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Review Article

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONISTS IN CARDIAC DISORDERS

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ABSTRACT

The active incretin hormone glucagon-like peptide-1 (GLP-1) is a 30-amino acid peptide that exerts glucoregulatory and insulinotropic actions by functioning as an agonist for the GLP-1 receptor (GLP-1R). In addition to its anti-diabetic effects, GLP-1 has demonstrated cardioprotective actions.the effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on myocardial function remain controversial. Whereas some promising observations have been reported in various animal models, the effects of GLP-1RAs on myocardial function in humans are more heterogeneous, while the positive effect on left ventricular ejection fraction (LVEF), if any, appears to be inconsistent and rather modest in most patients with HF. However, no increased risk of hospitalization for HF has been reported with GLP-1RAs in meta-analyses of phase-II/III trials Here we review the cardiovascular effects of the GLP-1 analogues currently approved for the treatment of type 2 diabetes, namely exenatide and liraglutide. We discuss their anti-hyperglycaemic efficacy, and offer a clinical perspective of their effects on cardiovascular risk factors such as body weight, blood pressure, heart rate and lipid profiles, as well as their potential consequences on cardiovascular events, such as arrhythmias, heart failure, myocardial infarction and death.

Keywords: Cardiovascular disease, clinical perspective, GLP-1 receptor agonists, type 2 diabetes, ischemic heart disease.

INTRODUCTION

Glucagon-like peptide-1 receptor (GLP-1R) agonists have been investigated for treating type 2 diabetes mellitus (T2DM) since the early 1990s because of their ability to enhance glucose-dependent insulin secretion. The cessation of GLP-1-stimulated insulin release when blood glucose concentrations are <55 mg/dL is probably responsible for the low incidence of severe hypoglycemia observed in phase III clinical trials of the GLP-1R agonists exenatide and liraglutide. Uniquely, GLP-1R agonists exert coordinated effects on mechanisms of glucose release and nutrient uptake, suppress inappropriately elevated glucagon secretion, slow gastric emptying, and increase satiety with the net result of reduced body weight. Weight loss and lower blood glucose concentrations may reduce patients' risk for cardiovascular disease (CVD).

In addition, GLP-1R agonists are hypothesized to have pleiotropic effects on the cardiovascular system. This is a particularly important research area for patients with T2DM since these individuals are at increased risk for CVD and recover from cardiovascular events less well than patients without diabetes. Type 2 diabetes is frequently associated with proatherogenic risk factors including hypertension, overweight or obesity, and dyslipidemia with elevated proinflammatory markers and procoagulant factors. However, patients with T2DM also demonstrate endothelial dysfunction and impaired vasodilatation, microvascular disease (particularly in the myocardial microcirculation, increased arterial stiffness, left ventricular hypertrophy, and cardiac fibrosis. To improve the cardiovascular outcomes of patients with T2DM, comprehensive risk reduction was recommended by a joint committee of the American Heart Association and the American Diabetes Association, specifically to achieve an HbA1C <7% or as close to normal (<6.0%) as possible without significant hypoglycemia, weight loss to reduce multiple CVD risk factors, aggressive management of hypertension, treatment of dyslipidemia, and therapy to prevent platelet aggregation.

GLP-1 Structure and Function:

GLP-1-(7-36) amide is a 30-amino acid cleavage product of pro-glucagon secreted by enteroendocrine L-cells in the gut. Oral ingestion of a meal is the primary physiological stimulus to GLP-1 secretion. GLP-1 is not secreted in response to an intravenous glucose infusion. GLP-1 has receptor-dependent and -independent actions. It causes glucose-dependent insulin release through binding the GLP-1 receptor (GLP-1R) on pancreatic beta cells. GLP-1 does not cause hypoglycemia as its insulinotropic effect does not occur at a blood glucose concentrations <70 mg/dl. GLP-1 has a number of other physiological effects which serve to lower plasma glucose levels. These include stimulation of insulin gene transcription in the beta cell and reduced gastric emptying. Enhancement of peripheral insulin sensitivity remain unproven with conflicting evidence. The GLP-1R is a 463-amino acid, G protein-coupled receptor found on the cell surface membrane of numerous tissues throughout the body. Its presence within the myocardium has remained controversial. Both mouse and primate studies have suggested that GLP-1R remains confined to the atria and possibly just the sinoatrial node. The location of the receptor is important in elucidating the mechanism of GLP-1 cardioprotection. Evidence of receptor-independent effects suggest that there may be an alternative receptor or perhaps actions that do not require a receptor discussed further below.

