks. No improvement in LVEF was observed with liraglutide treatment, which was actually associated with an increase in the rate of cardiac serious adverse events (ventricular tachycardia and atrial fibrillation). Furthermore, a substudy of 36 patients from the LIVE trial demonstrated that those with HF assigned to liraglutide treatment did not have increased rates of myocardial glucose utilization as assessed by FDG-PET⁹⁴. Therefore, individuals with severely reduced LV function (mean LVEF ~25% and 35% in the FIGHT¹⁰¹ and LIVE²⁹ trials, respectively) do not benefit from therapy with GLP1R

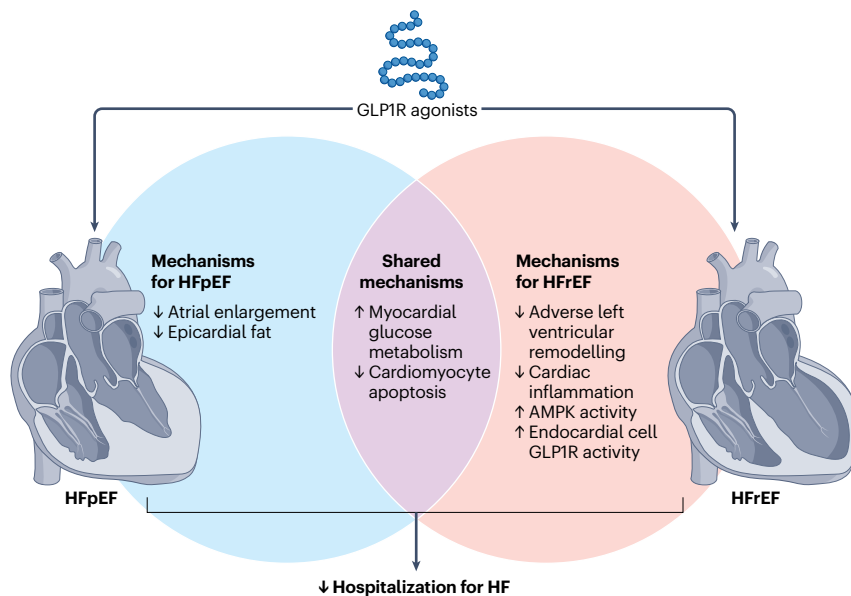


Fig. 5 | Actions and potential mechanisms of GLP1R agonists in HF. Glucagon-like peptide 1 receptor (GLP1R) agonists decrease the rate of hospitalization for heart failure (HF), which might reflect direct and indirect effects on the mechanisms underlying HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). In HFpEF, GLP1R agonists alleviate atrial enlargement and decrease epicardial fat depots. In HFrEF, GLP1R agonists decrease adverse left ventricular remodelling and cardiac inflammation, while increasing AMP-activated protein kinase (AMPK) activity, perhaps linked to increased endocardial cell GLP1R activity. GLP1R agonist-mediated mechanisms of action that seem to be shared between HFpEF and HFrEF include an increase in myocardial glucose metabolism and a decrease in cardiomyocyte apoptosis.

agonists and might even be at excess cardiovascular risk, probably due to increases in heart rate leading to supraventricular tachycardia.

