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Review Article

Semaglutide in Cardiovascular Disease: Integrating Mechanisms with Evidence from Major Clinical Trials

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of global morbidity and mortality, with a growing contribution from cardiometabolic disorders such as type 2 diabetes mellitus and obesity. Traditional glucose-lowering therapies have primarily focused on glycaemic control without demonstrating consistent cardiovascular benefit, leading to a paradigm shift toward therapies that target both metabolic and cardiovascular risk. Semaglutide, a long-acting glucagon-like peptide-1 receptor agonist, has emerged as a promising agent with integrated effects on glycaemic regulation, body weight, vascular function, and systemic inflammation. This review synthesizes current evidence on the role of semaglutide in cardiovascular disease, integrating mechanistic insights with findings from major clinical trials. Semaglutide improves insulin secretion, suppresses glucagon release, delays gastric emptying, and promotes sustained weight reduction through central appetite regulation. Beyond metabolic effects, it enhances endothelial function, reduces oxidative stress, and exerts anti-inflammatory actions that contribute to stabilization of atherosclerotic processes. Large cardiovascular outcome trials, including SUSTAIN-6 and SELECT, demonstrate significant reductions in major adverse cardiovascular events in both diabetic and non-diabetic populations, highlighting benefits independent of glycaemic control.

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Additionally, emerging evidence suggests favourable effects in obesity-related heart failure and broader cardiometabolic risk profiles. Despite these benefits, challenges related to long-term outcomes, comparative effectiveness, and accessibility remain. Overall, semaglutide represents a shift toward integrated cardiometabolic therapeutics, acting across multiple pathophysiological pathways and offering potential as a disease-modifying agent in cardiovascular care.

INTRODUCTION:

Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality worldwide, contributing substantially to the global healthcare burden despite advances in pharmacological and interventional therapies [26–28]. The rising prevalence of cardiometabolic disorders, particularly type 2 diabetes mellitus (T2DM) and obesity, has further amplified cardiovascular risk. Individuals with T2DM have a 2- to 4-fold higher risk of major adverse cardiovascular events (MACE), while obesity significantly contributes to atherosclerosis, heart failure, and adverse cardiac remodelling [26,27,29].

Traditionally, glucose-lowering therapies primarily focused on glycaemic control without demonstrating long-term cardiovascular benefit, prompting a paradigm shift toward cardiovascular outcome trials (CVOTs) [29]. This shift led to the emergence of drug classes such as sodium–glucose cotransporter-2 (SGLT2) inhibitors, which have demonstrated significant cardiovascular and renal benefits and are now recommended as first-line therapy in heart failure management [20,36]. Similarly, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have gained prominence due to their dual metabolic and cardiovascular effects [17,18,22,23].

Semaglutide, a long-acting GLP-1 receptor agonist with enhanced albumin binding and prolonged half-life, represents a major advancement within this class. It has demonstrated superior efficacy in glycaemic control and weight reduction compared to earlier GLP-1 RAs, along with additional pleiotropic effects including improvement in endothelial function, lipid modulation, and blood pressure reduction [10,21,23,30].

Recent large-scale randomized clinical trials have expanded the clinical relevance of semaglutide by demonstrating significant reductions in cardiovascular events not only in patients with T2DM but also in overweight and obese individuals without diabetes [1–3]. These findings challenge the traditional view of weight-loss therapies as purely metabolic interventions and highlight the evolving role of semaglutide in cardiovascular risk reduction.

Unlike earlier reviews that primarily focused on glycaemic outcomes or individual trials, this review integrates mechanistic insights, biomarker modulation, and evidence from major clinical trials, including emerging SELECT-era data, into a unified cardiometabolic framework. By synthesizing evidence across diabetic and non-diabetic populations, this article positions semaglutide as a disease-modifying therapy acting across the continuum of obesity, atherosclerosis, and cardiovascular disease[1-4] .Top of FormBottom of Form

2. DEFINING SEMAGLUTIDE ROLE IN CARDIOVASCULAR DISEASE:

Cardiovascular disease (CVD) encompasses a spectrum of interconnected conditions, including atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and obesity-related cardiac disorders [26,27,29]. These conditions are closely linked through shared pathophysiological mechanisms such as insulin resistance, systemic inflammation, endothelial dysfunction, and adverse cardiac remodelling, creating a continuous cardiometabolic disease spectrum [26,27,31,32]. Obesity and type 2 diabetes mellitus significantly accelerate this progression, increasing the risk of ischemic heart disease, myocardial infarction, and heart failure.

