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# After the LEADER trial and SUSTAIN-6, how do we explain the cardiovascular benefits of some GLP-1 receptor agonists?

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**Abstract**

Recent cardiovascular outcome trials – the LEADER with liragutide and SUSTAIN-6 with semaglutide – have shown significant reductions of major cardiovascular (CV) events with these glucagon-like peptide (GLP)-1 receptor agonists. Progressive separation of the treatment and placebo curves, starting clearly between 12 and 18 months of the trial period, and significant reductions in the risk of myocardial infarction and stroke, indicate that the beneficial CV effects observed with GLP-1 receptor agonists could be due to an antiatherogenic effect. So far, the reasons for such an effect of GLP-1 receptor agonists have not been entirely clear, although several hypotheses may be proposed. As the reductions in glycated haemoglobin and systolic blood pressure (SBP) in these trials were modest, and both trials lasted only a short period of time, reductions in hyperglycaemia and SBP are unlikely to be involved in the beneficial CV effects of GLP-1 receptor agonists. On the other hand, their effect on lipids and, in particular, the dramatic decrease in postprandial hypertriglyceridaemia may explain their beneficial CV actions. Reduction of body weight, including a significant decrease in visceral fat in patients using GLP-1 receptor agonists, may also have beneficial CV effects by reducing chronic proatherogenic inflammation. In addition, there are in-vitro data showing a direct anti-inflammatory effect with these agents that could also be involved in their beneficial CV effects. Moreover, studies in humans have shown significant beneficial effects on ischaemic myocardium after a very short treatment period, suggesting a direct effect of GLP-1 receptor agonists on myocardium, although the precise mechanism remains unclear. Finally, as a reduction in insulin resistance has been associated with a decrease in CV risk, it cannot be ruled out that the lowering of insulin resistance induced by GLP-1 receptor agonists might also be involved in their beneficial CV actions.



***Key words:*** *Cardiovascular; Myocardial infarction; GLP-1; Liraglutide; Semaglutide*

## 1. Introduction

Glucagon-like peptide (GLP)-1 receptor agonists are effective hypoglycaemic agents that are widely used. In recent years, considerable data have suggested that GLP-1 receptor agonists may have effects beyond their glucose-lowering actions, including a possible cardioprotective effect [1,2]. Some animal studies showed that GLP-1 receptor agonists could reduce the size of myocardial infarction (MI) [3,4] while, in humans, limited studies have reported reduced MI size after administration of these drugs, suggesting beneficial effects on the ischaemic heart [5–7]. Furthermore, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) have recently provided clear evidence of cardiovascular (CV) benefit with these GLP-1 receptor agonists. Both studies were conducted in patients with type 2 diabetes mellitus (T2DM) and a history of previous CV events (82–83%) or high CV risk (17–18%) [8,9]. In the LEADER trial, 3.5 years of treatment with liraglutide 1.8 mg/day was associated with a significant 13% reduction in the primary outcome (time to first major CV event: CV death, non-fatal MI, non-fatal stroke; $p = 0.01$), and a significant 14% reduction in MI (fatal and non-fatal; $p = 0.046$), 22% reduction in CV-related death ($p = 0.007$) and 15% reduction in total mortality ($p = 0.02$; Table 1) [8]. In SUSTAIN-6, 2 years of treatment with semaglutide, a long-acting GLP-1 receptor agonist administered once a week, resulted in a significant 26% reduction in the primary outcome (time to first major CV event: CV death, non-fatal MI, non-fatal stroke; $p = 0.02$), 39% reduction in non-fatal stroke ($p = 0.04$) and 35% reduction in revascularization procedures ($p = 0.003$; Table 1) [9].

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**Table 1**
Effects of glucagon-like peptide (GLP)-1 receptor agonists on primary and secondary cardiovascular (CV) outcomes in the LEADER trial and SUSTAIN-6

