Review

The Cardiovascular Physiology of Glucagon-like Peptide-1 Receptor Agonists: From Macro-level Outcomes to Micro-level Mechanisms

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The Cardiovascular Physiology of Glucagon-like Peptide-1 Receptor Agonists: From Macro-level Outcomes to Micro-level Mechanisms

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have instigated a paradigm shift in the management of cardiometabolic disease. Initially developed for glycemic control in type 2 diabetes, their therapeutic role has expanded dramatically following the demonstration of robust cardiovascular benefits in large-scale clinical trials. This review provides a comprehensive synthesis of the physiological mechanisms underlying the cardioprotective effects of GLP-1 RAs, moving beyond the clinical outcomes to explore the cellular and molecular pathways involved. We systematically deconstruct the effects of this drug class on the vasculature, where they mitigate atherosclerosis by improving endothelial function, attenuating vascular inflammation and oxidative stress, and favorably modulating plaque composition. We then delve into the complex and controversial effects on the myocardium, addressing the debate over GLP-1 receptor expression and detailing the interplay of direct and indirect actions on cardiomyocyte metabolism, ion homeostasis, and fibrosis. A central focus is the differential impact of GLP-1 RAs on heart failure (HF) phenotypes, clarifying their established benefits in HF with preserved ejection fraction (HFpEF)—largely through targeting obesity and inflammation—and their neutrality or potential for harm in HF with reduced ejection fraction (HFrEF). By integrating evidence from landmark trials with cutting-edge mechanistic studies, this review illuminates how GLP-1 RAs exert their profound cardiovascular effects and identifies critical unanswered questions that will shape the future of cardiometabolic medicine.

Keywords: glucagon-like peptide-1 receptor agonist; cardiovascular disease; atherosclerosis; heart failure; cardiomyocyte; endothelial function; inflammation

1. Introduction

The confluence of the global epidemics of obesity, type 2 diabetes (T2D), and atherosclerotic cardiovascular disease (ASCVD) represents one of the most significant public health challenges of the 21st century [1]. For decades, these conditions were often treated in silos, with antidiabetic therapies focused almost exclusively on achieving glycemic control [3]. This approach, while logical, created a profound therapeutic gap; many glucose-lowering agents had neutral or, in some cases, potentially adverse cardiovascular effects, failing to address the fact that cardiovascular disease is the leading cause of morbidity and mortality in patients with T2D [3]. The urgent need for therapies capable of simultaneously managing metabolic dysregulation and providing direct cardiovascular protection remained a paramount, yet largely unmet, clinical goal.

This landscape was fundamentally altered by the emergence of glucagon-like peptide-1 receptor agonists (GLP-1 RAs). This class of incretin-based therapies has transcended its original role as a glucose-lowering agent to become a cornerstone of cardiovascular risk reduction [4]. This transformation was driven by a series of landmark cardiovascular outcome trials (CVOTs) that unequivocally demonstrated that several agents within this class significantly reduce the incidence

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of major adverse cardiovascular events (MACE), including myocardial infarction (MI) and stroke, in high-risk patient populations [5]. The consistency and robustness of these findings have catalyzed a paradigm shift in clinical practice guidelines, which now endorse the use of GLP-1 RAs for their cardiovascular benefits, often independent of the baseline glycemic status or the need for additional glucose lowering [5].

While the clinical efficacy of GLP-1 RAs is now firmly established, a complete understanding of *how* these agents exert their profound cardioprotective effects requires a deeper exploration of their underlying physiological mechanisms. The purpose of this review is to synthesize the current state of knowledge, moving beyond the macro-level outcomes of clinical trials to the micro-level cellular and molecular pathways. This paper will systematically deconstruct the multifaceted actions of GLP-1 RAs, beginning with their effects on the vasculature and the pathogenesis of atherosclerosis. It will then navigate the complex and often controversial evidence regarding their direct and indirect effects on the myocardium. A central theme will be the analysis of their dichotomous role in heart failure, clarifying their established benefits in heart failure with preserved ejection fraction (HFpEF) and their contrasting neutrality or potential for harm in heart failure with reduced ejection fraction (HFrEF). By addressing key controversies, such as the precise cellular location of the GLP-1 receptor in the human heart, and identifying critical unanswered questions, this review aims to provide a comprehensive physiological framework for understanding this transformative drug class and to guide the next wave of research in cardiometabolic medicine [10].

