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Editorial

The Obesity-Heart Disease Connection: Is Weight Loss the New Cardiovascular Prevention?

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Obesity affects more than one billion people worldwide and is a major upstream driver of cardiovascular disease (CVD). Dysfunctional visceral adipose tissue acts as an active endocrine organ, promoting insulin resistance, lipotoxicity, systemic inflammation, and neurohumoral activation. These pathways link excess adiposity to a cardiometabolic continuum that includes type 2 diabetes, hypertension, heart failure with preserved ejection fraction (HFpEF), atrial fibrillation, and atherosclerotic cardiovascular disease. Recent cardiovascular outcome trials have moved obesity treatment from a lifestyle goal to an evidence-based strategy for cardiovascular risk reduction. In SELECT, semaglutide 2.4 mg reduced major adverse cardiovascular events by 20% in adults with overweight or obesity and established CVD without diabetes, leading to FDA approval for this indication in 2024. In obesity-related HFpEF, semaglutide improved symptoms and functional capacity in STEP-HFpEF, and tirzepatide reduced the composite of worsening heart failure events and cardiovascular death by 38% in SUMMIT. These benefits likely reflect both weight loss and weight-independent effects on myocardial metabolism, inflammation, natriuresis, and epicardial fat. In this Perspective, we review the mechanisms linking obesity to CVD, summarize key incretin-based outcome trials, and argue that sustained intentional weight loss, whether achieved through lifestyle intervention, pharmacotherapy, or metabolic surgery, should be recognized as a core component of cardiovascular prevention, with success measured by the prevention or resolution of obesity-related CVD rather than by weight change alone. Cost, inconsistent insurance coverage, and weight regain after discontinuation remain substantial barriers, and ongoing primary prevention trials such as SURMOUNT-MMO will deter-



KEYWORDS: Obesity, overweight, cardiovascular risk, primary prevention, cardiovascular disease, CVD

Introduction

Obesity is a major driver of heart disease, making effective obesity treatment and sustained weight loss important strategies for cardiovascular disease

prevention. More than one billion people worldwide live with obesity, and approximately 42% of U.S. adults met body mass index (BMI) criteria for obe

sity in 2017 and 2018.^{1,2,3} Recent frameworks from the American Association of Clinical Endocrinology (AACE) and the Lancet Diabetes & Endocrinology Commission move beyond BMI to emphasize excess adiposity and its clinical consequences.^{4,5} Excess fat mass and adipose tissue dysfunction promote metabolic, inflammatory, and hemodynamic disturbances that contribute to the development and progression of cardiovascular disease.⁶ This connection supports treating obesity itself alongside hypertension, dyslipidemia, and other cardiovascular risk factors, addressing an underlying cause rather than its consequences alone. Weight loss should therefore be recognized as a major component of cardiovascular prevention, not simply a lifestyle goal, with success measured by the prevention, improvement, or resolution of obesity-related cardiovascular disease rather than changes in body weight alone.

The Cardiometabolic Cascade: From Adipocyte to Atherosclerosis

The progression from excess adiposity to cardiovascular disease follows a series of interconnected pathophysiologic changes. Visceral adipose tissue is an active endocrine organ. It secretes pro-inflammatory cytokines, drives insulin resistance through adipokine dysregulation and excessive free fatty acid liberation, and promotes ectopic lipid deposition in the liver, skeletal muscle, and myocardium.⁶ Lipotoxicity occurs when fatty acid delivery exceeds tissues' capacity, leading to accumulation of toxic lipid species that can impair insulin signaling and promote oxidative and endoplasmic reticulum stress.⁷ The resulting cellular injury and myocardial dysfunction link abnormal adipose tissue function to cardiovascular disease. Over time, declining beta-cell function can lead to compensatory hyperinsulinemia insufficient to maintain normal glycemia leading to type 2 diabetes mellitus (T2D) in individuals with obesity. In a US study, adjusted relative risks of a T2D diagnosis were 2.5 for class I obesity (BMI 30–34.9 kg/m²), 3.6 for class II obesity (BMI 35–39.9 kg/m²), and 5.1 for class III (severe) obesity (BMI ≥40 kg/m²), compared with normal

