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Obesity As A Preponderant Cardiovascular Risk – Evidence For Clinical Practice: A Systematic Review

Maria Elizabeth Ferreira MD, Maurício De Melo Mattos MD,
Cristina Guimarães Pondè MD

Internal Medicine Department , Estacio De Sá University (IDOMED), Rio De Janeiro, Brazil ; Hospital Of Civil Servants In The State Of Rio De Janeiro, Brazil ; 3 Neurovida Clinic, Rio De Janeiro, Brazil .

Abstract
Objective: *To synthesize current evidence on the association between obesity and cardiovascular diseases (CVD), covering pathophysiology, clinical implications, and modern management strategies.*
Methodology: *A systematic review of scientific literature conducted across platforms such as PubMed, Cochrane, and international society guidelines (ESC, ACC, SBC), including studies in English, Spanish, and Portuguese.*
Results: *Obesity is a multifactorial chronic disease acting through a neuro-hormonal-inflammatory axis. Visceral and epicardial adipose tissue function as active endocrine organs, secreting pro-inflammatory cytokines (IL-6, TNFα) that promote atherogenesis and cardiac remodeling.*
Clinical Manifestations: *Obesity is causally linked to heart failure (specifically HFpEF), atrial fibrillation, coronary artery disease, and premature cardiovascular aging.*
Diagnosis: *Body Mass Index (BMI) alone is insufficient for risk stratification. The inclusion of anthropometric criteria, such as waist circumference and the assessment of intermuscular adipose tissue (IMAT), is recommended.*
Management: *Beyond lifestyle interventions, a new pharmacological era (GLP-1 and GIP agonists) has demonstrated a direct reduction in major adverse cardiovascular events (MACE), as evidenced by the SELECT and SUMMIT trials. Bariatric surgery remains the most effective option for sustained weight loss in severe cases.*
Conclusion: *Obesity must transition from being viewed merely as a comorbidity to being treated as a direct and modifiable therapeutic target in cardiological practice. A proactive and multidisciplinary management approach is essential to mitigate the global burden of cardiovascular disease.*
Keywords: *obesity; cardiovascular diseases; chronic inflammation; visceral adiposity; incretin therapies*

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I. Introduction: Obesity As A Chronic Disease And Causative Factor Of Cardiovascular Disease

Obesity has reached epidemic proportions globally and is formally recognized as a chronic disease by the World Health Organization (WHO) and the European and North American Commissions [1,2] . According to the American Obesity Society (ASO), obesity is a multifactorial chronic disease, recognized throughout life, through long-term positive energy imbalance, with the development of excess adiposity, leading to structural changes, physiological disorders, and functional modifications [1.] Obesity increases the risk of developing other chronic diseases (hypertension, coronary artery disease, dyslipidemia, diabetes mellitus, non-alcoholic fatty liver disease, atrial fibrillation, aortic stenosis, stroke, pulmonary embolism), in addition to being associated with premature mortality. Obesity is distinguished by various phenotypes, clinical presentations, and responses to treatment (similar to other chronic diseases) [2,3] .

This condition is causally linked to adverse health outcomes and reduced life expectancy. Alarmingly, most obesity-related deaths—approximately two-thirds—are attributable to cardiovascular disease (CVD), positioning excess weight as one of the most significant modifiable risk factors of our time [4,5] .

Recent epidemiological data reinforce the urgency of the problem. In 2021, it is estimated that 22.5% of adults in member countries of the European Society of Cardiology (ESC) were obese, a prevalence that has more than doubled in the last four decades. Globally, it is estimated that more than one billion people live with obesity, a public health crisis that overburdens health systems and compromises the quality of life of millions [3,5].