2. A New Standard of Care: Evidence from Cardiovascular Outcome Trials

The ascent of GLP-1 RAs as a primary tool for cardiovascular risk reduction is built upon a foundation of large, rigorously conducted, randomized controlled trials. These CVOTs evolved from regulatory requirements to demonstrate cardiovascular safety into powerful investigations that revealed profound therapeutic benefits, ultimately reshaping treatment algorithms for patients with and without T2D.

2.1. Overview of Landmark CVOTs and MACE Reduction

The journey of GLP-1 RAs in cardiovascular medicine began with trials designed primarily to rule out harm, but soon pivoted to demonstrating clear superiority. The **ELIXA** trial with lixisenatide, a short-acting agent, showed non-inferiority but not superiority for MACE reduction, yielding a neutral result [14]. However, the subsequent trials with long-acting agents painted a much different picture.

The watershed moment arrived with the **LEADER** (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial. In over 9,300 high-risk patients with T2D, liraglutide significantly reduced the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke by 13% compared to placebo (HR:0.87; 95% CI: 0.78-0.97). Crucially, it also demonstrated a 22% reduction in cardiovascular death and a 15% reduction in all-cause mortality, providing the first definitive evidence that a GLP-1 RA could not only prevent cardiovascular events but also save lives [14].

This groundbreaking finding was reinforced by a series of subsequent trials. The **SUSTAIN-6** (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) trial showed that subcutaneous semaglutide reduced the primary MACE endpoint by 26% (HR:0.74; 95% CI: 0.58-0.95), driven primarily by a significant reduction in nonfatal stroke [14]. The **PIONEER 6** trial later demonstrated the cardiovascular safety of oral semaglutide, with a directionally similar, albeit not statistically significant, 21% reduction in MACE, further solidifying the benefits of the semaglutide molecule [14].

The **REWIND** (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) trial with dulaglutide was particularly noteworthy. It enrolled a broader population of over 9,900 patients, of whom only 31% had established ASCVD, making it a mixed primary and secondary prevention cohort. Dulaglutide demonstrated a 12% reduction in the primary MACE outcome (HR:0.88; 95% CI:

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0.79-0.99), showing that the benefits extend to patients with multiple cardiovascular risk factors, not just those with prior events [14]. Additional trials, including **HARMONY Outcomes** with albiglutide (HR:0.78) and **AMPLITUDE-O** with efpeglenatide (HR:0.73), consistently reported significant reductions in MACE, cementing the class effect of long-acting GLP-1 RAs in mitigating atherothrombotic risk [14].

2.2. The SELECT Trial: Expanding the Paradigm Beyond Diabetes

Perhaps the most transformative study in the field has been the **SELECT** (Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity) trial. This landmark investigation shifted the focus entirely away from diabetes. It randomized over 17,600 patients with pre-existing ASCVD and overweight or obesity (BMI ≥27 kg/m^2) but *without* diabetes to receive semaglutide 2.4 mg or placebo [6].

The results were unequivocal: semaglutide reduced the primary composite MACE endpoint by a significant 20% (HR:0.80; 95% CI: 0.72-0.89) over a median follow-up of 3.3 years [6]. This finding was of monumental importance for several reasons. First, it definitively proved that the cardiovascular benefits of GLP-1 RAs are not merely a byproduct of improved glycemic control. By demonstrating efficacy in a normoglycemic population, the SELECT trial decoupled the cardiovascular effects from the antidiabetic effects, providing the strongest clinical evidence to date that other physiological mechanisms—such as weight reduction, anti-inflammatory actions, and direct vascular effects—are primary drivers of the observed benefit [6]. This has broadened the potential therapeutic application of these agents to a vast population of patients with obesity-related cardiovascular risk, irrespective of their diabetes status.

2.3. Effects on Secondary and Exploratory Endpoints

Beyond the primary MACE outcomes, the CVOTs have provided crucial insights into the broader cardiorenal effects of GLP-1 RAs. A consistent and clinically significant finding across multiple trials, including LEADER, SUSTAIN-6, and REWIND, has been a marked reduction in the risk of new or worsening nephropathy [14]. This demonstrates a clear renal-protective effect, adding another dimension to their systemic benefits.

