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GLP-1 Agonists Beyond Weight Loss: Cardiovascular Mechanisms

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Abstract

GLP-1 receptor agonists (GLP-1RAs) offer a promising treatment option for cardiovascular risk reduction through pathways outside of weight loss and glycemic control. There is significant evidence from cardiovascular outcome trials and preclinical studies that support the cardioprotective effects of GLP-1RAs through many mechanisms, including metabolic circuits, improving endothelial function, reducing systemic inflammation, cardiac remodeling by cardiac progenitor cells, and changing the gut microbiome composition. Additional evidence of cardiovascular benefit has also been observed in individuals without significant weight loss, supporting the use of GLP-1RAs in people with high cardiometabolic risk regardless of body weight or cardiovascular disease status. Taken together, these observations provide a foundation for a more practical and optimistic approach to cardiovascular prevention in metabolically vulnerable patients, moving beyond traditional definitions based on body mass index.

Keywords: GLP-1Ras; cardiovascular diseases; MACE; T2D; weight loss

Introduction

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) were developed primarily to enhance metabolic control in type 2 diabetes (T2D) and to treat obesity. These agents act by inducing glucose-dependent insulin secretion while simultaneously inhibiting glucagon secretion, delaying gastric emptying, and increasing feelings of fullness [1,2]. These actions lead to better metabolic control and weight loss, which is a factor leading to approval for obesity treatment [3,4]. As a result of cardiovascular outcome trials (CVOTs), GLP-1RAs have also been shown to reduce major adverse cardiovascular events (MACE) independent of weight loss [5-7]. Key trials, including LEADER, SUSTAIN-6, REWIND, and AMPLITUDE-O, have consistently demonstrated reductions in MACE rate in patients with T2D at elevated cardiovascular risk, with only modest weight loss [8-10].

Aside from their metabolic advantages, glucagon-like peptide receptor agonists (GLP-1RAs) provide cardiovascular protection by improving endothelial function, exerting anti-inflammatory effects, and repairing the myocardium through the activation of cardiac progenitor cells (CPCs) [11,12]. Furthermore, GLP-1RAs could affect the gut-heart axis by modulating microbial composition, inflammation, and myocardial metabolism in the gut, which may increase cardiovascular protection from these mechanisms [13,14]. Overall, these factors enable substantial cardiovascular protection, especially in individuals at high cardiometabolic risk, such as lean individuals (e.g., Asian Indians or Africans) who develop metabolic diseases at a lower BMI (body mass index) threshold and whose cardiovascular risk would be underestimated if an individual's risk was evaluated without taking sufficient consideration of BMI-based criteria [15,16].

As cardiovascular diseases (CVDs) and T2D become increasingly prevalent globally, we must prioritize the development of treatment modalities that can target both metabolic and cardiovascular risk factors simultaneously if they coexist. GLP-1RAs represent a novel treatment option that confers glycemic control alongside cardiovascular protection. Even more importantly, GLP-1RAs address mechanisms beyond weight loss and represent a fundamental component in the treatment of CVD risk in individuals with cardiometabolic risk, particularly in high-risk populations with multiple comorbidities that would otherwise be insignificant in a risk stratification process based on typical BMI [17,18].

Against this backdrop, this article will discuss the broadened role of GLP-1RAs in patients with metabolic risk factors who are at elevated cardiovascular risk, especially for individuals who do not meet traditional BMI cutoffs. The discussion in the article will primarily center on the mechanisms of cardioprotection of GLP-1RAs and their potential to inform the development of future treatments for cardiometabolic conditions.

Clinical Evidence Supporting Cardiovascular Protection

CVOTs have shown strong evidence for cardiovascular benefits of GLP-1RAs, demonstrating reductions in MACE that occurred independently of the weight loss and glycemic control effects [19,20]. In the LEADER trial, liraglutide was responsible for a 13% reduction in MACE among patients with T2D at high cardiovascular risk, with cardiovascular benefits observed prior to major improvements in glycemic control or weight loss [21]. This finding was significant, showing that GLP-1RAs can provide direct cardiovascular protection independent of metabolic improvements. Similarly, in the SUSTAIN-6 trial utilizing semaglutide, MACE was reduced by 26%, evidencing reduction in events such as nonfatal stroke and myocardial infarction [22]. Results of SUSTAIN-6 further demonstrated that GLP-1RAs reduce ischemic events even in the absence of robust weight loss. Finally, the REWIND trial with dulaglutide demonstrated a 12% reduction in MACE; importantly, the cardiovascular benefits experienced by individuals receiving GLP-1RAs were also evident in individuals with T2D but without established CVDS [23,24]. This suggests that GLP-1RAs may offer potential for the primary prevention of cardiovascular events and supports their early use in high-risk populations.