To guide effective prevention and treatment strategies, it is imperative to understand the complex mechanisms that link obesity to cardiovascular disease. The aim of this article is a systematic review, synthesizing current evidence on this association, from pathophysiology to clinical implications and management strategies, with the goal of informing clinical practice. If current trends persist, the decline observed in recent decades in deaths from Coronary Artery Disease (CAD) may stabilize, accompanied by an increase in other cardiovascular disorders, such as Heart Failure (HF) and Cardiomyopathy [5,6,7] .

II. Methodology

In this review, searches were conducted on the following scientific literature platforms: PubMed ; Cochrane; Lilacs ; BVS; European Society of Cardiology (ESC); American College of Cardiology (ACC); American Society of Endocrinology and Diabetes; Brazilian Society of Obesity; Harvard University Library; Web of Science. The descriptors Booleans candidates The search terms were : "obesity AND cardiovascular diseases"; obesity AND inflammation; obesity AND prevalent risk factors; cardio-reno-metabolic AND obesity; obesity medicine; visceral obesity AND chronic inflammation AND systemic repercussions; obesity AND cardiac remodeling AND failure; obesity AND comorbidities. The languages chosen were English, Spanish, and Portuguese. The selected articles included systematic reviews, guidelines , consensus statements, position papers , meta-analyses, and integrative reviews.

III. Classification Of Obesity

According to the WHO and other Endocrinology, Metabolism and Obesity Societies, obesity is classified according to the Body Mass Index (BMI) as follows (Table 1):

Table 1. Obesity Classification for adults ≥ 18 years old

25-29.9	Overweight
30-34.9	Mild obesity (I)
35-39.9	Moderate obesity (II)
40-49.9	Severe obesity (III)
≥ 50	Extreme obesity

Source: Brazilian and American Obesity Societies, 2025

New definition of Body Mass Index (BMI)

Currently, BMI alone is not sufficient to confirm obesity.7 In addition to BMI, confirmation must be made using anthropometric criteria, such as abdominal circumference (> 102 cm in men and > 88 cm in women), waist-to-hip ratio (≥ 0.85 in women and ≥ 0.90 in men). There are also other criteria, such as body fat percentage and bioimpedance, which are considered the gold standard, but are still very expensive.7,8 Therefore, for the diagnosis of obesity, the following should be considered:

BMI + 01 Anthropometric Criterion

OR

02 Anthropometric Criteria

However, if the BMI is > 40, excess adiposity can be diagnosed without further confirmation.

IV. Obesity As A Causal Factor In Cardiovascular Diseases

Obesity is a modifiable and predominant cardiovascular risk factor [7,9], showing a causal link with several chronic diseases, as shown in Table 1.

Table 1. Obesity as a modifiable and predominant cardiovascular risk factor and its causal relationship with major chronic diseases.

Cardiovascular Manifestation	Association/Causality	Important Findings
Coronary Artery Disease/Atherosclerosis	Causal Factor	Excessive adiposity accelerates atherosclerosis (2/3 of patients are overweight/obese)
Heart Failure	Causal Factor	Obesity as an independent risk factor. Each unit of BMI is associated with a 5% increase in risk in men and 7% in women. Strong association with HFpEF.
Arterial Hypertension (HTN)	Causal Factor	Adiposity as a causal risk factor in HTN
Atrial Fibrillation (AF)	Causal Factor	Obese people have a 50% risk.
Aortic Valve Stenosis (SA)	Observed association/uncertain causality	Increased BMI and abdominal obesity are associated with ischemic stroke.
Stroke (CVA)	Observed association/uncertain causality	Observational studies show an association, however randomized (Mendelian) studies have not shown a significant causal factor for all causes of ischemic stroke, suggesting caution in interpretation.
Pulmonary Embolism (PE)	Causal Factor	Adiposity may be a causal risk factor in PE.

V. Pathophysiology: Mechanisms Of Impact Of Obesity On The Cardiovascular System

Understanding the pathophysiology of obesity-related cardiovascular disease is of strategic importance for clinical practice.9 The association is complex and transcends traditional mediators such as hypertension, dyslipidemia, and diabetes.[10] It involves a multifactorial interaction of hemodynamic, metabolic, inflammatory and neurohormonal mechanisms that, together, promote structural and functional changes in the heart and blood vessels.