In stark contrast, the effect on hospitalization for heart failure (HHF) has been consistently neutral across most major CVOTs, with hazard ratios hovering around 1.0 [8]. This observation is critically important as it creates a clear point of divergence from another class of cardioprotective agents, the sodium-glucose cotransporter-2 (SGLT2) inhibitors, which show robust reductions in HHF. A critical pattern emerging from these trials is a clear divergence in outcomes: while GLP-1 RAs consistently reduce atherothrombotic events, their effect on HHF remains largely neutral. This dichotomy strongly suggests that the primary physiological mechanisms of this drug class are targeted towards the atherosclerotic process itself, rather than the hemodynamic and renal pathways typically associated with heart failure exacerbations. This distinction forms a central theme of this review and necessitates a separate and detailed exploration of the drug class's effects on the vasculature versus the failing heart.

Table 1. Summary of Major Cardiovascular Outcome Trials (CVOTs) for GLP-1 Receptor Agonists. *SC: Subcutaneous. Bolded values indicate statistical significance for superiority.*

Trial Name	Drug	Sample Size	Baseline ASCVD (%)	Follow-up (years)	Primary MACE Outcome (HR [95% CI])	HHF Outcome (HR [95% CI])
ELIXA [14]	Lixisenatide	6,068	100%	2.1	1.02 [0.89–1.17]	0.96 [0.75–1.23]
LEADER [14]	Liraglutide	9,340	81%	3.8	**0.87 [0.78–0.97]**	0.87 [0.73–1.05]
SUSTAIN-6 [14]	Semaglutide (SC)	3,297	83%	2.1	**0.74 [0.58–0.95]**	1.11 [0.77–1.61]

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EXSCEL [14]	Exenatide (weekly)	14,752	73%	3.2	0.91 [0.83–1.00]	0.94 [0.78–1.13]
REWIND [14]	Dulaglutide	9,901	31%	5.4	**0.88 [0.79–0.99]**	0.93 [0.77–1.12]
PIONEER 6 [14]	Semaglutide (oral)	3,183	85%	1.3	0.79 [0.57–1.11]	0.86 [0.48–1.55]
AMPLITUDE-O [14]	Efpeglenatide	4,076	90%	1.8	**0.73 [0.58–0.92]**	0.61 [0.38–0.98]
SELECT [6]	Semaglutide (SC)	17,604	100% (No Diabetes)	3.3	**0.80 [0.72–0.89]**	0.82 [0.71-0.96]

2.1.1. Subsubsection

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3. The Vasculature as a Primary Target: Mechanisms in Atherosclerosis

The consistent reduction of atherothrombotic events (MI and stroke) in CVOTs strongly points to the vasculature as a primary site of action for GLP-1 RAs. Atherosclerosis is a complex pathology driven by endothelial dysfunction, chronic inflammation, and lipid deposition within the arterial wall. Mechanistic studies have revealed that GLP-1 RAs mount a coordinated, multi-pronged attack on these core processes, intervening at multiple steps to halt or reverse the disease. This multi-target engagement likely explains the robustness of the MACE reduction seen in clinical trials, distinguishing these agents from therapies that target only a single pathway.

3.1. Improving Endothelial Function and NO Bioavailability

The endothelium is the critical interface between the blood and the vessel wall, and its dysfunction is the initiating event in atherogenesis. A healthy endothelium maintains vascular tone through the production of nitric oxide (NO), a potent vasodilator with anti-inflammatory and anti-proliferative properties. GLP-1 RAs have been shown to directly restore and enhance endothelial function [22].

The biological plausibility for this direct effect is strong, as GLP-1 receptors (GLP-1R) are expressed on human coronary artery endothelial cells (hCAECs) [23]. In vitro studies have demonstrated that activation of these receptors by agonists like exendin-4 and liraglutide triggers key intracellular signaling cascades. Specifically, receptor binding leads to the activation of both the protein kinase A (PKA) and the phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) pathways [23]. These pathways converge on the phosphorylation and subsequent activation of endothelial nitric oxide synthase (eNOS), the enzyme responsible for producing NO [23].

