THERAPEUTIC SPOTLIGHT

National Consensus on Semaglutide in Cardiology: From Clinical Evidence to Clinical Translation

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Abstract

Obesity is increasingly recognized as a chronic, relapsing, and progressive disease that acts as a major upstream driver of cardiovascular, kidney, and metabolic disorders, with South Asians experiencing heightened vulnerability at lower adiposity thresholds. Despite this, effective metabolic therapies remain underutilized in cardiology practice. Semaglutide, a GLP-1 receptor agonist, has emerged as a multisystem, disease-modifying agent with benefits that extend well beyond glycemic control. Accumulating evidence from the STEP (Semaglutide Treatment Effect in People with Obesity) program, the SELECT cardiovascular outcomes trial, the SOUL trial, heart failure with preserved ejection fraction (HFpEF) studies, and real-world cohorts underscores its relevance for cardiometabolic risk reduction and symptom improvement. Recognizing the need for India-specific guidance, a panel of cardiologists from across the country reviewed pivotal randomized trials, including STEP 1–8, STEP-HFpEF, STEP-HFpEF DM, STEP TEENS, SELECT, SOUL, SUSTAIN-6, and PIONEER-6, along with meta-analyses, observational data, and international recommendations to formulate practical, context-appropriate guidance for cardiology practice.

Across diverse studies, semaglutide consistently produces substantial reductions in body weight and visceral fat, accompanied by improvements in blood pressure, glycemic control, inflammatory markers, and hepatic steatosis. SELECT demonstrated a significant reduction in major adverse cardiovascular events in adults with overweight or obesity and established atherosclerotic cardiovascular disease (ASCVD), independent of diabetes status. Benefits of obesity-related HFpEF include meaningful gains in symptoms, exercise tolerance, and quality of life. Emerging data also support renal and hepatic protection across CKM domains. Findings from high-dose 7.2 mg studies highlight a dose-response continuum but call for careful assessment of tolerability. As international guidelines increasingly position GLP-1 receptor agonists as cardiometabolic therapies, Indian data emphasize the importance of early, phenotype-driven intervention.

Semaglutide represents a practice-changing therapy that addresses core pathophysiological drivers of ASCVD and HFpEF through integrated modulation of adiposity and metabolic dysfunction. Its cardiovascular efficacy, multisystem benefits, and suitability for South Asian phenotypes support broader incorporation into contemporary cardiology. This consensus offers a framework for evidence-based patient selection, contraindications, monitoring, maintenance strategies, and coordinated multidisciplinary implementation to ensure safe and effective use in Indian clinical practice.

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Introduction

Obesity has emerged as one of the defining cardiometabolic disorders of the modern era, with its prevalence increasing worldwide, including in India. Major global organizations such as the World Health Organization (WHO), American Medical Association (AMA), European Association for the Study of Obesity (EASO), and the World Obesity Federation now classify obesity as a chronic and relapsing condition. This disease-centered perspective reflects a deeper understanding that excessive adiposity arises from intricate biological processes rather than from lifestyle behaviors alone. Central mechanisms include disturbances in neurohormonal regulation, impaired energy balance, chronic inflammatory activation, and metabolic dysfunction.[1–3]

Recognizing obesity as a biological disease has important cardiovascular implications. Excess adiposity substantially elevates the risk for a wide spectrum of cardiovascular conditions, including early-onset atherosclerotic disease, heart failure with preserved ejection fraction (HFpEF), arrhythmias, sudden cardiac death, vascular inflammation, metabolic syndrome, and chronic kidney disease (CKD).[4,5] These associations are especially significant in India, where cardiovascular risk tends to emerge earlier and at lower body mass index (BMI) levels. The Indian cardiometabolic phenotype, marked by disproportionate visceral fat, pronounced insulin resistance, and lower lean mass further amplifies the cardiovascular impact of adiposity.

Therapeutic developments over the past decade have reshaped obesity care, with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) playing a particularly transformative role. Semaglutide, in particular, has gained prominence due to its robust and durable effects on appetite regulation, energy expenditure, systemic inflammation, and metabolic health.[6–8] Although first introduced for glycemic management in type 2 diabetes (T2DM), accumulating evidence has established its relevance far beyond glucose control, demonstrating sustained and clinically meaningful reductions in body weight.

In addition to weight loss, semaglutide favorably influences several biological pathways that contribute to cardiovascular disease. These include improvements in endothelial function, reductions in vascular inflammation and oxidative stress, enhancement of myocardial energetics, and favorable modulation of cardiac workload (Fig. 1).[9,10]

These mechanistic actions are supported by an expanding body of clinical research in populations with diabetes, obesity, and established cardiovascular risk. Notably, analyses from the SELECT trial indicate that the cardiovascular benefits of semaglutide occur independently of baseline adiposity and are not solely explained by weight reduction.[11] This evidence supports a shift in perception of GLP-1 RAs, from agents primarily used for weight loss to therapies capable of modifying cardiometabolic disease processes.

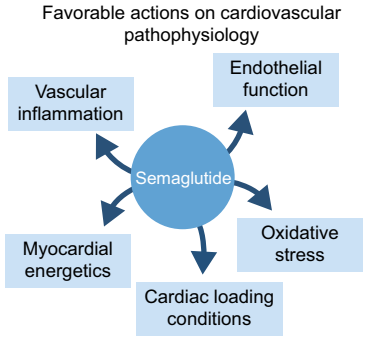

Fig. 1: Cardiovascular pathways beneficially modulated by semaglutide

Given India's substantial burden of obesity-driven cardiovascular disease and historically limited use of antiobesity medications, structured and context-specific clinical guidance is urgently needed. This national consensus aims to meet that need by integrating current scientific evidence, mechanistic understanding, and clinical trial data to guide the responsible use of semaglutide in cardiovascular practice.

The consensus seeks to:

- Frame obesity as a biologically mediated condition that fundamentally shapes cardiovascular risk.
- Outline the mechanistic and pathophysiological basis for GLP-1 RA therapy in cardiovascular care.
- Summarize evidence from major semaglutide trials relevant to cardiology; and
- Provide practical recommendations for the safe and effective incorporation of antiadiposity pharmacotherapy into routine cardiovascular management.

As evidence supporting semaglutide continues to evolve, it provides an opportunity for cardiology to more directly address upstream metabolic contributors to disease. This document intends to bridge emerging scientific knowledge with real-world clinical application in the Indian setting.

Methodology

This consensus was developed by a nationally represented panel of cardiologists during the National Consensus Meeting held on 12th October 2025, Mumbai, India. The panel conducted a structured evaluation of mechanistic studies, randomized clinical trials, real-world evidence, and international guidelines pertaining to semaglutide use in cardiometabolic care. This review was followed by expert deliberations to interpret the data in relation to the unique clinical and metabolic profile observed in Indian populations.

Consensus statements were developed through iterative discussion and refinement, aiming to harmonize global scientific principles with regional clinical needs and resource considerations. The resulting document reflects collective professional judgement and is intended to offer clear, evidence-based, and practice-oriented recommendations for integrating semaglutide into cardiovascular care pathways.

Obesity as a Chronic, Relapsing, Progressive Disease

Global Recognition of Obesity as a Disease

Over recent years, international consensus has shifted decisively toward classifying obesity as a complex chronic disease rather than a consequence of individual behavior. Leading authorities, including WHO, AMA, EASO, and World Obesity Federation, formally identify obesity as a long-term, progressive condition with distinct biological pathways and quantifiable health effects.[12–14] This reframing acknowledges the multifaceted interplay of genetic predisposition, neuroendocrine signaling defects, environmental influences, socioeconomic factors, and metabolic maladaptation, moving away from the outdated notion of obesity as a purely lifestyle-driven problem.