GLP-1 is cleaved by the enzyme dipeptidyl peptidase (DPP)-4 to GLP-1-(9-36) amide with a half-life of approximately 2 min. The biological role of this breakdown product is uncertain but it has reduced incretin activity. GLP-1 is further degraded by neutral endopeptidase to GLP-1 fragments whose biological activity is the subject of ongoing research. A number of pharmaceutical products have been developed to use the incretin effect of GLP-1 while avoiding the difficulties associated with its rapid breakdown to an apparently inactive form. These drugs include DPP-4 inhibitors such as sitagliptin, saxagliptin, and vildagliptin. all of which increase levels of native GLP-1 receptor agonists (GLP-1RA) such as exenatide and liraglutide.

Mechanism of GLP-1-Mediated Cardioprotection:

Many of the studies cited above have demonstrated aspects of cardioprotection that provide clues to how GLP-1 protects against IR injury. Several mechanisms have been proposed for GLP-1-mediated cardioprotection. A change in myocardial glucose utilization may result in increased metabolic efficiency and myocardial resistance to ischemia, thus limiting infarction. Vasodilation and reduction in systemic and/or pulmonary vascular resistance can also reduce cardiac work and ATP demand during ischemia. Finally, the pathways of ischemic preconditioning may be activated to increase cellular resistance to IR injury. These pathways may overlap, limiting lethal and nonlethal IR injury to various extents. Figure 1 offers an overview of a number of proposed mechanisms for GLP-1-mediated cardioprotection. Evidence for these mechanisms is reviewed below.

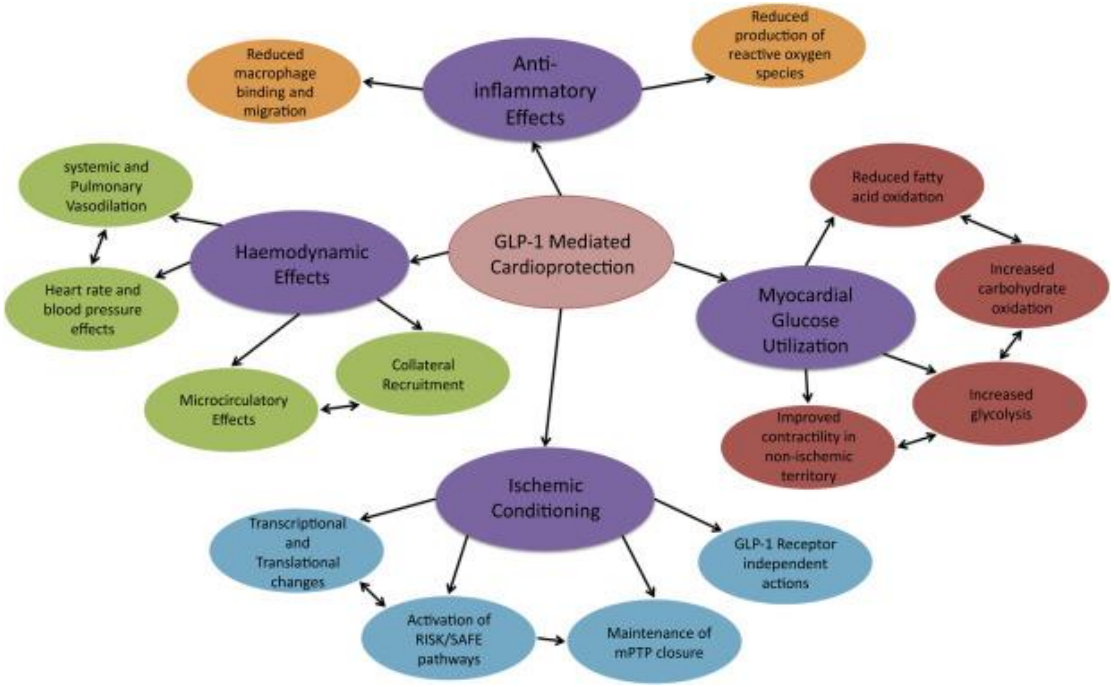

Figure 1: Possible Mechanism of GLP-1-Mediated Cardioprotection: A Complex Web GLP-1 cardioprotection appears to be mediated through a number of complex and interrelated cellular mechanisms. Figure 1 shows a number of proposed actions through which GLP-1 may exert its protective effect. Detailed physiological and biochemical studies are needed to tease out the relevant contributions of different actions