The resulting increase in NO bioavailability promotes vasodilation and contributes to an anti-atherogenic vascular environment. Beyond NO production, these signaling pathways also promote endothelial cell survival and proliferation while protecting them from lipoapoptosis (cell death induced by toxic lipids), a common feature in the metabolic dysregulation that accompanies T2D and obesity [22]. Furthermore, GLP-1 RAs can alleviate cellular stress within the endothelium by downregulating the unfolded protein response, another pathway implicated in endothelial dysfunction [23].

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3.2. Attenuating Vascular Inflammation and Oxidative Stress

Atherosclerosis is now understood to be, at its core, a chronic inflammatory disease [1]. GLP-1 RAs exert potent anti-inflammatory effects directly within the vessel wall, disrupting the cycle of inflammation that drives plaque progression. A key mechanism is the downregulation of the master inflammatory transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [23]. By inhibiting NF-κB, GLP-1 RAs reduce the expression of critical cell adhesion molecules, namely vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) [23]. These molecules act as docking sites on the endothelial surface for circulating monocytes; by reducing their expression, GLP-1 RAs effectively limit the recruitment of these inflammatory cells into the subendothelial space, a critical early step in lesion formation.

Once inside the vessel wall, monocytes differentiate into macrophages, which engulf oxidized lipids to become pro-inflammatory foam cells. GLP-1 RAs further intervene at this stage by modulating macrophage behavior, pushing them away from the inflammatory M1 phenotype and inhibiting foam cell formation [31]. This is complemented by a reduction in oxidative stress, another key driver of vascular inflammation. These drugs have been shown to decrease the production of reactive oxygen species (ROS) in vascular cells, partly through the inhibition of pro-oxidant enzymes like NADPH oxidase (NOX) [22].

3.3. Modulating Plaque Composition and Stability

The clinical benefit of GLP-1 RAs extends beyond simply preventing the formation of new atherosclerotic plaques; emerging evidence suggests they may also stabilize existing plaques, making them less vulnerable to rupture, the event that typically triggers an acute MI or stroke. This involves both direct effects on plaque components and indirect effects mediated by surrounding tissues.

A novel and important area of research focuses on the role of epicardial adipose tissue (EAT), a unique fat depot that directly encases the heart and coronary arteries. EAT is not merely a passive storage site but a metabolically active endocrine organ that can secrete pro-inflammatory and pro-atherogenic factors. Crucially, EAT has been shown to express GLP-1R [35]. Studies with semaglutide have revealed that it can directly modulate the secretome of EAT. Specifically, semaglutide treatment increases the secretion of the anti-thrombotic protein gelsolin while decreasing levels of the pro-inflammatory adipokine fatty acid-binding protein 4 (FABP4) [36]. This represents a localized anti-atherogenic mechanism, whereby the drug alters the immediate paracrine environment of the coronary arteries to be less thrombotic and inflammatory.

Preclinical studies in atherosclerosis-prone mouse models (ApoE-/- and LDLr-/-) provide further support, showing that both liraglutide and semaglutide significantly reduce the development of plaque lesions [27]. There is also evidence that these agents can alter plaque composition to favor a more stable phenotype, characterized by increased collagen content and a thicker fibrous cap, potentially through mechanisms involving the longevity-associated protein sirtuin 6 (SIRT6) [23]. These direct and localized effects are powerfully amplified by the well-established systemic benefits of GLP-1 RAs, including significant weight loss, improvements in lipid profiles (reductions in LDL-cholesterol and triglycerides), and lowering of systolic blood pressure, all of which contribute to a healthier vascular milieu and reduced atherosclerotic burden [25].

4. The Myocardium: A Complex Interplay of Direct and Indirect Effects

While the vascular benefits of GLP-1 RAs are well-supported and align closely with the atherothrombotic event reduction seen in CVOTs, their effects on the heart muscle itself are far more complex and have been the subject of considerable scientific debate. The central controversy revolves around the very presence and function of the GLP-1 receptor in ventricular cardiomyocytes. Reconciling conflicting data requires a nuanced examination of historical findings, modern molecular techniques, and the distinction between direct receptor-mediated effects and indirect physiological consequences.

