Beneficial Effects of Liraglutide beyond Glycaemic Control

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Abstract
Macrovascular complications are the leading cause of mortality among patients with type 2 diabetes. Thus, a very important goal in the treatment of type 2 diabetes is to reduce the risk of macrovascular complications and mortality. Hyperglycaemia, obesity and hypertension are well-known risk factors for vascular complications in patients with type 2 diabetes. Obesity is a common co-morbidity and an independent risk factor of cardiovascular disease (CVD). Hypertension is a condition associated with diabetes that increases the risk of cardiovascular complications and death. It has been demonstrated that decrease and control in blood pressure reduces the risk of macrovascular complications. Patients with type 2 diabetes have a decreased β-cell function, which is one of the reasons for disease progression. Current medications are able to improve glycaemic control, but they do not reverse the disease progression and often result in weight gain. Hence, new treatment approaches are needed for the treatment of type 2 diabetes. The role of the native glucagon-like peptide-1 (GLP-1) biology has generated new hope for the successful management of type 2 diabetes. Liraglutide is the first once-daily human GLP-1 analogue, which has been developed to address the unmet medical needs in the management of type 2 diabetes. This novel drug may offer additional advantages over other current antidiabetic medications. Clinical trials demonstrate that liraglutide reduces weight, lowers blood pressure and restores β-cell function, besides improving glycaemic control in patients with type 2 diabetes. The results also show that liraglutide is well tolerated with minimal risk of hypoglycaemia due to its glucose-dependent stimulation of insulin secretion. The overall clinical findings indicate that liraglutide is a treatment for type 2 diabetes, which improves β-cell function, and reduces the burden of type 2 diabetes and its vascular complications.

Introduction
In patients with type 2 diabetes, the risk of developing CVDs (such as coronary artery disease, peripheral arterial disease and diseases of the carotid vessels) is four times higher (approximately 15 years earlier) compared to those without diabetes. Furthermore, it has been observed that patients with type 2 diabetes have an increased risk of mortality related to CVD compared to people without diabetes who have had a previous myocardial infarction. Patients with type 2 diabetes generally carry a number of risk factors for cardiovascular disease, including hyperglycaemia, obesity, hypertension and reduced insulin effect. Each of the risk factors increases the risk of CVD and will multiply when >1 risk factor exists. In spite of the availability of numerous antidiabetic treatments, which are able to improve the glycaemic control in patients with type 2 diabetes, the treatments usually result in weight gain and hypoglycaemia, particularly for sulphonylureas (SUs) and insulin. It has been demonstrated that weight loss has beneficial effects on the cardiovascular system and reduces the risk of CVD. The association between obesity and hypertension is also well recognised. It has been shown that an increase of 10 kg body weight is associated with 3.0 mmHg and 2.3 mmHg increases in systolic and diastolic blood pressure, respectively. This elevation in blood pressure has been shown to result in an estimated 12% and 24% higher risk of coronary heart disease and stroke, respectively. The World Health Organization’s (WHO) classification of overweight and obesity in Asian populations is a body mass index (BMI) of 23.0 to 24.9 kg/m² and BMI ≥ 25.0 kg/m², respectively. In fact, more than 80% of patients with type 2 diabetes are overweight or obese. Diabetes and hypertension are related in many ways. Both are associated with an increased risk of cardiovascular mortality. Tight blood pressure control (<130/85 mmHg) has managed to decrease diabetes-associated mortality and cardiovascular complications in patients with type 2 diabetes. Hence, a multifactorial approach is utilised for improving the outcome of type 2 diabetes, adding other drugs besides antidiabetic medications to reduce the risk of hypertension and CVD. An association between hyperglycaemia (HbA1c or fasting and postprandial glucose levels) and CVDs has been demonstrated in many clinical trials, most prominently the DECODE study. Tight control of the glucose levels has shown to have positive impact in reducing the risk of microvascular complications, such as retinopathy and nephropathy, in patients with type 2 diabetes. Despite these data, it remains unclear whether a strict glycaemic control will prevent macrovascular complications such as stroke and myocardial infarction. However, clinical trials show that improved glucose control has beneficial effects on preventing myocardial infarction with different consequences on cardiovascular death, but with an increased risk of hypoglycaemia.