Visceral Obesity, Chronic Inflammation, and Systemic Repercussions

Visceral obesity (abdominal fat) is the **most metabolically active** fat depot and carries the greatest burden of metabolically unhealthy obesity ("apple-shaped" or "male-type" phenotype), increasing cardiometabolic risk [11,12] .

Hemodynamic and Structural Cardiac Changes

Excess weight imposes a direct hemodynamic overload on the cardiovascular system. Obesity leads to an increase in total blood volume and, consequently, cardiac output to meet the greater metabolic demand of adipose tissue. Over time, this chronic volume overload results in adverse cardiac structural adaptations.

The consequences include the development of eccentric left ventricular hypertrophy (LVH), left atrial dilation, and diastolic dysfunction, which can occur even in the absence of hypertension. In more advanced cases, there is an accumulation of fat within the myocardium itself—a condition known as "obesity cardiomyopathy" or "*adipositas cordis* " — can lead to cellular dysfunction, conduction defects, and ultimately, heart failure [11-13.]

The Central Role of Adipose Tissue: Inflammation, Lipotoxicity , and Paracrine Effects

It is crucial to differentiate adipose tissue deposits. Subcutaneous fat is considered metabolically less active compared to visceral (abdominal) fat, the accumulation of which is strongly associated with cardiometabolic risk. Visceral fat functions as an active endocrine organ, secreting a variety of pro-inflammatory cytokines (such as interleukin-6 and tumor necrosis factor alpha) and adipokines , which establish a state of chronic low-grade inflammation. The validation of inflammation as a causal mechanism in atherosclerosis, as demonstrated in studies such as CANTOS, solidifies the importance of this process [13,14] .

Brazilian and international guidelines from 2025 (such as those from the SBC and the ESC Consensus) focus on what we call the neuro-hormonal-inflammatory axis [15] .

Adipose tissue, especially visceral adipose tissue, acts as an immune organ, driving low-grade systemic inflammation through the secretion of bioactive cytokines (adipokines) such as TNFα and IL-6. IL-6 released by adipose tissue stimulates the production of C-Reactive Protein (CRP) in the liver. Elevated levels of high-sensitivity CRP (hsCRP) are associated with increased CV risk [8,14] . The chronic inflammatory state directly contributes to the pathogenesis of atherosclerosis. Epicardial fat (EFT) is a particular form of visceral fat deposited around the heart and subepicardial coronary arteries. EFT is a good substitute for visceral obesity. It provides free fatty acids and is a source of local production of inflammatory mediators, contributing to coronary atherogenesis , regardless of BMI or diabetes. EFT is metabolically and physiologically important. This paracrine interaction is facilitated by proximity to adjacent coronary arteries (outside-to-inside signaling), in which TAE provides free fatty acids and produces inflammatory cytokines that contribute to said coronary atherogenesis , regardless of BMI or diabetes [13-15] .

In cardiac remodeling, TAE can also mediate deleterious effects of obesity and inflammation in the myocardium, being associated with arrhythmias (such as atrial fibrillation). In intermuscular adiposity (IMAT): Fat infiltration in skeletal muscle (IMAT) reflects muscle quality and is associated with inflammation and coronary microvascular dysfunction (CMD), identifying a cardiometabolic risk phenotype. Increased thoracic intermuscular fat (IMAT) has been associated with an increased risk of CV events, being a discriminator of cardiometabolic risk, even in the absence of traditional visceral adiposity [5,6,10] .