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4.1. The GLP-1 Receptor in the Human Heart: A Contentious Presence

The question of whether GLP-1 RAs can act directly on heart muscle cells has been a moving target. Early investigations using techniques like reverse transcription-polymerase chain reaction (RT-PCR) and certain antibodies suggested that GLP-1R mRNA and protein were expressed in all four chambers of the human heart, including the ventricular myocardium [26]. The presence of GLP-1R in the sinoatrial node is well-established and provides a clear explanation for the consistent chronotropic (heart rate-increasing) effect of these drugs observed in clinical studies [38].

However, the evidence for ventricular cardiomyocyte expression has become more tenuous under closer scrutiny. More recent and rigorous studies, employing highly specific monoclonal antibodies and advanced techniques like in situ hybridization, have struggled to definitively localize GLP-1R protein within human ventricular cardiomyocytes [38]. This has led to the hypothesis that many previously observed "direct" cardiac effects might actually be mediated indirectly, for instance, through activation of the autonomic nervous system, which then acts on the heart [41].

A potential resolution to this controversy has emerged from the application of **single-cell RNA sequencing (scRNA-seq)**, a powerful technology that allows for gene expression analysis on an individual cell basis. This approach has provided a more granular map of GLP-1R expression in the heart. Multiple scRNA-seq datasets from both mouse and human hearts have converged on a key finding: while *GLP1R* expression is very low or undetectable in cardiomyocytes, it is consistently and predominantly expressed in **cardiac endothelial cells and endocardial cells** [43]. This insight reframes the debate entirely. It suggests that GLP-1 RAs can exert profound effects on the heart not by acting on the muscle cells directly, but by binding to their receptors on the adjacent endothelium and endocardium. These cells, in turn, can communicate with the underlying cardiomyocytes through the release of paracrine signaling molecules (such as NO), creating an "indirect-but-local" mechanism of action. This model can account for many of the observed myocardial benefits without requiring robust receptor expression on the cardiomyocytes themselves.

4.2. Modulation of Myocardial Metabolism and Mitochondrial Function

Regardless of the precise cellular target, GLP-1 RAs clearly influence the metabolic state of the myocardium. In pathological states like diabetic cardiomyopathy, the heart becomes overly reliant on fatty acid oxidation, which is less oxygen-efficient and can lead to the accumulation of toxic lipid intermediates. Studies have shown that liraglutide can promote a beneficial metabolic shift by increasing myocardial glucose oxidation [45]. This effect appears to be indirect, likely mediated by augmented insulin secretion, which subsequently enhances the activity of pyruvate dehydrogenase, the rate-limiting enzyme for glucose oxidation [45].

At a subcellular level, GLP-1 RAs offer significant protection to mitochondria, the powerhouses of the cardiomyocyte. In vitro studies demonstrate that these agents can shield mitochondria from damage induced by inflammatory stimuli (e.g., interleukin-1β) or lipotoxicity [34]. They act to preserve the mitochondrial membrane potential, maintain ATP production, and reduce the generation of damaging ROS [34]. A key signaling molecule implicated in mediating these mitochondrial benefits is

AMP-activated protein kinase (AMPK), a central regulator of cellular energy homeostasis. Liraglutide has been shown to activate AMPK, and blocking this pathway abolishes its protective effects, indicating that AMPK activation is a critical downstream mechanism [34].

4.3. Direct Effects on Cardiomyocyte Ion Homeostasis and Contractility

While the receptor expression debate continues, a recent and provocative study has provided compelling evidence for a direct effect of semaglutide on the fundamental machinery of cardiomyocyte function. This research, using isolated human ventricular cardiomyocytes from patients with both HFrEF and an HFpEF-like phenotype, demonstrated that semaglutide directly modulates cellular ion handling [47].

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Specifically, semaglutide was shown to reduce the pathological **late sodium current (INa,L)**, an aberrant inward current that contributes to ionic imbalance and arrhythmias in the failing heart. It also decreased diastolic **sarcoplasmic reticulum (SR) Ca^{2+} leak**, another key driver of arrhythmias and contractile dysfunction [47]. The functional consequence of these ionic effects was a significant improvement in systolic Ca^{2+} transients and an enhancement of myocardial contractility [47]. These effects were mediated through the GLP-1R and were comparable in magnitude to those achieved with inhibition of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), a central signaling hub in cardiac pathology [47]. These findings provide a novel and direct mechanistic basis for how GLP-1 RAs could improve cardiac function. However, they also create a fascinating paradox: if semaglutide directly improves contractility in failing cells, why have clinical trials in HFrEF patients been neutral or even suggested potential harm? This discrepancy underscores the critical difference between the behavior of an isolated cell and the integrated physiology of a whole organism, where other systemic effects of the drug, such as increased heart rate, may counteract or override any direct cellular benefit.