Patients with type 2 diabetes suffer from progressive β-cell failure, which in turn leads to reduced insulin secretion, insulin gene expression and eventually apoptosis of the β cells. It has been demonstrated that the β-cell mass is reduced by 50% (compared to normal population) at diagnosis of type 2 diabetes. The β-cell dysfunction and the failure in the insulin secretory response are two major causes for the progression of diabetes.
is suggested that if the β-cell mass and function can be preserved, the progression of the disease can be delayed or even prevented.13

There is a need for new treatment approaches that address all these unmet needs in the management of type 2 diabetes.

GLP-1 is an incretin hormone produced and released from L cells of the distal small intestine and the colon in response to meal ingestion. When GLP-1 is secreted, it stimulates insulin secretion and decreases glucagon secretion in a glucose-dependent manner. GLP-1 also reduces gastric motility and emptying and thereby reduces appetite and food intake.4,14,15 In addition to the blood glucose-lowering effect, animal studies demonstrated that GLP-1 inhibited β-cell apoptosis, enhanced proliferation and promoted the neogenesis of β-cells.12 Moreover, clinical trials in patients with type 2 diabetes also indicated that GLP-1 has positive effects on the myocardium function and the endothelial function.17 The combination of these functions makes GLP-1 an attractive pharmacological approach for the treatment of type 2 diabetes.

However, a major drawback with the endogenous GLP-1 as a medical treatment is its short half-life (<1.5 min), which is mainly due to a rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4).4,15

**Liraglutide**

Liraglutide is a human GLP-1 analogue (97% amino acid homology to native human GLP-1), which has a pharmacokinetic profile suitable for once-daily administration, as evidenced with a half-life of approximately 13 h.4,14,15,16 Results from phase 2 and 3 clinical trials consistently showed that liraglutide is an effective drug, in terms of lowering plasma glucose concentration, and reducing weight and blood pressure. Clinical trials also showed that once daily administration of liraglutide increased insulin secretion and restored normal β-cell responsiveness to hyperglycaemia. Treatment with liraglutide was safe and well-tolerated. Moreover, the risk of hypoglycaemia was significantly lower with liraglutide as compared with currently available antidiabetic drugs. This is mainly because liraglutide stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner.12

**Liraglutide Effects on Cardiovascular Risk**

The LEAD trials (six large randomised, controlled phase 3 trials, conducted in 41 countries, in which approximately 2700 patients received liraglutide) showed that liraglutide was superior to most of the active comparators with respect to improved glycaemic control, weight loss, reduced systolic blood pressure (SBP) and lower plasma concentration of CVD biomarkers. These beneficial effects of liraglutide can be translated to clinically meaningful effects on cardiovascular risk in patients with type 2 diabetes. In fact, results from the LEAD trials showed a lower rate of major adverse cardiovascular events in the liraglutide group (18.0/1000 subject years of exposure) compared to the rate in the total comparator group (active comparator + placebo; 19.6/1000 subject years of exposure), active comparator group (18.8/1000 subject years of exposure) and placebo (19.3/1000 subject years of exposure).6

**Hyperglycaemia**

A meta-analysis of several prospective trials demonstrated that in patients with type 2 diabetes, an increase of 1% in glycated haemoglobin A1c (HbA1c) can be translated to an estimated increase of 18% in the risk of coronary heart disease and stroke.10 Another meta-analysis of randomised clinical trials showed that in comparison with standard treatments, intensive intervention could lower HbA1c by 0.9%. This resulted in a reduction of 17% and 15% in the rate of events of non-fatal myocardial infarction and coronary heart disease, respectively. Intensive glycaemic control had no significant effect on stroke.19

The LEAD trials demonstrated that liraglutide improved glycaemic control (reduction in HbA1c by up to 1.6%) without increasing the risk of hypoglycaemia.4,14,15,16,20
complications in patients with type 2 diabetes by its effect of significantly improving glycaemic control.

