Potential cardiovascular benefits of GLP-1 analogues: evidence and implications for type 2 diabetes management

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Glucagon-like peptide-1 (GLP-1) analogues are an injectable therapy used in the management of type 2 diabetes. These drugs seem to reduce cardiovascular risk factors and clinical trial data seems to suggest that liraglutide and semaglutide reduce cardiovascular risk in patients with type 2 diabetes and concomitant atherosclerotic cardiovascular disease. The search for agents such as these (and SGLT2 inhibitors) that not only manage diabetes but also reduce cardiovascular risk has resulted in a paradigm shift in the way diabetes can be managed.

Keywords: type 2 diabetes, GLP-1 analogues, LEADER, SUSTAIN-6, ELIXA, liraglutide, semaglutide

Introduction

Glucagon-like peptide-1 (GLP-1) receptor analogues are modified forms of the GLP-1 molecule that are structurally homologous to human GLP-1 but are resistant to degradation by the dipeptidyl peptidase-4 (DPP-4) enzyme. This results in a longer duration of action. Examples of the GLP-1 analogues include: albiglutide, exenatide, liraglutide, semaglutide and lixisenatide. These analogues work by increasing circulating levels of GLP-1 which increases insulin secretion, decreases glucagon secretion, enhances satiety and delays gastric emptying. These analogues work by increasing circulating levels of GLP-1 which increases insulin secretion, decreases glucagon secretion, enhances satiety and delays gastric emptying. These analogues have been considered to be an ideal agent in the management of type 2 diabetes mellitus (T2DM) because they not only reduce blood glucose levels, have durable effects on glycaemic control and beta-cell function but also have an effect on cardiovascular risk factors.

Table I: CVD risk factors and targets for patients with T2DM

| Traditional CVD risk factors | Targets |
|-----------------------------|---------|
| Smoking                     | Complete cessation |
| Dyslipidaemia               | Total cholesterol < 4.5 mmol/L |
|                            | LDL cholesterol < 1.8 mmol/L |
|                            | HDL cholesterol > 1.0 mmol/L (men) or > 1.2 mmol/L (women) |
|                            | Triglycerides < 1.7 mmol/L |
| Obesity                     | < 94 cm (men); < 90 cm (men of South Asian descent); < 80 cm (women) |
| BMI                         | < 25 kg/m²* |
| Hypertension                | < 140 mmHg |
| Diastolic blood pressure    | < 90 mmHg |

* value may differ based on ethnicity

Potential cardiovascular risk reduction benefits

The potential for cardiovascular benefits of GLP-1 analogues can be linked to their improvements in vascular endothelial function, reduction in vascular inflammatory markers, a reduction in brain natriuretic peptide levels (BNP) as well as reductions in blood pressure (BP), lipid levels and weight.

Vascular endothelial function

Data suggests that vascular endothelial dysfunction may precede clinically evident macrovascular complications. This is due to various factors including abnormal glucose rise and lipid metabolism and other factors. With regards to glucose rise and lipids it seems that postprandial changes in glucose levels and lipid metabolism are particularly important risk factors for vascular endothelial dysfunction. Exenatide improves vascular endothelial dysfunction by reducing postprandial glucose excursions and prevents postprandial rises in serum triglyceride levels.

Vascular inflammatory markers and brain natriuretic peptide (BNP)

GLP-1 analogues like liraglutide have shown potential to reduce plasminogen activator inhibitor (PAI) levels and BNP levels. High PAI levels are known to decrease fibrinolysis and increase the risk of atherosclerosis, whilst high BNP levels are considered a risk marker for heart failure (HF). Thus GLP-1 analogues could potentially reduce the risk for atherosclerosis and HF. Increased GLP-1 levels reduce IL-6, prostaglandin F2α, ICAM-1,
MCP-1, TNFα and inflammatory markers within monocytes. Increased GLP-1 receptor signalling has demonstrated robust cardio protection in the form of decreased infarct size, preservation of ventricular function, improved survival and reduced levels of creatinine kinase MB and hep-ann-1.4