Within India, where central adiposity and adiposity-linked cardiometabolic disease are highly prevalent, organizations such as the Research Society for the Study of Diabetes in India (RSSDI) have adopted this disease framework. Despite increasing acceptance, national guidance remains fragmented, highlighting the need for cardiology leadership to position obesity as a primary therapeutic target for cardiovascular risk reduction.[15]

Why Obesity Constitutes a Disease: Core Biological Mechanisms

Obesity arises from disturbances in finely regulated systems governing feeding behavior, energy expenditure, nutrient storage, inflammatory balance, and metabolic homeostasis. The combined disruption of neurohormonal, endocrine, immune, and metabolic pathways produces a self-sustaining and progressive state that seldom reverses without structured intervention.

Neurohormonal Dysregulation: Dysfunction of The Brain–Gut–Adipose Circuit

In individuals living with obesity, key hypothalamic networks responsible for regulating hunger and satiety become resistant or poorly responsive to metabolic cues.[16] Although leptin levels rise in proportion to fat mass, its normal satiety-promoting actions are blunted. The brain perceives a starvation signal despite elevated leptin, driving increased appetite and defending a

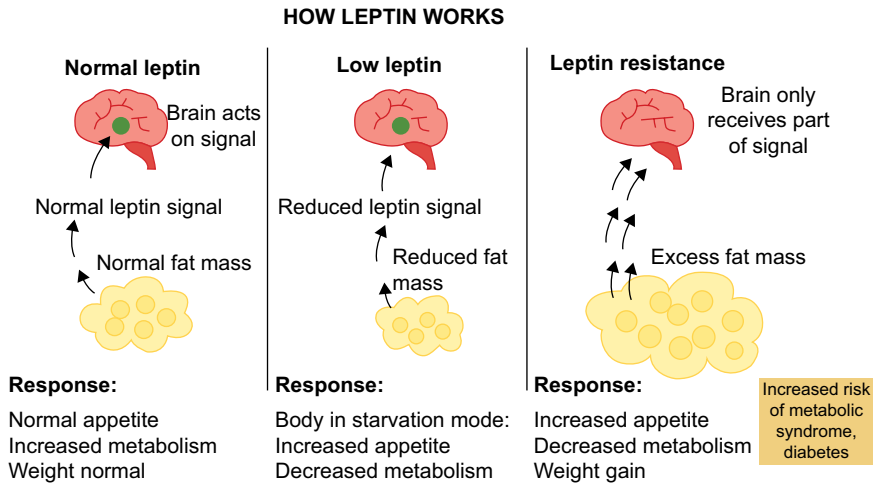

Fig. 2: Leptin signaling states and their physiological effects

higher body weight "set point." Central insulin resistance further reduces anorexigenic signaling (Fig. 2).

Hormones derived from gut that promote satiety, such as GLP-1, peptide YY (PYY), and cholecystokinin, are reduced, while orexigenic pathways (e.g., ghrelin) may become overactive. These alterations are compounded by heightened dopamine-mediated reward responses to calorie-dense foods, closely resembling addiction biology.

Together, these changes create a neurobiological environment favoring sustained caloric intake and undermining the durability of weight loss achieved through lifestyle efforts alone.

Adipose Tissue Dysfunction and Low-grade Chronic Inflammation

As adipose tissue expands, it undergoes a pathological transformation into an active, proinflammatory organ. Hypertrophic adipocytes become hypoxic, recruit macrophages and immune cells, and generate persistent inflammatory signalling.[17] Characteristic alterations include:

- ↑ IL-6 and TNF-α: drivers of hepatic CRP production, endothelial dysfunction, insulin resistance, and atherogenesis.
- ↑ CRP: both a marker and mediator of chronic inflammation; strongly associated with atherosclerotic cardiovascular disease (ASCVD) risk.
- ↓ Adiponectin: Leading to impaired insulin sensitivity, endothelial function, fatty liver disease, and vascular stiffness.
- Leptin excess/resistance: promoting sympathetic overactivity, thrombogenicity, and vascular inflammation.

These changes contribute to dysglycemia, atherogenic dyslipidemia (hypertriglyceridemia, reduced HDL-C, small dense LDL particles), mitochondrial dysfunction, and ectopic fat deposition in major organs, including the liver, heart, pancreas, and kidneys.[18] This pathophysiologic milieu aligns with the emerging cardiovascular–kidney–metabolic (CKM) disease continuum endorsed by the American Heart Association.[19]

Multisystem Clinical Impact (>200 Obesity-associated Conditions)

Untreated obesity contributes to over 200 recognized clinical complications.[20] Cardiometabolic disorders account for the greatest impact, including hypertension, premature coronary artery disease, heart failure (notably HFpEF), atrial fibrillation, other arrhythmias, ischemic stroke, progressive CKD, and T2DM, often manifesting at lower BMI thresholds in South Asian individuals.

Beyond cardiometabolic conditions, obesity increases susceptibility to obstructive sleep apnea, infertility, osteoarthritis, numerous malignancies, and metabolic dysfunction–associated steatohepatitis (MASH), which itself acts as a significant cardiovascular risk amplifier.[20]

Chronicity and Relapse Biology

A defining feature of obesity is its propensity to relapse. Following weight loss, especially through lifestyle modification alone, the body activates multiple compensatory mechanisms aimed at restoring prior weight. These include reductions in resting metabolic rate exceeding what is predicted by loss of mass, increased metabolic efficiency of skeletal muscle, rises in ghrelin and decreases in GLP-1 and PYY, heightened hunger, and reduced satiety.[21–23] These adaptations collectively promote weight regain, often surpassing the initial baseline weight. This "weight-regain physiology" mirrors homeostatic compensation seen in other chronic illnesses and underscores the need for sustained long-term management strategies.

Evidence-based Treatment Modalities Exist

Classifying obesity as a disease is also justified by the availability of effective treatments that modify its trajectory. While lifestyle modification remains foundational, its long-term effectiveness is limited by compensatory biological responses.[24] Modern pharmacotherapies, particularly semaglutide and tirzepatide, directly target neurohormonal and metabolic dysfunction. These agents enhance satiety and reduce hedonic eating, improve insulin sensitivity, reduce systemic inflammation, and improve multiple cardiometabolic parameters.[8] Semaglutide preferentially reduces visceral adiposity, preserves lean-mass proportion, improves handgrip strength, and lowers the prevalence of sarcopenic obesity.[25] Metabolic/bariatric surgery remains the most potent option for those eligible, with long-term improvements in diabetes remission, cardiovascular outcomes, and overall mortality.

Clinical Definition and Cardiovascular Relevance

In line with WHO criteria, obesity is best understood as abnormal or excessive fat accumulation that impairs health.[26] This definition transcends BMI and incorporates visceral adiposity, ectopic lipid deposition, metabolic dysfunction, and target-organ involvement. For cardiovascular practice, this reframing is critical. It elevates obesity from a behavioral label or cosmetic concern to a central, modifiable risk factor requiring systematic identification, early intervention, and long-term medical management.

Obesity and Cardiovascular Disease: Mechanistic Pathways

Obesity influences cardiovascular health through a network of interconnected biological processes that together generate hemodynamic strain, metabolic derangement, chronic inflammation, structural cardiac and vascular alterations, and progressive CKM dysfunction. These pathways do not operate in isolation; rather, they interact and amplify one another, establishing excess adiposity as an active causal factor in cardiovascular disease rather than a simple correlate or background risk condition.