Additionally, the concept of lipotoxicity describes how the deposition of ectopic fat—that is, outside of adipose tissue—in organs such as the heart, liver, and skeletal muscle leads to cellular dysfunction. This cellular dysfunction is particularly relevant in tissues not traditionally seen as primary fat depots, such as skeletal muscle, where intermuscular fat infiltration has emerged as a powerful and independent predictor of cardiovascular events. Local deposits, such as epicardial (around the heart) and perivascular (around the coronary vessels) fat, exert direct paracrine effects, contributing to local coronary inflammation and the progression of atherosclerotic plaque [14,15] .

Additional Systemic Mechanisms

In addition to hemodynamic changes and the direct effects of adipose tissue, obesity triggers multiple systemic mechanisms that amplify cardiovascular risk:

- **Endothelial Dysfunction:** Obesity impairs the function of the endothelium, the inner layer of blood vessels, and this is one of the earliest events in the atherosclerosis cascade [2,3] .
- **Neuro-hormonal activation:** There is an increase in the tone of the sympathetic nervous system and an elevation in leptin and insulin concentrations, in addition to chronic activation of the renin-angiotensin-aldosterone system, both contributing to increased blood pressure, cardiac stress with cardiac remodeling [6,8,15].
- **Prothrombotic State :** Obesity is associated with an increase in pro-coagulant factors, such as fibrinogen and plasminogen activator inhibitor-1 (PAI-1), and increased platelet adhesiveness, which raise the risk of acute thrombotic events, such as myocardial infarction [2,4] .
- **DMC:** The risk of DMC (defined as impaired coronary flow reserve in the absence of obstructive CAD) is also increased in obesity and is independently associated with high BMI and adverse outcomes.
- **Obstructive Sleep Apnea (OSA):** OSA is a critical and highly prevalent mediator in patients with obesity. It independently contributes to hypertension, arrhythmias (especially atrial fibrillation), and myocardial ischemia during sleep [5,9] .

These interconnected pathophysiological mechanisms result in a broad spectrum of clinical manifestations that increase cardiovascular morbidity and mortality in individuals with obesity.

VI.Clinical Manifestations: The Spectrum Of Cardiovascular Diseases Associated With Obesity

The complex pathophysiological processes triggered by excess adiposity manifest clinically as a wide spectrum of cardiovascular diseases, ranging from atherosclerotic disease to arrhythmias and heart failure, significantly increasing morbidity and mortality, and accelerating the cardiovascular aging process.

Atherosclerotic Cardiovascular Disease (ACVD)

Obesity is a robust and independent risk factor for the development of CVD, including coronary artery disease (CAD) and cerebrovascular disease. Although some of this risk is mediated by traditional factors such as hypertension and dyslipidemia, obesity exerts direct effects that accelerate atherosclerosis. Diagnosing CVD in obese patients can be challenging, as exercise stress tests may be limited by low aerobic capacity, and imaging studies such as myocardial scintigraphy (SPECT) and echocardiography may present technical artifacts that compromise diagnostic accuracy [1-4] .

Heart Failure (HF)

Obesity is a well-established risk factor for the development of heart failure, doubling the risk compared to normal-weight individuals, as demonstrated in the Framingham Heart Study. The association is particularly strong with heart failure with preserved ejection fraction (HFpEF), due to increased ventricular wall thickness and fibrosis, leading to left ventricular stiffness, with consequent diastolic dysfunction and left atrial enlargement. In fact, obesity is more strongly associated with the risk of developing HFpEF than heart failure with reduced ejection fraction (HFrEF). The clinical diagnosis of HF in obese patients also presents challenges, such as the difficulty in assessing signs of congestion and the observation that natriuretic peptide (BNP/NT- proBNP) levels are typically lower, which can lead to underdiagnosis [11,14,16] .