and, indeed, determine whether some of these are “red-herrings.”

Myocardial glucose utilization:

A change in myocardial glucose utilization is consistent with the physiological role of an incretin hormone. Fatty acids are the main fuel for energy production in the heart, although the omnivorous myocyte will use a number of different sources for ATP production. Glucose is the most oxygen-efficient source of ATP and is the preferred substrate when insulin and glucose levels are high, as in the post-prandial state. Glucose is preferentially metabolized in ischemic tissues and this is facilitated by augmentation of glucose uptake through up-regulation of the glucose transporters GLUT1 and GLUT4 to the cell surface membrane. Ischemic myocardium relies increasingly on anaerobic respiration through glycolysis, and if ischemia is prolonged intracellular levels of lactate and Ca2+ rise, the pH falls, and ultimately initiates the apoptotic cascade. Increasing substrate availability through increased concentrations of glucose and/or insulin can protect by delaying the initiation of this cascade, the so-called glucose-insulin-potassium (GIK) effect. GIK therapy was among the earliest cardioprotective interventions to be investigated, but its benefit remains uncertain and controversial. Some data have shown reduction in infarct size when given during acute myocardial infarction. However, these benefits may have been mitigated by clinical problems including risks of hypoglycemia and hyperkalemia. Lack of a clear cardioprotective benefit in subsequent larger studies such as DIGAMI II (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2) has limited the translation of the GIK effect into clinical practice.

Increased glucose uptake by the myocardium has been shown to be beneficial in IR injury. In a canine model of dilated cardiomyopathy, GLP-1 was shown to increase myocardial glucose uptake. This was associated with an improvement in myocardial performance. GLP-1 reduced levels of lactate and pyruvate in a porcine model of IR injury, suggesting alteration of myocardial glucose utilization. Of note, infarct size was not affected by GLP-1 in that model. Additionally, albiglutide produced an increase in myocardial glucose uptake and a shift from fatty acid to carbohydrate oxidation during IR injury in rats. In an ex vivo rat model, chronic treatment with DPP-4 inhibitors reduced infarct size in a glucose-dependent manner. Conversely, a number of recent human studies have cast doubt on changes in myocardial glucose utilization as the mechanism behind GLP-1-mediated cardioprotection. A study of 20 nondiabetic patients given a 48-h subcutaneous infusion of GLP-1 did not show any significant change in metabolic parameters. Furthermore, coronary sinus sampling in humans subjected to brief coronary artery occlusion demonstrated no significant change in myocardial glucose extraction when GLP-1 was infused. In healthy volunteers, GLP-1 did not affect overall myocardial glucose utilization in either normo- or hypoglycemic states. The subgroup of volunteers with a high baseline level of glucose utilization had a reduced level in response to GLP-1. In contrast, those with low baseline level were found to exhibit increased glucose utilization.

Pharmacokinetics:

Exenatide:

Exenatide was the first GLP-1 mimetic approved by the FDA, in April 2005. Several recent studies

provided additional clinical utilities for exenatide, demonstrating increased β-cell function and significant reduction of daily insulin doses in insulin-treated type 2 diabetic patients. It is a synthetic, 39-amino acid peptide (molecular formula form of the exendin-4 molecule isolated from the salivary gland secretions of the Gila monster. It shares 53% similarity with human GLP-1 but is resistant to enzymatic degradation by DPP-4. Exenatide is administered twice daily within 60 min of morning and evening meals. The duration of effect of exenatide is therefore considerably longer than that of native GLP-1, although twice-daily administration is required.After subcutaneous (s.c.) administration, exenatide reaches peak plasma concentrations in 2.1 h, with a half-life of approximately 2 h. DPP-4-resistant exenatide is measurable in plasma for up to 10 h following s.c. injection, warranting twice-daily dosage for full glycaemic control. Exenatide is eliminated by glomerular filtration with subsequent proteolytic degradation; hence it is contraindicated in patients with end-stage renal disease. The most common adverse effects reported with exenatide treatment are diarrhoea, nausea and vomiting . Exenatide is not recommended in patients with severe gastrointestinal disease.