Hemodynamic Overload Associated with Excess Adiposity

Increased adipose tissue requires greater blood flow to sustain metabolic needs. The resulting rise in circulating blood volume and cardiac output imposes continuous mechanical stress on the myocardium. Left ventricular (LV) wall tension increases, prompting concentric remodeling early in the course of weight gain. Over time, the combination of elevated preload and afterload impairs diastolic relaxation, raises LV filling pressures, and predisposes to pulmonary venous congestion—hemodynamic features characteristic of HFpEF.[27] These abnormalities can occur even in normotensive individuals, demonstrating that adiposity itself operates as a persistent hemodynamic stressor. This pattern has contributed to recognition of an "obesity-associated HFpEF phenotype," in which excess adiposity is a primary initiating and perpetuating factor.

Metabolic Dysregulation as a Catalyst for Cardiovascular Injury

Insulin resistance is a hallmark metabolic defect accompanying obesity and acts as a unifying mechanism behind multiple cardiometabolic disturbances.[28] With declining insulin responsiveness, hepatic glucose output increases, peripheral glucose disposal diminishes, and progression toward T2DM accelerates. Obesity is also closely linked with an atherogenic lipid profile, including elevated triglycerides, low HDL-C, and an abundance of small, dense LDL particles, changes that promote endothelial injury, lipid accumulation in macrophages, and rapid plaque formation.[29] Lipotoxicity resulting from ectopic fat accumulation further injures nonadipose tissues, including myocardium, liver, skeletal muscle, and kidneys. Myocardial lipid deposition impairs contractility and energetics; hepatic steatosis fuels systemic inflammation; and renal lipotoxicity accelerates CKD. These metabolic insults collectively establish the mechanistic bridge between excess adiposity and accelerated atherosclerosis, heart failure (both HFpEF and HFrEF), and CKM deterioration long before clinical symptoms emerge.

Chronic Inflammation and Endothelial Dysfunction

Obesity, especially when dominated by visceral fat, generates a persistent inflammatory state. Adipose depots become infiltrated by macrophages and other immune cells and adopt a proinflammatory phenotype.[30] Visceral adipose tissue, in particular, releases cytokines such as IL-6 and TNF-α, which stimulate hepatic CRP production and propagate systemic inflammation. This inflammatory milieu has multiple vascular consequences, including reduced nitric oxide availability and impaired vasodilator function, increased arterial stiffness, enhanced thrombogenicity, and accelerated atherosclerotic plaque development and destabilization.

Inflammation originating from visceral fat also disrupts myocardial microvascular function, a mechanism now considered central to the pathobiology of obesity-related HFpEF. Thus, chronic inflammation serves as a unifying process linking adiposity with coronary artery disease, arrhythmias, heart failure, and diffuse vascular dysfunction.

Structural and Adipose-mediated Cardiac and Vascular Changes

Beyond systemic metabolic and inflammatory effects, adiposity alters cardiovascular structure directly through the behavior of local fat depots, primarily epicardial adipose tissue (EAT) and perivascular adipose tissue (PVAT).

Epicardial adipose tissue, located in immediate proximity to the myocardium and coronary arteries, expands substantially in obesity and becomes metabolically active. This depot secretes inflammatory mediators and free fatty acids that diffuse into adjacent tissues, promoting microvascular dysfunction, myocardial fibrosis, and reduced myocardial compliance.

Perivascular adipose tissue, surrounding major vessels, produces proinflammatory adipokines that penetrate the vascular wall, accelerating atherosclerosis and impairing vasoreactivity.

Additionally, obesity contributes to increased LV mass, altered chamber geometry, impaired systolic–diastolic coupling, and heightened susceptibility to arrhythmias. These changes illustrate how adiposity directly remodels cardiac and vascular structures, compounding metabolic and inflammatory injury.[31,32]

Clinical Manifestations of Adiposity-Driven Pathophysiology

The combination of hemodynamic stress, metabolic dysfunction, chronic inflammation, and structural remodeling translates into markedly elevated cardiovascular risk. Large cohort studies, including the Framingham Offspring Study, UK Biobank, and multinational registries, consistently demonstrate higher incidence of coronary artery disease, myocardial infarction, atrial fibrillation, ischemic stroke, cardiovascular mortality, and both HFpEF and HFrEF in individuals with obesity.[33] Among these outcomes, the relationship between obesity and HFpEF is particularly strong, with adiposity increasingly recognized as a principal upstream contributor to HFpEF onset and progression. Obesity also accelerates renal decline, increases albuminuria, and reinforces the CKM disease continuum.

South Asian Phenotype: Cardiometabolic Risk at Lower BMI

South Asians exhibit a distinctive cardiometabolic profile characterized by greater visceral adiposity, disproportionately high ectopic fat deposition in organs such as the liver and pericardium, pronounced insulin resistance, and reduced skeletal muscle mass.[34] As a result, cardiometabolic risk, including diabetes and premature myocardial infarction, emerges at lower BMI values compared to other populations. This phenotype highlights the need to incorporate markers beyond BMI when assessing obesity-related cardiovascular risk in India. Measurements such as waist circumference, waist–hip ratio, and biochemical markers of metabolic dysfunction provide more accurate risk stratification in this population.

Semaglutide: Biological Rationale and Therapeutic Scope

Overview and Rationale for GLP-1 RAs in Cardiometabolic Disease

The advent of GLP-1 RAs has transformed the therapeutic landscape for obesity and cardiometabolic disorders. Semaglutide, a long-acting GLP-1 RA characterized by high receptor affinity and a prolonged elimination half-life of about 168 hours (≈7 days), was initially developed for glucose regulation in T2DM.[35] Subsequent research has greatly expanded its clinical relevance, demonstrating benefits extending well beyond glycemic control. These include profound and durable weight reduction, improvement in multiple cardiometabolic risk factors, reduction of systemic inflammation, and protective effects across cardiovascular, hepatic, and renal systems.

Semaglutide's broad therapeutic activity is rooted in its capacity to influence central appetite regulation, correct neurohormonal disturbances, enhance metabolic efficiency, and mitigate the pathological consequences of excess adiposity. Unlike lifestyle interventions that are limited by biological counter-regulatory mechanisms, semaglutide acts on upstream drivers of obesity and metabolic dysfunction, making it useful across

patients with obesity, metabolic syndrome, diabetes, or cardiovascular disease.

Modulation of Central Appetite Regulation

A defining feature of semaglutide is its influence on neural pathways that govern appetite, satiety, and reward-driven eating. Neuroimaging studies show that GLP-1 RAs dampen activity in hypothalamic and cortico-limbic networks that are typically hyperresponsive to food cues in people with obesity.[36] These regions integrate both homeostatic and pleasure-related components of feeding behavior. Through activation of GLP-1 receptors in these brain areas, semaglutide reduces hunger and premeal drive, increases satiety following food intake, decreases craving and reward responses to calorie-dense foods, and restores synchrony between gut-derived signals and central appetite control.