4.4. Attenuation of Cardiac Fibrosis and Adverse Remodeling

Cardiac fibrosis, the excessive deposition of extracellular matrix, is a final common pathway in many forms of heart disease, leading to myocardial stiffening and dysfunction. In preclinical models of myocardial infarction, GLP-1 RAs have been shown to inhibit the development of myocardial fibrosis and attenuate adverse ventricular remodeling [48]. These anti-fibrotic effects are thought to be secondary to the potent anti-inflammatory and anti-apoptotic actions of the drugs [26]. By reducing inflammation and preventing cardiomyocyte death in the aftermath of an ischemic injury, GLP-1 RAs can mitigate the stimulus for subsequent fibrotic repair, thereby helping to preserve the structural and functional integrity of the heart and prevent the long-term progression to heart failure.Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Interventionary studies involving animals or humans, and other studies that require ethical approval, must list the authority that provided approval and the corresponding ethical approval code.

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5. GLP-1 Receptor Agonists in Heart Failure: A Tale of Two Phenotypes

The clinical trial data for GLP-1 RAs in heart failure (HF) present a stark and instructive contrast. While the overall effect on HHF in the major CVOTs was neutral, dedicated HF trials have revealed a clear divergence: GLP-1 RAs are emerging as a breakthrough therapy for HFpEF, particularly the obesity-related phenotype, but have proven to be ineffective and potentially unsafe in HFrEF. This tale of two phenotypes provides a powerful lesson in the heterogeneity of heart failure and underscores the importance of matching therapeutic mechanisms to specific underlying pathophysiology. The success of these agents in HFpEF strongly supports the hypothesis that their primary clinically relevant benefits are driven by their profound systemic metabolic and anti-inflammatory effects, rather than by a direct positive inotropic action on the heart.

5.1. Clear Benefits in Heart Failure with Preserved Ejection Fraction (HFpEF)

For decades, HFpEF remained a major clinical challenge with no effective pharmacotherapies. This syndrome is now recognized as being highly heterogeneous, with a prominent phenotype

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driven by obesity, metabolic dysfunction, and a state of chronic, low-grade systemic inflammation [29]. The landmark STEP-HFpEF and STEP-HFpEF DM trials represented a major therapeutic breakthrough. In these studies, treatment with semaglutide led to dramatic improvements in the primary endpoints: patient-reported symptoms, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) score, and physical function, assessed by the 6-minute walk test. These benefits were accompanied by substantial weight loss and were observed in obese patients with HFpEF both with and without co-existing T2D [50]. The remarkable success of GLP-1 RAs in this context stems from their unique ability to target the core pathophysiological drivers of the obesity-related HFpEF phenotype. The mechanisms of benefit are multi-faceted and synergistic:

- Targeting Adiposity: GLP-1 RAs induce significant weight loss, which reduces the overall hemodynamic burden on the heart. Critically, they also appear to reduce visceral and epicardial adipose tissue (EAT), the metabolically active and pro-inflammatory fat depots that are strongly implicated in promoting myocardial stiffness and diastolic dysfunction [52].

- Targeting Inflammation: HFpEF is increasingly viewed as an inflammatory disease. GLP-1 RAs directly counter this by exerting potent systemic and local anti-inflammatory effects, reducing levels of inflammatory markers like C-reactive protein and inhibiting pro-inflammatory signaling pathways [29].

- Targeting Vascular Dysfunction: Many patients with HFpEF suffer from coronary microvascular dysfunction. By improving endothelial function and NO bioavailability, GLP-1 RAs can address this component of the disease, improving myocardial perfusion [31].

By simultaneously addressing excess adiposity, systemic inflammation, and vascular dysfunction, GLP-1 RAs are almost perfectly suited to treat this common and debilitating form of heart failure.