Liraglutide:

Liraglutide is structurally similar to natural GLP-1(7–37) with 97% identical amino acid residues to natural hormone. It differs at position 28 with Arg instead of Lys and in addition palmitic acid is conjugated via glutamate spacer at Lys in position 20. This fatty acid conjugation provides the prolonged duration of action facilitated by binding to serum albumin as well self-association at the subcutaneous space. Furthermore, the tight albumin binding action protects liraglutide sequence from DPP-4 and NEP enzymatic degradation. The mean plasma half-life in humans is 11–13 h. Once daily human dose of 1.2 mg provides good glycemic control and with increasing doses up to 1.8 mg show significant improvements in HbA1c reduction compared to exenatide (1.1% vs. 0.79%). Further increase in dose of up to 3 mg of liraglutide gave ~ 6% weight reduction in overweight Type 2 diabetics compared to placebo.

Possible Advantages in Cardiovascular Risk Factors:

Endothelial Function:

Endothelial dysfunction is a pathological process that links diabetic macro- and microvascular disease. Studies conducted in humans observed that the infusion of native GLP-1 in healthy volunteers improved the blood flow in the forearm induced by the secretion of acetylcholine, as measured by plethysmography. In fasting T2DM subjects with stable coronary artery disease, a notable improvement was found in endothelial function after the infusion of GLP-1, as demonstrated by an increase in flow-mediated vasodilation of the brachial artery during a hyperinsulinaemic clamp. Similarly, in an observational study of 20 diabetic subjects receiving metformin, exenatide treatment (twice daily) for 16 weeks improved flow-mediated vasodilation of the brachial artery after 5 minutes of ischaemia, as determined by ultrasound, compared with patients receiving glimepiride.

It is unclear whether the beneficial endothelial effects that are attributed to native GLP-1 are mediated by an endothelial GLP-1R. Many of these studies do not control for the effects of GLP-1 on increasing insulin secretion and decreasing glucose, so the improvement in endothelial function could be by indirect mechanisms.

The intra-arterial infusion of GLP-1 in obese subjects with metabolic syndrome improved acetylcholine- and sodium nitroprusside-induced forearm blood flow only in the presence of an intra-arterial infusion of insulin. In contrast, infusion of GLP-1 into the femoral artery after fasting in healthy subjects improved the flow, independently of insulin. Moreover, GLP-1 promotes vasodilation of isolated mesenteric arteries in the absence of insulin in a nitric oxide synthase-dependent manner. Liraglutide attenuates induction of plasminogen activator inhibitor type-1 (PAI-1) and vascular adhesion molecule (VAM) expression in human vascular endothelial cells (hVECs) in vitro. Therefore, it may protect against endothelial dysfunction, an early abnormality in vascular disease in diabetic patients. In vitro studies demonstrated GLP-1R-mediated inhibition of PAI-1 and VAM expression. Liraglutide treatment also increased nitric oxide synthase (eNOS) activity and reduced intercellular adhesion molecule (ICAM-1) expression in the aortic endothelium, another GLP-1R-dependent effect. All these studies therefore identify a potential molecular mechanism of protection by GLP-1R-mediated liraglutide against endothelial dysfunction. Further studies are required to evaluate the direct and indirect actions of the GLP-1 RAs against native GLP-1 on endothelial function or vascular smooth muscle cells in diabetic and nondiabetic subjects. They should specify whether part or all the observed effects attributed to GLP-1 are mediated by GLP-1R, GLP-1 (9-36) or degradation products that exert vasodilatory effects independent of GLP-1R function.