In this context, therapeutic strategies targeting multiple components of this interconnected pathway are essential. Semaglutide, a glucagon-like peptide-1 receptor agonist, has emerged as a promising agent with benefits extending beyond glycaemic control. Its effects on weight reduction, metabolic regulation, vascular function, and inflammation position it as a potential disease-modifying therapy across the cardiometabolic continuum, supporting its expanding role in cardiovascular risk reduction [1,4,17,31]

3. EPIDEMIOLOGICAL STATUS OF CARDIOVASCULAR DISEASE:

Cardiovascular diseases remain the leading cause of mortality globally, accounting for approximately 17.9 million deaths annually [14,15]. The burden is disproportionately increasing in low- and middle-income countries, driven by rapid urbanization, sedentary lifestyles, and dietary changes. Type 2 diabetes mellitus and obesity are major contributors, with individuals with diabetes exhibiting a 2–4-fold increased risk of major adverse cardiovascular events. Globally, over 537 million adults live with diabetes, while obesity affects more than 650 million individuals, highlighting the scale of the cardiometabolic crisis.

In India, the coexistence of diabetes and obesity further amplifies cardiovascular risk, contributing to a significant rise in morbidity and mortality. Despite advances in therapeutic strategies, substantial residual cardiovascular risk persists, underscoring the need for integrated interventions targeting multiple metabolic and vascular pathways [14,15]. In the Indian context, the burden of cardiometabolic disease is particularly pronounced due to genetic predisposition, early onset of type 2 diabetes mellitus, and a high prevalence of central obesity [39,40]. Individuals of South Asian origin tend to develop cardiovascular risk factors at lower body mass index levels compared to Western populations [38]. Despite the growing clinical need, the use of advanced therapies such as semaglutide is often limited by cost, accessibility, and healthcare disparities [33]. Therefore, while semaglutide demonstrates substantial cardiometabolic benefits, its real-world impact in India will depend on improved affordability, wider availability, and integration into context-specific treatment strategies.

4. MECHANISTIC BASIS OF CARDIOMETABOLIC BENEFITS:

Semaglutide exerts cardiometabolic benefits through integrated metabolic, vascular, renal, and inflammatory mechanisms mediated via GLP-1 receptor activation [22,23,30]. These multi-organ effects converge to reduce cardiovascular risk across diverse patient populations [23,30,31]. The integrated mechanistic pathways are illustrated in Figure 1.

4.0 Pharmacological Profile of Semaglutide:

Semaglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist structurally modified to enhance stability and prolong systemic exposure [22,23]. It shares high homology with native GLP-1 but incorporates specific amino acid substitutions that confer resistance to degradation by dipeptidyl peptidase-4 and promote strong albumin binding, resulting in an extended half-life of approximately one week [22,23]. These pharmacokinetic properties enable once-weekly dosing and sustained receptor activation. Semaglutide is available in both subcutaneous and oral formulations and exhibits high receptor affinity, translating into potent and prolonged metabolic effects [22,23,24]

4.1 Pancreatic and Glycaemic Effects: Semaglutide exerts its primary action through activation of the glucagon-like peptide-1 (GLP-1) receptor on pancreatic β-cells, enhancing glucose-dependent insulin secretion via cyclic adenosine monophosphate signaling [22,23]. This allows effective glycaemic control with a low risk of hypoglycaemia compared to conventional therapies [13,22].

In parallel, semaglutide suppresses inappropriate glucagon secretion, thereby reducing hepatic glucose output and improving both fasting and post-prandial glycaemia [22,23]. GLP-1 receptor activation also supports β-cell function by reducing oxidative stress and apoptosis, contributing to sustained glycaemic control [22,23].

Across the SUSTAIN and PIONEER programs, semaglutide consistently demonstrated significant reductions in HbA1c across diverse populations [4,10,11,12]. However, cardiovascular benefits extend beyond glycaemic control, involving additional metabolic and systemic mechanisms [1,4,17].