Arrhythmias and Thromboembolic Disease

There is strong causal evidence linking obesity to atrial fibrillation (AF), the most common sustained arrhythmia in clinical practice. Left atrial dilation, a consequence of the hemodynamic changes of obesity, serves as a structural substrate for AF. Furthermore, obesity increases the risk of sudden cardiac death, an association that may be mediated by alterations such as obesity cardiomyopathy (in advanced degrees of obesity), by fat infiltration in the myocardium leading to myocardial fibrosis, as well as structural remodeling (left ventricular hypertrophy, epicardial fat) and prolongation of the QTc interval on the electrocardiogram. Finally, obesity also significantly increases the risk of venous thromboembolism (VTE) due to the prothrombotic state and venous stasis.[10,16]

Accurate assessment of cardiovascular risk in these patients requires an approach that goes beyond traditional metrics, considering body fat distribution and its metabolic effects.

Associated Factors and Comorbidities:

a. Type II Diabetes Mellitus (DM II) : Approximately 80-85% of individuals with DM II are also overweight or obese. Insulin resistance – strongly associated with visceral fat – initiates or accelerates the atherogenic process.

b. Dyslipidemia : obesity is associated with an atherogenic phenotype: elevated triglycerides, small and dense LDL particles (prone to oxidation), and low HDL-c.

c. Obstructive Sleep Apnea (OSA) : highly prevalent in obese individuals. OSA is an independent risk factor for hypertension, heart failure, and cardiovascular events, contributing to myocardial ischemia and activation of the sympathetic nervous system, in addition to pro-coagulant factors [15,16] .

VII. Cellular Mechanisms And Premature Aging

Obesity mimics and accelerates aging processes (premature cardiovascular aging) at the molecular and cellular levels [4,5,10] .

• **Mitochondrial Dysfunction and Oxidative Stress:** Obesity induces mitochondrial dysfunction and redox imbalance (increased Reactive Oxygen Species - ROS). Mitochondrial dysfunction and oxidative stress are characteristics shared with aging.

• **Toxic Lipids (Lipotoxicity):** The accumulation of lipids in non-adipose cells, such as cardiomyocytes, can lead to cell dysfunction or death, a phenomenon known as lipotoxicity .

• **Obesity Cardiomyopathy (*Adipose) (Cordis*):** Fatty infiltration in the myocardium (fatty heart) can lead to **fibrosis** and deterioration of diastolic or systolic function.

• **Cellular Senescence:** Obesity accelerates cellular senescence in adipose tissue and the cardiovascular system of young models. Senescence is a contributing factor to cardiac and vascular dysfunction [12,14] .

VIII. Clinical Assessment Of Adiposity And Cardiovascular Risk

An accurate assessment of adiposity is fundamental for risk stratification and to guide therapeutic interventions. Although it is a useful screening tool at the population level, Body Mass Index (BMI) is insufficient to capture the heterogeneity of individual cardiovascular risk, making a more detailed assessment necessary.

Limitations of BMI and the "Obesity Paradox"

The main limitation of BMI is that it does not differentiate between fat mass and lean mass, nor does it provide information about the distribution of body fat. A muscular individual may be classified as "overweight" by BMI, while another with a normal BMI may have excess visceral fat and a high cardiometabolic risk.

" *obesity paradox* **"** emerges , where observational studies suggest that overweight or mildly obese patients with established cardiovascular disease may have a more favorable prognosis than their normal-weight peers. However, this observation likely does not reflect a protective effect of fat, but rather methodological biases, unmeasured confounding factors, or the inadequacy of BMI itself as a risk metric in populations with chronic disease [9,15] .

Assessment of Central and Ectopic Adiposity

Measures that assess central and ectopic adiposity offer a more accurate risk stratification than BMI alone [6,7] .

Metric	Clinical Relevance
Waist Circumference (WC)	It is a simple and effective indicator of visceral adiposity, predicting cardiovascular risk better than BMI. ESC guidelines recommend that weight gain should be avoided for waist circumferences >94 cm in men and >80 cm in women.
Waist-to-Hip Ratio (WHR)	Another measure of central adiposity that complements WC in assessing the risk associated with fat distribution.
Intermuscular Muscle Adiposity (IMAT)	The IMAT, assessed by imaging exams, reflects muscle quality and has emerged as a new and potent predictor of coronary microvascular dysfunction and adverse cardiovascular events, independent of BMI and other fat depots. Evidence shows that each 1% increase in the fat-muscle fraction (FMF) confers a 7% increase in the risk of major adverse cardiovascular events (MACE).