Semaglutide also induces a transient delay in gastric emptying during early treatment, enhancing postprandial fullness without producing clinically meaningful long-term motility impairment. Collectively, these central and peripheral effects reduce energy intake sustainably, supporting substantial weight loss even in individuals with chronic obesity or prior resistance to dietary interventions.[37]

Restoration of Metabolic Homeostasis and Reduction of Adiposity

Semaglutide improves metabolic health through mechanisms that depend on and extend beyond weight reduction. Studies in both diabetes and obesity populations reveal improvements in insulin sensitivity, fasting insulin, hepatic glucose output, and indices of insulin resistance, alongside favorable changes in triglycerides, atherogenic lipoproteins, and metabolic flexibility.[38]

The drug also reduces systemic inflammation, reflected by declines in CRP and multiple cytokine-related markers.[39] These effects derive from a combination of reduced adipose inflammation, improved GLP-1 signaling, decreased ectopic lipid accumulation, and enhanced metabolic function. A notable benefit is its ability to reduce visceral adipose tissue and ectopic fat depots including hepatic, intramuscular, and epicardial fat which are central drivers of cardiometabolic deterioration.[40,41] Improvements in endothelial function, autonomic balance, and blood pressure have been documented even in cases where weight loss does not fully explain metabolic gains, indicating additional weight-independent actions.[8]

Cardiac and Vascular Benefits Beyond Weight Loss[42]

Accumulating evidence suggests that semaglutide's cardioprotective actions extend well beyond its impact on body weight. In the SELECT trial, conducted in adults with overweight or obesity but without diabetes, semaglutide significantly reduced major adverse cardiovascular events (MACE).[11] This finding confirms that semaglutide's cardioprotective effects are not contingent on glycemic control and likely reflect a combination of improved endothelial function and nitric oxide bioavailability, reduced vascular inflammation and oxidative stress, decreased epicardial adipose tissue activity, improved myocardial energetics, lower systemic congestion and filling pressures, and attenuation of chronic inflammation.

In obesity-related HFpEF, semaglutide has shown consistent improvements in exercise tolerance, functional status, quality of life, and biomarkers of congestion and inflammation.[43] Because HFpEF is driven by the interplay of hemodynamic load, chronic inflammation, and coronary microvascular dysfunction, conditions closely linked to excess adiposity, semaglutide offers a mechanistically coherent therapeutic option where traditional cardiology treatments often provide limited benefit.

Hepatic, Renal, and Multiorgan Protective Effects

Semaglutide also confers significant hepatic benefits. Phase 3 data from 2025 indicate improvements in steatosis, inflammation, and fibrosis-related markers in metabolic dysfunction-associated steatohepatitis (MASH/NASH).[44–46] These improvements reflect reductions in lipotoxicity, enhanced metabolic efficiency, and lower ectopic lipid burden.

Renal benefits are consistently observed across trials, including reductions in albuminuria, slower decline in estimated glomerular filtration rate, and diminished renal inflammation.[47–49] These findings are highly congruent with the CKM disease framework, positioning semaglutide as a therapy that addresses interconnected organ systems rather than isolated metabolic endpoints.

In addition, reductions in oxidative stress, inflammatory burden, and markers of endothelial dysfunction contribute to a coherent picture of multiorgan protection.

Semaglutide as a Comprehensive Cardiometabolic Therapy

The collective mechanistic and clinical evidence positions semaglutide as far more than a weight-loss medication. By influencing central appetite pathways, re-establishing metabolic balance, reducing visceral and ectopic fat, lowering inflammation, and providing proven cardiovascular benefits, including in HFpEF, semaglutide modifies the upstream biological processes that drive cardiometabolic disease.

Its emerging role in metabolic liver disease and CKD further underscores its broad therapeutic potential. As evidence continues to expand, semaglutide is poised to become a cornerstone therapy across the cardiometabolic spectrum, especially in countries such as India, where obesity-related cardiovascular disease is escalating, and utilization of antiobesity pharmacotherapy remains limited.

Evidence Base: Semaglutide Clinical Trials

Semaglutide is supported by an extensive clinical development program covering obesity, T2DM, cardiovascular outcomes, heart failure with preserved ejection fraction (HFpEF), liver disease, and renal endpoints. Across heterogeneous populations and study designs, the accumulated data show reproducible, clinically meaningful effects, positioning semaglutide not only as a leading antiobesity agent but also as a therapy that modifies disease processes across the CKM continuum.

The STEP Program: Establishing Weight-loss Efficacy

The STEP (Semaglutide Treatment Effect in People with Obesity) trials (STEP 1–8 plus STEP TEENS and related studies) established weekly subcutaneous semaglutide 2.4 mg as an effective pharmacologic option for weight management (Table 1). Across these trials, semaglutide produced large, sustained reductions in body weight with high responder rates.

Key findings from the STEP series include:

- Mean relative weight loss in the active arms typically ranged from about 13% to 16% at primary endpoints (most commonly 68 weeks), with placebo groups showing modest losses (≈2–6%) (Fig. 3).
- A high proportion of participants on semaglutide achieved clinically important weight-loss thresholds (≥5%, ≥10%), with responder rates substantially higher than those with comparators. (Fig. 4).
- Benefits were observed across adults (with and without diabetes), adolescents (STEP TEENS), and diverse geographic groups, including East Asian cohorts.

Table 1: Overview of clinical trial evidence for semaglutide 2.4 mg in obesity and overweight management: STEP 1–8 and STEP TEENS

Trial	*Population included*	*Number enrolled (male/female)*	*Duration of trial*	*Age (years)*	*Intervention (dose)*	*Comparator*	*Primary endpoint*	*Key results (Primary)*	*Main safety signals*
STEP 1[50]	Adults with obesity (BMI ≥30) or overweight (BMI ≥27 + ≥1 comorbidity); no diabetes	1961 (≈508 M/1453 F)	68 weeks	46–47	Semaglutide 2.4 mg weekly	Placebo	% weight change; ≥5% weight loss	−14.9% vs −2.4%; 86% vs 31% achieved ≥5% loss	GI AEs, gallbladder disease, and rare pancreatitis
STEP 2[51]	Adults with T2DM; BMI ≥27; HbA1c 7–10%	1210 (sex not specified)	68 weeks	Not reported	Semaglutide 2.4 mg weekly vs 1.0 mg	Placebo	% weight change; ≥5% loss	−9.6% vs−3.4%; 69% vs 29%	GI AEs were higher with 2.4 mg
STEP 3[52]	Adults with obesity/overweight; no diabetes; intensive behavioral therapy	611 (116 M/495 F)	68 weeks	46 ± 13	Semaglutide 2.4 mg weekly	Placebo	% weight change; ≥5% loss	−16% vs−5.7%; 87% vs 48%	GI AEs; 3% discontinuation
STEP 4[53]	Adults with obesity after a 20-week semaglutide run-in	803 (169 M/634 F)	20-week run-in + 48-week randomized	46 ± 12	Continued semaglutide 2.4 mg	Placebo (after run-in)	% weight change from week 20→68	−7.9% vs +6.9% (difference −14.8 pts)	GI AEs; similar serious AEs
STEP 5[54]	Adults with obesity/overweight; no diabetes	304 (68 M / 236 F)	104 weeks	47 ± 11	Semaglutide 2.4 mg weekly	Placebo	% weight change; ≥5% loss	−15.2% vs−2.6%; 77% vs 34%	GI AEs; gallbladder events; rare hypoglycaemia
STEP 6[55]	East Asian adults (Japan, Korea); BMI ≥27 + comorbidities or ≥35; ~25% with T2DM	401 (253 M / 148 F)	68 weeks	51 ± 11	Semaglutide 2.4 mg or 1.7 mg	Placebo	% weight change; ≥5% loss	−13.2% (2.4 mg) vs−2.1%; 83% vs 21%	GI AEs; ~3% discontinuation; no pancreatitis
STEP 7[56]	Predominantly East Asian adults; overweight/obesity with/without T2DM	375 (sex not given)	44 weeks	Not reported	Semaglutide 2.4 mg	Placebo	% weight change; ≥5% loss	−12.1% vs−3.6%; 85% vs 31%	GI AEs (67% vs 36%)
STEP 8[57]	Adults with obesity/overweight; no diabetes; head-to-head vs liraglutide	338 (73 M / 265 F)	68 weeks	49 ± 13	Semaglutide 2.4 mg weekly	Liraglutide 3.0 mg daily	% weight change (semaglutide vs liraglutide)	−15.8% vs−6.4% (difference −9.4 pts)	GI AEs; lower discontinuation with semaglutide
STEP TEENS[58]	Adolescents 12–<18 yrs; BMI ≥95th percentile (or ≥85th + comorbidity)	201 (76 M / 125 F)	68 weeks + run-in	15.4 ± 1.6	Semaglutide 2.4 mg weekly	Placebo	% BMI change	−16.1% vs +0.6%	GI AEs; cholelithiasis (4%); no pancreatitis

