EFFECT OF LIRAGLUTIDE ON CARDIOVASCULAR RISK FACTORS AND FUNCTION

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Abstract

Cardiovascular disease is the major cause of death in diabetes. This results from a cluster of risk factors, including high glucose, obesity, hypertension and dyslipidaemia. Liraglutide is the first native GLP-1 analogue and represents a breakthrough approach in type 2 diabetes treatment. Previous data from the LEAD™ programme have shown liraglutide to be a potent glucose regulator, but also to induce weight loss, lower blood pressure, and potentially show improvements in lipid levels, amongst other markers of cardiovascular risk. GLP-1 has also been shown to have an effect on the renal system, as well as the vascular system. Other cardio-protective effects of GLP-1 were proved in animal models: improves cardiac function in heart failure, functional recovery following myocardial ischemia, endothelium dysfunction, increases myocardial glucose uptake and reduces infarct size. Cardiovascular safety of liraglutide was assessed using existing clinical data. The incidence ratio for adjudicated broad/serious major adverse cardiovascular events (MACE) associated with liraglutide was 0.73 (95% CI 0.38–1.41) versus all comparator drugs, within cardiovascular safety limits defined by the United States Food & Drug Administration.

keywords: cardiovascular risk factors, cardiovascular safety, cardio protective effects GLP-1, Liraglutide, type 2 diabetes mellitus

Introduction

IDF fact sheet: Diabetes and cardiovascular disease [1]

Cardiovascular disease (CVD) is the major cause of death in diabetes, accounting for some 50% of all diabetes fatalities, and much disability. On average, people with type 2 diabetes will die 5-10 years before people without diabetes and most of this excess mortality is due to cardiovascular disease. People with type 2 diabetes are over twice as likely to have a heart attack or stroke as people who do not have diabetes. Indeed, people with type 2 diabetes are as likely to suffer a heart attack as people without diabetes.
who have already had a heart attack. Strokes occur twice as often in people with diabetes and hypertension as in those with hypertension alone. People with diabetes are 15-40 times more likely to have a lower limb amputation compared to the general population. People with diabetes have two to four times the risk of developing atherosclerosis compared to people without diabetes.

This results from a cluster of risk factors (Figure 1), including high glucose, obesity, hypertension, and dyslipidaemia [2].

Figure 1. Risk factors for cardiovascular disease.

Only around 10% of people with type 2 diabetes are controlled on risk factors such as high glucose, hypertension and dyslipidaemia [3]. Therefore, there is a significant unmet medical need to control these cardiovascular risk factors when treating type 2 diabetes mellitus.

Liraglutide effect on cardiovascular risk factors in patients with type 2 diabetes

Liraglutide is the first native GLP-1 analogue [4] and represents a breakthrough approach in type 2 diabetes treatment. It acts by potently stimulating insulin secretion in a glucose-dependent manner, reducing inappropriately elevated glucagon levels, slowing gastric emptying and reducing appetite, which in turn reduces food intake [4].

Previous data from the LEAD trials have shown liraglutide to be a potent glucose regulator, but also to induce weight loss, lower blood pressure, and potentially show improvements in lipid levels, amongst other markers of cardiovascular risk [4, 5, 6, 7, 8, 9]:

- Reduction in HbA1c of 1.0-1.6 %
- Reduction in body weight of 2-3 kg
- Reduction in systolic blood pressure (SBP) between 2-6 mmHg
- Indications of improvement in lipids and other markers of cardiovascular risk: Total cholesterol (TC), low density lipoprotein cholesterol (LDL), triglycerides (TG), free
fatty acids (FFA), brain natriuretic peptide (BNP), C-reactive protein (CRP), vascular cell adhesion molecule-1 (VCAM), plasminogen activator inhibitor-1 (PAI-1)

- Very low risk of hypoglycaemia

**Liraglutide improved emergent cardiovascular disease risk markers across the LEAD trials**

Plutzky et al. [10] assessed the impact of liraglutide on lipids and other cardiovascular risk markers. A meta-analysis (ANCOVA) of the six trials comparing liraglutide 1.8 mg once daily (OD) with common type 2 diabetes therapies (glimepiride, rosiglitazone, insulin glargine, exenatide) and placebo (n=3967) was conducted.