The Concept of "Metabolically Healthy Obesity" (WHO)

The concept of "metabolically healthy obesity" (MHO) refers to individuals with obesity who do not present the classic components of metabolic syndrome (such as hypertension, dyslipidemia, or insulin resistance). However, this term can be misleading. Although individuals with MHO have a lower cardiovascular risk than those with "metabolically unhealthy" obesity, they still present an increased risk compared to metabolically healthy individuals of normal weight. Therefore, MHO should be considered a high-risk transitional state, as prospective data demonstrate that these individuals have a significantly higher probability of progressing to a metabolically unhealthy state and developing cardiovascular risk factors compared to normal-weight individuals [1,5,8] .

Once the risk has been properly assessed, it is crucial to implement effective, evidence-based management strategies for weight loss.

Traditional Risk Factors Exacerbated by Obesity

Obesity exacerbates traditional risk factors [1,2,3,4,9,11] :

• Insulin Resistance and Dyslipidemia: Visceral fat causes insulin resistance and an atherogenic lipid profile: hypertriglyceridemia, small and dense LDL particles, and low HDL concentration. Insulin resistance initiates or accelerates the atherogenic process.

• Obstructive Sleep Apnea (OSA): OSA, common in obese individuals, induces acute and chronic stress (hypoxia, hypercapnia), which predisposes to myocardial ischemia and is linked to increased sympathetic activation and pro-coagulant factors.
• Leptin: Hyperleptinemia (increased leptin, a sign of resistance) has possible effects on increased sympathetic activity, thrombosis potency, and increased blood pressure and heart rate.

In summary, obesity is an "accelerator" of aging and cardiovascular disease, integrating complex mechanisms ranging from the local secretion of inflammatory toxins by ectopic adipose tissue to hemodynamic overload and structural remodeling of the myocardium.

IX. Management Strategies: The Impact Of Weight Loss On Cardiovascular Health

Weight loss is a fundamental pillar in the treatment of obesity and in reducing cardiovascular risk. Modern approaches are multifaceted and integrate lifestyle interventions, the use of advanced pharmacotherapy and, in selected cases, bariatric procedures, aiming for significant and sustained weight loss [4,9] .

Fundamentals of Management: Lifestyle Interventions

Lifestyle changes remain the foundation for weight management.

1. **Dietary Interventions:** The main focus of dietary interventions is to achieve a caloric deficit, typically of 500-750 kcal per day. Different dietary patterns, such as the Mediterranean diet, have been shown to induce modest weight loss (5-10%) and significantly improve cardiovascular risk factors. The main challenge, however, is long-term adherence, which requires ongoing support and behavioral strategies.
2. **Physical Activity:** Although the effect of physical activity alone on weight loss is modest, its role is crucial for multiple reasons. Regular physical activity is essential for maintaining weight loss, improves cardiometabolic health independently of weight loss, and helps preserve muscle mass during weight loss. Robust evidence shows that regular physical activity reduces the incidence of cardiovascular risk factors in overweight or obese individuals.

Pharmacotherapy: A New Era in the Treatment of Obesity

The field of pharmacotherapy for obesity has undergone a paradigm shift. While older therapies, such as orlistat , offered modest results (weight loss of approximately 2.9 kg more than placebo) and were limited by side effects, the new generation of incretin -based therapies has fundamentally transformed the management of obesity. These new agents provide efficacy comparable to surgical procedures and, for the first time, have demonstrated a direct reduction in cardiovascular outcomes in patients without diabetes [1-3,12] .

The new generation of drugs, **GLP-1 receptor agonists (GLP-1 RAs) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists** , represent a significant advance [16,17,18] .