HbA1c, glycated hemoglobin; Pts/pts, percentage points; SEM/SD, standard error / standard deviation, WC, waist circumference

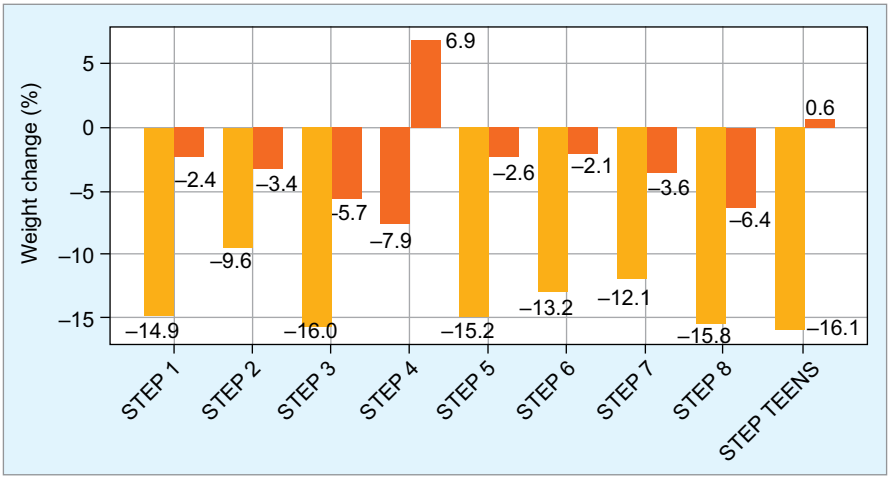

Fig. 3: Weight reduction across STEP trials: Semaglutide vs Comparator

- Safety signals were consistent across studies: gastrointestinal effects were the most frequent adverse events, with cholelithiasis and rare pancreatitis reported infrequently; discontinuation rates rose with intolerable GI effects in some trials.
- Collectively, the STEP program demonstrates robust and reproducible weight-loss efficacy for semaglutide 2.4 mg across age groups and ethnicities.

Cardiometabolic Trials Beyond Weight Loss

Semaglutide's evidence base now spans nearly a decade, evolving from early cardiovascular safety trials in diabetes (SUSTAIN-6, PIONEER-6) to large-scale outcome trials in obesity, HFpEF, and nondiabetic ASCVD. Together, these studies establish semaglutide as a multisystem cardiometabolic therapy with benefits extending well beyond glucose lowering (Table 2).

Cardiovascular Outcomes: From Safety to Proven Risk Reduction

Across the major semaglutide cardiovascular outcome trials (Fig. 5), consistent reductions in MACE were observed irrespective of diabetes status or route of administration. SUSTAIN-6[59] and PIONEER-6[60] first established cardiovascular

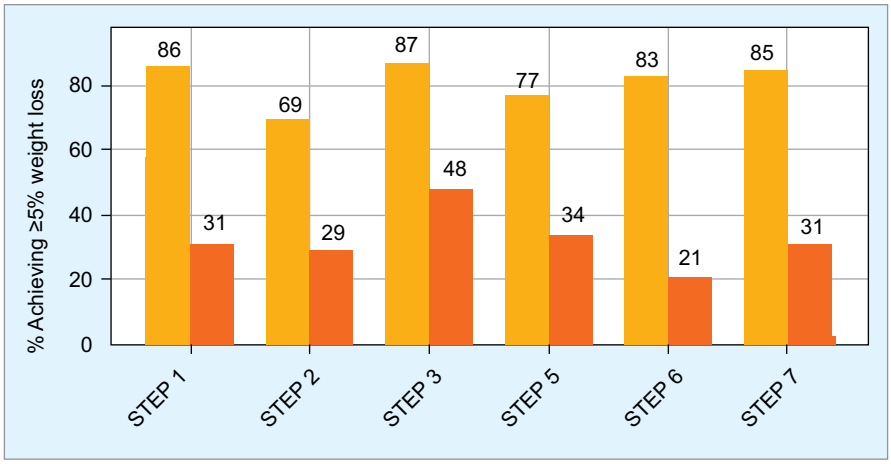

Fig. 4: Proportion achieving > 5% weight loss across STEP trials

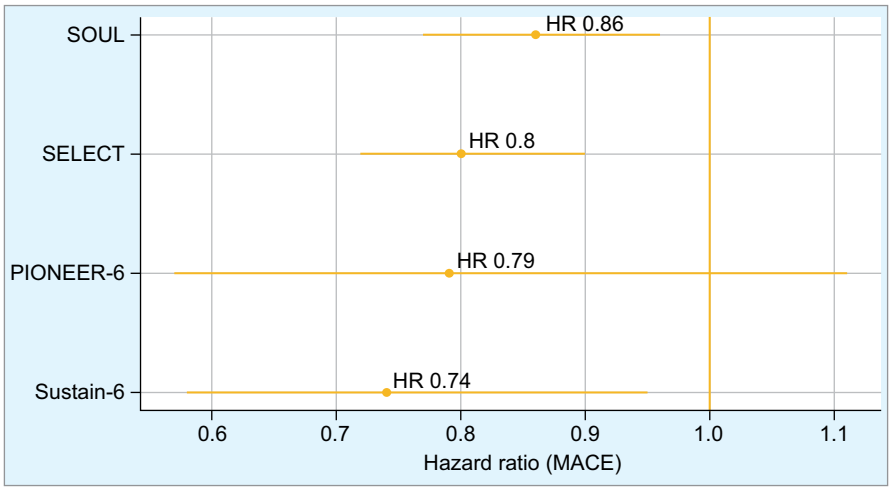

Fig. 5: CV outcomes with Semaglutide: composite MACE across major CV trials

safety in high-risk T2DM populations, with SUSTAIN-6 demonstrating a significant 26% MACE reduction (HR 0.74) and PIONEER-6 confirming noninferiority (HR 0.79). Building on these findings, SELECT delivered the first definitive CV benefit in nondiabetic patients, showing a 20% MACE reduction (HR 0.80) in over 17,000 adults with established ASCVD, independent of glycaemia or baseline adiposity.[61] The prespecified adiposity-trajectory analysis further demonstrated that only one-third of the CV benefit was mediated by waist reduction, supporting additional anti-inflammatory and cardiometabolic mechanisms.[11] Most recently, SOUL confirmed a 14% MACE reduction (HR 0.86) with oral semaglutide in T2DM patients with ASCVD or CKD, reinforcing that both injectable and oral formulations provide clinically meaningful cardiovascular protection beyond glucose lowering.[62]