4.2 Central and Gastrointestinal Mechanisms of Weight Reduction: Semaglutide induces clinically meaningful weight loss through central and gastrointestinal pathways [22,23]. It delays gastric emptying, leading to early satiety and reduced caloric intake [22].

At the central level, activation of GLP-1 receptors in appetite-regulating regions reduces hunger and food intake, resulting in sustained weight reduction [23].

Clinical trials across the SUSTAIN, PIONEER, and STEP programs demonstrate dose-dependent weight

loss, ranging from 4–6 kg in type 2 diabetes to 10–15% body weight reduction in obesity (6-10) .

This weight reduction improves insulin sensitivity, blood pressure, lipid profile, and systemic inflammation, thereby contributing to cardiovascular risk reduction [17,18,31]. The SELECT trial further established that these effects translate into significant reductions in major adverse cardiovascular events even in individuals without diabetes [2].

4.3 Vascular, Endothelial, and Anti-Inflammatory Effects: Semaglutide improves endothelial function by enhancing nitric oxide availability and reducing oxidative stress, thereby restoring vascular homeostasis [30,31].

It also exerts anti-inflammatory effects by reducing circulating inflammatory markers such as C-reactive protein and pro-inflammatory cytokines, contributing to stabilization of atherosclerotic plaques and attenuation of disease progression [31,32].

These vascular and anti-inflammatory actions, partly independent of glycaemic control, play a key role in reducing cardiovascular risk and may explain the early separation of event curves observed in clinical trials [1,2,17,18].

4.4 Renal and Systemic Cardiometabolic Effects: Semaglutide promotes natriuresis through renal GLP-1 receptor activation, leading to modest reductions in intravascular volume and blood pressure [30,31]. These hemodynamic effects occur early and are only partially explained by weight loss [17,18,31].

In addition, semaglutide improves lipid metabolism, including reductions in low-density lipoprotein cholesterol and triglycerides, contributing to a more favourable cardiometabolic profile [17,18,31].

Clinical evidence indicates that these combined effects on blood pressure, lipids, and metabolic parameters contribute cumulatively to cardiovascular risk reduction across populations [1,2,17,18].

Integrated Biological Mediators of Cardiovascular Protection

Beyond direct receptor-mediated effects, semaglutide modulates key biological mediators that link metabolic improvement to cardiovascular outcomes. Sustained weight loss, reduced inflammatory burden, improved blood pressure, and favourable lipid changes collectively act as intermediate drivers of cardiovascular protection [17,18,30,31].

Emerging evidence also suggests beneficial effects on myocardial structure and function, including improvements in ventricular remodelling and diastolic function, particularly in obesity-related heart failure [31,32].

These integrated effects provide a mechanistic bridge between molecular actions and the reduction in major adverse cardiovascular events observed in large outcome trials [1,2,17,18].

Thus, semaglutide acts across multiple levels of the cardiometabolic continuum, targeting metabolic dysregulation, vascular dysfunction, inflammation, and hemodynamic stress simultaneously. This multi-layered mechanism provides a strong biological basis for the consistent and sustained cardiovascular benefits observed in clinical trials [1,2,4,5].

5. CLINICAL CARDIOVASCULAR EVIDENCE: The mechanistic framework described above is substantiated by large cardiovascular outcome trials demonstrating that semaglutide translates cardiometabolic effects into meaningful reductions in hard clinical endpoints [1,2,4,5,17,18]. Evidence from both diabetic and non-diabetic populations consistently supports its role as a cardiovascular risk–modifying therapy.

5.1 Cardiovascular Outcome Trials in Type 2 Diabetes (SUSTAIN-6)

The SUSTAIN-6 trial, a randomized, double-blind, placebo-controlled cardiovascular outcomes study, evaluated once-weekly subcutaneous semaglutide in patients with type 2 diabetes at high cardiovascular risk [1,4]. The study population included individuals with established cardiovascular disease, chronic kidney disease, or multiple risk factors, reflecting a real-world high-risk cohort [1,4,29].

Semaglutide significantly reduced the primary composite endpoint of major adverse cardiovascular events (MACE)—cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke—by **26% compared with placebo** over a median follow-up of approximately two years [1]. Notably, a pronounced reduction in

non-fatal stroke was observed, suggesting potential preferential effects on cerebrovascular and atherosclerotic pathways [30,31,32].