| | LEADER | SUSTAIN-6 |
|---|---|---|
| Study duration (years) | 3.5 | 2.0 |
| GLP-1 receptor agonist: molecule | Liraglutide | Semaglutide |
| GLP-1 receptor agonist: dose | 1.8 mg/day | 0.5 or 1.0 mg/week |
| Patients (n) | 9340 | 3297 |
| Major CV events[a] | ↓ 13% ($p$ = 0.01) | ↓ 26% ($p$ = 0.02) |
| Myocardial infarction | ↓ 14% ($p$ = 0.046) | ↓ 15% (NS; $p$ = 0.38) |
| Non-fatal stroke | ↓ 11% ($p$ = 0.30; NS) | ↓ 39% ($p$ = 0.04) |
| Coronary revascularization | ↓ 9% ($p$ = 0.18; NS) | Not available |
| Coronary + peripheral revascularization | Not available | ↓ 35% ($p$ = 0.003) |
| Hospitalization for heart failure | ↓ 13% ($p$ = 0.14; NS) | → ($p$ = 0.57; NS) |
| CV death | ↓ 22% ($p$ = 0.007) | → ($p$ = 0.92; NS) |
| Total mortality | ↓ 15% ($p$ = 0.02) | → ($p$ = 0.79; NS) |

[a]CV death, non-fatal myocardial infarction, non-fatal stroke.
LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.
↓: decrease; →: no effect; NS: not significant

There are some similarities, but also some differences, between the results of these two trials (Table 1). One major similarity was the significant reduction in major CV outcomes with liraglutide. However, the significant reduction in CV death and total mortality in LEADER was not observed in SUSTAIN-6. This difference could be due to both the shorter duration of SUSTAIN-6 and its smaller number of included patients, leading to considerably fewer deaths compared with the LEADER trial (122 *vs* 497, respectively). A notable difference between the two trials was the significant reduction in non-fatal stroke in SUSTAIN-6, but not in LEADER. Although the reasons for this discrepancy are still unknown, it may be supposed that the greater reduction in systolic blood pressure in SUSTAIN-6 compared with LEADER (-2.6 mmHg *vs* -1.2 mmHg, respectively) is perhaps part of the explanation.

Nevertheless, further studies are needed to clarify the dramatic effect of semaglutide on stroke. It is important to note that, in LEADER, the curves for liraglutide and placebo diverged at between 12 and 18 months, which is similar to what is observed in clinical prospective trials of statins, whereas in SUSTAIN-6, the curves for semaglutide and placebo diverged progressively throughout the study. While this suggests that the decrease in major CV events observed with GLP-1 receptor agonists could be due to an antiatherogenic effect, so far, the reasons behind this beneficial effect have not been entirely elucidated, although several hypotheses may be considered. Thus, the present review discusses the potential mechanisms that might explain the CV benefits of GLP-1 receptor agonists summarized in Fig. 1.

## 2. Effects on CV risk factors

### *2.1. Lipids*

#### *2.1.1. Effects of liraglutide on fasting lipids*

Significant variations in lipid parameters are observed in type 2 diabetes mellitus (T2DM) patients treated with GLP-1 receptor agonists. In a 3.5-year open-label study, exenatide b.i.d. reduced low-density lipoprotein (LDL) cholesterol by 6% and triglycerides (TGs) by 12%, while increasing high-density lipoprotein (HDL) cholesterol by 24% [10]. Five-year data from the DURATION study showed a significant reduction in LDL cholesterol (-9.8%) and TGs (-12%), and a significant increase in HDL cholesterol (+4.3%), with 2-mg exenatide once a week [11], while a meta-analysis of six trials of liraglutide reported reductions in total cholesterol (-0.13 mmol; $p < 0.01$), LDL cholesterol (-0.20 mmol; $p < 0.0001$), free fatty acids (-0.09 mmol; $p < 0.0001$) and TGs (-0.20 mmol; $p < 0.01$) compared with baseline in the intention-to-treat population [12].

#### *2.1.2. Effects of liraglutide on postprandial lipids*

The most striking effect of GLP-1 receptor agonists on lipids is the significant reduction in postprandial hypertriglyceridaemia. In healthy volunteers, GLP-1 infusion abolished postprandial lipidaemia [13]. In subjects with impaired glucose tolerance and recent-onset T2DM, a single subcutaneous