Heart Failure and Severe Obesity Studies

Dedicated HFpEF trials (STEP-HFpEF programs) testing semaglutide 2.4 mg in obese patients with HFpEF showed meaningful improvements in patient-reported symptoms (KCCQ), exercise capacity, congestion biomarkers, and body weight compared with placebo.[9,10] These studies report fewer serious adverse events in the semaglutide arms and consistent tolerability profiles dominated by transient GI complaints. In severe-obesity cohorts, semaglutide produced substantial reductions in fat mass while largely preserving or improving functional muscle strength and reducing the prevalence of sarcopenic obesity.[25]

Dose-response and Comparative Data

Phase 3B data (e.g., STEP-UP) and head-to-head comparisons demonstrate a dose-response relationship for semaglutide, with higher weekly doses achieving greater mean weight loss that approaches the effects seen with metabolic surgery in magnitude for some individuals. In direct comparisons, semaglutide produced larger weight reductions than liraglutide 3.0 mg and showed superior tolerability in terms of discontinuation rates.[63]

Real-world Evidence: SCORE and STEER Studies

Early real-world data consistently support the cardiovascular benefits of semaglutide observed in SELECT. In the SCORE study, a large, matched cohort of >9,300 semaglutide 2.4 mg users with overweight or obesity and established ASCVD showed substantial reductions in cardiovascular events versus 18,600 non-users, including a ~57% lower risk of MACE-3 (MI, stroke, all-cause death) and ~45% lower risk of MACE-5 (adding HF hospitalization and revascularization).[64]

Complementing this, the STEER study, a 21,250-patient real-world cohort of individuals with overweight/obesity and established ASCVD without diabetes found that semaglutide was associated with a 57% reduction in revised MACE-3 compared with tirzepatide (HR 0.43; 95% CI 0.24–0.78). Event rates were 4.4 vs 10.3 per 1,000 patient-years for semaglutide and tirzepatide, respectively.[65]

Together, SCORE and STEER highlight the robustness, reproducibility, and clinical relevance of semaglutide's cardioprotective effects in routine practice, reinforcing its role in secondary cardiovascular prevention among people with obesity-related ASCVD. No new safety signals were identified in the available reports.

Safety and Tolerability

Across cardiovascular, HFpEF, obesity and real-world cohorts, semaglutide demonstrates a consistent safety pattern: GI adverse events remain the leading tolerability issue; dose-dependent but typically transient; Cholelithiasis risk is modestly increased across weight-loss trials; retinopathy progression appears limited to rapid glucose lowering in T2DM (seen in SUSTAIN-6), serious adverse events are generally not increased, and in HFpEF and CVOTs are often reduced compared with placebo. Overall, semaglutide maintains a favorable cardiometabolic safety profile.

Patient Selection, Contraindications, and Guideline Recommendations

Who Should Receive Semaglutide in Cardiology?

Clinical indications and practical considerations for semaglutide use in cardiometabolic care are summarized in Table 3.

Safety, Contraindications, and Practical Use of Semaglutide

Safety considerations, contraindications, and practical use of semaglutide are summarized in Table 4.

Table 2: Chronological summary of major semaglutide cardiometabolic and obesity clinical trials

Trial	*Population*	*Sample size (M/F)*	*Duration*	*Age*	*Intervention*	*Comparator*	*Primary endpoint*	*Key results (Primary outcome)*	*Main safety signals*
SUSTAIN-6[59]	Adults ≥50 yrs with T2DM + established CVD/CKD/HF, or ≥60 yrs with ≥1 CV risk factor; HbA1c ≥7%; 20-country double-blind CVOT	3297 (60.7% M/39.3% F)	104 weeks + 5-week follow-up	Mean 64.6 ± 7.4 yrs	Semaglutide 0.5 or 1.0 mg SC weekly	Placebo	3-point MACE (CV death, nonfatal MI, nonfatal stroke)	MACE: 6.6% vs 8.9% → HR 0.74 (95% CI 0.58–0.95) → noninferior and superior (p=0.02). Stroke HR 0.61; MI HR 0.74	GI AEs common; retinopathy complications ↑ (HR 1.76); nephropathy ↓ (HR 0.64); serious AEs lower vs placebo; similar pancreatitis/malignancy; mild HR increase
PIONEER-6[60]	T2DM adults ≥50 yrs with CVD/CKD or ≥60 yrs with ≥1 CV risk factor; double-blind event-driven CVOT	3183 (68.4% M / 31.6% F)	Median 15.9 months	Mean 66 ± 7 yrs	Oral semaglutide 14 mg daily (titrated)	Placebo	Time to first MACE	MACE: 3.8% vs 4.8% → HR 0.79 (95% CI 0.57–1.11) → noninferior ($p < 0.001$)	GI discontinuations ↑ (6.8% vs 1.6%); serious AEs lower; CV death ↓ (HR 0.49); retinopathy similar; hypoglycemia mainly when combined with insulin/SU
SEMALEAN[25]	Severe obesity (BMI ≥40) with comorbidity; real-world cohort assessing DXA, muscle function, REE	115 enrolled; 106 completed (31.1% M / 68.9% F)	12 months	Mean 52 ± 12 yrs	Semaglutide 2.4 mg weekly	None (uncontrolled)	Body weight, body composition, muscle function, REE	Weight:– 9.8% (M7) and– 12.7% (M12); Fat mass–14% →–19%; lean mass initially–3 kg then stable; strength ↑; sarcopenic obesity ↓ 49%→33%	GI AEs primary cause of dropout; 1 cholecystitis; no pancreatitis; 1 renal-worsening event
STEP-HFpEF[9]	HFpEF (LVEF ≥45%), BMI ≥30, NYHA II–IV; KCCQ-CSS <90	529 (263 sema / 266 placebo; 56.1% F)	52 weeks	Median 69 yrs	Semaglutide 2.4 mg weekly	Placebo	KCCQ-CSS change;% weight change	KCCQ: +16.6 vs +8.7 → Δ +7.8 pts ($p < 0.001$); Weight:– 13.3% vs–2.6% → Δ–10.7 pts ($p < 0.001$)	Serious AEs lower (13.3% vs 26.7%); GI discontinuation ↑; HF events 1 vs 12 (HR 0.08); no new safety signals
STEP-HFpEF DM[10]	HFpEF with T2DM, BMI ≥30, elevated filling pressures	616 (310 sema / 306 placebo; 44.3% F)	52 weeks + follow-up	Median 69–70 yrs	Semaglutide 2.4 mg weekly	Placebo	KCCQ-CSS change;% weight change	KCCQ: +13.7 vs +6.4 → Δ +7.3 pts ($p < 0.001$); Weight:– 9.8% vs–3.4% → Δ–6.4 pts ($p < 0.001$)	Serious AEs lower (17.7% vs 28.8%); HF events 7 vs 18 (HR 0.40); GI AEs ↑; no ↑ hypoglycemia/retinopathy
SELECT[61]	Adults ≥45 yrs with established CVD, BMI ≥27, without diabetes	17,604	Mean follow-up 39.8 months	Typically, mid-60s	Semaglutide 2.4 mg weekly	Placebo	3-point MACE	MACE reduced by 20%: 6.5% vs 8.0% → HR 0.80 (95% CI 0.72–0.90)	Higher AE-related discontinuation (16.6% vs 8.2%); GI events dominant; overall safety consistent with class
SELECT prespecified adiposity analysis[11]	Same SELECT population; analyses by adiposity and waist change	17,604 (sex distribution variable; mixed male majority)	39.8 months	Median ≈61 yrs	Semaglutide 2.4 mg weekly	Placebo	MACE	20% MACE reduction across all adiposity levels; benefit not dependent on early weight loss; waist reduction modestly mediated benefit (≈33%)	No increase in SAEs with greater weight/waist change; GI events primary cause of discontinuation; placebo pts with high unintentional weight loss had ↑ mortality
SOUL[62]	T2DM ≥50 yrs with ASCVD and/or CKD, HbA1c 6.5–10%; double-blind CVOT across 33 countries	9650 (≈4825/ arm; female 22–31%)	Mean 47.5 months	Median 65–67 yrs	Oral semaglutide up to 14 mg daily	Placebo	Time to first MACE	MACE ↓ 14%: HR 0.86 (95% CI 0.77–0.96); benefit consistent with/without SGLT2i	Serious AEs ≈placebo; no ↑ severe hypoglycemia or DKA; GI AEs class-consistent
STEP UP[63]	Obesity (BMI ≥30) without diabetes; 11-country Phase 3b randomized study	1407 (approx. 74% F)	72 weeks	Mean 47 ± 12 yrs	Semaglutide 7.2 mg weekly	Semaglutide 2.4 mg and placebo	% weight change;% achieving ≥ 5% weight loss	Weight:– 18.7% (7.2 mg) vs–15.6% (2.4 mg) vs–3.9% (placebo); ETD–3.1% vs 2.4 mg (p <0.0001); ≥5% WL OR 12.1	High GI AEs (70.8%); dysesthesia ↑ (22.9%); serious AEs 6.8% (similar to placebo/2.4 mg)

