The GLP-1 receptor agonists: what's all the (cardiovascular) hype about?

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Abstract

Over four million people in South Africa are estimated to have diabetes. People diagnosed with diabetes have an increased risk of developing cardiovascular disease. Safety trials conducted on novel hypoglycaemic agents suggest that glucagon-like peptide-1 receptor agonists may afford cardiovascular benefits in this at-risk population. Selection of an agent from this class, as add-on treatment to metformin, should be individualised and based on accessibility, affordability, convenience of the dosing schedule, and tolerability.

Keywords: GLP-1 receptor agonists, cardiovascular disease, hypoglycaemic agents

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Introduction and epidemiology

Over four million people in South Africa are estimated to have diabetes.[1] People living with diabetes (PLWD) have an increased risk of microvascular and macrovascular disease, with an estimated prevalence of coronary artery disease among PLWD of 8.7% in South Africa.[1] The pathogenesis of increased risk of atherosclerotic cardiovascular disease in diabetes is multifactorial, and related to hyperglycaemia, hyper-insulinaemia, dyslipidaemia, inflammation, increased reactive oxygen species, endothelial dysfunction, hypercoagulability, and vascular calcification.[2] Mitigation of this increased risk requires lifestyle modification, glycaemic control and pharmacological management. Therefore, an understanding of the cardiovascular benefits and risks associated with the classes of anti-diabetic drugs utilised in type 2 diabetes mellitus is essential.[2]

Previously, a statistically significant reduction in HbA1c and short-term safety data was all that was required for approval of a glucose-lowering drug by regulatory authorities such as the US Food and Drug Administration (FDA). Safety signals of increased cardiovascular risk and cardiac failure with thiazolidinediones and sulphonylureas led to a change in policy for drug development.[3] Since 2008, the FDA has mandated that all new drugs developed for glycaemic control be assessed for safety with cardiovascular outcome trials (CVOT), evaluating the risk of major adverse cardiac events (MACE).[3] This composite endpoint includes myocardial infarction (MI), cerebrovascular accident (CVA), and cardiovascular mortality events, while some trials also include unstable angina and revascularisation events.[4] According to the FDA, an investigational hypoglycaemic agent is deemed to have an unacceptable level of risk if the upper bound of the 95% confidence interval (95% CI) for the hazard ratio (HR) of MACE exceeds 1.8 if the study is conducted preregistration, or 1.3 if conducted post-approval.[3,5]

Consequent to FDA requirements, we now have a body of evidence looking at the cardiovascular safety of newer hypoglycaemic agents, including the glucagon-like peptide-1 (GLP-1) receptor agonists.

Mechanism of action

Incretin hormones are released by the gut in response to an oral glucose load. Incretins, specifically GLP-1, reduce glucose levels through three important mechanisms: Firstly, GLP-1 stimulates insulin secretion, and this secretion is more pronounced during hyperglycaemia. During normo- or hypoglycaemia, GLP-1 stimulation of insulin secretion is reduced providing protection from further decreases in blood glucose.[6] Secondly, GLP-1 decreases the secretion of glucagon with a subsequent reduction in hepatic gluconeogenesis.[6] Thirdly, GLP-1 delays gastric emptying, reducing the postprandial increase in glucose and promoting satiety with resultant decrease in food intake.[6]

Endogenous GLP-1 has a short duration of action of 1–2 minutes and is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) enzymes and cleared renally. To increase the duration of effect, GLP-1 analogues with longer half-lives were developed, that are not subject to degradation by DPP-4.

GLP-1 receptor agonists bind to the GLP-1 receptor and stimulate glucose-dependent insulin release to reduce blood glucose levels. As a class, GLP-1 agonists reduce HbA1c by 0.9–1.2% without clinically significant increased risk of hypoglycaemia, unless combined with insulin or sulphonylureas.[7] Furthermore, the effects of GLP-1 agonists on gastric emptying, satiety and resultant weight reduction are exploited in the medical management of obesity. Exenatide, liraglutide, dulaglutide, and semaglutide are GLP-1 receptor agonists registered for use in South Africa by the South African Health Product Registration Authority for the treatment of type 2 diabetes. Lixisenatide is a GLP-1 receptor agonist available in combination with insulin glargine.[8] These agents remain costly with single exit prices ranging from R350 to R2 400 depending on agent and dose, however, evidence from well-resourced settings suggests that these agents may still be cost-effective for patients

that have failed monotherapy with metformin.[9,10] Local data would be required to assess the cost-effectiveness and affordability of these agents in South Africa.

Effects on atherosclerotic cardiovascular disease

In addition to their glucose-lowering effects, the GLP-1 agonists reduce the risk of cardiovascular disease via a reduction in atherosclerotic plaque formation and rupture, inflammation, and vasoconstriction.[11] Matrix metalloproteinase-2 (MMP2), an enzyme produced by vascular cells, promotes arterial remodelling in atherosclerosis. MMP2 concentrations are increased in patients with type 2 diabetes and cardiovascular risk factors. A previous animal study showed that MMP2 expression was reduced in diabetic rats after exenatide or GLP-1 administration using an adenovirus vector.[12] Improved endothelial function may also be related to an increase in nitric oxide production and reduced reactive oxidative species production in response to GLP-1 receptor agonists.[11] Other direct effects of the GLP-1 receptor agonists include the decreased expression of inflammatory cytokines and a reduction in systolic blood pressure, which appear independent of the degree of weight loss.[6] Atherosclerotic cardiovascular disease risk is further attenuated via a reduction in low-density lipoprotein (LDL) and triglycerides, a reduction in body weight, an increase in adiponectin (an adipokine protein known for its anti-inflammatory effects), and a reduction in albuminuria.[11]