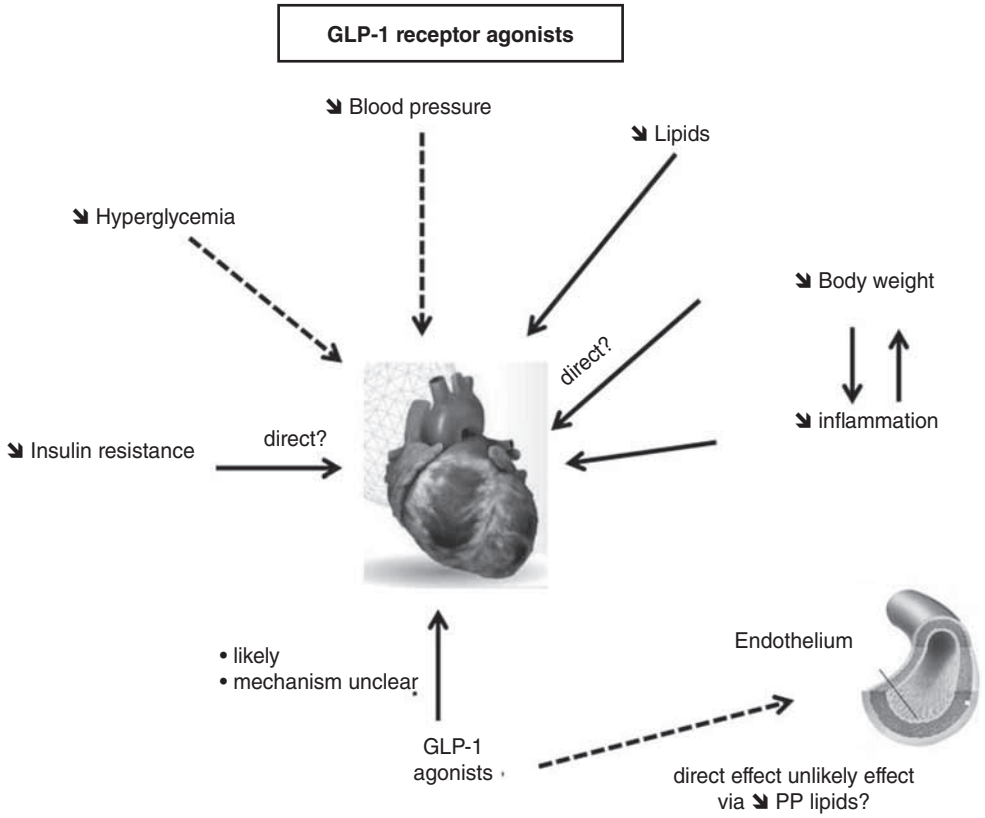


**Fig. 1.** Summary of the mechanisms that may explain the cardiovascular benefits of GLP-1 receptor agonists. Solid lines indicate the likely mechanisms; dotted lines indicate those unlikely to play major roles.

injection of the GLP-1 agonist exenatide (10 µg) was shown to markedly reduce postprandial increases in TGs, apolipoprotein (Apo) B48 and ApoC-III compared with a placebo [14], and as this effect was observed after just a single exenatide injection, it indicates that it was independent of its effect on body weight. On the other hand, 3 weeks of treatment with liraglutide (1.8 mg/day) compared with a placebo in patients with T2DM significantly reduced postprandial excursions of TGs and ApoB48 after a fat-rich meal, independently of gastric-emptying [15]. In fact, in hamsters and mice, exenatide decreased plasma TG-rich lipoprotein (TRL)-containing ApoB48, and reduced the secretion of ApoB48 in hamster enterocyte cultures [16]. Conversely, blockade of GLP-1 receptor signaling by the antagonist exendin-(9-39) or by genetic elimination of GLP-1 signaling in GLP-1 receptor knock-out (KO) mice enhanced ApoB48 TRL secretion [16]. In healthy humans, 4–6 weeks of treatment with exenatide significantly suppressed plasma concentrations and production rates of ApoB48 TRL [17]. In patients with T2DM, it has recently been reported that 6 months of treatment with liraglutide significantly reduced ApoB48 production and increased ApoB48 catabolism, leading to significant decreases in plasma ApoB48 [18].

Although GLP-1 receptor agonists have only a relatively modest effect on LDL cholesterol, they can induce a major reduction in postprandial hyperlipidaemia, an important feature of diabetic dyslipidaemia [19], as it is known to be atherogenic [20]. Thus, the effect of GLP-1 receptor agonists on postprandial hyperlipidaemia could be one factor involved in their beneficial CV effects.