The AMPLITUDE-O trial, relating to epigenotype (a long-acting GLP-1RA), added further support for a class-wide cardiovascular benefit for GLP-1RAs, with a reported 27% reduction in MACE. This study supports the class-wide use of GLP-1RAs for cardiovascular protection, including higher-risk groups [25]. The SELECT trial also extended benefits to semaglutide, reporting a significant reduction of approximately 33% for MACE in overweight and obese patients, regardless of baseline obesity or early weight loss. In this trial, about one-third of the benefit was attributed to waist circumference measurements, indicating that GLP-1RAs provide cardioprotective benefits when weight loss does not occur [26]. This is particularly important for individuals with leaner phenotypes, such as Asian Indians, who exhibit greater cardiometabolic susceptibility relative to their BMI levels. These individuals have not only a greater tendency to develop metabolic disorders (e.g., insulin resistance and dyslipidemia) but also a predisposition to CVD at lower BMI levels that are not measured with standard BMI-based risk modeling [27,28].

Moreover, GLP-1RAs have shown important cardiovascular benefits in members of the obese and the normal-weight groups with T2D who are less likely to experience a weight loss response from treatment [29, 30]. The weight-independent decrease in MACE in these patients gives further justification to recommending semaglutide (Ozempic) and other GLP-1RAs in higher-risk populations [31, 32]. Taken together, the above findings demonstrate the clinical relevance of GLP-1RAs as treatment options that are not in the weight-basis treatment dimension, including adults with high cardiometabolic risk at low BMI, who were less likely to qualify for therapies aimed at decreasing cardiovascular outcomes secondary to obesity.

Mechanistic Insights into Cardiovascular Benefits

As discussed previously, GLP-1RAs improve glycemic control by boosting insulin secretion, inhibiting glucagon secretion, and delaying gastric emptying, thereby reducing excursions of glucose and lipid levels after meals. These mechanisms decrease metabolic strain to the vasculature and myocardium, improve insulin responses, are beneficial in energy metabolism, and ultimately help to preserve endothelial and myocardial function [33, 34]. In addition, GLP-1RAs may also help improve vascular health by augmenting endothelial function, increasing nitric oxide bioavailability, promoting vasodilation, and decreasing arterial stiffness and inflammation [35, 36]. Collectively, these processes enhance vascular compliance and minimize atherosclerosis by reducing further injury to the endothelium, the first step in plaque development. Importantly, GLP-1RAs stabilize atherosclerotic plaques and reduce the likelihood of rupturing, a major initiating factor for acute cardiovascular incidents such as myocardial infraction and stroke, by decreasing oxidative stress and cytokines that promote inflammation, such as TNF-α (Tumor Necrosis Factor-alpha) and IL-6 (Interleukin 6).

GLP-1RAs have also shown beneficial effects in preclinical models of heart failure with preserved ejection fraction (HFpEF), specifically in situations involving obesity-related pathophysiology [37,38]. The effects of GLP-1RA extend beyond weight loss but have been demonstrated through transcriptomic and proteomic studies, with improvements in left ventricular (LV) cytoskeletal biology and immune function in visceral adipose tissue and activation of certain processes that improve myocardial resilience,

vascular compliance, and endothelial health, leading to an overall cardioprotective effect [39,40]. Notably, available evidence demonstrates that GLP-1RAs also impact myocardial regenerative capacity, promote atherosclerotic plaque stabilization, and tissue repair [41,42].

CPCs are stem cell-like cells that have the ability to differentiate into vascular cells and cardiomyocytes and play an important role in myocardial repair after ischemic injury [43, 44]. GLP-1RAs improve CPC survival, proliferation, and differentiation, supporting cardiac repair and restoring vascular integrity, which stabilizes plaques [45,46]. GLP-1 secretion is subject to modulation by the gut microbiota, in particular, through short-chain fatty acids (SCFAs), enteric hormones, and signaling to gut microbes [47,48]. In this respect, SCFAs produced by the gut microbiota may enhance recruitment of CPCs via a gut-heart axis and activate CPCs to assist in tissue repair.

Additionally, GLP-1RAs can also modify the gut microbiota composition, reducing systemic inflammation and metabolic endotoxemia. This enhances gut immunological function and improves vascular and endothelial health, ultimately optimizing cardiac metabolism [49-51]. As a result, GLP-1RAs can stabilize atherosclerotic plaques and lower the risk of adverse cardiovascular outcomes. They achieve this by reducing inflammation, improving vascular function, and modulating gut-heart axis signaling. Together, these effects highlight the role of GLP-1RAs in myocardial repair and overall cardiovascular stability.

In summary, GLP-1RAs provide cardiovascular protection that goes beyond weight loss and involves a complicated interplay of metabolic, vascular, regenerative, and microbiota mechanisms, which all have impacts on cardiovascular health and disease. These effects are especially important in lean individuals at elevated risk for cardiometabolic disease, where assessments of risk that are based on obesity status alone can potentially underestimate the overall burden of disease. GLP-1RAs are a novel and specific therapeutic approach to managing atherosclerotic CVD through mechanisms that include plaque stabilization, improved endothelial function, and reduced inflammation, particularly in high-risk lean groups.

