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NOVEL WEIGHT-LOSS MEDICATIONS AND THEIR CARDIOVASCULAR BENEFITS: A COMPREHENSIVE REVIEW

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ABSTRACT:

The global obesity pandemic necessitates effective pharmacological interventions. This review examines the cardiovascular benefits of novel weight-loss medications, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual/triple incretin receptor agonists. Through systematic analysis of recent clinical trials and mechanistic studies, we demonstrate that agents like semaglutide and tirzepatide not only promote significant weight reduction (15-24%) but also confer substantial cardiovascular protection. Key benefits include reduced major adverse cardiovascular events (20% risk reduction), improved blood pressure control (4-7 mmHg systolic reduction), enhanced lipid profiles, and decreased heart failure hospitalization rates. These effects stem from both weight-dependent and weight-independent mechanisms, including direct cardioprotective actions, improved endothelial function, and reduced systemic inflammation. While gastrointestinal side effects remain common, the risk-benefit profile

favors use in high-cardiovascular-risk obese populations.

Intraduction

The global obesity pandemic represents one of the most pressing public health challenges of the 21st century. Characterized not merely as a condition of excess weight but as a complex, chronic, and relapsing disease, obesity is a primary and modifiable risk factor for cardiovascular diseases (CVD), the leading cause of mortality worldwide. For decades, the therapeutic arsenal against obesity has been limited, often yielding modest efficacy or burdened by safety concerns that restricted their widespread use, particularly in patients at the highest cardiovascular risk. While lifestyle modifications remain the cornerstone of management, their long-term success is often hindered by the powerful physiological and metabolic adaptations that sustain excess weight. This persistent clinical gap has driven an urgent need for effective, safe, and sustainable pharmacological interventions. The last decade has witnessed a paradigm shift with the emergence of novel agents targeting the incretin system—most notably, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and the newer dual and triple incretin receptor agonists (e.g., glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 and glucagon/GIP/GLP-1 receptor agonists). These medications have moved beyond the primary goal of weight reduction, demonstrating profound and clinically significant benefits for cardiovascular health. Landmark cardiovascular outcomes trials (CVOTs), initially designed to confirm safety, have instead revealed that agents like semaglutide and tirzepatide can significantly reduce major adverse cardiovascular events (MACE) in high-risk populations. This suggests a multifaceted mode of action involving both weight-dependent mechanisms (e.g., reduced visceral adiposity, lowered blood pressure, improved lipid metabolism) and weight-independent, direct cardioprotective effects (e.g., enhanced endothelial function, reduced inflammation, and direct myocardial effects). This comprehensive review synthesizes the current evidence on the cardiovascular benefits of these novel weight-loss pharmacotherapies. We will systematically analyze data from pivotal clinical trials and mechanistic studies to elucidate the extent of cardioprotection offered, explore the underlying physiological pathways, and discuss the implications for clinical practice in managing obesity as a critical strategy for cardiovascular risk reduction. By doing so, we aim to provide a clear overview of how these

groundbreaking therapies are reshaping the therapeutic landscape at the intersection of cardiology and metabolic medicine.

Literature Review

1. Introduction and Evolution of Obesity Pharmacotherapy

Obesity, recognized as a chronic, relapsing, progressive disease by the American Medical Association in 2013 and the World Obesity Federation, represents a complex neuroendocrine-metabolic disorder characterized by dysregulated energy homeostasis. The historical trajectory of pharmacotherapy reveals successive waves of agents developed to modulate appetite, energy expenditure, or nutrient absorption, each constrained by limitations in efficacy, safety, or mechanistic scope.

1.1 The Cardiovascular Safety Imperative The withdrawal of fenfluramine-phentermine and sibutramine (2010) due to cardiovascular and valvular toxicity established a rigorous safety paradigm. This culminated in the 2008 FDA guidance requiring large-scale cardiovascular outcomes trials (CVOTs) for all new antidiabetic and anti-obesity therapies. These CVOTs, initially conceived as safety probes, inadvertently became discovery platforms for unexpected cardioprotection, catalyzing a paradigm shift in therapeutic development.

2. Mechanistic Foundations: Incretin Physiology and Beyond

2.1 The GLP-1 Receptor System Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L-cells postprandially. Beyond its classic glucoregulatory actions (glucose-dependent insulin secretion, glucagon suppression), its receptors are widely distributed in the brain (nucleus tractus solitarius, arcuate nucleus), heart, vasculature, and immune cells. This broad expression underpins its pleiotropic effects. Long-acting GLP-1 receptor agonists (RAs) induce weight loss primarily via central anorexigenic signaling through pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons and inhibition of neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons in the hypothalamus.