### *2.2. Blood pressure*

In human trials, treatment with GLP-1-receptor agonists is associated with reductions in blood pressure (BP). Over 82 weeks of exenatide b.i.d. treatment, systolic/diastolic BP fell significantly *vs* baseline in 314 overweight patients with T2DM. Average decreases were -1.3/-2.7 mmHg (95% CI: -3.1 to +0.5/-3.8 to -1.7 mmHg), with even greater changes observed in the quartile of patients who lost the most weight (on average: -3.9/-4.4 mmHg) [21]. A large meta-analysis of patients using exenatide reported significant reductions in systolic BP compared with both placebo (-5.24 mmHg, $p < 0.00001$) and insulin glargine (-3.46 mmHg, $p < 0.00001$), and in diastolic BP compared with placebo (-5.91 mmHg, $p < 0.00001$) and sitagliptin (-0.99 mmHg, $p < 0.00001$) [22]. In another large meta-analysis, liraglutide at 1.2 mg/day lowered systolic BP compared with placebo and glimepiride treatment, with mean differences of -5.60 mmHg ($p < 0.00001$) and -2.38 mmHg ($p = 0.05$), respectively. In addition, liraglutide at 1.8 mg/day also reduced systolic BP *vs* placebo and glimepiride, with mean differences of -4.49 mmHg ($p < 0.00001$) and -2.62 mmHg ($p < 0.00001$), respectively [22]. In the LEADER trial, a mean systolic BP reduction of 1.3 mmHg *vs* placebo was

observed while, in SUSTAIN-6, systolic BP was -2.5 mmHg and -0.9 mmHg lower in patients using semaglutide 1 mg or 0.5 mg, respectively, *vs* placebo [8,9].

Weight loss may have contributed to the BP decrease observed with GLP-1 receptor agonists. However, systolic BP changes were seen early in these trials and preceded weight loss, suggesting a direct effect of GLP-1 receptor agonists on BP. It has been suggested that the BP-lowering effect of GLP-1 receptor agonists could be due to direct stimulation by GLP-1 of atrial natriuretic peptide (ANP) secretion, leading to increased natriuresis [23].

Nevertheless, the reduction in systolic BP observed with GLP-1 receptor agonists appears to be too modest to be a major factor behind the significant decrease in major CV events noted with liraglutide. However, the BP-lowering observed with semaglutide may have contributed to its overall benefit, and especially the risk of stroke, as seen in SUSTAIN-6.

Yet, it has recently been shown that the BP-lowering effect of sodium – glucose cotransporter *2* (SGLT2) inhibitors (which is more pronounced than with GLP-1 receptor agonists) may only partially explain the cardioprotective effects observed with empagliflozin in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) [24,25]. This reinforces the idea that the BP-lowering effect of GLP-1 receptor agonists is likely to be only a minor factor in any explanation of their CV benefits.

## 3. Reduction of hyperglycaemia

In LEADER, the mean $HbA_{1c}$ level with liraglutide was 0.4% lower than with placebo whereas, in SUSTAIN-6, the mean $HbA_{1c}$ level was 0.7% lower with semaglutide 0.5 mg and 1% lower with semaglutide 1 mg than with placebo [8,9]. Previous prospective studies have shown that the reduction in hyperglycaemia needs time to induce a significant decrease in CV events [26]. For instance, in the *United Kingdom Prospective Diabetes Study* (UKPDS), a significant reduction in MI was observed only in the long-term report after a median follow-up of 17 years [27] and, in the *Veterans Affairs Diabetes Trial* (VADT), a significant 17% decrease in the primary CV outcome (heart attack, stroke, new or worsening congestive heart failure, amputation for ischaemic gangrene or CV death) was reported only after a median follow-up of 9.8 years [28], whereas the first VADT report, after a median 6.25 years of follow-up, showed no significant effects on this primary outcome [29].

Nevertheless, the effect of a decrease in hyperglycaemia on the reduction of CV events cannot be totally ruled out in either LEADER or SUSTAIN-6, despite its being an unlikely major contributing factor, given the short durations of those studies: 3.5 years and 2 years, respectively.