5.2. Neutrality and Caution in Heart Failure with Reduced Ejection Fraction (HFrEF)

In stark contrast to the success in HFpEF, the story of GLP-1 RAs in HFrEF is one of neutrality and caution. HFrEF is a distinct syndrome primarily characterized by impaired systolic function (pump failure) and the activation of adverse neurohormonal pathways, leading to high sympathetic tone. Dedicated trials in patients with stable, established HFrEF, such as the FIGHT and LIVE trials with liraglutide, failed to show any benefit in clinical stability, exercise capacity, or left ventricular function [51]. More concerningly, these trials raised potential safety signals, with a numerically higher rate of serious cardiac adverse events in the liraglutide groups [55]. Meta-analyses have since confirmed that GLP-1 RAs do not reduce HF outcomes in patients with established HF and may even be harmful in those with advanced disease (NYHA Class III-IV) or severely reduced ejection fraction [20].

Several physiological hypotheses have been proposed to explain this lack of benefit and potential for harm in HFrEF:

- Adverse Chronotropic Effects: A consistent physiological effect of GLP-1 RA therapy is a modest but persistent increase in heart rate of 3-5 beats per minute [40]. In a healthy heart, this is of little consequence. However, in the context of HFrEF, where the heart is already failing and under high sympathetic stress, elevated heart rate is a well-established negative prognostic factor. The increased myocardial oxygen demand associated with a faster heart rate could be detrimental, potentially negating or overriding any other potential benefits of the drug [42].

- Lack of Favorable Hemodynamic Effects: A key mechanism of benefit for other successful HFrEF therapies, such as SGLT2 inhibitors, is their ability to induce osmotic diuresis and reduce plasma volume, thereby decreasing cardiac preload and congestion. GLP-1 RAs do not

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appear to share these robust hemodynamic effects, limiting their utility in the volume-overloaded state typical of HFrEF.

- Pathophysiological Mismatch: The primary drivers of HFrEF progression often involve extensive myocyte loss, adverse remodeling, and profound neurohormonal activation. The primary mechanisms of GLP-1 RAs—metabolic optimization and inflammation reduction—may be less effective at targeting these core features of HFrEF compared to their effectiveness against the metabolic drivers of HFpEF.

The divergent outcomes in HFpEF and HFrEF underscore that heart failure is not a monolithic entity. The success of GLP-1 RAs in HFpEF validates the concept of phenotype-specific therapy, where treatments are rationally selected to target the dominant underlying pathophysiology of a specific disease subtype.

6. Unanswered Questions and Future Directions

The rapid evolution of GLP-1 RAs from metabolic drugs to cardiovascular powerhouses has answered many questions but has also opened new avenues of inquiry. The field is poised for further discovery, with several critical unanswered questions guiding the next phase of research.

6.1. Definitive Localization and Function of the Cardiac GLP-1R

While scRNA-seq has pointed towards endothelial and endocardial cells as the primary sites of GLP-1R expression in the ventricles, the functional consequences of this localization are not fully understood [12]. What specific paracrine signals are released from these cells upon GLP-1R activation? How do these signals communicate with cardiomyocytes to modulate metabolism and function? Advanced techniques such as spatial transcriptomics and proteomics will be essential to map these cellular communication networks within the heart.

6.2. Disentangling Direct vs. Indirect Effects

A central challenge remains in quantifying the relative contributions of the various mechanisms to the overall cardiovascular benefit. How much of the MACE reduction is attributable to weight loss, versus direct anti-inflammatory effects, versus improved endothelial function? The SELECT trial demonstrated benefit in a non-diabetic population, and the HARMONY trial showed benefit with minimal weight loss, providing crucial clues that the effects are not solely dependent on glucose control or weight reduction [6]. However, designing studies to precisely parse out these intertwined pathways in humans remains a significant methodological challenge.

6.3. The Next Frontier: Dual and Tri-Agonists

The development of unimolecular multi-agonists represents the next therapeutic frontier. Dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonists, such as tirzepatide, have already demonstrated superior efficacy for weight loss and glycemic control compared to GLP-1 RAs alone [56]. The ongoing SURPASS-CVOT will provide definitive data on the cardiovascular profile of tirzepatide. Key questions include whether the addition of GIP agonism will alter the cardiovascular effects. For instance, will it have a different impact on heart failure phenotypes or provide even greater anti-atherosclerotic benefit? The physiology of these next-generation agents is a major area of active investigation.