Preclinical studies

GLP1R agonists are protective against experimental HF in several species, including mice, rats, pigs and dogs^{88,106–110}. Infusions of native GLP1 (1.5 pmol/kg/min) increased LVEF and systolic function in dogs subjected to rapid pacing-induced HF^{106,107}. Furthermore, a 3-month infusion of native GLP1 (1.5 pmol/kg/min) improved LVEF and survival, while decreasing adverse LV remodelling, in spontaneously hypertensive and HF-prone (SHHF) male rats aged ≤ 1 year¹⁰⁹. GLP1R agonists also confer robust cardioprotection against chronic ischaemia-induced HF; 1 week of treatment with liraglutide (75 μ g/kg twice daily) before permanent LAD coronary artery occlusion markedly improved the survival of male C57BL/6J mice with or without T2DM⁸⁸. Moreover, liraglutide treatment decreased adverse LV remodelling and improved LV stroke volume in a preclinical model of obesity-induced cardiomyopathy involving high-fat diet supplementation for 20 or 32 weeks in male C57BL/6J mice¹⁰⁸. Pretreatment with liraglutide (30 μ g/kg twice daily) for 1 week increased LVEF assessed by pressure–volume loop conductance catheters, decreased cardiac fibrosis, and decreased myocardial mRNA expression of ANP and B-type natriuretic peptide¹⁰⁸. Similarly, in an obesogenic swine model subjected to chronic regional ischaemia via placement of an ameroid occluder around the LAD coronary artery, liraglutide treatment for 30 days (0.005–0.015 mg/kg) improved cardiac power and efficiency assessed using invasive haemodynamic measurements¹¹⁰. In a mouse model of experimental T2DM (high-fat diet plus low-dose streptozotocin), liraglutide treatment (30 μ g/kg) improved diastolic dysfunction as reflected by an increased mitral E/A ratio and decreased E/e' ratio¹¹¹, and also preserved LVEF in mice with T2DM subjected to transverse aortic constriction surgery¹¹². In addition, liraglutide treatment at a much higher dose (1 mg/kg once daily) for 12 weeks alleviated cardiac hypertrophy, atrial enlargement and diastolic dysfunction as indicated by an increase in global longitudinal strain in female mice (aged ~ 2 years) subjected to experimental HF with preserved ejection fraction (HFpEF) in response to high-fat diet supplementation plus angiotensin II infusion¹¹³.

Several mechanisms have been proposed for the GLP1R-dependent improvement in HF (Fig. 5), including reduced inflammation. Liraglutide therapy in male C57BL/6J mice fed a high-fat diet for 32 weeks had decreased myocardial expression of TNF and nuclear localization of nuclear factor- κ B¹⁰⁸. Furthermore, an increased level of 5'AMP-activated protein kinase (AMPK) might also contribute to the liraglutide-mediated reversal of obesity-induced cardiomyopathy given that co-treatment of mice with the AMPK inhibitor compound C abolished the GLP1R agonist-induced increase in LVEF¹⁰⁸. Decreases in cardiomyocyte apoptosis are also observed in response to GLP1R agonist treatment in preclinical studies of HF as reflected by the decreased expression levels of cleaved caspase 3 in the hearts of SHHF rats¹⁰⁹ and mice⁸⁸ subjected to LAD coronary artery occlusion. These mice also had increased myocardial expression of pro-survival factors (such as AKT phosphorylated at Ser473)⁸⁸. As noted, the actions of liraglutide pretreatment (75 μ g/kg twice daily for 1 week) to improve survival and LVEF and to attenuate adverse LV remodelling in response to permanent LAD coronary artery occlusion require the presence of GLP1Rs in endothelial (most probably cardiac) or haematopoietic cells that also express the TEK receptor tyrosine kinase³³.

GLP1R agonists consistently increase myocardial glucose metabolism in animals, and native GLP1 infusion increases myocardial glucose uptake both in dogs with rapid pacing-induced HF and in SHHF rats^{107,109}. Using radioisotopes to measure flux through glucose oxidation, researchers demonstrated that direct treatment of mouse isolated working hearts with liraglutide had no effect on glucose oxidation¹¹¹. This observation is consistent with the negligible expression of GLP1R in murine ventricular cardiomyocytes³³. By contrast, robust increases in glucose oxidation were observed when isolated working hearts were studied from mice that had been previously treated with liraglutide in vivo, and this effect was preserved in mice with T2DM¹¹¹. Nevertheless, metabolic findings from preclinical studies are not universally replicated in humans with HF treated with either albiglutide¹⁰² or liraglutide⁹⁴. However, these patients had advanced HF, which is often characterized by myocardial insulin resistance¹¹⁴. This trait might mask the actions of GLP1R agonists on myocardial glucose metabolism,

which is likely to be indirect and dependent on increases in insulin secretion. Furthermore, 96% of participants in the FIGHT¹⁰¹ trial and 100% of those in the LIVE trial²⁹ were receiving β -blockers. These drugs might also have masked the capacity of GLP1R agonists to stimulate myocardial glucose metabolism because β -blockers increase myocardial glucose oxidation in patients with NYHA class II or III HF¹¹⁵. The species-specific differences in cellular localization of cardiac *GLP1R* or *Glp1r* mRNA expression (Fig. 4), which is more easily detectable in human than in mouse cardiomyocytes³³, highlights the importance of studying GLP1R agonists in humans with HFpEF versus HF with reduced ejection fraction (Fig. 5) as well as with HF of ischaemic versus non-ischaemic origin.