## 4. Anti-inflammatory actions of GLP-1

Several in-vitro and animal studies have shown anti-inflammatory effects with both GLP-1 and GLP-1 receptor agonists [30–34]. Exendin-4 directly reduced l*ipopolysaccharide* (LPS)-induced secretion of cytokines [tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10] in human monocytes from non-diabetic individuals, effects that were blocked by coadministration of the GLP-1 receptor antagonist exendin-(9-39), suggesting that GLP-1 had a direct effect on the immune system [30]. In-vitro liraglutide reduced the expression of vascular cell adhesion molecule (VCAM)-1 in human aortic endothelial cells after stimulation by LPS or TNF-α through a calcium- and adenosine monophosphate-activated protein kinase (AMPK)-dependent mechanism [31], and decreased monocyte adhesion to TNF-α-activated endothelial cells [32]. Also, GLP-1 and GLP-1 receptor agonists both reduced vascular monocyte adhesion and foam-cell formation in mice [32–34], while the anti-inflammatory action of GLP-1 was abolished by coadministration of the GLP-1 receptor antagonist exendin-(9-39), suggesting a direct effect of GLP-1 [34]. Liraglutide administered for 7 days to C57BL/6 mice fed a high-fat diet reduced heart inflammation and lipid accumulation with no significant weight loss [32], whereas treatment with taspoglutide, another GLP-1 agonist, did not significantly change plaque area and macrophage accumulation in ApoE KO mice [35].

Some data also suggest anti-inflammatory actions with both GLP-1 and GLP-1 receptor agonists in humans [36]. Infusions of native GLP-1 in patients with type 1 diabetes mellitus (T1DM) reduced the plasma increases of IL-6, intercellular adhesion molecule (ICAM)-1 and markers of oxidative stress [nitrotyrosine, 8-iso-prostaglandin F2α (PGF2α)] induced by both hypoglycaemia and hyperglycaemia [37]. In non-obese patients with T2DM, GLP-1 reduced plasma levels of IL-6, ICAM-1, PGF2α and nitrotyrosine [38] whereas, in obese T2DM patients, exenatide reduced circulating levels of IL-2, monocyte chemotactic protein (MCP)-1, serum amyloid A and matrix metallopeptidase (MMP)-9, with no significant weight loss [39]. Eight weeks of treatment with liraglutide reduced soluble cluster of differentiation 163 (sCD163) and the production of proinflammatory cytokines (IL-1β, IL-6, TNF-α) in peripheral blood cells in obese patients with T2DM and psoriasis, and increased levels of the anti-inflammatory adipokine adiponectin, independently of reductions in body weight, fructosamine and $HbA_{1c}$ [40].

Although there are data indicating that the anti-inflammatory effects of GLP-1 and GLP-1 receptor agonists may be direct, it should be borne in mind that many of their observed anti-inflammatory effects may have been confounded by parallel decreases in body weight, blood glucose and free fatty acids, as reported in several studies. Thus, GLP-1 receptor agonists reduce chronic CV inflammation through both direct and indirect effects, and their anti-inflammatory effects could be part of their beneficial CV actions.

## 5. Effect on weight loss

In addition to their effects on blood glucose control, GLP-1 receptor agonists have demonstrated positive effects on body

weight. A meta-analysis of 27 trials showed significant mean weight loss with GLP-1 receptor agonists *vs* placebo: exenatide 2 mg/week: -1.62 kg; exenatide 20 µg: -1.37 kg; liraglutide 1.2 mg: -1.01 kg; and liraglutide 1.8 mg: -1.51 kg [41]. Another meta-analysis of 18 trials involving T2DM patients reported a mean body weight decrease of -2.8 kg with GLP-1 receptor agonists *vs* control groups [42], while Robinson et al. [43], in a larger meta-analysis of 32 trials of either exenatide or liaglutide, reported a mean body weight decrease of -3.31 kg *vs* an active control and -1.22 kg *vs* placebo.

In the Liraglutide Effect and Action in Diabetes (LEAD-2) trial, the weight loss associated with liraglutide treatment was primarily the result of decreases in both visceral and subcutaneous fat tissue [44]. Six months of treatment with exenatide also significantly reduced both visceral and subcutaneous fat in drug-naïve T2DM patients [45]. It is well known that adipose tissue, particularly visceral adipose tissue, is associated with increased chronic inflammation and that a modest elevation of inflammation-related molecules in the circulation can contribute to a substantially increased risk of CV disease [46]. Indeed, it has also been shown that weight loss improves the inflammatory profile of obese subjects by decreasing proinflammatory factors and increasing anti-inflammatory molecules [47]. In an interventional study of obese women, body-weight reduction was associated with a significant fall in serum concentrations of IL-6, IL-18 and C-reactive protein (CRP), whereas adiponectin levels were significantly increased [48]. After 1 year of a multidisciplinary programme of weight reduction in obese subjects who achieved a loss of ≥ 10% of their original weight, a significant reduction in plasma cytokines (TNF-α, IL-6) and vascular adhesion molecules was observed, along with an improved vascular response to L-arginine [49].