**Blood pressure and lipid levels**

GLP-1 analogues have proven effects on reducing both systolic and diastolic BP and also seem to reduce serum triglyceride levels.2,10-12 The magnitude of change in systolic and diastolic BP seems to differ based on the GLP-1 analogue and the study but there is evidence that GLP-1 analogues reduce BP.1,9 Courrèges et al.3 noted that liraglutide reduced systolic BP (SBP) by 8 mmHg and reduced serum triglyceride levels by 22% when compared to the placebo. In other studies, liraglutide was able to reduce systolic BP between 2.5–5 mmHg from baseline depending on the dose, while diastolic BP was reduced from 0–1.7 mmHg from baseline.2 Exenatide had similar effects on systolic BP reduction from 2.9–4.7 mmHg and diastolic BP from 0–1.9 mmHg in the Duration Trials.2 Albiclutide reduced systolic BP by 1.5 mmHg and diastolic BP by 1 mmHg at 104 weeks in the Harmony-3 trial.13 It is clear that the systolic BP changes are more substantial than the diastolic BP changes which are almost negligible.

With regards to reduction in cholesterol, the reduction in triglycerides, LDL-C and total cholesterol vary depending on the type of GLP-1 analogue used and the dose being studied.2,3 Clearly, the reduction in triglycerides seem to be the most pronounced whilst the drugs have minimal effects on total cholesterol and LDL-C.2 Table II illustrates the effects of selected GLP-1 analogues on serum lipid levels

**Weight loss**

Obesity and abdominal obesity are cardiovascular risk factors.3 The use of GLP-1 analogues has proven weight reduction effects.2,10-12,14,15 The amount of weight loss seems to vary depending on the agent used and the dose at which it is used.13 The higher the dose of the GLP-1 analogues, the greater the weight loss.2 Liraglutide at a dose higher than the maximum dose used for diabetes, i.e. a dose of 3 mg daily, produced a mean weight loss of 7.2 kg at 20 weeks compared to 4.1 kg in patients who used orlistat and 2.8 kg in patients taking the placebo.16 A meta-analysis of 21 trials comparing 3,395 patients receiving a GLP-1 analogue
| Study | Population and Sample Size | Primary and secondary endpoints | Results | Comments | Conclusion |
|-------|-----------------------------|---------------------------------|---------|----------|------------|
| LEADER trial | International, multi-centred randomised controlled trial. Participants were randomised to liraglutide 0.6 mg subcut daily and titrated after 2 weeks to a maximum of 1.8 mg based on tolerance (median dose 1.78 mg) or standard of care. Sample size: 9 340 Mean age: 64.3 ± 7.2 yrs. Non-inferiority trial for primary efficacy outcome followed by superiority according to ITT analysis. Duration of diabetes: 12.8 ± 8 yrs. Average HbA1c: 8.7 ± 1.6%. BMI: 32.5 ± 6.3 kg/m². SBP: 135.9 ± 17.8 mmHg. DBP: 77.1 ± 10.2 mmHg. If patient did not reach recommended target for glycaemic control (HbA1c ≤ 7% or individualised target at investigator’s discretion), addition of anti-hyperglycaemic agents (except GLP-1-A, DPP4-I, and pramlintide) including insulin, were permitted. | 1. **Primary endpoint** Composite time to event analysis of first occurrence of death from CV causes, nonfatal MI and stroke. 2. **Expanded endpoints** Death from CV causes. All-cause mortality. Non-fatal MI. Non-fatal stroke. Hospitalisation for HF. | 1. **Primary endpoint** Composite outcome significantly reduced with HR = 0.87 (95% CI 0.78–0.97, p = 0.01 for superiority and < 0.001 for non-inferiority). 2. **Expanded endpoints** Death from CV causes significantly reduced with HR = 0.78 (0.66–0.93, p = 0.007). All-cause mortality reduced with HR = 0.85 (95% CI 0.74–0.97, p = 0.02). No significant reduction in non-fatal MI HR 0.88 (95% CI 0.75–1.03, p = 0.11). No significant reduction in non-fatal stroke with HR = 0.89 (95% CI 0.72–1.11, p = 0.30). No significant reduction in hospitalisation for HF with HR = 0.87 (95% CI 0.73–1.05, p = 0.14). | | Liraglutide was the first GLP-1 analogue to demonstrate a positive CV outcome in an RCT. Similar to other CV outcome trials like SUSTAIN-6 and ELIXA, liraglutide had a neutral effect on hospitalisation for HF. Liraglutide is a treatment option for patients with established CVD disease to reduce both CV mortality and all-cause mortality. |