6.4. Long-Term Effects in Broader Populations

With the expanding use of GLP-1 RAs for obesity management in younger, non-diabetic, and lower-risk populations, understanding their long-term cardiovascular effects and safety profile is paramount [59]. Will the benefits observed in high-risk secondary prevention trials translate to

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primary prevention over many decades of use? Monitoring the real-world impact of this widespread adoption will be crucial.

6.5. Elucidating the HFrEF Paradox

The neutral-to-negative findings in HFrEF warrant further investigation [11]. Is the adverse signal driven solely by the increase in heart rate, or are other mechanisms at play? Could there be specific subgroups of HFrEF patients, such as those with a significant co-existing inflammatory or metabolic component to their disease, who might still derive benefit? Resolving this paradox is essential for defining the precise boundaries of safe and effective use for this drug class in patients with heart failure.

7. Conclusions

The story of GLP-1 receptor agonists in cardiovascular medicine is one of remarkable and rapid transformation. In little more than a decade, they have evolved from being niche glucose-lowering therapies to indispensable tools for cardiovascular risk reduction, fundamentally altering the management of patients with cardiometabolic disease. The wealth of evidence from large-scale cardiovascular outcome trials is unequivocal: GLP-1 RAs significantly reduce the burden of atherosclerotic cardiovascular events. This review has synthesized the evidence suggesting that this clinical benefit is not a happy accident of metabolic improvement but is instead driven by a powerful and synergistic combination of indirect systemic effects and direct physiological actions on the vasculature, which collectively attenuate endothelial dysfunction, quell inflammation, and promote a more stable plaque phenotype.

The clinical implications of these findings are profound. GLP-1 RAs have established a new pillar of care for the secondary prevention of ASCVD in patients with T2D. With the landmark SELECT trial, this benefit has been extended to the vast and growing population of patients with obesity and established cardiovascular disease, independent of diabetes status. Furthermore, their proven efficacy in the STEP-HFpEF program has provided the first truly effective pharmacotherapy for the obesity-related phenotype of HFpEF, a condition for which treatment options were previously scarce and ineffective. This success highlights the critical importance of a phenotype-driven approach to heart failure management.

While much has been learned, the physiological narrative of GLP-1 RAs is still being written. The ongoing exploration of their precise molecular mechanisms, the resolution of controversies surrounding their direct cardiac effects, and the advent of next-generation multi-agonist therapies promise to further revolutionize the treatment of cardiometabolic disease [2]. The journey of GLP-1 RAs serves as a powerful testament to the value of investigating therapies beyond their primary endpoint, a path that has led to one of the most significant advances in cardiovascular medicine in recent history.

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Abbreviations

The following abbreviations are used in this manuscript:

ACC	Acetyl-CoA Carboxylase
AMPK	5′ Adenosine Monophosphate-activated Protein Kinase
ASCVD	Atherosclerotic Cardiovascular Disease
cAMP	Cyclic Adenosine Monophosphate
CVOT	Cardiovascular Outcome Trial
DPP-4	Dipeptidyl Peptidase-4
EAT	Epicardial Adipose Tissue
eNOS	Endothelial Nitric Oxide Synthase
ERK1/2	Extracellular Signal-regulated Kinase 1/2
GLP-1	Glucagon-Like Peptide-1
GLP-1R	Glucagon-Like Peptide-1 Receptor
GLP-1RA	Glucagon-Like Peptide-1 Receptor Agonist
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
ICAM-1	Intercellular Adhesion Molecule 1
IL-1β	Interleukin-1 Beta
IL-6	Interleukin-6
MACE	Major Adverse Cardiovascular Events
MCP-1	Monocyte Chemoattractant Protein-1
MI	Myocardial Infarction
MMP	Matrix Metalloproteinase
NF-κB	Nuclear Factor Kappa-light-chain-enhancer of Activated B cells
NO	Nitric Oxide
PI3K	Phosphoinositide 3-Kinase
PKA	Protein Kinase A
ROS	Reactive Oxygen Species
SGLT2i	Sodium-Glucose Cotransporter-2 Inhibitor
SMC	Smooth Muscle Cell
T2DM	Type 2 Diabetes Mellitus
TNF-α	Tumor Necrosis Factor-alpha
VCAM-1	Vascular Cell Adhesion Molecule 1
VSMC	Vascular Smooth Muscle Cell

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