Cardiovascular benefits emerged early and were sustained throughout follow-up, supporting mechanisms beyond glycaemic control [1,4,5]. These findings established semaglutide as a glucose-lowering agent with proven cardiovascular benefit and influenced guideline-directed therapy in high-risk diabetic populations [20,37,38,39].

5.2 Cardiovascular Outcomes in Obesity Without Diabetes (SELECT)

The SELECT trial extended these findings to a non-diabetic population, evaluating semaglutide 2.4 mg in overweight or obese individuals with established cardiovascular disease [2,6,7,8,9]. This large randomized trial demonstrated a **20% relative risk reduction in MACE**, confirming that cardiovascular benefits are independent of glycaemic control [2].

Importantly, SELECT represents the first large-scale evidence that pharmacological weight reduction alone can reduce hard cardiovascular outcomes [2,6,7,8,9]. These findings redefine obesity as a modifiable cardiovascular risk factor and position semaglutide as a disease-modifying therapy in cardiometabolic medicine [2,17,18,31].

A comparative overview of these landmark trials is presented in **Table 1**

5.3 Critical Appraisal

Despite robust evidence from randomized controlled trials, certain limitations remain. Follow-up durations, although sufficient to demonstrate cardiovascular benefit, may not fully capture long-term effects on disease progression and mortality. Additionally, direct comparative data with other GLP-1 receptor agonists and cardioprotective therapies are limited. These gaps highlight the need for further investigation to better define the long-term and comparative effectiveness of semaglutide across diverse cardiovascular phenotypes.

Another important consideration is the relative contribution of weight loss versus direct pleiotropic effects in mediating cardiovascular benefits, which remains incompletely understood. Furthermore, real-world data on long-term adherence, safety, and effectiveness across diverse populations are still evolving. Cost and accessibility also represent important challenges, particularly in resource-limited settings, potentially affecting widespread implementation.

These considerations highlight the need for longer-duration studies, comparative trials, and real-world evidence to better define the role of semaglutide across the cardiovascular disease continuum.

6. Translational Impact Across Cardiovascular Phenotypes

Beyond trial endpoints, semaglutide demonstrates clinically meaningful benefits across major cardiovascular disease phenotypes by targeting shared cardiometabolic pathways [1,2,17,18,31]. The integration of mechanistic and clinical evidence is illustrated in **Figure 2**, which outlines the continuum from molecular effects to phenotype-level outcomes.

Atherosclerotic Cardiovascular Disease (ASCVD)

The strongest evidence supports semaglutide in ASCVD, where it significantly reduces MACE, particularly non-fatal stroke [1,4,17,18]. These benefits are linked to improvements in endothelial function, reduction in vascular inflammation, and stabilization of atherosclerotic plaques [30,31,32]. This positions semaglutide as an effective strategy for secondary prevention in high-risk populations.

Heart Failure

Semaglutide demonstrates phenotype-specific benefits in heart failure, with the most consistent evidence observed in obesity-related heart failure with preserved ejection fraction (HFpEF) [31,32]. Clinical trials report improvements in symptoms, exercise capacity, and quality of life, supported by favourable effects on cardiac structure and diastolic function [31,32].

In contrast, evidence in heart failure with reduced ejection fraction (HFrEF) remains limited, showing neutral to modest effects without safety concerns [31]. These findings highlight the importance of metabolic and obesity-driven mechanisms in determining therapeutic response.

Obesity-Related Cardiovascular Risk

Semaglutide substantially reduces obesity-driven cardiovascular risk through sustained weight loss of approximately 10–15%, accompanied by improvements in blood pressure, lipid profiles, insulin resistance, and systemic inflammation [6,7,8,9,17,18,31,40]. These upstream effects contribute to downstream reductions in cardiovascular events, as demonstrated in the SELECT trial [2].

Emerging evidence also suggests favourable effects on myocardial remodelling and vascular stiffness, reinforcing its role as a therapy targeting the root drivers of cardiometabolic disease [31,32,33,34].

A comprehensive summary of phenotype-specific clinical effects, mechanisms, and strength of evidence is provided in **Table 2**.

7.Safety and Tolerability Profile:

Despite its broad cardiometabolic benefits, evaluation of safety remains essential for long-term clinical application. Semaglutide is generally well tolerated, with a favourable risk–benefit profile demonstrated across large randomized trials and real-world analyses [1,2,6,10,17,18].