Composite endpoint reduction was driven primarily by a decrease in CV mortality as the others were non-significant. For the expanded endpoints only death from CV causes and all-cause mortality were significant. Despite a numerical increase in pancreatic carcinoma in patients using liraglutide, this result was not significant with p = 0.06. Control group compared to liraglutide group, received more insulin and SU. This could explain the increased incidence of hypoglycaemia in the control group. The number needed to harm for acute gallstone disease was 84 per 3.8 years. This study had the largest sample size of any CV outcome trial for a GLP-1 and the longest duration. It was a well-designed RCT that was blinded with external adjudication for all outcomes. 97% of the liraglutide group and 96.6% of the control group completed the study thus attrition was low. Results of this study indicated the use of liraglutide for CVD risk reduction can only be used in patients with established CVD disease. |
| Study             | Population and sample size | Primary and secondary endpoints | Results                                                                 | Comments                                                                 | Conclusion                                                                 |
|-------------------|-----------------------------|--------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|
| SUSTAIN-6 trial   | Sample size: 2,735.         | 1. Primary endpoint          | Composite outcome significantly reduced with HR = 0.74 (95% CI 0.58–0.95, p = 0.02 for superiority and < 0.001 for non-inferiority). | NNT for semaglutide to prevent one composite outcome over 2 years was 44. | Semaglutide is the second GLP-1 analogue to demonstrate a positive CV outcome in an RCT. |
|                   | International, randomised   | 2. Expanded endpoints        | Composite outcome significantly reduced with HR = 0.74 (95% CI 0.62–0.89, p = 0.002). | Trial was powered to show non-inferiority and may have been \underpowered to show superiority. | Similar to other CV outcome trials like LEADER and ELIXA, semaglutide had a neutral effect on hospitalisation for HF. |
|                   | double blind, placebo       |                                | Comport of all-cause mortality, non-fatal MI or non-fatal stroke significantly reduced with HR = 0.77 (95% CI 0.61–0.97, p = 0.03). | Patients were followed up for a relatively short duration to truly see CV risk reductions especially when considering that the LEADER trial took 1 year to show meaningful results. | Semaglutide is a treatment option for patients with established CVD disease to reduce both CV mortality and all-cause mortality. |
|                   | controlled trial.           |                                | No significant changes in either all-cause mortality with HR = 1.05 (95% CI 0.74–1.50, p = 0.79) or CV mortality with HR = 0.98 (95% CI 0.65–1.48, p = 0.92). | No significant reductions in non-fatal MIs, non-fatal strokes or hospitalisation for unstable angina. |                                                                       |
|                   | Patients were randomised to receive either semaglutide 0.5 mg or 1 mg subcut once weekly or placebo. |                                | Reduction in need for revascularisation in patients using semaglutide when compared to the control with HR = 0.65 (95% CI 0.50–0.86, p = 0.003). | No significant increase in hospitalisation for HF with HR = 1.11 (95% CI 0.77–1.61, p = 0.57). |                                                                       |
|                   |                             |                                | No significant reductions in non-fatal MIs, non-fatal strokes or hospitalisation for unstable angina. |                                                                       |                                                                       |
|                   |                             |                                | Significant increase in retinopathy complications with HR = 1.76 (95% CI 1.11–2.78, p = 0.02). |                                                                       |                                                                       |
|                   |                             |                                | No significant differences between either group in terms of either acute pancreatitis, gallbladder disorders, pancreatic cancer or thyroid cell carcinoma. |                                                                       |                                                                       |
compared to 3 016 patients receiving different controls noted a weight reduction between 0.2–7.2 kg.12

Cardiovascular outcomes trials

There have been three large cardiovascular outcome trials of note, which investigated the cardiovascular safety of GLP-1 analogues in patients with T2DM.1 These are discussed in significant detail in Table III.