After 26 weeks, TC, LDL, FFA and TG levels all decreased significantly from baseline with liraglutide \((p<0.01\) for all).

Decrease in TC was significantly greater with liraglutide \((p<0.01\) than with rosiglitazone, glargine or placebo; decrease in LDL was significantly greater with liraglutide \((p<0.05\) than with rosiglitazone, glimepiride or glargine.

Compared with baseline, high density lipoprotein cholesterol (HDL) fell significantly with all interventions except rosiglitazone. Versus baseline, liraglutide significantly decreased levels of BNP and high sensitivity C-reactive protein (hsCRP) – 2 key biomarkers of cardiovascular risk \((p<0.01\). apolipoprotein B (Apo B) levels did not change significantly with any treatments.

In conclusion, liraglutide significantly improved the lipid profile, and reduced BNP and hsCRP levels, in type 2 diabetes patients over 26 weeks. Liraglutide may have potential cardiovascular benefits in type 2 diabetes addition to its documented effects on glycaemic control, weight and SBP.

**Liraglutide, may have beneficial effects on blood vessels, the heart and the kidney**

In addition to reducing cardiovascular risk factors, studies indicate that the native GLP-1, and its analogue, liraglutide, may have beneficial effects on blood vessels, the heart and the kidney [11, 12, 13]. The benefits include the improvement of vascular endothelial function, protecting the heart under ischemic conditions, and increases in diuresis and sodium excretion [11, 12, 13].

**GLP-1 improves endothelial function in patients with type 2 diabetes and coronary artery disease**

It is well known that type 2 diabetes subjects are characterized by impaired endothelial-dependent relaxation, which may be a consequence of a disturbed synthesis or increased destruction of nitric oxide (NO) or a combination thereof [14].

Endothelial dysfunction is strongly associated with insulin resistance and type 2 diabetes mellitus and may be causing the angiopathy typifying this debilitating disease [15].

Intervention affecting both endothelial dysfunction and insulin resistance may prove useful in patients with type 2 diabetes.

Nyström et al. [16] investigated GLP-1’s effect on endothelial function and insulin sensitivity (IS) in two groups: 1) 12 type 2 diabetes patients with stable coronary artery disease and 2) 10 healthy subjects with normal endothelial function and IS. Subjects underwent infusion of recombinant GLP-1 or saline in a random crossover study. Endothelial function was measured by
postischemic flow-mediated vasodilation (FMD) of brachial artery, using ultrasonography. IS \([10^-4 \text{ dl} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})/\mu\text{U/ml}\]) was measured by hyperinsulinemic isoglycemic clamp technique. In type 2 diabetic subjects, GLP-1 infusion significantly increased relative changes in brachial artery diameter from baseline FMD (%) \((3.1 \pm 0.6 \text{ vs. } 6.6 \pm 1.0\%, P < 0.05)\), with no significant effects on IS \((4.5 \pm 0.8 \text{ vs. } 5.2 \pm 0.9, P = \text{NS})\). In healthy subjects, GLP-1 infusion affected neither FMD(%) \((11.9 \pm 0.9 \text{ vs. } 10.3 \pm 1.0\%, P = \text{NS})\) nor IS \((14.8 \pm 1.8 \text{ vs. } 11.6 \pm 2.0, P = \text{NS})\).

Nyström et al [16] concluded that GLP-1 improves endothelial dysfunction but not insulin resistance in type 2 diabetic patients with coronary heart disease. This beneficial vascular effect of GLP-1 adds yet another salutary property of the peptide, increasing its clinical utility in type 2 diabetic patients, in whom endothelial dysfunction is a salient feature that adversely affects their survival.

GLP-1 Improves functional recovery following myocardial ischemia

Nikolaidis et al [17] investigated the safety and efficacy of a 72-hour infusion of GLP-1 \((1.5 \text{ pmol/kg per minute})\) added to background therapy in 10 patients with acute myocardial infarction (AMI) and left ventricular (LV) ejection fraction (EF) <40% after successful primary angioplasty compared with 11 control patients. Echocardiograms were obtained after reperfusion and after the completion of the GLP-1 infusion. Baseline demographics and background therapy were similar, and both groups had severe LV dysfunction at baseline \((\text{LVEF}=29 \pm 2\%)\). GLP-1 significantly improved LVEF \((29 \pm 2\% \text{ to } 39 \pm 2\%, P < 0.01)\), global wall motion score indexes \((1.94 \pm 0.11 \rightarrow 1.63 \pm 0.09, P < 0.01)\), and regional wall motion score indexes \((2.53 \pm 0.08 \rightarrow 2.02 \pm 0.11, P < 0.01)\) compared with control subjects. The benefits of GLP-1 were independent of AMI location or history of diabetes.