7.1 Common Adverse Effects

Gastrointestinal adverse events are the most frequently reported side effects of semaglutide, particularly during treatment initiation and dose escalation [6,10]. The most common include nausea, vomiting, and diarrhoea, which are typically mild to moderate in severity and transient in nature [6,10].

These effects are mechanistically related to delayed gastric emptying and central appetite regulation mediated by GLP-1 receptor activation [22,23]. While reduced appetite contributes to weight loss, it may temporarily affect oral intake during early treatment phases [22,23].

Importantly, most gastrointestinal symptoms are self-limiting and decline over time with continued therapy. Gradual dose escalation and appropriate patient counselling significantly improve tolerability and minimize treatment discontinuation [6,10]. Long-term data indicate that these effects do not compromise sustained cardiometabolic benefits [6,10].

7.2 Rare but Clinically Relevant Risks

Rare adverse events have been reported but remain infrequent in large trials and pooled analyses [17,18].

Acute pancreatitis has been observed rarely; however, current evidence does not demonstrate a consistent increase in risk compared with placebo [17,18]. Caution is advised in patients with a prior history of pancreatitis, although the absolute risk remains low relative to clinical benefits [17,18].

Gallbladder-related events, including cholelithiasis and cholecystitis, have been reported, particularly in the context of rapid weight loss [6,7]. These are likely secondary to alterations in bile composition and gallbladder motility rather than direct drug toxicity and are generally manageable [6,7].

A modest increase in resting heart rate has also been observed, likely related to autonomic modulation. Importantly, this has not been associated with increased arrhythmic risk or adverse cardiovascular outcomes [1,2].

Overall, these rare events do not significantly alter the favourable safety profile of semaglutide in high-risk populations [1,2,17,18].

7.3 Cardiovascular Safety

Semaglutide has demonstrated a robust cardiovascular safety profile across large outcome trials in both diabetic and non-diabetic populations [1,2]. It is not associated with increased risk of major adverse cardiovascular events, arrhythmias, sudden cardiac death, or heart failure exacerbation [1,2].

Cardiac safety analyses show no clinically meaningful effects on cardiac conduction or arrhythmia risk [1,2]. Although a small increase in resting heart rate is observed, it has not translated into increased cardiovascular mortality or adverse outcomes [1,2].

Importantly, no signal of worsening heart failure or adverse ventricular remodelling has been identified, including in patients with obesity-related heart failure with preserved ejection fraction (HFpEF) [2,31]. Evidence from SUSTAIN, PIONEER, and SELECT consistently supports cardiovascular safety across formulations and patient populations [1,2].

8.COMPARISON WITH OTHER GLP-1 RECEPTOR AGONISTS

Following the demonstration of cardiovascular efficacy and safety, it is important to position semaglutide within the broader GLP-1 receptor agonist (GLP-1RA) class. While cardiovascular benefit is observed across multiple agents, differences exist in the magnitude of metabolic and clinical effects [10,17].

Head-to-head evidence from the SUSTAIN-7 trial demonstrated that semaglutide provides greater reductions in HbA1c and body weight compared with dulaglutide [10]. Similar superiority over liraglutide has been reported in comparative analyses [10,17]. These effects are attributed to its higher receptor potency, prolonged half-life, and enhanced central appetite regulation [10,17].

Cardiovascular outcome trials have shown benefit with semaglutide (SUSTAIN-6), liraglutide (LEADER), and dulaglutide (REWIND) [1,13]. However, pooled analyses suggest that semaglutide demonstrates among the greatest reductions in major adverse cardiovascular events, with a notable effect on non-fatal stroke [17,18]. Consistent benefit across varying baseline risk has also been observed [4,5].

Semaglutide further offers practical advantages, including once-weekly dosing and an oral formulation, alongside the most pronounced weight reduction within the class [6,7,8,9,10].

A structured comparison of key agents, including differences in formulation, cardiovascular outcomes, metabolic effects, and clinical applicability, is summarized in **Table 3.**

Overall, while GLP-1 receptor agonists exhibit a class effect for cardiovascular benefit, semaglutide demonstrates greater magnitude and consistency across glycaemic, weight, and cardiovascular outcomes, supporting its preferential role in patients with obesity, type 2 diabetes, and established cardiovascular disease [1,2,17,18]. However, the absence of direct head-to-head cardiovascular outcome trials warrants cautious interpretation of comparative superiority.