BMI (18.5–24.9 kg/m²).⁶

Obesity also promotes hypertension through multiple, partially overlapping mechanisms. Activation of the renin-angiotensin-aldosterone system, heightened sympathetic outflow, increased renal sodium avidity, and compression of the kidneys by excess perirenal and renal sinus fat collectively raise systemic vascular resistance and blood pressure.⁸ Together, these mechanisms make excess adiposity, particularly visceral adiposity, an important contributor to hypertension. These processes contribute to a substantial proportion of the hypertension burden that is attributable to excess adiposity.⁸

Heart failure with preserved ejection fraction (HFpEF) represents perhaps the most mechanistically rich expression of obesity-driven cardiac disease. Pericardial and epicardial fat accumulation impairs ventricular compliance, elevates filling pressures, and promotes chronic low-grade myocardial inflammation.⁹ Experimental evidence suggests that myocardial lipotoxicity promotes oxidative stress and cardiomyocyte apoptosis through pathways including PINK1/Prdx2 dysregulation, amplifying inflammation and fibrotic remodeling that increase myocardial stiffness and impair diastolic function.¹⁰ The resulting HFpEF with obesity phenotype is characterized by volume overload, concentric remodeling, metabolic inflexibility, and systemic inflammation. It frequently overlaps with hypertension, is pathophysiologically distinct from lean HFpEF, and contributes substantially to the growing HFpEF burden in developed nations.⁹

Atrial fibrillation (AF) links obesity-related structural remodeling to arrhythmic disease. Obesity promotes AF through several convergent mechanisms: atrial enlargement secondary to elevated filling pressures, epicardial fat infiltration into the atrial myocardium, autonomic dysregulation, and a profibrotic environment driven by adipokines and inflammatory mediators.¹¹ Epicardial adipose tissue further exerts direct paracrine effects on the atrial myocardium through secretion of adipokines, including Activin A, promoting interstitial fibrosis and facilitating the electrophysiologic substrate for AF.¹² Landmark data from the Framingham Heart Study demonstrated a 4% higher AF

risk associated with each 1-kg/m² increase in BMI after adjustment for cardiovascular risk factors.¹¹ A subsequent meta-analysis found an approximately 49% increased risk of developing AF in individuals with obesity compared with those without obesity, with risk escalating in parallel with BMI.¹³ AF augments stroke risk and accelerates the progression of underlying heart failure.¹⁴ Together, these effects complete a vicious cycle that is increasingly difficult to interrupt once established.

These metabolic and inflammatory pathways link obesity to atherosclerotic cardiovascular disease (ASCVD) [Figure 1], providing a biological rationale for weight loss as a strategy for cardiovascular prevention. Obesity-associated dyslipidemia, characterized by hypertriglyceridemia, elevated small dense LDL particles, and reduced HDL cholesterol, compounds endothelial dysfunction driven by oxidative stress and systemic inflammation.⁶ Together, these processes create a permissive environment for accelerated plaque formation.

Premature myocardial infarction, unstable angina, and ischemic stroke disproportionately burden individuals with obesity, often occurring a decade earlier than in lean counterparts.⁶

GLP-1 and GIP Receptor Agonists: Interrupting the Cascade at Its Source

Long recognized for its role in postprandial insulin secretion and glucose homeostasis, the incretin system has emerged as an important therapeutic target in cardiovascular prevention. Foundational evidence came from the LEADER and SUSTAIN-6 trials, which demonstrated reductions in major adverse cardiovascular events with liraglutide and semaglutide, respectively, in patients with T2D at high cardiovascular risk.^{15,16} These trials established GLP-1 receptor agonism as a cardiovascular-protective class, though whether benefit extended to populations without diabetes remained unanswered.