Emerging GLP1R agonist-based therapies

The GIP–GLP1R co-agonist tirzepatide is the most effective GLP1-based drug so far developed for T2DM and obesity. In the ongoing SURPASS CVOT¹¹⁶, the safety of tirzepatide versus dulaglutide is being assessed in 13,299 patients with T2DM, aged >40 years, with confirmed atherosclerotic CVD. Analysis of the limited number of cardiovascular events across the SURPASS trials in patients with T2DM revealed evidence for cardiovascular safety, with a hazard ratio of 0.8 for four-point MACE (cardiovascular death, MI, stroke and hospitalization for unstable angina) and a hazard ratio of 0.9 for all-cause mortality, favouring tirzepatide¹¹⁷. The cardiovascular safety of tirzepatide is also being assessed in individuals with obesity in the SURMOUNT-MMO trial¹¹⁸.

Mechanistically, little evidence exists to inform the cardiovascular biology or long-term safety of selective GIP receptor (GIPR) agonism in humans^{6,119}. GIPR expression is detectable, albeit at low levels, in the human atria and ventricles, in ventricular and atrial cardiomyocytes, adipocytes and pericytes³³. Activation of GIPR signalling reduces experimental inflammation and atherosclerosis in mice¹²⁰, whereas loss of GIPR signalling exacerbates them¹²¹. Paradoxically, the loss of cardiomyocyte GIPR signalling improves survival in acute ischaemic cardiac injury¹²², whereas GIPR agonism attenuates cardiac hypertrophy in hypertensive cats¹²³.

Several glucagon–GLP1 co-agonists (such as cotadutide, mazdutide and pemvidutide) and the glucagon–GLP1–GIP tri-agonist retatrutide¹²⁴ are being investigated in patients with metabolic disorders, principally obesity and NASH. Amgen has presented promising phase I clinical data for AMG133, a GIPR antagonist–GLP1R agonist antibody combination, in individuals with obesity. The long-acting amylin analogue cagrilintide is being co-formulated with semaglutide for the treatment of obesity and T2DM. This combination is more effective than either agent alone for glucose control and weight loss¹²⁵. Beyond the putative benefits of weight loss in reducing BP, circulating lipids and inflammation, these GLP1-based medicines will require scrutiny to ascertain their cardiovascular safety in the relevant patient populations. Several investigational, small-molecule GLP1R agonists, such as danuglipron, PF-07081532 and orforglipron, are also progressing through clinical development¹²⁶. The extent to which these agents might have differential pharmacodynamic activity in the cardiovascular system cannot be predicted and requires ongoing scrutiny.

Conclusions

Emerging clinical trial¹⁵ and real-world¹²⁷ data, together with complementary mechanisms of action⁶², support the use of GLP1R agonists for the prevention of cardiovascular events in patients with T2DM. Whether GLP1R agonists are an effective therapeutic option for individuals with HFpEF or peripheral artery disease¹²⁸ will be revealed by

the findings of ongoing trials. Although most clinical trial data have highlighted the cardiovascular benefits of GLP1R agonists in patients with T2DM and established CVD, these agents also seem to be promising in the context of primary prevention of CVD¹⁴. Progress continues in the identification of precision medicine approaches to identify people with heightened glycaemic responses to GLP1R agonists¹²⁹. However, our understanding is limited as to whether some individuals might be more sensitive than others to the cardioprotective actions of GLP1R agonists. Furthermore, the cardiovascular benefits of GLP1R agonists have been determined predominantly in patients with T2DM, and the cardiovascular safety of these drugs in individuals with obesity or NASH remains to be established. Understanding both the direct and indirect actions of GLP1R agonists in the cardiovascular system requires further refinement and application of tools and techniques used to detect translated and functional GLP1R protein. Finally, it seems reasonable to question whether future clinical trials should study individuals with atherosclerotic CVD but without T2DM or obesity to determine whether those with residual cardiovascular risk might also benefit from treatment with GLP1R agonists.

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Competing interests

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