2.2 Dual and Triple Hormone Receptor Agonism: A Polypharmacology Approach The evolution from single to multi-agonist therapies represents a strategic response to the redundant pathways maintaining energy homeostasis. Tirzepatide (GIP/GLP-1 RA) exploits complementary signaling: GIP receptor agonism may potentiate GLP-1's central anorectic effects via cross-talk in the ventral tegmental area and nucleus accumbens, while also enhancing adipocyte insulin sensitivity and lipid storage in a potentially metabolically

beneficial manner. Retatrutide (GLP-1/GIP/glucagon RA) adds a thermogenic component via glucagon receptor-mediated hepatic energy expenditure, mitochondrial uncoupling, and lipolysis.

Methodology

This comprehensive review was conducted in accordance with established principles for narrative and systematic reviews in cardiovascular and metabolic medicine. The primary objective was to synthesize evidence on the cardiovascular benefits of novel weight-loss medications, with a focus on glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as semaglutide and dual/triple incretin receptor agonists including tirzepatide (GLP-1/GIP RA) and emerging agents like retatrutide (GLP-1/GIP/glucagon RA).

Search Strategy - A systematic literature search was performed using major electronic databases, including PubMed/MEDLINE, Embase, Cochrane Library, and ClinicalTrials.gov, from inception through December 2025. Search terms included combinations of keywords and MeSH terms such as: "GLP-1 receptor agonist*", "semaglutide", "tirzepatide", "retatrutide", "incretin mimetic*", "obesity pharmacotherapy", "weight loss medication*", "cardiovascular outcomes", "major adverse cardiovascular events", "MACE", "heart failure", "blood pressure", "lipid profile", "inflammation", "endothelial function", combined with "clinical trial*", "randomized controlled trial", "CVOT", "cardiovascular outcome* trial", and "obesity" OR "overweight". Reference lists of key publications, including landmark trials and prior meta-analyses, were hand-searched for additional relevant studies. Grey literature sources, such as conference abstracts from major cardiology and endocrinology meetings (e.g., American Heart Association, European Society of Cardiology, American Diabetes Association), were also reviewed.

Inclusion and Exclusion Criteria - Studies were included if they met the following criteria: (1) randomized controlled trials (RCTs), including phase 2/3 cardiovascular outcomes trials (CVOTs), weight-management trials with cardiovascular endpoints or substudies, or mechanistic studies; (2) evaluation of GLP-1 RAs (e.g., semaglutide) or dual/triple incretin agonists (e.g., tirzepatide, retatrutide) in adults with obesity/overweight, with or without type 2 diabetes; (3) reporting of cardiovascular outcomes (e.g., major adverse cardiovascular events [MACE: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke], heart failure hospitalizations, blood pressure changes, lipid profiles, inflammatory markers) or relevant mechanistic data (e.g., endothelial function, direct cardioprotective effects); and (4) published in English. Exclusion criteria

encompassed non-human studies, observational data without RCT-level evidence for primary outcomes, trials of older anti-obesity agents without incretin-based mechanisms, and studies lacking cardiovascular or cardiometabolic endpoints.

Priority was given to large-scale CVOTs such as SELECT (semaglutide 2.4 mg weekly in patients with overweight/obesity and established cardiovascular disease without diabetes), SURPASS-CVOT (tirzepatide vs. dulaglutide in type 2 diabetes with atherosclerotic cardiovascular disease), and phase 2/3 trials for tirzepatide (e.g., SURMOUNT series) and retatrutide. Smaller mechanistic studies and meta-analyses were incorporated to elucidate weight-independent effects.

Data Extraction and Synthesis Data were extracted independently by reviewers using standardized forms, including trial design, population characteristics (e.g., age, BMI, baseline cardiovascular risk, diabetes status), intervention details (dose, duration, titration), comparator (placebo or active control), primary and secondary cardiovascular endpoints, key safety outcomes (e.g., gastrointestinal adverse events), and mechanistic insights. Risk of bias was assessed qualitatively using criteria from the Cochrane Collaboration tool, focusing on randomization, blinding, attrition, and reporting bias. Given the heterogeneity in trial populations (with vs. without diabetes) and endpoints, a narrative synthesis was employed, supplemented by quantitative summaries (e.g., relative risk reductions, hazard ratios, mean changes in blood pressure/lipids) from pivotal trials where appropriate. No formal meta-analysis was performed due to differences in comparators, follow-up durations, and patient phenotypes.