**Obesity**

Animal studies and clinical trials have shown that liraglutide reduces body weight. It is postulated that the mechanism for weight loss is due to decreased gastric motility, which delays gastric emptying, and in turn leads to reduction in appetite and food intake.  

In all LEAD trials, substantial body weight loss was observed after approximately eight weeks of treatment and was maintained to the end of the trials. A dose-dependent trend in weight reduction with liraglutide was observed.  

Gastrointestinal disorders were the most frequently reported adverse events for liraglutide in the LEAD trials. However, these events occurred in the beginning of treatment and were transient. Thus, beneficial effects on weight with liraglutide are not related to gastrointestinal disorders, since substantial weight loss occurred only after cessation of gastrointestinal side effects.

Furthermore, data from LEAD-1, LEAD-2 and LEAD-5 were analysed with respect to body weight change in response to liraglutide. Patients from these three trials were stratified by their baseline BMI. After 26 weeks of treatment with liraglutide, weight loss occurred in all BMI groups treated with liraglutide, with the greatest decrease in body weight in patients with the highest baseline BMI.  

Clinical evidence shows that liraglutide induces and sustains weight loss, especially in overweight patients, and may thereby have beneficial cardiovascular effects.

**Hypertension/SBP**

Reductions in SBP with liraglutide were consistently seen in all LEAD trials. It was observed that with regard to reduction in SBP, liraglutide was superior to most active comparators such as sulfonylurea, rosiglitazone, insulin glargine and exenatide. (Figure 1).  

SUs stimulate the endogenous insulin secretion through binding to an ATP-dependent K+ channel on the cell membrane and is usually used as an alternative to metformin or in combination with metformin (when metformin does not achieve the glycaemic targets). SUs are often associated with increased body weight and hypoglycaemia.  

In LEAD-3, both doses of liraglutide (1.2 mg and 1.8 mg) reduced the SBP greater than glimepiride. SBP reduced by 0.7 mmHg in the glimepiride monotherapy group, while it was 2.1 mmHg in the liraglutide 1.2 mg group, and 3.6 mmHg in the liraglutide 1.8 mg group. The estimated difference between the liraglutide 1.2 mg and the glimepiride + metformin group was not statistically significant.  

In LEAD-2, in combination with metformin, liraglutide 1.2 mg and 1.8 mg treatment resulted in significant reductions in SBP of 2–3 mmHg, whereas an increase of 0.4 mmHg was observed in the glimepiride + metformin group.

Both trials demonstrated that liraglutide was significantly superior to glimepiride (except liraglutide 1.2 mg + metformin vs. glimepiride + metformin in LEAD-3) in reducing SBP. This can be translated to a lower cardiovascular risk with liraglutide than SUs and that liraglutide is advantageous in the early treatment of type 2 diabetes.

Thiazolidinediones (TZDs) increase insulin sensitivity by binding to the peroxisome proliferator-activated receptor gamma (PPAR-gamma) and are used in addition to metformin or other antidiabetic treatments when monotherapy or combination therapies fail. Common side effects associated with TZDs are oedema and weight gain.

In LEAD-1, reductions in SBP were observed with all treatments, with more pronounced and dose-dependent reductions with liraglutide 1.2 mg 2.6 mmHg, and 1.8 mg 2.8 mmHg (both in combination with SU). These changes were not significantly different from rosiglitazone + SU treatment (0.9 mmHg).

Furthermore, LEAD 4 showed that when adding liraglutide (1.2 mg or 1.8 mg) to metformin + rosiglitazone treatment, SBP significantly reduced when compared with metformin + rosiglitazone alone. The difference between the treatments was 5.6 mmHg (liraglutide 1.2 mg) and 4.5 mmHg (liraglutide 1.8 mg).

Current guidelines advise the use of basal insulin (both as monotherapy and as combination with oral antidiabetic drugs [OADs]) when combination therapy of OADs fails to maintain the glycaemic control. Insulin glargine is a well-characterised, once-daily insulin analogue.