Coronary Ischaemia:

A great many preclinical and clinical studies show that the GLP-1 RAs have a cardioprotective effect. Nevertheless, many of these do not distinguish whether the mechanism by which this effect occurs is direct, through the GLP-1R, indirect via other pathways, or whether they could be potential effects of GLP-1 (9-36). A beneficial effect of the infusion of GLP-1 (for 72 hours) has been observed in patients with acute myocardial infarction (AMI) and left ventricular dysfunction after reperfusion, with improved ejection fraction and ventricular wall motion. Acute infusion of GLP-1, 30 minutes before a dobutamine stress cardiac ultrasound and 30 minutes afterwards prevented the development of postischaemic myocardial dysfunction. investigated the effects of a 6-hour infusion of exenatide compared with placebo during the 15 minutes prior to reperfusion in patients about to undergo a coronary intervention to treat ST-segment elevation myocardial infarction (STEMI). Exenatide was effective in reducing the size of the infarct in relation to the ischaemic area and increased the myocardial salvage index measured by cardiac magnetic resonance 90 days postinfusion. In contrast, patients treated with exenatide had no reduction in mortality or improvement in left ventricular contractility. Post hoc analyses revealed that a trend towards a smaller final infarct size in patients treated with exenatide versus placebo (13 ± 9 versus 17 ± 14 g;). This cardioprotection described with exenatide was observed in both diabetic and nondiabetic patients. Complementary evidence of the cardioprotective effect of exenatide was obtained in a study that included 58 patients with STEMI and thrombolysis. Compared to placebo, the exenatide group showed an improvement in left ventricular function at 6 months and a reduction in the infarct size at one month.

Liraglutide also demonstrated cardioprotection in a trial with 96 patients with STEMI who underwent

percutaneous coronary angioplasty. Liraglutide treatment (0.6 mg for two days, 1.2 mg for two days and 1.8 mg for three days) was compared with placebo, finding a better myocardial salvage index in the liraglutide treatment arm (0.66 ± 0.14 versus 0.55 ± 0.15;), smaller infarct size (15 ± 12 versus 21 ± 15;), and lower high-sensitivity C-reactive protein levels. Thus, native GLP-1 and GLP-1 RAs together produce favourable effects in patients with coronary artery disease, which were initially attributed to direct effects on the myocardium. New findings that call into question GLP-1R expression in the ventricular cardiomyocytes support the hypothesis that this beneficial effect on the myocardium could be mediated by a process independent of the GLP-1R.

Heart Failure:

Promising experimental studies in animal models have generated high expectations of the possible benefit of GLP-1 RAs in patients with T2DM and heart failure. Until the moment, there are no published studies in which the effect on heart failure of GLP 1 agonists is the primary objective. Hospital admissions due to heart failure have been explored as secondary objectives. However, there are several clinical trials completed and pending for publication which explore this, such as functional impact of GLP-1 for heart failure treatment (FIGHT), liraglutide and heart failure in type 2 diabetes, evaluating the use of exenatide in people with type 2 diabetes and diastolic heart failure, incretin-based drugs and the risk of heart failure, effects of exenatide in type 2 diabetic patients with congestive heart failure. Meta-analyses of phase II/III clinical trials of exenatide, liraglutide, albiglutide, and dulaglutide have shown that they do not increase the risk of hospitalization for heart failure, confirming the findings of cardiovascular safety trials, which we will review later. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, in particular, showed a significant 12% reduction in the expanded composite outcome comprising the primary endpoint plus coronary revascularizations and hospitalizations for angina and heart failure. However, there was no significant benefit on heart failure admissions [57]. For the moment, clinical data have demonstrated a neutral effect on the incidence of hospitalization for heart failure; nevertheless, this has to be explored as a primary objective in future trials.

Blood pressure and heart rate:

Hypertension, defined as SBP > 140 mmHg and DBP > 90 mmHg, is a frequent comorbidity in T2D contributing to CVD risk. Stringent blood pressure control has been shown to reduce CV events and all-cause mortality.63,64 A reduction of 5.6 mmHg resulted in an 18% decrease in the risk of death from CV disease in patients with diabetes.65 Accordingly, SBP and DBP are important considerations in the continuum of care in T2D. Exenatide, both as Exenatide and liraglutide has a favourable effect on blood pressure, primarily SBP. A pooled data analysis from six clinical trials investigating Exenatide in T2D patients for six months revealed significantly greater reductions in SBP with Exenatide compared with placebo (difference of −2.8 mmHg) or insulin (difference of −3.7 mmHg). This decrease was greater in patients with a baseline SBP of ≥ 150 mmHg. There were no significant changes in DBP, although a small correlation was found between weight loss and reductions in SBP ($r = 0.09$, $p = 0.02$). In a smaller double-blind placebo-controlled pilot study comparing Exenatide twice daily versus placebo for 12 weeks in patients already on metformin and/or a TZD, significant

reductions in 24 h, daytime and night-time SBP were observed in patients receiving Exnatide without accompanying changes from baseline in DBP or mean 24 h HR. Exnatide significantly reduced SBP, with mean reductions ranging from −3 to −5 mmHg. Active comparators sitagliptin, pioglitazone and insulin glargine failed to significantly reduce SBP from baseline. Meanwhile, mean HR increased by four beats per minute (bpm) compared with baseline in patients receiving Exenatide, but not in the insulin glargine group. It remains unclear whether this magnitude of change in HR holds any clinical significance in patients treated with this agent. While the DURATION investigators noted no association between changes in HR and SBP, it remains unclear whether the observed increases in HR are in any way related to the mechanisms that cause reduced SBP. The latter may include improved endothelial function, natriuresis and/or diuresis. In a small pilot study, patients with impaired glucose tolerance or early onset T2D manifest improved post-prandial endothelial function after a single injection of exenatide 10 μg versus placebo, following a high-fat meal. Improved endothelial function has also been demonstrated in small human studies using native GLP-1. A pre-clinical study in rats has demonstrated that exenatide can induce natriuresis and diuresis with accompanying increases in glomerular filtration rate and renal blood flow. Although these mechanisms have yet to be confirmed in humans, one small clinical study with native GLP-1 supports the notion that GLP-1 receptor activation can reduce renal sodium absorption.

Whether used as a monotherapy or in combination with other agents, liraglutide consistently reduced SBP across the LEAD 1–5 trials, with SBP falling by means of 2.7 to 6.6 mmHg from baseline with liraglutide 1.2 and 1.8 mg doses. This reduction was even evident in patients with well-controlled blood pressures at baseline (min–max: 128/76–134/81 mmHg). The same trend was reported from a meta-analysis of all six Phase III LEAD studies examining the specific effect of liraglutide on SBP. In this analysis, the magnitude of SBP reductions observed with liraglutide was greatest in subjects with the highest baseline SBP. For subjects in the highest quartile of baseline SBP (> 140 ≤ 190 mmHg) the fall in SBP was 11.4 mmHg with liraglutide 1.2 and 1.8 mg doses versus 7.7 mmHg with placebo ($p < 0.0001$). This effect on SBP occurred early and was maintained over time. In a model (adjusted for quartile of baseline SBP) examining longitudinal effects, reductions in SBP began within two weeks of treatment onset, preceded any weight loss (which occurred after eight weeks of therapy) and were maintained over the entire 26 weeks of the study periods. The reductions in SBP observed in the LEAD trials were not accompanied by any statistically significant changes in DBP. While patients in the six LEAD trials did experience small reductions in DBP across all treatments groups, e.g. 0.7 to 1.4 mmHg in LEAD-1, there were no significant reductions between groups. Like Exenatide, liraglutide once daily resulted in small but statistically significant increases in HR. Addition of liraglutide to combination therapy resulted in HR increases ranging from 2 to 3 bpm, as compared with active comparator or placebo.

Dyslipidaemia:

Given the insulin resistance and metabolic disorder in patients with T2DM, dyslipidaemia is an important and common comorbidity. The typical lipid profile of a T2DM patient, known as atherogenic dyslipidaemia, includes a decrease in HDL cholesterol (HDL-C) and an increase in LDL cholesterol (LDL-C), total

cholesterol, and triglycerides. The combination of dyslipidaemia and poor glycaemic control plays an essential role in the development of atherosclerosis. According to the Quebec Cardiovascular Study, the combination of diabetes, high LDL-C, and high apolipoprotein B confers a 20-fold risk of developing cardiovascular episodes. It is interesting to note that several clinical trials with GLP-1 Receptor Agonists have described an improved lipid profile due to as yet unknown mechanisms. No clinical trials have been conducted that evaluate the different doses and impact on lipid profiles of each GLP-1 Reeptor Agonist. Additionally, most trials were not specifically designed to look at the effect of GLP-1 Receptor Agonists on lipid profile. The majority are head-to-head trials in which the GLP-1 agonist is compared to placebo or other treatments, such as an active comparator, mainly exenatide and liraglutide.