Thus, the possibility that the significant reduction in body weight associated with liraglutide treatment may have a beneficial CV effect by reducing chronic proatherogenic inflammation cannot be excluded, although the effect is likely to be minor. Indeed, in the Look AHEAD trial, an intensified lifestyle intervention reduced body weight (-2.6 kg *vs* control group), but with no significant reduction in CV outcomes [50].

## 6. Direct effects on myocardium

### *6.1. Effects of native GLP-1*

Several studies have shown a beneficial effect of native GLP-1 on the heart [51]. GLP-1 *in vitro* increased intracellular cyclic AMP in rat cardiomyocytes [52] while, in murine cardiomyocytes, GLP-1 protected cells against apoptosis induced by staurosporine, palmitate or ceramide, a cytoprotective effect mainly mediated by phosphatidylinositol 3-kinase (PI3K) and partially dependent on extracellular signal-regulated kinase (ERK) 1/2 [53]. In wild-type mouse hearts subjected to ischaemia – reperfusion, GLP-1 significantly increased functional recovery and cardiomyocyte viability [54]. Such effects were also observed in GLP-1-Receptor KO mice, suggesting that some cardioprotective effects of native GLP-1 may be mediated through a mechanism independent of the known GLP-1 receptors [54]. Indeed, in that study the GLP-1 metabolite, GLP-1-(9-36), also showed significant cardioprotective effects [54]. In Wistar – Kyoto rat hearts, GLP-1 increased glucose uptake by increasing nitric oxide (NO) production and glucose transporter (GLUT)-1 translocation [55]. In the same model, GLP-1 also enhanced recovery after a 30-min low-flow ischaemia protocol, with significant improvement in left ventricular (LV) end-diastolic pressure and LV developed pressure, and also showed that the GLP-1-mediated increase in glucose uptake was through a non-Akt-dependent mechanism distinct from the action of insulin [55].

In conscious dogs with advanced dilated cardiomyopathy, Nikolaïdis et al. [56] showed that a 48-h infusion of GLP-1 could significantly increase stroke volume and cardiac output, while significantly decreasing LV end-diastolic pressure, heart rate and systolic vascular resistance. GLP-1 also increased myocardial insulin sensitivity and myocardial glucose uptake [56]. In rats subjected to ischaemia – reperfusion, GLP-1 dramatically decreased infarct size, an effect that was abolished by a GLP-1 receptor antagonist [57], while data from a study in dogs by Moberly et al. [58] indicated that acute intracoronary administration of GLP-1 preferentially augments glucose metabolism in ischaemic myocardium, independently of its effects on cardiac contractile function or coronary blood flow. In swine, GLP-1, but not its metabolite GLP-1-(9-36), increased cardiac output during ischaemia by increasing ventricular preload without changing cardiac inotropy [59]. In non-diabetic rats, an infusion of native GLP-1, started 10 min prior to the induction of ischaemia and continued for 24 h until the end of the reperfusion period, significantly reduced infarct size while increasing myocardial glucose uptake in the normal heart, and induced metabolic substrate switching by increasing the ratio of carbohydrate *vs* fat oxidation in the non-ischaemic myocardium of ischaemic hearts [60]. A possible direct effect of GLP-1 on the heart is also suspected, as mice with genetic deletion of GLP-1 receptors display increased LV thickness, impaired LV contractility and diastolic dysfunction after insulin administration, as well as reduced LV contractility after epinephrine infusion [61].

A few studies have analyzed the effects of native GLP-1 on human hearts *in vivo*. Thrainsdottir et al. [62] examined six diabetic patients with congestive heart failure of ischaemic etiology, treated with subcutaneous infusions of 3–4 pmol/kg/min of recombinant GLP-1 for 72 h, and reported a trend towards myocardial improvement. In one exploratory study, a 72-h GLP-1 infusion improved regional and global LV function in 10 patients with acute MI and severe diastolic dysfunction after successful primary angioplasty, increasing the LV ejection fraction (LVEF) from 29 ± 2% to 39 ± 2% ($p < 0.01$). In addition, the in-hospital mortality rate was reduced in patients with acute MI and LV dysfunction (27% *vs* 10%, respectively) after successful reperfusion [63]. In a pilot study of 20 patients with normal LV function and

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