Glucagon-like peptide-1 receptor agonists as anti-inflammatory agents: A potential mode of cardiovascular benefits

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Cardiovascular outcomes trials (CVOTs), initially mandated to ensure the safety of novel glucose-lowering medications, have unexpectedly shown encouraging cardiovascular (CV) benefits of Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in people with type 2 diabetes mellites (T2DM)[(1)].

GLP-1 RAs improve glycaemic control through their insulinotropic properties. However, the mechanisms by which these agents reduce adverse cardiovascular events remain unclear. Whilst large randomised trials have provided safety and positive outcome data, the mechanisms of these benefits require further exploration if there is to be broader utilisation and further applications of these agents.

Potentially, some benefits of GLP-1 RAs could be explained by better control of non-glycaemic CV risk factors such as blood pressure and weight[(2)]. However, in the HARMONY trial, albiglutide was associated with a significant reduction in major adverse cardiovascular events (MACE) without substantial differences in body weight or blood pressure compared to placebo[(3)]. Whilst there might be some positive effects of GLP-1RAs on heart failure (HF), the data are inconsistent. None of the CVOTs included heart failure in the primary composite outcome, and details about baseline left ventricular ejection fraction (LVEF), or concurrent HF therapies during the trials weren't clear[(4)]. Furthermore, one can argue that other GLP-1RA's favourable hemodynamic effects may contribute to this finding.

On the other hand, in a recent network meta-analysis, which included seven hundred and sixty-four trials, GLP-1RAs reduce cardiovascular mortality, non-fatal myocardial infarction,

and non-fatal stroke. There was a remarkable benefit in non-fatal stroke, which has not been observed with the sodium-glucose co-transporter-2 (SGLT2) inhibitors (the other class of glucose-lowering drugs to have shown CV benefit)[5]. Those outcomes suggest that GLP-1RAs may exhibit CV protection through anti-atherosclerotic properties.

Systemic and localized inflammation are now recognized as an active part of atherosclerosis pathophysiology and play an essential role in plaque instability and the risk of myocardial infarction[6]. Chronic hyperglycemia and insulin resistance are associated with higher than normal inflammatory responses, putting people with T2DM at higher risk for CV adverse outcomes than their non-diabetic counterparts[7,8].

Currently, some of the available biomarker data points toward an anti-inflammatory role of GLP-1-based therapies. Within this context, liraglutide, in combination with metformin, was found to decrease plasma C-reactive protein (CRP) levels in patients with coronary artery disease (CAD) and newly diagnosed T2DM[9]. Similarly, liraglutide treatment in people with T1DM resulted in a decrease in the levels of IL-6, IL-8, IL-10, and INF-γ after 26 weeks of treatment versus placebo, although this decrease was only significant for IL-6[10]. To explore this anti-inflammatory role further, Jensen et al. (in this issue of Atherosclerosis) examined the impact of the long-acting GLP-1RA, semaglutide on the atherosclerotic burden in a rabbit model using multimodality positron emission tomography and computed tomography (PET/CT)[11]. Here, the authors report a significantly decreased uptake of [^{18}F]FDG and [^{64}Cu]Cu-DOTATATE tracers imaging activated macrophages and cellular metabolism within the aorta in the semaglutide group when compared to the saline placebo group. The animal models used in the trial did not have diabetes, and fasting blood glucose did not differ between groups either at baseline or at follow-up, which is further evidence that the cardiovascular benefits of GLP-1RAs are not directly related to glucose-lowering. This was the first in vivo CT PET study to investigate the anti-inflammatory role of GLP-1RAs.

Although these anti-inflammatory effects may have beneficial cardioprotection in people with diabetes mellitus, supporting data in humans are neither extensive nor consistent.

The localised role of GLP-1RA on coronary arteries has been investigated recently. In a sub-study of the LIRAFLAME trial, the authors examined the anti-inflammatory effect of liraglutide on coronary arteries using a combined [64Cu]Cu-DOTATATE PET and CT coronary angiogram in 30 participants with T2DM[12]. After 26 weeks of treatment, there was a significant reduction in [64Cu]Cu-DOTATATE uptake in the coronary arteries in the liraglutide group compared to placebo. In an on-going randomised control study, Hamal et al. aim to investigate the impact of 1-year treatment with subcutaneous semaglutide on coronary plaque volumes and progression rate using CT coronary angiography in patients with T2DM[13].

Interestingly, patients' baseline characteristics appear to be an essential determining factor in detecting the anti-atherosclerotic prosperities of GLP-RAs. In two recent large randomised controlled trials, liraglutide and semaglutide showed remarkable CV benefits compared to placebo when added to people with T2DM[14,15]. In both trials, participants either had established CV disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease) or had a high CV risk profile. In a more low to moderate risk population with T2DM, liraglutide had little effect on vascular inflammation assessed as [18F]-fluorodeoxyglucose uptake compared with placebo[16]. This supports the hypothesis that GLP-1RAs' anti-atherosclerotic benefits are best utilised in populations at high CV risk.

In line with this, consensus statements from the American Diabetic Association and the American College of Cardiology now acknowledge the role of GLP-1RAs in people with T2DM and existing or at high risk of developing atherosclerotic cardiovascular disease[17,18]. The most up to date European Society of Cardiology guidelines (2019) have gone a step further and recommended either GLP- 1RAs or SGLT-2 inhibitors as a first-line therapy –

even before metformin to people with T2DM and prevalent atherosclerotic cardiovascular disease or high/very high CV risk profile[19]. However, these recommendations are not universal. The National Institute of Clinical Excellence in the United Kingdom advocate a stepwise, personalised approach in T2DM in which GLP-1RAs can be introduced as an 'add-on' after a number of standard therapies if required to achieve adequate glycaemic control[20]. One reason for this heterogenicity is the absence of a clear, defined mechanism for the cardiovascular protection of the GLP-1 mimetic agents. The study by Jansen et al. is a useful addition to the existing trial data. However, more mechanistic insight is still required to gain a better understanding of these agents and their cardiovascular benefits.

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