ELIXA trial

The ELIXA trial investigating the use of lixisenatide in 6 068 patients who recently suffered an acute coronary syndrome (ACS) noted that lixisenatide had a neutral effect on cardiovascular risk.12 The medication did not produce any significant cardiovascular risk reduction but also posed no excessive harm to patients with T2DM who had an ACS event.12

LEADER trial

The LEADER trial was a landmark trial in the search for a type 2 diabetic agent with potential cardiovascular risk reduction benefits. A total of 9 340 patients were randomised in a blinded manner to either a placebo group or liraglutide (at a dose 1.8 mg daily) and the cardiovascular safety of liraglutide was investigated.10 The dose of 1.8 mg of liraglutide was superior to conventional treatment and was associated with a 13% relative risk reduction in the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke (3-point MACE) at a median 3.8-year follow-up compared to the placebo. Importantly, the target group selected for this trial were high cardiovascular risk patients.10

This trial demonstrated that liraglutide produced a significant cardiovascular reduction in high-risk cardiovascular patients with T2DM. Liraglutide did not improve glycaemic control to any greater extent when compared to the placebo meaning the results of cardiovascular disease (CVD) risk reduction was not linked to improved glycaemia. The primary outcome was driven by a reduction in cardiovascular mortality and all-cause mortality. There were no differences in the rate of non-fatal MI, non-fatal stroke, and hospitalisation for HF, which was not dissimilar to the ELIXA or SUSTAIN-6 trial.10,12 The number needed to treat (NNT) to prevent one composite outcome or cardiovascular death or all-cause mortality with liraglutide 1.8 mg over 3.8 years were 66,104 and 98 respectively.10 An important point to note is that the Kaplan Meier curve for the 3-point MACE only deviated from the control after one year.4

SUSTAIN-6 trial

The SUSTAIN-6 trial (a randomised controlled trial which investigated a similar cohort of patients to the LEADER trial) found that semaglutide reduced the primary composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke, at a median 2.4-year follow-up, by 26% compared to the placebo (HR 0.74; 95% CI 0.58–0.95).11

Heart failure (HF) data

As discussed previously, GLP-1 analogues reduce BNP levels, which is a marker for HF, so the question becomes is there any potential reduction in HF when using GLP-1 analogues? A meta-analysis conducted by Li et al.16 of 20 randomised controlled trials noted that GLP-1 analogues had no significant effect on the incidence of HF (HR 0.62; 95% CI 0.32–1.22). This is not dissimilar to the results of the SUSTAIN-6, LEADER and ELIXA trial.10–12

Overall thoughts on trial data

It is important to note that in both the LEADER and SUSTAIN-6 trial, patients without established CVD did not benefit significantly from the GLP-1 analogues used in terms of CVD risk.10,11 To date there are no studies published which investigated the cardiovascular outcomes of exenatide that have demonstrated significant benefit. The LEADER trial has come under scrutiny by authors such as Cohen and Beckley19 who noted that patients receiving lixisenatide were also on more cardio-protective medications at baseline compared to patients receiving the placebo. Considering that the population group included in this trial were patients with either established CVD or had CVD risk factors; it is not unimaginable for them to have background cardio-protective medication and with such a large sample size such differences can be expected at baseline and not be considered as significant.20 Furthermore, Cohen and Beckley19 also noted that the results of the LEADER trial are incongruent with those of ELIXA. That said, Cohen and Beckley19 can be forgiven as the results of the SUSTAIN-6 trial were yet to be published. The results of SUSTAIN-6 were congruent with LEADER.11

The results of these trials have forced the American Diabetes Association (ADA) to rethink its guidance regarding the management of type 2 diabetes. GLP-1 analogues and SGLT2 (sodium glucose-like transporter 2) inhibitors with proven cardiovascular risk reduction benefits are now considered as second-line added on therapy (after diet, exercise and metformin) in patients with established atherosclerotic cardiovascular disease.21 Additionally, GLP-1 analogues are also now considered to be the first-line injectable therapy that must be started prior to basal insulin.21 The South African Guidelines already acknowledge the cardiovascular benefits of certain GLP-1 analogues and it is a possibility that in a future iteration they may follow the ADA guidelines with similar recommendations.

Conclusions

It is clear that GLP-1 analogues have pleiotropic effects that extend to aspects of cardiovascular risk reduction and also reduce cardiovascular risk factors such as BP, cholesterol and weight. They also have effects on endothelial function and vascular inflammatory markers. They signal a potential for CVD risk reduction. Whilst the ELIXA trial demonstrated CVD risk neutrality for lixisenatide, the LEADER and SUSTAIN-6 trials demonstrated distinct CVD risk reduction benefits with liraglutide and semaglutide respectively. However, this was only in patients with established CVD. The results of these
studies prompted the ADA to change their guidelines and ask practitioners to consider the use of GLP-1 analogues in patients with established atherosclerotic CVD if they fail on lifestyle modification and metformin.

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