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GLP-1 RECEPTOR AGONISTS: CARDIOVASCULAR BENEFIT BEYOND WEIGHT LOSS

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Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death worldwide. As smoking rates continue to decline, the rising incidence of type 2 diabetes mellitus (T2DM) and obesity –hallmarks of the ongoing metabolic epidemic– has emerged as the predominant driver of ASCVD in contemporary populations[1].

Approximately 80%-85% of individuals with T2DM have overweight or obesity; conversely, people with obesity are nearly three times more likely to develop T2DM than those with normal weight, underscoring the strong interrelation between these conditions[2].

Obesity is a chronic, multifactorial disease characterized by ectopic, dysfunctional fat accumulation that increases cardiovascular risk through interconnected hemodynamic, metabolic, and inflammatory mechanisms[2]. Excessive and dysfunctional visceral adipose tissue triggers chronic low-grade inflammation, marked by increased secretion of pro-inflammatory cytokines (such as tumor necrosis factor-α and interleukin-6), oxidative stress mediators, and altered adipokine profiles. This inflammatory milieu plays a central role in linking obesity to ASCVD risk by promoting endothelial dysfunction, insulin resistance, disordered lipid metabolism, and hypertension, thereby accelerating atherosclerotic plaque formation, enhancing plaque vulnerability, and ultimately increasing the likelihood of cardiovascular events[3,4].

Over the past decade, a paradigm shift has occurred in the management of T2DM and obesity, moving beyond the traditional focus on metabolic control toward a contemporary framework centered on cardiovascular risk reduction. In this context, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as key contributors to this paradigm shift, initially supported by robust evidence demonstrating cardiovascular benefits in patients with T2DM[5], and more recently in those with overweight or obesity (body mass index [BMI] ≥ 27 kg/m²) without diabetes, as shown in the SELECT trial. In this study, among 17 604 individuals with pre-existing cardiovascular disease in addition to the characteristics mentioned, once-weekly subcutaneous semaglutide (2.4 mg) reduced the composite cardiovascular endpoint –including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke– by 20%, corresponding to an absolute risk reduction of 1.5% over a mean follow-up of approximately 40 months. Notably, participants treated with semaglutide experienced a mean body weight reduction of 9.39% over a 24-month treatment period[6].

Although BMI –a weight-based measure– is widely used in population studies, it has notable limitations for accurately diagnosing obesity at the individual level. It does not differentiate fat from lean mass or assess fat distribution, leading to possible under- or overestimation of adiposity. Complementary assessments, such as waist circumference, additional anthropometric indices (including waist-to-height and waist-to-hip ratios), together with physical examination, are essential for enhancing accuracy, as they enable a more reliable identification of central adi-

posity and provide a more precise reflection of cardiometabolic risk[7].

Additionally, from a therapeutic standpoint, weight loss should not be viewed as the only goal of intervention. Emerging evidence indicates that lifestyle interventions combining increased physical activity with a balanced diet can mitigate obesity-related risk even in the absence of significant weight loss. Such interventions lead to reductions in visceral fat, improvements in cardiometabolic profiles, and gains in skeletal muscle mass and cardiorespiratory fitness, ultimately translating into meaningful clinical benefit[8].

A recent prespecified analysis of the SELECT trial provided important insights, suggesting that the cardioprotective benefits of semaglutide extend beyond weight reduction and may involve additional mechanisms[9]. The findings supporting this concept are summarized below. First, cardiovascular outcomes did not differ between semaglutide-treated patients who achieved ≥5% weight loss and those who did not. Similar observations have been reported with other GLP-1 RAs, which have demonstrated cardiovascular outcome benefits despite minimal or no associated weight loss[10]. Second, a clear temporal dissociation was observed, with the cardiovascular benefit emerging early, preceding significant weight loss. Third, the benefits of semaglutide were independent of baseline measures of adiposity. Fourth, cardiovascular outcomes were more closely associated with changes in waist circumference than with overall body weight. Supporting this observation, a phase 4, placebo-controlled trial showed that liraglutide 3.0 mg plus lifestyle intervention significantly reduced visceral adipose tissue –quantified by magnetic resonance imaging– over 40 weeks in adults with overweight or obesity at high cardiovascular risk but without diabetes[11]. Although waist circumference offers a better approximation of total adiposity than body weight, it cannot differentiate between subcutaneous and visceral fat, the latter being the compartment associated with increased cardiovascular risk[2]. This limitation may partly explain why, in the SELECT mediation analysis, reductions in central adiposity accounted for only up to 33% of the observed major adverse cardiovascular events (MACE) risk reduction with semaglutide. Alternatively, other mechanisms beyond changes in adiposity may contribute to the cardiovascular benefits reported.