Quality Assessment and Evidence Grading Evidence quality was evaluated based on trial design (e.g., event-driven, double-blind, multicenter), statistical power, adherence to regulatory CVOT standards (e.g., FDA 2008 guidance), and consistency across studies. Landmark trials like SELECT and SURPASS-CVOT were considered high-quality due to their large sample sizes (>13,000–17,000 participants), long-term follow-up (median ~3–4 years), and adjudication of cardiovascular events by independent committees. This methodology ensured a balanced, evidence-based synthesis of the cardiovascular benefits of these novel agents, highlighting both established clinical outcomes and emerging mechanistic understanding to inform clinical practice in high-risk obese populations.

Results

The reviewed evidence from landmark cardiovascular outcomes trials (CVOTs), phase 2/3 weight-management studies, and supporting mechanistic investigations demonstrates

robust cardiovascular benefits associated with novel incretin-based weight-loss medications, including GLP-1 receptor agonists (e.g., semaglutide) and dual/triple receptor agonists (e.g., tirzepatide and retatrutide). These agents achieve substantial weight reduction while conferring protection against major adverse cardiovascular events (MACE), improvements in cardiometabolic risk factors, and potential direct cardioprotective effects beyond weight loss.

Cardiovascular Outcomes in Key Trials In the SELECT trial (semaglutide 2.4 mg weekly vs. placebo in 17,604 patients with overweight/obesity and established cardiovascular disease but without diabetes), semaglutide significantly reduced the primary composite endpoint of MACE (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Over a mean follow-up of approximately 40 months, MACE occurred in 6.5% of the semaglutide group versus 8.0% in the placebo group, corresponding to a 20% relative risk reduction (hazard ratio [HR] 0.80; 95% CI 0.72–0.90; P<0.001). Benefits were consistent across baseline adiposity levels, with prespecified analyses indicating that only about one-third of the MACE reduction was mediated by changes in waist circumference or body weight, supporting substantial weight-independent mechanisms. All-cause mortality showed a directional benefit (HR 0.81; 95% CI 0.71–0.93), and heart failure composite events were reduced (HR 0.82; 95% CI 0.71–0.96). For tirzepatide (dual GLP-1/GIP receptor agonist), the SURPASS-CVOT trial (tirzepatide vs. dulaglutide in patients with type 2 diabetes and atherosclerotic cardiovascular disease) confirmed noninferiority for the primary MACE endpoint over a median 4-year follow-up, with events in 12.2% versus 13.1% (HR 0.92; 95% CI 0.83–1.01; P=0.003 for noninferiority). While superiority was not achieved (P=0.09), numerical reductions were observed in cardiovascular death (5.6% vs. 6.2%; HR 0.89) and other components. Real-world evidence and meta-analyses of SURPASS program data further support tirzepatide's favorable cardiovascular profile, with reduced risks of acute coronary syndrome, heart failure, stroke, MACE, and all-cause mortality compared to other GLP-1 receptor agonists or controls in patients with type 2 diabetes. Emerging triple incretin agonists like retatrutide (GLP-1/GIP/glucagon) have shown promising cardiometabolic improvements in phase 2 and initial phase 3 trials (e.g., TRIUMPH-4), including dose-dependent weight loss up to 24–28.7% at higher doses (12 mg) over 48–68 weeks, alongside reductions in systolic blood pressure (up to 14 mmHg), non-HDL cholesterol, triglycerides, and high-sensitivity C-reactive protein. While dedicated large-scale CVOTs for retatrutide are ongoing, these early findings suggest enhanced

potential for cardiovascular risk mitigation through additive effects on energy expenditure, lipolysis, and inflammation.

Effects on Cardiometabolic Risk Factors Across trials, these agents consistently improved blood pressure (systolic reductions of 4–14 mmHg), lipid profiles (e.g., lowered LDL cholesterol and triglycerides), and inflammatory markers. Semaglutide and tirzepatide reduced heart failure hospitalizations and events, particularly in populations with preserved ejection fraction. Weight-independent benefits, including enhanced endothelial function, reduced systemic inflammation, and direct myocardial/vascular effects via incretin receptor expression in cardiac and vascular tissues, contribute to the observed cardioprotection.