Exenatide in both twice-daily doses of 5 μg and 10 μg and in the extended-release formulation and liraglutide 1.8 mg have shown a reduction in total cholesterol levels. The lowering effect seems more marked with extended-release exenatide and liraglutide 1.8 mg. In terms of lowering triglyceride values, liraglutide (1.2 mg and 1.8 mg) has been found to be more effective. In a meta-analysis of the LEAD trials (liraglutide clinical development program), it was observed that, in all of them, treatment with liraglutide reduced LDL-C (−7.73 mg/dL), total cholesterol (−5.03 mg/dL), and triglycerides, compared with standard treatment. The LEAD-6 study found a reduction in triglycerides of −15.7 mg/dL, compared with twice-daily exenatide. Moreover, decreases in HDL-C were observed, except in patients on combined treatment with TZD.

In the DURATION studies (with extended-release exenatide), reductions of between 4.64 and 34.8 mg/dL were found in total cholesterol compared with standard tatment. These reductions were much greater than with twice-daily exenatide. No changes were observed in HDL-C levels. In a 3-year follow-up trial that compared twice-daily exenatide with placebo, the group treated with exenatide were found to have reductions of −6% in LDL-C values, −5% in total cholesterol, and− 12% in triglycerides. Another study, the EUREXA trial, also showed reductions in triglycerides and improvement in HDL-C with twice-daily exenatide compared to glimepiride. A modest improvement in the lipid profile of a patient with T2DM can produce a significant impact from a clinical point of view; nevertheless, the mechanism has not been clearly identified. One possible explanation could be improved glycaemic control, which would reduce insulin resistance and hepatic triglyceride synthesis. Another possible action could be mediated by GLP-1Receptor in the intestinal mucosa, resulting in reduced secretion of apolipoprotein B48, present in the chylomicrons, with a consequent reduction in plasma triglycerides. The beneficial effects of liraglutide could be related to modulation of the expression of certain genes related to lipid and glucose metabolism. Furthermore, in studies performed with exenatide, this agent was seen to suppress the production of intestinal lipoproteins by acting directly on their synthesis, independently of changes in weight, satiety, or gastric emptying. It is important that new trials should be carried out that include all GLP-1 agonists and their effect on the lipid profile as the primary objective and that they explore the mechanism by which this improvement occurs.

Arrhythmias:

Assessment of the QT interval is an important CV safety outcome to consider for drugs under clinical

development. The QT interval is defined as the time it takes from the start of ventricular depolarisation (i.e. the start of the Q or R wave on the surface electrocardiogram (ECG)) to the end of ventricular repolarisation (i.e. the end of the T wave on the ECG). QT prolongation can predispose to malignant ventricular arrhythmias (e.g. torsade des pointes), which are often drug-induced. As such, thorough QT studies are used to assess the potential for developing such arrhythmias after long-term exposure to new therapeutics. A study specifically examining the effects of exenatide on QT interval has appeared recently. This randomised, placebo-controlled study of healthy subjects included three cross over treatment periods with exenatide (10 µg) and placebo. QT intervals corrected for HR (QTcF) and individually (QTcI) were analysed for change between pre- and post-treatment values. Based on both QTc assessments, exenatide did not show a clinically significant prolongation in QT as compared with placebo. An earlier study on the effects of liraglutide on QT intervals reached the same conclusions for this GLP-1R agonist. This placebo-controlled, double-blind cross over study with healthy participants assessed the effects of liraglutide 0.6, 1.2, and 1.8 mg doses versus placebo once daily for seven days each. Four correction methods were used to assess the change in QTc interval from baseline. The study concluded that liraglutide did not cause any significant increase in QTc interval.