Evidence for benefit in atherosclerotic cardiovascular disease

Several meta-analyses ("critically low" quality rating)[13] have reported a beneficial class effect of various GLP-1 agonists on MACE.[14-17] Of these, one meta-analysis examined all GLP-1 receptor agonist CVOTs published before June 2021 and included the results of 60 080 patients followed up from between 1.3 to 5.4 years. In this study, pooled analysis found that the risk of MACE was reduced by 14% (HR 0.86; 95% CI 0.79–0.94; $p = 0.006$) in GLP-1 agonist treatment groups, as compared to placebo. Treatment with GLP-1 agonists was associated with a 16% reduction in risk of MACE (HR 0.84; 95% CI 0.79–0.90; $p < 0.001$) in patients with established cardiovascular disease (secondary prevention population). In comparison, patients without established cardiovascular disease (primary prevention population) had a non-significant 6% reduction in risk of MACE (HR 0.94; 95% CI 0.83–1.06; $p = 0.33$).[17] Another meta-analysis ("critically low" quality rating)[13] which published a similar 14% reduction in risk of MACE (HR 0.86; 95% CI 0.80–0.93; $p < 0{\cdot}0001$), reported a number needed to treat of 65 (95% CI 45–130) patients over three years to prevent one event.[16]

Despite the lack of robust evidence for use in the primary prevention population, the latest guideline from the American Diabetes Association recommends the use of a GLP-1 receptor agonist to reduce the risk of MACE in people living with type 2 diabetes and established atherosclerotic cardiovascular disease, as well as those with multiple risk factors for cardiovascular disease.[18]

For individual components of MACE, GLP-1 receptor agonist treatment was associated with statistically significant reductions in risk of cardiovascular mortality and non-fatal stroke, but not non-fatal MI.[17] In stand-alone trials, exenatide (EXSCEL trial) and lixisenatide (ELIXA trial) failed to demonstrate a cardiovascular benefit, despite no difference to placebo in terms of safety.[19,20] Conversely, liraglutide (LEADER trial), semaglutide (SUSTAIN-6 trial), and dulaglutide (REWIND trial) all demonstrated benefit, but head-to-head trials examining superiority between agents in the class are lacking.[21-23] It is uncertain if this disparity in cardiovascular benefit across agents relates to differences in study design alone or to the inherent pharmacodynamic and pharmacokinetic properties of each agent.[11] For example, exenatide and lixisenatide are based structurally on exendin-4 (a hormone found in the saliva of the Gila monster that mimics GLP-1), whereas albiglutide, dulaglutide, liraglutide, and semaglutide are structurally similar to endogenous GLP-1.[16]

Safety and adverse effects

Common adverse effects associated with GLP-1 receptor agonists are gastrointestinal, including nausea, vomiting, and diarrhoea, which may contribute to reported discontinuation rates of between 4.5 and 13.2% across trials.[6,8] Gastrointestinal adverse events may be the result of direct effect on the central nervous system, in addition to delayed gastric emptying and increased smooth muscle activity and motility in the colon. The frequency appears to be dose-related and more prevalent when combined with metformin.[24] In a meta-analysis examining adverse effects, nausea, vomiting and study withdrawal rates were found to be lower with the longer-acting GLP-1 agonists, such as liraglutide and dulaglutide, as compared to the shorter-acting agents lixisenatide and exenatide. Semaglutide was not included in this meta-analysis as it was not yet registered for use in diabetes at the time the analysis was conducted.[24]

Based on preclinical studies, concerns of increased risk of pancreatitis, pancreatic cancer, cholecystitis, and medullary thyroid cancer associated with GLP-1 receptor agonists, have led to the exclusion of participants with a history of these conditions from subsequent clinical trials. The pathophysiological mechanism of these serious complications is related to the expression of GLP-1 receptors by thyroid C cells and the pancreatic duct.[6,11] Three meta-analyses ("critically low" quality)[13] did not show an increased incidence of pancreatitis, pancreatic cancer, or thyroid cancer associated with GLP-1 receptor agonist use.[14-16] Importantly, most trials for these agents were of limited duration, excluded patients at increased risk for these conditions, and were not powered to detect these rare events.

Overall, these results suggest that GLP-1 receptor agonists are safe to use, however, pharmacovigilance is ongoing.[25] For example, a registry to monitor the incidence of medullary thyroid carcinoma associated with GLP-1 agonist use has been mandated by the FDA as a specific post-marketing requirement.[26] It remains prudent to avoid the use of GLP-1 receptor agonists in patients with a history

of pancreatitis, pancreatic cancer, medullary thyroid cancer, or multiple endocrine neoplasia type 2 (MEN 2).[7,8]

Conclusion

Meta-analyses of pooled data for GLP-1 receptor agonists suggest a class protective effect in PLWD for atherosclerotic cardiovascular disease. In randomised controlled trials, liraglutide, semaglutide, and dulaglutide (all approved for use in South Africa) have demonstrated a reduction in MACE. Extending the use of these agents for the primary prevention of atherosclerotic cardiovascular disease in PLWD currently lacks robust evidence, and the cost-effectiveness of this indication is debatable. GLP-1 receptor agonists may be a useful adjunctive treatment option to metformin in patients with uncontrolled diabetes, established atherosclerotic cardiovascular disease, obesity, and problematic hypoglycaemia. However, the decision to initiate GLP 1 agonist therapy should be individualised and based on affordability.

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Conflict of interest

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