Safety Considerations Gastrointestinal adverse events (nausea, vomiting, diarrhea) were the most common, dose-related, and generally mild to moderate, often mitigated by gradual titration. Discontinuation rates due to adverse events were higher with active treatment (e.g., 16.6% vs. 8.2% in SELECT), but no major increases in serious cardiovascular or other safety signals were identified. In summary, semaglutide provides definitive evidence of cardiovascular event reduction in high-risk obese populations without diabetes, while tirzepatide demonstrates at least equivalent cardioprotection to established GLP-1 receptor agonists in diabetes populations with established disease. Emerging agents like retatrutide offer superior weight loss with favorable cardiometabolic profiles, positioning incretin-based therapies as transformative options for reducing cardiometabolic risk in obesity management. These findings support prioritizing such agents in high-cardiovascular-risk obese individuals, pending ongoing trial data for broader indications.

Discussion

The novel incretin-based weight-loss medications, particularly GLP-1 receptor agonists (GLP-1 RAs) such as semaglutide and dual/triple incretin agonists like tirzepatide and retatrutide, represent a transformative advancement in obesity management and cardiovascular risk reduction. The evidence synthesized in this review highlights their capacity to deliver substantial weight loss alongside meaningful cardioprotection, reshaping treatment paradigms for high-risk obese populations. The SELECT trial provides the strongest level of evidence for semaglutide's cardiovascular superiority in patients with overweight or obesity and established cardiovascular disease (CVD) but without diabetes. With a 20% relative reduction in major adverse cardiovascular events (MACE; HR 0.80, 95% CI 0.72–0.90), semaglutide demonstrates clear event-driven benefit over placebo, including directional improvements in cardiovascular death and reductions in heart failure

events. Recent prespecified analyses from SELECT further underscore that these effects are largely independent of baseline adiposity and the magnitude of weight loss achieved. Benefits persist across weight categories, with only modest mediation by changes in body weight or waist circumference (approximately one-third of MACE reduction attributable to adiposity measures), reinforcing the presence of direct, weight-independent cardioprotective mechanisms. These include improved endothelial function, reduced systemic inflammation, anti-atherogenic effects, and potential direct actions on cardiac and vascular tissues via GLP-1 receptor expression.

Tirzepatide, as a dual GLP-1/GIP receptor agonist, extends this paradigm in populations with type 2 diabetes and atherosclerotic CVD. The SURPASS-CVOT trial, with results published in late 2025, confirmed noninferiority to dulaglutide (a proven cardioprotective GLP-1 RA) for the primary MACE endpoint over a median 4-year follow-up (HR 0.92, 95% CI 0.83–1.01; P=0.003 for noninferiority), with numerical reductions in cardiovascular death, myocardial infarction, and stroke, alongside a nominally lower all-cause mortality. While superiority was not statistically achieved (P=0.09), tirzepatide exhibited greater metabolic improvements, including superior HbA1c reduction, weight loss, blood pressure lowering, and favorable lipid changes compared to dulaglutide. These findings position tirzepatide as at least equivalent in cardiovascular protection to established GLP-1 RAs, with added advantages in cardiometabolic risk factor modification that may translate to broader long-term benefits. Emerging triple agonists like retatrutide (GLP-1/GIP/glucagon) show even greater weight loss potential (up to 24–28% in phase 2/3 trials) and promising improvements in cardiometabolic parameters, including substantial systolic blood pressure reductions (up to 14 mmHg), lipid profile enhancements, and decreased inflammatory markers. However, dedicated large-scale cardiovascular outcomes trials (e.g., TRIUMPH-Outcomes) remain ongoing, with results not yet available as of early 2026. Early data suggest favorable safety and enhanced energy expenditure via glucagon-mediated mechanisms, but definitive event reduction evidence awaits completion of these event-driven studies.

The observed cardiovascular benefits likely arise from a combination of weight-dependent pathways (reduced visceral fat, improved insulin sensitivity, lower blood pressure, and better lipid metabolism) and weight-independent effects (direct anti-inflammatory actions, enhanced nitric oxide bioavailability, improved myocardial energetics, and vascular protection). These multifaceted mechanisms explain why event

reductions often exceed what would be expected from weight loss alone and support the use of these agents in high-cardiovascular-risk obese individuals, even when modest weight reduction is achieved. Clinically, these therapies shift obesity from a cosmetic concern to a treatable cardiometabolic disease modifiable with pharmacotherapy. In high-risk populations, incretin mimetics should be prioritized alongside lifestyle interventions, particularly given their favorable risk-benefit profile despite common gastrointestinal side effects (typically manageable with titration). Ongoing trials and real-world evidence will further clarify comparative efficacy (e.g., tirzepatide vs. semaglutide head-to-head), long-term durability, and applications in primary prevention or additional comorbidities like heart failure with preserved ejection fraction. In conclusion, semaglutide establishes definitive cardiovascular event reduction in non-diabetic obese patients with CVD, tirzepatide confirms comparable or potentially enhanced protection in diabetic high-risk groups, and triple agonists like retatrutide herald even greater potential. These agents are poised to become cornerstone therapies at the cardiology-metabolic interface, offering holistic risk reduction beyond traditional approaches and underscoring the profound interplay between obesity pharmacotherapy and cardiovascular health.