SAEs, serious adverse events; DXA, dual-energy X-ray absorptiometry; REE, resting energy expenditure, NYHA, New York Heart Association; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NT-proBNP, N-terminal Pro, B-type Natriuretic Peptide; ASCVD, atherosclerotic cardiovascular disease; WC, waist circumference, WHR, waist–hip ratio, ETD, estimated treatment difference, OR, odds ratio, IQR, interquartile range; DKA, diabetic ketoacidosis; SU, sulfonylurea; SGLT2i, sodium–glucose cotransporter-2 inhibitor

Table 3: Clinical indications and practical use of semaglutide in cardiometabolic care

Clinical scenario	*Why semaglutide is appropriate*	*Key considerations*
Established ASCVD with overweight/obesity	SELECT showed MACE reduction in nondiabetic ASCVD	Assess frailty, sarcopenia, and nutrition
Obesity-related HFpEF	STEP-HFpEF improved symptoms, congestion, and exercise capacity	Monitor volume status; titrate alongside diuretics
CKM multimorbidity (obesity + diabetes/HTN/dyslipidemia)	Addresses multiple upstream drivers: adiposity, insulin resistance, inflammation	Coordinate with existing cardiometabolic therapies (statins, ARBs/ACEi/ARNI, BB, SGLT2i, etc.)
South Asian visceral-adiposity phenotype	High visceral fat at lower BMI supports earlier pharmacotherapy	Use WC/WHR/body composition rather than BMI alone
Secondary prevention with weight-sensitive symptom burden	Weight loss improves hemodynamics, angina, and dyspnea	Avoid excessive weight loss, especially in older adults
Need for sustained, meaningful weight loss	STEP trials show ~15% loss with 2.4 mg weekly; late-stage 2025 data show ~20% or greater weight loss with the investigational 7.2 mg weekly dose	Long-term therapy is usually required for maintenance

Table 4: Safety, Contraindications, and Practical Use of Semaglutide

Category	*Contraindication/caution*	*Clinical notes for cardiologists*
Absolute contraindications	Personal/family history of medullary thyroid carcinoma or MEN2	Avoid in all cases
	Pregnancy or breastfeeding	Stop 2 months prior to conception
Use with caution	Prior pancreatitis	Not absolute; monitor symptoms closely
	Gallbladder disease or post-cholecystectomy	Risk increases with rapid weight loss; counsel proactively
	Diabetic retinopathy (long-standing/poorly controlled)	Avoid rapid glycemic drops; slower titration
	Significant GI disease, gastroparesis	May worsen symptoms; consider alternatives
	Advanced HF or borderline volume status	Appetite suppression can worsen nutrition; monitor hydration
	Frailty, sarcopenia, low BMI, but high visceral fat	Assess muscle mass; ensure nutritional support
	Patients on high-dose diuretics	Monitor BP, volume depletion risk
Special considerations	Older adults (>75 yrs)	Individualize goals; slower titration

MEN2, Multiple endocrine neoplasia type 2

Table 5: Summary of contemporary (2024–2025) guideline and consensus recommendations on semaglutide in cardiometabolic and heart failure care

Guideline/position statement	*Consensus statements/recommendations*
2025 ACC scientific statement on obesity in HF[66]	In patients with BMI ≥30 kg/m^2 and HFpEF, semaglutide-induced weight loss improves symptoms and functional capacity. HF event reduction evidence is limited, but biomarker trends are favorable. Monitor renal function, electrolytes, and volume status during dose escalation.
2024 ESC consensus on obesity and CVD[27]	Semaglutide is recommended for T2DM + ASCVD to reduce CV events (Class I, Level A). It may be considered in overweight/obese CCS patients without diabetes to reduce CV mortality, MI, and stroke (Class IIa, Level B).
2025 AACE consensus statement[67]	Preferred for diabetes prevention, strong weight loss, and improvements in lipids, BP, and inflammation. Only obesity drug proven to reduce MACE in non-diabetic obesity. Favored in CKD (slows eGFR decline) and beneficial in knee OA with >5% weight loss.
2025 ADA standards of care in diabetes (obesity section)[68]	For people with diabetes and overweight/obesity, semaglutide is a preferred therapy due to high weight-loss efficacy and glycemic + cardiometabolic benefits independent of weight loss.

Guidelines Recommendation/ Statements

Table 5 summarizes contemporary (2024–2025) guideline and consensus recommendations.

Comprehensive Checklist for Semaglutide Use in Cardiometabolic Practice

Table 6 presents a comprehensive clinical checklist for the initiation and monitoring of semaglutide.

Consensus Statements—Semaglutide in Cardiology (2025)

1. Obesity is recognized as a chronic, relapsing, progressive disease, and active treatment of adiposity is a core component of cardiovascular prevention and long-term disease modification.
2. Semaglutide is a cardiometabolic therapy, acting beyond glucose lowering, with reproducible reductions in adiposity, improvement in cardiometabolic markers, and demonstrated cardiovascular event reduction.
3. Evidence from SELECT confirms that semaglutide 2.4 mg weekly reduces major adverse cardiovascular events in adults with overweight/obesity and established ASCVD irrespective of diabetes, supporting cardiology-led initiation in secondary prevention.
4. The SOUL cardiovascular outcome trial demonstrates that oral semaglutide confers cardiovascular benefit in T2DM

Table 6: Comprehensive clinical checklist for semaglutide initiation and monitoring

1. Baseline assessment before prescribing semaglutide	
Domain	*Required evaluation*
Anthropometry	Weight, BMI, waist circumference (>90 cm men; >80 cm women)
Metabolic profile	Fasting glucose, HbA1c, lipid profile (fasting), serum creatinine, eGFR, LFTs (ALT, AST), T3, T4, TSH (fasting)
Cardiovascular evaluation	BP, HR, ECG, echocardiography, abdominal ultrasound, eye checkup with retinal examination (rule out retinopathy)
Other screening	Pregnancy test (if applicable), History of pancreatitis, gallbladder disease, thyroid carcinoma, MEN2

2. Indication Confirmation

- T2DM–inadequate glycemic control on oral therapy
- Obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) + > 1 weight-related comorbidity—hypertension, TDM, dyslipidemia, OSA etc.
- Cardiovascular risk reduction in in T2DM with established CVD, overweight or obesity
- Pediatric patients >12 years with obesity for chronic weight management
- Consideration in metabolic syndrome or NAFLD/MAFLD (off-label evidence-based use)