9. FUTURE DIRECTIONS

With established cardiovascular benefits across both diabetic and non-diabetic populations, future research on semaglutide is increasingly focused on expanding its role across the cardiovascular disease continuum.

One key area of investigation is heart failure. While semaglutide has demonstrated clinically meaningful benefits in obesity-related heart failure with preserved ejection fraction (HFpEF), its role in heart failure with reduced ejection fraction (HFrEF) remains incompletely defined. Ongoing studies are expected to clarify whether semaglutide exerts true disease-modifying effects or primarily improves outcomes through metabolic optimization.

Another emerging direction is its potential role in post –myocardial infarction remodelling. Given its anti-inflammatory, endothelial, and metabolic effects, early initiation following acute coronary syndromes may attenuate adverse ventricular remodelling and reduce progression to heart failure, representing a shift toward early cardiometabolic intervention.

In the context of primary prevention, future trials are likely to evaluate semaglutide in individuals with obesity and cardiometabolic risk factors prior to the onset of overt cardiovascular disease. Such strategies may redefine prevention paradigms by targeting upstream drivers of atherosclerosis, heart failure, and diabetes.

Combination therapy represents another promising avenue. The integration of semaglutide with SGLT2 inhibitors, which exert complementary effects on hemodynamic and renal pathways, may offer additive or synergistic cardiovascular protection. Ongoing studies will help define optimal sequencing and combination strategies.

A critical unresolved question is whether the cardiovascular benefits of semaglutide are predominantly weight-mediated or partially independent through direct vascular and anti-inflammatory mechanisms. Addressing this distinction will be essential in determining whether semaglutide should be conceptualized primarily as an anti-obesity therapy with cardiovascular benefit or as a direct cardiometabolic disease-modifying agent.

Key future research priorities include:

- Defining phenotype-specific benefits across heart failure subtypes
- Evaluating long-term outcomes and mortality impact
- Expanding evidence in primary prevention populations
- Establishing optimal combination and sequencing strategies
- Clarifying mechanistic pathways underlying cardiovascular benefit.

CONCLUSION

Semaglutide represents a paradigm shift in cardiometabolic therapeutics, extending beyond glycaemic control to target fundamental drivers of cardiovascular disease. Through integrated effects on body weight, systemic inflammation, blood pressure, lipid metabolism, and myocardial remodelling, it provides comprehensive cardiovascular protection across a broad spectrum of clinical phenotypes, including atherosclerotic cardiovascular disease, obesity-related heart failure, and high-risk cardiometabolic populations.

Robust evidence from large-scale cardiovascular outcome trials confirms its safety and its ability to significantly reduce major adverse cardiovascular events in both diabetic and non-diabetic individuals. Comparative data further position semaglutide among the most effective GLP-1 receptor agonists in terms of metabolic efficacy and cardiovascular risk reduction.

Importantly, semaglutide challenges traditional therapeutic boundaries by bridging metabolic and cardiovascular disease management. Rather than acting solely as a glucose-lowering or weight-reducing agent, it emerges as a therapy that modifies upstream pathophysiological processes driving cardiovascular risk.

As ongoing research continues to explore its role in heart failure, post–myocardial infarction remodelling, primary prevention, and combination cardioprotective strategies, semaglutide is poised to play a central role in integrated cardiometabolic care.

Ultimately, the evolving evidence raises a pivotal question: whether semaglutide should be viewed as a metabolic therapy with cardiovascular benefits, or as a true cardiovascular disease–modifying agent acting across the entire cardiometabolic continuum.

The answer to this question will shape future therapeutic strategies and redefine the boundaries of cardiovascular prevention and treatment.