- **Mechanism and Efficacy:** Drugs such as semaglutide (GLP-1RAs) and tirzepatide (GIP) act on brain and gastrointestinal receptors to reduce appetite and increase satiety, leading to substantial weight loss, which can reach 15-20% of initial body weight. They are nominated at ICFEP in patients obese / overweight .

The action of Tirzepatide acts on various organs and systems: in the Central Nervous System (CNS) it increases satiety and curbs food intake, thereby reducing body weight; in the pancreas, it acts by increasing insulin and glucagon; in subcutaneous adipose tissue, it increases insulin sensitivity, increases blood flow and reduces pro-inflammatory infiltration; systemically, it acts to reduce hyperglycemia and triglyceride levels; in skeletal muscle, it acts to increase insulin sensitivity, greater metabolic flexibility, and reduce the accumulation of ectopic lipids; in the stomach, it acts by delaying gastric emptying and increasing white adipose tissue.

Semaglutide (GLP-1 RAs) acts: in the CNS by increasing satiety and reducing food intake (which contributes to weight loss); in the pancreas, by increasing insulin levels and decreasing glucagon levels; in the stomach, by slowing gastric emptying; systemically, by reducing hyperglycemia; and finally, in the liver, by increasing insulin sensitivity, reducing hepatic glucose production, and reducing the accumulation of ectopic lipids.

Below is a comparative table of new anti-obesity medications and their respective actions in protecting arterial blood pressure.

Table 2. Comparison of Arterial Protection (Semaglutide and Tirzepatide)

Mechanism	GLP-1 (Semaglutide)	GLP-1 + GIP (Tirzepatide)
Weight Loss	High	**Very High**
Reduction of Systemic Inflammation	Yes	**Yes (Enhanced)**
Improvement of Adipose Tissue Function	Moderate	**High (via GIP)**
Improvement of Adipose Tissue Function	Moderate	**High (via GIP)**

There are also other anti-obesity drugs, such as Orlistat (a lipase inhibitor that blocks absorption at the level of the gastrointestinal tract); Bupropion/ naltrexone (a norepinephrine reuptake inhibitor); Phentermine and Topiramate (which act as sympathomimetic modulators), but they have little effect on body weight loss and should be used with caution, mainly due to the scarce scientific evidence in terms of cardiovascular safety, as well as long-term cardiovascular risk [19,20] .

- **Evidence of Cardiovascular Outcomes:** The SELECT clinical trial marked a turning point. In this study, semaglutide at a dose of 2.4 mg per week reduced the incidence of major cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) by 20% (HR 0.80) in patients with pre-existing cardiovascular disease and overweight/obesity, but without diabetes. This was the first study to demonstrate a cardiovascular outcome benefit of a weight-loss medication in this population. The SURMOUNT-1 study (Tirzepatide vs. placebo) showed maintenance of weight loss in patients for three years, in addition to a 94% reduction in type II diabetes mellitus (DM II) [16,17] .
- **Impact on Heart Failure: The STEP** -HFpEF studies demonstrated that semaglutide significantly improved heart failure symptoms, quality of life, and exercise capacity in patients with HFpEF and obesity, consolidating its role in the management of this complex condition [1,2,19,20] .

Table 3 summarizes the clinical evidence and respective mechanisms of action of new anti-obesity therapies on cardiovascular risk.

Table 3. Clinical Evidence and Mechanisms of New Incretin Therapies in Cardiovascular Risk

Drug (Class)	Target Organs and Systems	Key Clinical Trials (RCTs)	Key Cardiovascular Outcomes and Protection
Semaglutide (GLP-1 RA)	Central nervous system (CNS), pancreas, stomach, liver, and adipose tissue.	**SELECT** ; **STEP- HFpEF**	20% reduction in MACE (non-fatal CV death, MI, and stroke); improvement in symptoms and functionality in HFpEF.
Tirzepatide (GIP + GLP-1 RA)	Central nervous system (CNS), pancreas, skeletal muscle, subcutaneous adipose tissue, and stomach.	**SURMOUNT-1** ; **SUMMIT** ; **SURPASS-CVOT**	94% reduction in the risk of type 2 diabetes; direct myocardial protection; maintenance of weight loss for 3 years.
Retatrutida (GIP/GLP-1/Glucagon)	Cardiovascular risk biomarkers	**TRIUMPH** (Phase 3)	Significant impact on cardiovascular risk biomarkers (under study).