OBESITY: THE UPSTREAM DRIVER OF CARDIOVASCULAR DISEASE

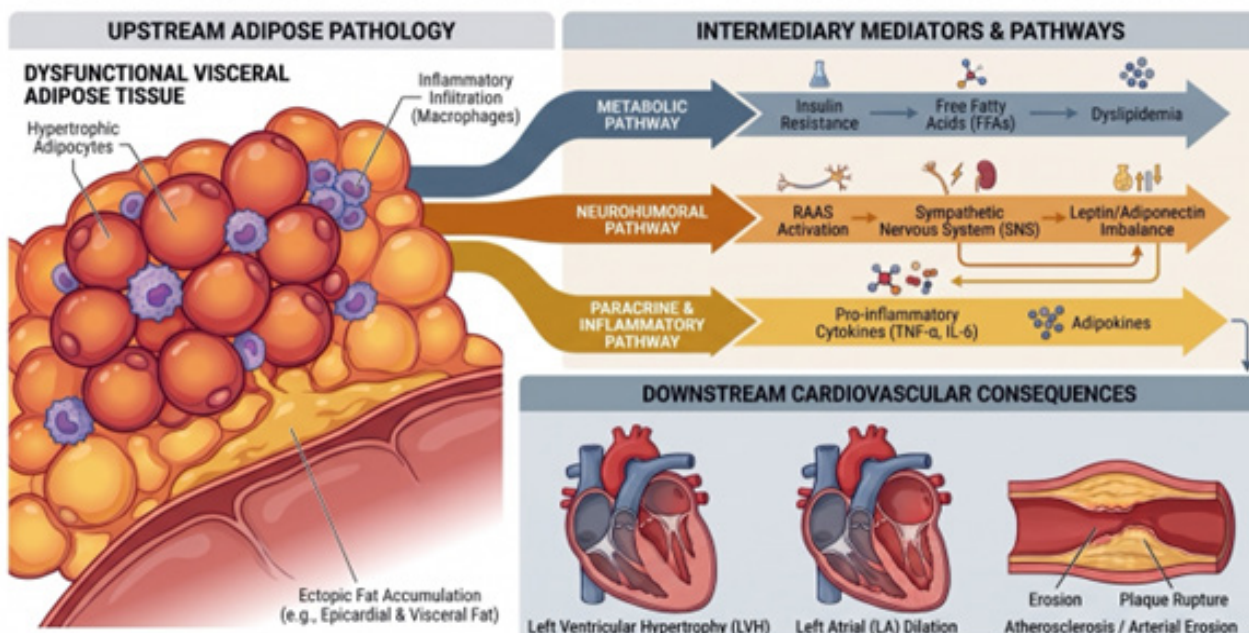


FIGURE 1. Obesity as an upstream driver of cardiovascular disease. Visceral adipose dysfunction tissue activates metabolic, neurohumoral, and inflammatory pathways that promote left ventricular hypertrophy, left atrial dilation, and atherosclerosis.

The SELECT trial was the inflection point. In over 17,600 adults with overweight or obesity with established cardiovascular disease but without T2D, weekly subcutaneous semaglutide 2.4 mg reduced the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke by 20% relative to placebo.¹⁷ This benefit emerged in a population without diabetes, establishing that GLP-1 receptor agonism confers cardiovascular protection through mechanisms beyond glycemic control. A subsequent mediation analysis of SELECT suggests that semaglutide's cardiovascular benefits may extend beyond weight loss and improvements in measured cardiovascular risk factors.¹⁸ Although additional protective mechanisms remain uncertain, these findings support viewing semaglutide as a cardiovascular risk reduction therapy rather than solely a weight loss medication. SURPASS-CVOT compared the dual GIP/GLP-1 receptor agonist tirzepatide with dulaglutide, an agent with established cardiovascular benefit, in more than 13,000 patients with T2D and ASCVD. Tirzepatide was noninferior to dulaglutide for the composite of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.92; 95.3% CI, 0.83–1.01; $P=0.003$ for noninferiority), although superiority was not established ($P=0.09$).¹⁹

The STEP-HFpEF trial demonstrated that semaglutide 2.4 mg improved Kansas City Cardiomyopathy Questionnaire scores, six-minute walk distance, and body weight in patients with obesity-related HFpEF.²⁰ These effects correlated with the magnitude of weight reduction and persisted regardless of baseline diabetes status.²⁰ The SUMMIT trial subsequently demonstrated similar benefits with tirzepatide, the dual GLP-1/GIP receptor agonist.²¹ Tirzepatide produced a 38% reduction in the composite of worsening heart failure events and cardiovascular death compared to placebo, with improvements in functional capacity and quality of life.²¹ Collectively, these trials establish obesity-targeted pharmacotherapy as an active disease-modifying strategy in heart failure, not merely an adjunct to standard care [Table 1].

Beyond caloric restriction, GLP-1 and GIP receptor agonists modulate cardiac energy utilization, attenuate myocardial lipotoxicity, promote natriuresis,

and reduce epicardial fat volume.²² They also suppress inflammatory signaling pathways implicated in endothelial dysfunction and atrial remodeling.²² Cardiovascular risk reduction likely reflects both weight loss-mediated benefits and weight-independent pleiotropic effects, although their relative contributions remain under investigation.