Integrated Perspective and Implications

GLP-1RAs operating as a "cardiovascular hub" involves various pathways related to cardiovascular protection, including metabolic, vascular, regenerative, and gut-brain pathways. Semaglutide has shown significant cardiac and metabolic benefits in preclinical models of heart failure (HF) with HFpEF, notably without inducing weight loss. These effects are likely mediated through improved myocardial function, left ventricular remodeling, and enhanced vascular compliance and endothelial function [52,53]. Although these observations are in preclinical models, they are corroborated by clinical data from the SELECT trial indicating that semaglutide protects the cardiovascular health in humans who are overweight and/or obese, regardless of baseline adiposity and/or very early on with weight loss [54,55].

These results provide evidence for GLP-1RAs, particularly in individuals with high cardiometabolic risk and lean individuals who may not realize the full benefits of a weight-loss-based therapy. SELECT trial data show that semaglutide substantially reduces MACE independent of weight loss, further enhancing its clinical value in populations with high cardiometabolic risk, even with a lower BMI. In addition, while the effect of GLP-1RAs on weight loss may be modest or attenuated among obese and normal-weight individuals with T2D, the reduction in MACE is a strong rationale for Ozempic use among T2D individuals [56]. These results provide evidence for the cardiovascular risk-reduction potential of GLP-1RAs across clinical settings.

Knowledge Gaps and Future Directions

Meanwhile, insights into the mechanism of GLP-1RAs continue to evolve. However, the pathways linking GLP-1RAs to the activation of CPCs and the gut-heart axis remain incompletely characterized. Further research is needed to assess the effects of GLP-1RAs in lean or non-diabetic patients at cardiovascular risk, as well as to explore long-term cardiovascular outcomes after the completion of clinical trials. Ongoing trials, such as STEP-HFpEF and STEP-HFpEF-DM, along with investigations into the role of dual GLP-1/GIP RAs, may provide valuable information regarding the role of GLP-1RAs in HF with HFpEF and other CVDs [57-60].

Future research should seek to improve our understanding of CPC activation and the immune- and metabolic-related pathways that can be modulated by the microbiota, with particular emphasis on translating preclinical observations to clinical outcomes that better define the cardioprotective effects of GLP-1RAs. Longitudinal studies will be critical to confirm weight-independent cardiovascular improvements associated with GLP-

1RAs by measuring other biomarkers and mechanistic pathways, including inflammatory markers, endothelial function, and CPC outcome. Expanding the diversity of participant recruitment will also yield better generalizability of results, especially among participants within the continuum of the quality of adiposity, including participants from marginalized and resource-limited areas with malnutrition and underweight. This approach will help define how GLP-1RAs provide cardiovascular protection beyond weight loss.

Lastly, it is important to conduct long-term trials to determine the broader clinical utility of GLP-1RAs in the prevention of MACE among people who do not lose weight. As HF continues to rise globally, there is growing interest in evaluating the benefits of GLP-1RAs in individuals with both HFrEF and HFpEF, regardless of T2D status. However, studies evaluating GLP-1RAs, especially in an HF population, have generally been small, underpowered, and inconsistent in their findings, leading to an unclear role for GLP-1RAs in HF care. Therefore, robust, large clinical trials are needed to evaluate the safety, effectiveness, and long-term effects of GLP-1RAs in people with HF, with and without T2D. These will allow us to understand the mechanisms, in addition to weight loss, that GLP-1RAs may also improve outcomes in cardiovascular disease in this growing patient population, especially their effects on metabolic, vascular, and other pathways related to HF progression.

Conclusion

GLP-1RAs provide cardiovascular benefits beyond weight loss through multiple pathways, including metabolic, vascular, regenerative (via CPCs), and gut microbiota-related mechanisms. Semaglutide has been shown to improve cardiac structure, function, and cardiometabolic outcomes in preclinical HFpEF models. Notably, the SELECT trial findings in a non-diabetic population highlight that GLP-1RAs offer similar benefits to cardiometabolic health without requiring weight loss. This evidence supports the clinical use of GLP-1RAs in cardiometabolically vulnerable populations at high risk, including those with lower BMI, and underscores the role of Ozempic in lowering cardiovascular risk, regardless of body weight changes. GLP-1RAs promote a holistic approach to cardiometabolic health, potentially reflecting a new paradigm that is relevant to diverse populations, including lean or "normal" BMI phenotypes, such as Asian Indians, who may be at risk of cardiovascular issues despite having a "normal" BMI.

Declarations

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Conflict of Interest

The author declares no conflict of interest.

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