Source: *Prepared based on data from Lincoff et al. (2024), Heerspink et al. (2024) and Rosenstock et al. (2026).*

Bariatric Surgery

Bariatric surgery remains the most effective intervention for inducing significant (25-30%) and sustained long-term weight loss in appropriately selected individuals. Consistent observational studies associate bariatric surgery with a robust reduction in all-cause mortality, cardiovascular mortality, and the incidence of events such as myocardial infarction and stroke [11,15] .

The two most common types of surgical procedures are:

a. Vertical sleeve gastrectomy: removes 70-80% of the stomach, including the greater curvature and gastric fundus; 4-6 incisions are required, either by video or robotic surgery; the surgery lasts about an hour; a relative contraindication is Gastroesophageal Reflux Disease (GERD).
b. Gastrojejunostomy: also called "gastric bypass (Roux-en-Y)"; it is performed by creating a gastric "pouch" (shaped like an "egg") that divides the intestine (50-150 cm from the jejunum); the surgery lasts about 4-6 hours, requiring 4-6 incisions. Contraindications: use of non- steroidal anti-inflammatory drugs (NSAIDs); smoking; patients using psychiatric medications.

These management strategies, when carefully integrated, offer an unprecedented opportunity to mitigate the impact of obesity on cardiovascular health.

X. Conclusion: Integrating Obesity Management Into Cardiovascular Practice

The growing body of evidence is driving a fundamental paradigm shift: obesity should not be viewed merely as a comorbidity or risk factor, but as a direct and modifiable therapeutic target for cardiovascular risk reduction. Addressing obesity should be an integral and proactive part of cardiovascular practice.

The main findings and practical recommendations for healthcare professionals are [11-14,16,17,20] :

1. **Comprehensive Assessment:** It is crucial to go beyond BMI in the routine assessment of cardiovascular risk. The use of central adiposity measures, such as waist circumference, should be incorporated into clinical practice. In specific contexts, novel markers of ectopic adiposity, such as intermuscular muscle fat (IMAT), may offer even more refined risk stratification.

2. **Lifestyle as a Foundation:** Dietary interventions to achieve a calorie deficit, and especially the promotion of regular physical activity, remain the foundation for the prevention and treatment of obesity. These strategies must be consistently promoted and supported, as they are essential for long-term success.
3. **Incorporation of Pharmacotherapy:** Based on robust evidence from clinical outcome trials, such as the SELECT study, GLP-1 receptor agonists (specifically semaglutide) should be considered a proven therapy for the secondary prevention of cardiovascular disease in overweight or obese patients with established CVD.
4. **Multidisciplinary Approach:** Effective obesity management requires a multidisciplinary and patient-centered approach. The combination of behavioral strategies (psychological and nutritional support), pharmacological strategies, and, when indicated, surgical strategies, is the most effective way to achieve and maintain long-term weight loss, resulting in lasting cardiovascular benefits.

The transition of obesity from a "comorbidity" to a "direct therapeutic target" is supported by the ability of new therapies to intervene in the inflammatory axis. By reducing the volume and metabolic activity of visceral and epicardial fat, these drugs not only promote weight loss but also interrupt the mechanisms of lipotoxicity and microvascular dysfunction that lead to major cardiovascular events.

In summary, proactive management of obesity by cardiologists and other healthcare professionals is no longer optional, but an essential necessity to mitigate the growing global burden of cardiovascular disease.

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