Conclusion

The novel incretin-based pharmacotherapies reviewed here—primarily GLP-1 receptor agonists (e.g., semaglutide) and dual/triple incretin receptor agonists (e.g., tirzepatide and retatrutide)—have fundamentally altered the management of obesity and its associated cardiometabolic complications. By achieving substantial, sustained weight reduction (often 15–25% or more) while demonstrating clear cardiovascular event reduction and improvements in multiple risk factors, these agents address obesity not as an isolated condition but as a central driver of cardiovascular disease (CVD). Semaglutide provides the most definitive evidence of direct cardiovascular event reduction in high-risk populations without diabetes, as demonstrated by the SELECT trial. With a consistent 20% relative risk reduction in major adverse cardiovascular events (MACE; HR 0.80, 95% CI 0.72–0.90) over extended follow-up (median ~40 months), including benefits in cardiovascular death, myocardial infarction, stroke, and heart failure events, semaglutide's effects persist across adiposity levels. Recent prespecified analyses confirm that only a portion of this protection is mediated by weight loss, with substantial contributions from weight-independent mechanisms such as reduced inflammation, enhanced endothelial function, improved lipid

metabolism, blood pressure lowering, and direct cardioprotective actions on cardiac and vascular tissues.

Tirzepatide extends these benefits into populations with type 2 diabetes and established atherosclerotic CVD. The SURPASS-CVOT trial (published December 2025) established noninferiority to dulaglutide—a GLP-1 RA with proven cardioprotection—for the primary MACE endpoint over a median 4-year follow-up (HR 0.92, 95% CI 0.83–1.01; P=0.003 for noninferiority), with numerical advantages in cardiovascular death, myocardial infarction, stroke, and all-cause mortality (HR ~0.84–0.89 in key components). Tirzepatide also delivered superior metabolic outcomes, including greater reductions in HbA1c, body weight (~6–7% more than dulaglutide), blood pressure, triglycerides, and renal risk markers, positioning it as a highly effective option with at least equivalent—and potentially enhanced—cardiovascular protection in high-risk diabetic patients. Emerging triple incretin agonists like retatrutide offer even greater weight loss potential (up to 24–28% in phase 2/3 trials) and favorable cardiometabolic profiles, including pronounced improvements in blood pressure, lipids, inflammation, and energy expenditure through glucagon-mediated mechanisms. While dedicated large-scale cardiovascular outcomes trials (e.g., TRIUMPH-Outcomes) are ongoing and recruiting, with primary completion expected in the coming years, early data support a promising trajectory for broader risk reduction.

These therapies highlight the interconnected pathophysiology of obesity, type 2 diabetes, and CVD, where incretin mimetics exert pleiotropic effects beyond glycemic control and weight loss. Benefits arise from both weight-dependent pathways (reduced visceral adiposity, insulin sensitization) and direct, weight-independent actions (anti-inflammatory, vasodilatory, anti-atherogenic, and myocardial protective effects via receptor expression in relevant tissues). In clinical practice, these agents should be prioritized in obese individuals at high cardiovascular risk—whether with or without diabetes—alongside lifestyle interventions. Their favorable risk-benefit profile, despite manageable gastrointestinal side effects, supports broader adoption to prevent MACE, heart failure hospitalizations, and related complications. Future research, including head-to-head comparisons, long-term durability studies, primary prevention trials, and applications in additional comorbidities (e.g., heart failure with preserved ejection fraction, chronic kidney disease), will further refine their role. Ultimately, these groundbreaking medications represent a paradigm shift, transforming obesity pharmacotherapy into a cornerstone strategy for cardiovascular risk reduction. By targeting the root metabolic drivers of CVD, incretin-based therapies offer

holistic, disease-modifying benefits that promise to significantly improve outcomes and reduce the global burden of cardiometabolic disease in the years ahead.

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