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

B. Vergès [1 2], B. Charbonnel [3]

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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.

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], [6], [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].

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.

Section snippets

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…

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…

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], [31], [32], [33], [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…

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*…

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 –…

GLP-1 and endothelium function

In several in-vitro studies, GLP-1 induced endothelial-dependent relaxation [74], [75], an effect that is NO-dependent [75]. Also, in-vitro GLP-1 decreased reactive oxygen species (ROS) generation and subsequently reduced VCAM-1 mRNA levels in human umbilical vein endothelial cells (HUVECs) exposed to advanced glycation end-products (AGEs) [76], while several human studies reported beneficial effects with GLP-1 on endothelium function. In healthy non-diabetic subjects, GLP-1 infusion enhanced…

GLP-1 receptor agonists and insulin resistance

Several human studies using the euglycaemic – hyperinsulinaemic clamp test have clearly shown that GLP-1 receptor agonists can significantly improve insulin sensitivity, which appears to be only partly mediated by weight reduction, so suggesting a direct effect [90], [91], [92]. This is reinforced by in-vitro studies showing that GLP-1 receptor agonists can enhance the insulin-signaling pathway [93], [94]. It is well established that insulin resistance is associated with increased CV risk [95], …

Reduction in hypoglycaemia?

Hypoglycaemia is associated with an increased risk of CV events [98] and, as GLP-1 receptor agonists are known to reduce the risk of hypoglycaemia compared with insulin and sulphonylureas, it seems plausible that this effect could be linked to their CV benefits. However, this is actually unlikely because, although fewer hypoglycaemic events were observed in patients using liraglutide in the LEADER trial [8], the rate of hypoglycaemia in patients using semaglutide was similar to that with a…

Are CV effects similar in all GLP-1 receptor agonists?

As the prospective Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial failed to show any reduction of major CV events with lixisenatide in T2DM patients after acute coronary syndrome, it must be acknowledged that the CV effects are not the same in all GLP-1 receptor agonists [99]. While the reason(s) behind these discrepancies still need to be fully elucidated, it is likely that the different CV effects are due to differences in pharmacokinetics [100]. Lixisenatide has a very…

Conclusion

In conclusion, the LEADER trial and SUSTAIN-6 have clearly demonstrated, in T2DM patients at high CV risk, the beneficial CV actions of the GLP-1 receptor agonists liraglutide and semaglutide, most probably due to antiatherogenic effects. So far, the reasons behind this benefit are not entirely clear. Nevertheless, several hypotheses have been proposed, including the reduction of postprandial lipids, of body weight and visceral fat, and of chronic inflammation, as well as the possible direct…

Disclosure of interest

During the past 5 years, B. Charbonnel has received fees for consultancy, speaking, travel or accommodation from AstraZeneca, Boehringer-Ingelheim, Janssen, Lilly, Merck-Sharpe & Dohme, Novartis, Novo-Nordisk, Sanofi, Takeda.

During the past 5 years, B. Vergès received consulting fees and honoraria for lectures from AstraZeneca/Bristol-Myers Squibb, Bayer Pharma, Kowa, Lilly, Merck Sharp Dohme, Novartis, Novo Nordisk, Sanofi, Servier and Takeda.…

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