3. Contraindications and cautions

- Personal/family history of medullary thyroid carcinoma (MTC)
- Multiple endocrine neoplasia syndrome type 2 (MEN2)
- History of pancreatitis (use with caution)
- Severe GI disease (e.g., gastroparesis)
- Hypersensitivity to semaglutide

4. Patient Counselling

- Mechanism: GLP-1 analog slows gastric emptying, increases satiety, lowers glucose
- Long term benefits: ↓ HbA1c (≈1–1.5%), ↓ Weight reduction (≈5–15%), ↓major adverse cardiovascular events (MACE), potential renal protection
- Common side effects: Nausea, vomiting, diarrhea, constipation
- Rare adverse effects: Pancreatitis, gallstones, retinopathy (transient worsening)
- Injection technique if SC formulation
- Gradual dose escalation to minimize GI intolerance

5. Dosing schedule–subcutaneous semaglutide

Phase	*Weeks*	*Dose (weekly SC)*
Step 1	1–4	0.25 mg
Step 2	5–8	0.5 mg
Step 3	9–12	1.0 mg
Step 4	13–16	1.7 mg
Maintenance	≥17	2.4/1.7 mg
If patient cannot tolerate a dose, delay escalation for +4 weeks		

6. Maintenance dose	
Indication	Maintenance dose
CV risk reduction or weight reduction	2.4 mg weekly preferred; 1.7 mg acceptable if not tolerated
MASH (F2–F3)	2.4 mg weekly (can reduce to 1.7 mg if intolerant)

7. Monitoring during therapy	
Time point	*Monitoring components*
At 1–3 months	GI tolerance, adherence, Weight, BP, HR, Fasting glucose, HbA1c
At 6 months and annually	HbA1c, renal/liver function, lipid profile, evaluate for retinopathy (especially in rapid HbA1c reduction)

8. Concomitant therapy adjustments

- If on insulin or sulfonylurea → reduce dose to avoid hypoglycemia
- Avoid combination with DPP-4 inhibitors
- Compatible with SGLT2 inhibitors, metformin, statins, and ACEi

9. Red flags–when to stop semaglutide

- Persistent severe GI intolerance
- Symptoms suggestive of pancreatitis (abdominal pain, nausea, vomiting)
- Vision changes (possible retinopathy)
- Thyroid nodule or dysphonia (evaluate for MTC)

Contd…

10. Follow-up and lifestyle reinforcement

- Nutritional diet, physical activity, sleep, and hygiene
- Reinforce adherence and dose titration tolerance
- Routine follow-up every 1 month

11. Follow-up monitoring parameters

Parameter	*Rationale*
Weight, BMI, waist	Efficacy
HR and BP	Risk of increased resting HR
Renal function	AKI risk due to volume depletion
GI tolerance	Most common cause for discontinuation
Gallbladder symptoms	Risk of cholelithiasis/cholecystitis
Mood changes/suicidal behavior	Package-insert warning
Diabetic retinopathy	May worsen with rapid glucose drop
Hypoglycemia (if on insulin/SU)	Package-insert warning

DPP-4, dipeptidyl peptidase-4; NAFLD, nonalcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; SGLT2, sodium–glucose cotransporter-2

with ASCVD/CKD, extending GLP-1RA cardio protection across formulations.

5. The STEP program and 2025 high-dose data demonstrate durable, clinically meaningful adiposity reduction, with larger weight loss at higher doses, requiring balanced consideration of efficacy, tolerability, and long-term safety.
6. In obesity-related HFpEF, semaglutide improves symptoms, exercise capacity, congestion profiles, and quality of life, and should be considered as part of a multidisciplinary HFpEF treatment pathway.
7. Semaglutide supplements but does not replace guideline-directed therapies for ASCVD, heart failure, diabetes, hypertension, and dyslipidemia.
8. Patient selection must be phenotype-based, integrating waist circumference, waist-to-hip ratio, visceral adiposity markers, metabolic profile, and clinical context rather than BMI alone.
9. Prescribing must respect contraindications, including a history of medullary thyroid carcinoma or MEN2, pregnancy and lactation, and apply caution in pancreatitis, gallbladder disease, retinopathy, gastroparesis, frailty, sarcopenia, and advanced HF.
10. Baseline and longitudinal monitoring should include weight trajectory, blood pressure, glycemic shifts, renal and hepatic function, and ophthalmic assessment in selected patients.
11. Clinicians should provide structured counselling on predictable gastrointestinal effects, slow titration strategies, nutritional support, and measures to enhance adherence and tolerability.
12. Given the high likelihood of weight regain after discontinuation, semaglutide should be positioned as long-term therapy within chronic disease management frameworks.
13. Care should follow a shared-care model, coordinated across cardiology, endocrinology, obesity medicine, nephrology, hepatology, and mental-health services.
14. In the Indian and South Asian context, earlier pharmacologic intervention is appropriate due to higher visceral adiposity and cardiometabolic risk at lower BMI, necessitating culturally and resource-aligned implementation strategies.
15. Access, affordability, and reimbursement remain major determinants of real-world impact; policy alignment is needed to recognize obesity as a cardiometabolic condition warranting therapy coverage.
16. Observational comparisons between semaglutide and dual-agonists (e.g., tirzepatide) are hypothesis-generating but not definitive; until randomized CVOTs are available, therapy choice should reflect evidence strength, tolerability, and patient preferences.
17. The panel supports Indian registry development and prospective real-world data to evaluate safety, adherence, metabolic durability, cardiovascular outcomes, and economic impact.
18. Clinicians must watch for red-flag symptoms, persistent vomiting, dehydration, acute abdominal pain, or sudden visual changes and institute prompt evaluation.
19. Education and workforce training are required to modernize cardiology practice, align with international obesity guidelines, and improve competency in long-term adiposity management.
20. Priority research areas include head-to-head cardiovascular outcome trials versus dual-agonists, long-term safety of very-high-dose regimens, Indian cost-effectiveness modelling, and mechanistic studies in HFpEF, CKD, hepatic steatohepatitis, and sarcopenic obesity.

Conclusion

Semaglutide has reshaped cardiometabolic medicine, evolving from a glucose-lowering drug into a multi-organ, disease-modifying therapy. Evidence from STEP, SELECT programs, HFpEF trials, and emerging liver-disease studies demonstrates consistent benefits across weight, inflammation, endothelial function, metabolic risk factors, and cardiovascular outcomes, including proven MACE reduction in people without diabetes. While higher-dose regimens continue to be evaluated, the 2.4 mg formulation currently represents the evidence-based dose for cardioprotection. Collectively, these findings firmly position adiposity as a modifiable driver of ASCVD and establish semaglutide as a central therapy across the cardiovascular–kidney–metabolic spectrum. Its effectiveness across diverse populations, including Indians with high visceral adiposity and premature CVD, highlights broad applicability. At the same time, optimal use requires careful patient selection, monitoring for tolerability, attention to GI, biliary, and retinal risks, and coordinated interdisciplinary care. Implementation in India must consider ethnic risk, cost, and access to ensure equitable benefit.

As comparative data with emerging incretin-based therapies evolve, semaglutide remains the agent with the most robust cardiovascular outcome evidence. Its integration into routine practice offers an opportunity to change disease trajectories at both individual and population levels. Semaglutide should now be regarded as a foundational key therapy for appropriately selected patients, embedded within

chronic disease management pathways and supported by system-wide infrastructure to reduce the growing burden of obesity-related cardiovascular disease.

Disclosure

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