GLP-1 RAs exert a range of pleiotropic actions that directly modulate systemic and vascular inflammation and endothelial function. These agents lower circulating concentrations of key pro-inflammatory cytokines –including tumor necrosis factor-α, interleukin-1β, and interleukin-6– while increasing anti-inflammatory mediators such as adiponectin, thereby attenuating the systemic inflammatory milieu that promotes atherogenesis. In this context, GLP-1 RAs significantly reduced C-reactive protein concentrations in individuals with overweight or obesity –independently of baseline BMI, body weight, and glycemic status– compared with placebo. At the vascular level, GLP-1 RAs reduce immune cell infiltration into the arterial wall and downregulate molecules involved in monocyte–macrophage adhesion and matrix degradation[2,4,12].

Moreover, GLP-1 receptors are expressed on endothelial cells, where GLP-1 RAs enhance nitric oxide bioavailability and activate endothelial nitric oxide synthase, thereby improving endothelial function and reducing oxidative stress. Furthermore, GLP-1 RAs diminish the production and activation of angiotensin II, exerting additional favorable effects on both endothelial and vascular smooth muscle cells[12].

Collectively, the previously described pleiotropic mechanisms of GLP-1 RAs converge to mitigate vascular inflammation, promote collagen deposition and development of a thicker fibrous cap, and reduce foam cell formation –features characteristic of enhanced plaque stability[12].

Beyond these vascular effects, emerging evidence indicates that GLP-1 RAs exert meaningful kidney protective effects. In a recent trial involving non-diabetic adults with chronic kidney disease and overweight or obesity, semaglutide 2.4 mg weekly for 24 weeks achieved a clinically significant 52.1% reduction in albuminuria compared with placebo[13]. These kidney protective actions –which appear consistent across varying degrees of glycemic control and excess adiposity– together with additional effects, including modest reductions in systolic blood pressure and improvements in lipid profiles, may further contribute, at least in part, to improved cardiovascular outcomes irrespective of metabolic control[6,14].

Prior to the publication of the SELECT trial, the cardiovascular benefits of GLP-1 RAs had been demonstrated primarily in populations with diabetes, where improvements in glycemic control predominantly confounded the contribution of other mechanisms –such as those previously described– through which these agents may reduce cardiovascular risk. In this context, analyses from the SELECT trial have shown that 66.4% of participants met criteria for prediabetes (HbA1c ≥5.7%), and semaglutide reduced the relative risk of progression to diabetes by 73%. Moreover, the cardiovascular benefits were independent of baseline HbA1c or glycemic changes, underscoring pleiotropic effects not solely mediated by glucose regulation[15].

In conclusion, GLP1 RAs have redefined the management of T2DM and obesity, acting not only through weight reduction and glycemic control but also as genuine disease-modifying agents. With respect to obesity treatment, these advances emphasize the need to move beyond a BMI-centric approach for the indication of pharmacological or metabolic surgical interventions, and to shift therapeutic targets away from weight alone. Looking ahead, emerging multi-receptor agonists such as tirzepatide have demonstrated substantially greater weight loss than GLP-1 RAs[4]. Further research is needed to clarify the cardiovascular impact of these agents and to determine how they will consequently reshape the therapeutic algorithm for obesity in the near future.

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