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AUTHOR CONTRIBUTIONS:

Supervision: Dr. Akif Ahamad Baig; Conceptualization, manuscript drafting, and editing: Yenduri Harikrishna Vignesh and Muhammed Sumayya Qatun; Literature review and data collection: Kothapalli Akanksha; Final approval of the manuscript: All authors**.**

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Table-1: Major Cardiovascular Outcome Trials Evaluating Semaglutide

Feature	SUSTAIN-6	SELECT
Population	Type 2 diabetes with high CV risk	Overweight/obese without diabetes + established CVD
Sample size	Approx 3,300 patients	Approx 17,500 patients
Semaglutide dose	0.5 mg / 1.0 mg weekly (SC)	2.4 mg weekly (SC)
Comparator	Placebo + standard care	Placebo + standard care
Median follow-up	Approx 2 years	Approx 5 years
Primary endpoint	MACE (CV death, non-fatal MI, non-fatal stroke)	MACE (CV death, non-fatal MI, non-fatal stroke)
Relative Risk Reduction	26% reduction in MACE	20% reduction in MACE
Key notable finding	Significant reduction in non-fatal stroke	First obesity drug to reduce hard CV outcomes

Table-2: Clinical Cardiovascular Effects of Semaglutide Across Major Phenotypes

Clinical Phenotype	Key Evidence Base	Primary Clinical Effects	Dominant Mechanisms	Strength of Evidence
Atherosclerotic Cardiovascular Disease (ASCVD)	Cardiovascular outcome trials in high-risk T2DM populations	↓ Major adverse cardiovascular events (MACE) ↓ non-fatal stroke Early event curve separation	↓ Plaque inflammation ↑ Endothelial nitric oxide bioavailability ↓ Oxidative stress Plaque stabilization	Strong outcome-based evidence
Heart Failure with Preserved	Randomized HFpEF trials in	↑ Symptom improvement ↑ 6-minute walk distance	↓ Visceral adiposity ↓ Inflammation ↑ Diastolic	Growing randomized evidence

EF (HFpEF)	obesity-related HF	↑ Quality of life ↓ LV mass	function Mild natriuresis	(strongest in obesity-related HFpEF)
Heart Failure with Reduced EF (HFrEF)	Subgroup and observational data	Neutral to mildly beneficial outcomes No signal of harm	Indirect metabolic benefit Weight loss Anti-inflammatory effects	Limited evidence; further trials needed
Obesity-Related Cardiovascular Risk	Obesity and SELECT trial data	↓ MACE (non-diabetic population) ↓ Blood pressure ↓ Insulin resistance	Sustained 10–15% weight loss ↓ Systemic inflammation ↓ Arterial stiffness Improved metabolic flexibility	Landmark evidence (first weight-loss CV outcome benefit)

Table-3: Comparison of Semaglutide with Other GLP-1 Receptor Agonists: Evidence from Major Trials and Key Studies

Aspect	Semaglutide	Liraglutide	Dulaglutide	Key Supporting Evidence
Formulation	Subcutaneous (weekly); Oral (daily)	Subcutaneous (daily)	Subcutaneous (weekly)	PIONEER-6 design and guidance documents
Primary CV Outcome Trial	SUSTAIN-6, SELECT, PIONEER-6	LEADER	REWIND	Verma et al. comparative analysis
Population Studied	T2DM with high CV risk; Obesity without diabetes; PAD subgroups	T2DM with established CV disease	T2DM with CV risk factors	LEADER vs SUSTAIN-6 PAD analysis
MACE Reduction	Significant reduction (26% in SUSTAIN-6; 20% in SELECT)	Significant reduction	Significant reduction	SUSTAIN-6, SELECT; LEADER; REWIND
Non-fatal Stroke Reduction	Significant reduction	Neutral	Neutral	SUSTAIN-6 vs LEADER comparison
Weight Loss Efficacy	**Highest (10–15%)**	Moderate	Modest	STEP program outcomes
HbA1c Reduc-	**Greatest reduction**	Moderate	Moderate	Practical and pooled

tion				analyses
Peripheral Artery Disease (PAD)	Strong CV benefit in PAD sub-group	CV benefit, less pronounced	Limited PAD-specific data	Verma et al.
Cardiometabolic Risk Reduction	Strong improvement in weight, BP, lipids	Moderate	Moderate	STEP, RESET1 pro-tocol
Oral Option Available	**Yes**	No	No	PIONEER-6 design; clinical guidance
Heart Failure Evidence	Benefit in HFpEF; neutral in HFrEF	Neutral	Neutral	Bibliometric & HF trend analyses
Cost-effective-ness in CVD	**Cost-effective** in obesity + CVD	Not established	Not established	Economic evaluation study
Research Volume & Trend	Highest growth & impact	High	Moderate	Bibliometric analyses