Death:

The long-term cardiovascular mortality associated with GLP-1 receptor agonists has not been extensively evaluated due to the relatively recent availability of these drugs on the market. One study set in the United Kingdom evaluated the life-expectancy associated with exenatide versus insulin glargine, as add-on therapies in T2D patients inadequately controlled on combination OADs after 35 years of treatment. Using a computer simulation model of diabetes (CORE model) and data from a published head-to-head 26-week trial of exenatide versus insulin glargine in 549 patients, it was demonstrated that exenatide was associated with both improvements in life expectancy and quality-adjusted life-expectancy. When compared with insulin glargine, life expectancy improved by 0.057 years with exenatide, while quality-adjusted life years improved by 0.442. The authors attributed the difference between life expectancy and quality-adjusted life expectancy to the impact of exenatide's body-weight lowering effect on improving lifestyle. The long-term cardiovascular morbidity and mortality effects of treatment with liraglutide were also simulated using the CORE diabetes cohort model, with data extracted from LEAD-1.85 Simulating a hypothetical cohort of 5000 patients per treatment (liraglutide 1.2, 1.8 mg, rosiglitazone 4 mg, all added to glimepiride), this model estimated that the survival rates would be 15% and 16% higher for liraglutide 1.2, 1.8 mg respectively than rosiglitazone after 30 years of treatment. Projected rates of cardiovascular death would be 69.7%, 68.4% and 72.5% for liraglutide 1.2, 1.8 mg and rosiglitazone respectively.

Major adverse cardiovascular events:

In a pooled analysis of 15 Phase II–III clinical trials of liraglutide, including a total of 6638 patients, of which 4257 were exposed to liraglutide, the rates of reported major adverse cardiovascular events (MACEs) comprising cardiovascular death, myocardial infarction and stroke, favoured liraglutide versus standard OAD comparators. MACEs were assessed using Medical Dictionary for Regulatory Activities (MEDRA) search terms

combined with serious adverse events reported by investigators. Of note, these trials represented relatively short periods of follow-up, with a low total number of adjudicated MACEs (n = 39). Thus while the incidence ratio of 0.73 revealed by this analysis favoured liraglutide over comparators (with the upper 95% confidence limit of 1.41), larger studies with longer durations of follow-up are needed to more fully establish the cardiovascular safety of this agent. Similarly, in a meta-analysis of Exenatide including T2D patients representing patient-years of exenatide exposure (with an average exposure of 24 weeks), no increase in CV risk was associated with Exenatide use. The exposure adjusted incidence rate of MACEs for patients treated with exenatide was 18.73 per 1000 patient-years, and 23.17 per 1000 patient-years for the pooled-comparator group (placebo or insulin treated). Again, while the hazard ratios (0.7) and relative risk reductions suggest that exenatide may improve cardiovascular outcomes, such small and short duration studies were not designed to test the longer term safety profiles of this class.

CONCLUSION

Here we have reviewed the published literature, including recent meetings abstracts, to provide a predominantly clinical perspective on the pharmacokinetics, anti-hyperglycaemic efficacy and cardiovascular risk factor and outcomes profiles of exenatide and liraglutide, the two widely available GLP-1Receptor agonists currently in use for the treatment of T2D. These powerful and well tolerated injectable agents effectively lower hyperglycaemia in patients with T2D, without increasing the incidence of hypoglycaemia. They have additional salutary effects such as reductions in body weight and SBP, while generally improving lipid profiles and other biomarkers of cardiovascular disease. Although they likely achieve these additional effects through a combination of mechanisms that include appetite suppression, reduced body fat, natriuresis, diuresis and improved endothelial function, further studies are needed to better understand their clinical significance. Similarly, the clinical significance and physiological mechanisms underlying the small but statistically significant increases in mean resting HR produced by both GLP-1Receptor agonists remain unknown. Having said this, QT intervals are not prolonged by these drugs, and early meta-analyses of the short-term clinical trials conducted to date and retrospective studies of large registry data suggest that the cardiovascular outcomes of diabetic treated with these agents are better than those not treated with them. Finally, promising validation of pre-clinical studies that showed cardioprotective and vasodilatory effects of these drugs is beginning to emerge in clinical studies. Already underway, the large randomised, double-blind, placebo-controlled studies on the long-term cardio-*/vascular safety.

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