The main objective of the LEAD-5 trial was to compare the efficacy and safety of liraglutide in combination with glimepiride and metformin versus insulin glargine added to glimepiride and metformin combination therapy. A significant reduction of 4.0 mmHg in SBP was observed with liraglutide, whereas an increase of 0.54 mmHg was seen with insulin glargine. The estimated treatment difference was significant.

These findings, with regard to SBP reduction, suggest a relatively favourable cardiovascular benefit of liraglutide compared with insulin glargine.

Exenatide is a twice-daily GLP-1 receptor agonist, which is recommended for patients who are inadequately controlled with metformin, SUs or a combination of both. It is also used in combination with TZD, with and without metformin.

In LEAD-6, the decrease in SBP with liraglutide 1.8 of 2.5 mmHg was greater (but not statistically significant) than with exenatide of 2.0 mmHg. The data from LEAD-6 indicate that the overall tolerance was better with liraglutide than exenatide, which suggests that liraglutide should be a treatment option under the same guidelines.

Although hypertension is associated with obesity, the beneficial effects on SBP with liraglutide were not related to weight loss. Across the six LEAD trials, the reductions in SBP occurred after approximately 2 weeks of treatment and before substantial weight loss.

All LEAD trials demonstrated that once-daily administration of liraglutide reduced SBP to the extent that was superior to some of the current antidiabetic agents. Hence, the risk of CVD in patients with type 2 diabetes could be lowered with once-daily administration of liraglutide.

**Biomarkers of CVDs**

A number of established cardiovascular biomarkers can be associated with a high risk of CVD. Elevated levels of inflammatory biomarkers such as plasminogen activator inhibitor-1 (PAI-1) and high sensitivity C-reactive protein (hsCRP) have been demonstrated to be associated with a higher risk of CVD. B-type natriuretic peptide (BNP) is a marker of left ventricular dysfunction, and increased levels are also an indication of increased risk for CVDs, particularly heart failure.
Table 1: The effects of liraglutide on β-cell markers in the LEAD trials

<table>
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<tr>
<th>Publication</th>
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<td>Efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study</td>
<td>Nauck M, et al.</td>
<td>Diabetes Care 2009</td>
<td>Lira 1.8 mg+MET vs. GLM+MET</td>
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<td>Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone in patients with type 2 diabetes (LEAD-1 SU)</td>
<td>Marre M, et al.</td>
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Lira = liraglutide, GLM = glimepiride, MET = metformin, ROS = rosiglitazone, INS = insulin glargine, EXE = exenatide.
↑: Significant treatment difference with liraglutide compared with comparator.
↔: No significant treatment difference with liraglutide compared with comparator.
a: Proinsulin-to-C-peptide ratio.

Liraglutide Effects on β Cells

In vitro, liraglutide was found to enhance the proliferation rate of rats’ β cells and prevent the β cells from cytokine- and FFA-mediated apoptosis. In animal models with type 2 diabetes, liraglutide had the potential to promote β-cell proliferation and increase β-cell mass. Early phase 2 trials showed that once-daily liraglutide significantly improved the β-cell function (measured as proinsulin-to-insulin ratio, maximal secretion capacity and first-phase insulin secretion) in patients with type 2 diabetes.

Following the encouraging results from phase 2 trials with liraglutide, β-cell function (measured as homeostatic model for assessment of β-cell function [HOMA-B] index and/or proinsulin-to-insulin ratio) was assessed and compared with various comparators in all LEAD trials.

The overall results from the LEAD trials demonstrated beneficial effects on β-cell function, which is in line with the results from phase 2 trials. The LEAD trials showed the trend that β-cell function as measured by homeostasis model assessment index of β-cell function (HOMA-B) and proinsulin-to-insulin ratio were improved with liraglutide compared to the comparators (Table 1).