GLP-1 was well tolerated, with only transient gastrointestinal effects.

When added to standard therapy, GLP-1 infusion improved regional and global LV function in patients with AMI and severe systolic dysfunction after successful primary angioplasty.

Many studies have shown that role of GLP-1 goes beyond regulation of glucose homeostasis and appetite regulation. GLP-1 has also been shown to have an effect on the renal system, where it plays a role in water and electrolyte homeostasis, as well as the vascular system.

Other cardio protective effects of GLP-1 were proved in animal models [18-23]:

- GLP-1 improves cardiac function in heart failure [18]
- GLP-1 increases myocardial glucose uptake [19]
- GLP-1 improves functional recovery following myocardial ischemia [20, 21]
- GLP-1 reduces infarct size [22, 23]

Cardiovascular safety of liraglutide assessed in a patient-level pooled analysis of phase 2–3 liraglutide clinical development studies [24]

Cardiovascular safety of liraglutide was assessed using existing clinical data. Patient-level results from all completed phase 2 and 3 studies from the liraglutide clinical development programme were pooled to determine rates of major adverse cardiovascular events (MACE):
cardiovascular death, myocardial infarction, stroke. MACE were identified by querying the study database using Medical Dictionary for Regulatory Activities (MedDRA) terms combined with serious adverse events recorded by study investigators. Broad, narrow, and custom groups of MedDRA queries were used. Candidate events from each query were independently adjudicated post hoc. In 15 studies (6638 patients; 4257 liraglutide treated), there were 114 patients with MACE identified using the broad MedDRA query. Of these, 44 were classified as serious adverse events and 39 were adjudicated as MACE. The incidence ratio for adjudicated broad/serious MACE associated with liraglutide was 0.73 (95% CI 0.38–1.41) versus all comparator drugs (metformin, glimepiride, rosiglitazone, insulin glargine, placebo), within cardiovascular safety limits defined by the United States Food & Drug Administration for diabetes therapies under current investigation.

It should be noted that the cardiovascular safety of liraglutide will be prospectively evaluated in the international LEADER™ trial, which is enrolling 9000 patients with type 2 diabetes and a broad range of cardiovascular risk, including known coronary heart disease. Patients will be randomised 1:1 to liraglutide or placebo and will be followed for up to 5 years for adjudicated macrovascular events including non-fatal MI, stroke, and cardiovascular death.

Conclusions

Liraglutide is a novel treatment developed to improve glycaemic control in patients with type 2 diabetes mellitus. Liraglutide is the first native GLP-1 analogue [4] and represents a breakthrough approach in type 2 diabetes treatment.

During the large clinical development programme, liraglutide has shown positive effects on cardiovascular risk factors.

In patients with type 2 diabetes, liraglutide reduced blood pressure and weight and showed indications of positive effects on lipids and other CV risk factors [4-10]

- Improves glycaemic control with a low risk of hypoglycaemia
- Decreases body weight and body fat
- Reduces SBP
- Shows indications of positive changes on lipid-profile
- Shows indications of reduction of CV risk markers, such as plasminogen activator inhibitor-1, brain natriuretic peptide and C-reactive protein

Liraglutide, may have beneficial effects on blood vessels, the heart and the kidney [11,12,13]

GLP-1 improves endothelial function in patients with type 2 diabetes and coronary artery disease [16]

GLP-1 improves functional recovery following myocardial ischemia[17].

In animal models, other cardioprotective effects of GLP-1 are [18-23]:

- Improves cardiac function in heart failure
- Increases myocardial glucose uptake
- Improves functional recovery following myocardial ischemia
- Reduces infarct size

The incidence ratio for adjudicated MACE was <1.0 compared with total comparator and the upper 95% CI was <1.8, within cardiovascular safety limits predefined by the US FDA for diabetes therapies under current investigation [24].
REFERENCES


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