Reconceptualizing Weight Loss as Cardiovascular Prevention

The traditional architecture of cardiovascular prevention was built around managing downstream risk factors individually: lipid-lowering, antihypertensive, and glucose-lowering therapies. Sustained intentional weight loss, achieved through lifestyle interventions, pharmacotherapy, or metabolic surgery, broadens this approach by reducing excess adiposity and improving multiple cardiometabolic risk factors simultaneously. GLP-1 and dual GLP-1/GIP receptor agonists represent one approach within this broader therapeutic strategy. They complement behavioral modification, bariatric surgery, and targeted management of individual comorbidities, acting on upstream adiposity-driven pathophysiology rather than only its downstream manifestations. Integrating weight management into cardiovascular prevention offers an opportunity to address the underlying adiposity-related disease alongside established treatment of its complications.⁶

This shift carries implications for clinical practice. The 2025 ACC Concise Clinical Guidance supports incorporating obesity pharmacotherapy into cardiovascular care and provides a framework for selecting treatment according to the patient's clinical profile. It emphasizes that pharmacotherapy need not await failure of lifestyle interventions, which should continue alongside medication.²³ SELECT has already translated into regulatory action: in March 2024, the FDA approved semaglutide to reduce major adverse cardiovascular events in adults with established cardiovascular disease and overweight or obesity, without requiring a diagnosis of diabetes.²⁴ Ongoing trials in high-risk primary prevention cohorts, including the SURMOUNT-MMO trial of tirzepatide, will test whether

TABLE 1. Key GLP-1 and GIP/GLP-1 Receptor Agonist Cardiovascular Outcome Trials (Published and Ongoing)

TRIAL (YEAR)	AGENT	POPULATION	PRIMARY OUTCOME	KEY RESULT	STATUS
LEADER (2016)	Liraglutide	T2D + ASCVD	3-P MACE	HR 0.87; p=0.01 superiority	Published
SUSTAIN-6 (2016)	Semaglutide SC 0.5/1 mg	T2D + high CV risk	3-P MACE	HR 0.74; p<0.001 NI	Published
SELECT (2023)	Semaglutide SC 2.4 mg	Overweight/obesity + ASCVD, no T2D	3-P MACE	HR 0.80; 20% RRR; p<0.001	Published
STEP-HFpEF (2023)	Semaglutide SC 2.4 mg	HFpEF + obesity	KCCQ + 6MWT	KCCQ +7.8 pts; 6MWT +20 m	Published
SUMMIT (2024)	Tirzepatide	HFpEF + obesity	Worsening HF/CV death	HR 0.62; 38% reduction; p=0.026	Published
SURPASS-CVOT (2025)	Tirzepatide vs dulaglutide	T2D + ASCVD	3-P MACE	HR 0.92; p=0.003 NI; superiority NS	Published
SURMOUNT-MMO (ongoing)	Tirzepatide	Obesity, no T2D — primary prevention	CV death/HF/MI/stroke	Ongoing	Ongoing

T2D, type 2 diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; MACE, major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke); NI, noninferiority; NS, not significant; RRR, relative risk reduction; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; 6MWT, six-minute walk test; SC, subcutaneous; HR, hazard ratio.

these benefits extend further upstream.²⁵ Practical barriers remain real. The annualized cost of semaglutide 2.4 mg in the United States exceeds \$15,000.²⁶ Insurance coverage is inconsistent, and weight regain upon discontinuation is well-documented.^{26,27} These limitations do not diminish the scientific signal. They demand, however, that any prevention strategy also address the structural determinants of access and adherence.

Conclusion

The interconnected pathways linking obesity to insulin resistance, T2D, hypertension, HFpEF, AF, and ASCVD form a cardiometabolic continuum that offers multiple opportunities for prevention and treatment. Clinical trials of semaglutide and tirzepatide demonstrate that obesity pharmacotherapy can reduce major cardiovascular events or worsening heart failure in selected populations, supporting the integration of obesity treatment

into cardiovascular prevention and care. Effective obesity treatment and sustained weight loss are major components of cardiovascular prevention. The question before the cardiovascular community is no longer whether treating obesity matters for the heart, but how quickly clinical practice, guidelines, and health systems will make obesity treatment a core component of cardiovascular prevention.

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