In comparison with glimepiride (LEAD 3): Improvements (increases) in HOMA-B were seen in all treatment groups.
although no significant differences in HOMA-B and in the proinsulin-to-insulin ratio were seen between liraglutide and SU monotherapy.9,15

In comparison with glimepiride (LEAD 2); HOMA-B was significantly improved in the liraglutide 1.2 mg and 1.8 mg groups (all in combination with metformin). Similar improvement in HOMA-B was obtained in the glimepiride group (in addition to metformin), while no change was observed with metformin monotherapy. Proinsulin-to-insulin ratio decreased (improved) from baseline in all liraglutide groups. The reductions in liraglutide groups were comparable to the reduction seen in the glimepiride group, but significantly different from the reduction seen in the metformin monotherapy group.9,16

In comparison with TZDs (LEAD-1): HOMA-B was increased in 1.2 mg and 1.8 mg liraglutide groups compared to the rosiglitazone group (all in combination with SU). The only statistically significant difference in HOMA-B improvement was found between liraglutide 1.2 mg and glimepiride monotherapy.9,14 Reductions in proinsulin to insulin ratio were greater with both liraglutide 1.2 mg and 1.8 mg groups (in combination with SU) as compared to either rosiglitazone (in combination with SU) or SU monotherapy.14

In comparison with metformin + TZDs (LEAD-4): HOMA-B increased by about 27% in both liraglutide 1.2 mg and 1.8 mg groups (all in combination with metformin + TZDs), while it was only 6% compared with metformin + rosiglitazone. The improvement (decrease) in proinsulin-to-insulin ratio was greater in both liraglutide groups (all in combination with metformin + TZDs) than in the metformin + TZDs group.9,18

In comparison with insulin glargine (LEAD-5): The liraglutide 1.8 mg group (in combination with metformin + glimepiride) significantly improved HOMA-B. The improvement in proinsulin-to-C-peptide ratio was greater with liraglutide than that with insulin glargine (in combination with metformin + glimepiride) or metformin + glimepiride treatment.19

In comparison with exenatide (LEAD-6): Once-daily liraglutide 1.8 mg was associated with greater improvement in HOMA-B than with twice-daily administration of exenatide (both in combination with metformin ± SU). The decreases in proinsulin to insulin ratio were comparable between two treatments.16

HOMA-B is calculated on the basis of the fasting plasma glucose and insulin. Any drug that can increase the fasting plasma insulin level and reduce the fasting plasma glucose will increase HOMA-B. Glimepiride is an insulin secretagogue, which increases fasting plasma insulin concentration and improves fasting glycaemic control. Therefore, it is not a surprise to see that in LEAD-3 and -2 trials, increase in HOMA-B in the liraglutide groups was comparable with glimepiride.

Road Ahead: The LEADER™ Trial

Since liraglutide has shown a favourable effect on cardiovascular risk factors such as hyperglycaemia, overweight, hypertension and insulin resistance, it can be strongly anticipated that liraglutide has beneficial effects on cardiovascular events in patients with type 2 diabetes. However, a further long-term trial on cardiovascular outcome with liraglutide is needed. LEADER™ (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) is a long-term, multicentre, international, randomised, double-blind, placebo-controlled, phase 3b trial. Approximately 9000 patients will be included over a period of 5 years. The trial aims to assess the effect of liraglutide on cardiovascular outcome and will compare liraglutide added to standard of care with standard of care alone in patients with type 2 diabetes. In India, it is planned to recruit 200 patients to this trial.

Conclusions

Clinical evidence has consistently shown that beyond improving glycaemic control, once-daily liraglutide offers additional benefits such as weight loss, reduced blood pressure, improved HOMA-B and proinsulin-to-insulin ratio in patients with type 2 diabetes. To some extent, treatment with liraglutide also reduced plasma concentration of PAI-1, BNP, and high-sensitivity C-reactive protein (hsCRP), which are risk factors (biomarkers) for CVD. This can be translated to clinically meaningful cardiovascular benefits with liraglutide. The findings also signify that liraglutide can improve and may preserve the β-cell function, thereby halting the progression of type 2 diabetes.

These findings support that liraglutide could represent an early strategy to reduce the burden of diabetes and its complications. It addresses significant unmet medical needs within type 2 diabetes – both short and longer term by going beyond glycaemic control.

However, long-term trials are needed to confirm the beneficial effects that liraglutide has on the cardiovascular outcome. If confirmed by the long-term LEADER™ trial, liraglutide could play an important role in the future management of type 2 diabetes and its vascular complications.

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