Review Article

# Emerging therapeutic strategies for obesity management for cardiovascular risk reduction in resource-limited settings: A review focusing on semaglutide

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## Abstract

Obesity represents a major contributor to cardiovascular disease burden, particularly in resource-limited settings where prevention, early detection, and long-term management remain challenging. Excess adiposity promotes cardiometabolic dysfunction through interconnected pathways involving insulin resistance, chronic low-grade inflammation, dyslipidemia, neurohormonal activation, and adverse cardiac remodeling, ultimately increasing the risk of heart failure, ischemic heart disease, stroke, and major adverse cardiovascular events. Among emerging therapeutic targets, incretin-based pathways have gained particular attention because they address both weight reduction and cardiovascular risk modification. Semaglutide, a glucagon-like peptide-1 receptor agonist, has become one of the most clinically relevant agents in this field, with evidence showing substantial reductions in body weight and improvements in glycemic control, visceral adiposity, systemic inflammation, blood pressure, and cardiometabolic risk markers. Data further support the potential role of semaglutide in reducing cardiovascular events, including among individuals with obesity and established cardiovascular disease without type 2 diabetes. The aim of the review is to synthesize current mechanistic and clinical evidence on semaglutide as an emerging therapeutic strategy in obesity management for cardiovascular risk reduction, while briefly contextualizing its role among other novel anti-obesity pharmacotherapies. Particular attention is also given to the relevance of semaglutide in resource-limited settings. Understanding organ-specific mechanisms and prioritizing scalable interventions may support more effective cardiovascular disease risk reduction strategies in obesity within resource-constrained healthcare systems.

**Keywords**: Obesity, cardiovascular disease, GLP-1 receptor agonist, semaglutide, resource-limited settings

## Introduction

Obesity places a substantial burden on overstretched health systems and has become a major public health challenge, particularly in developing regions [1]. In 2022, over one billion

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individuals met criteria for obesity (body mass index (BMI) ≥30), representing about one in eight adults, and 43% of adults were classified as overweight or obese [2]. Rapid population growth, urbanization, and lifestyle transitions have created conditions that fuel a projected obesity epidemic across Southeast Asia within the next decade [3]. In Indonesia, a recent national survey demonstrated consistently increasing prevalence, with obesity affecting 23.4% of adults [4]. Although diet modification, physical activity, pharmacologic therapy, and bariatric procedures are recognized strategies for weight reduction, effective implementation requires sensitivity to cultural and public health dynamics [5]. In Indonesia, higher body weight may be perceived as a sign of prosperity or health, shaping attitudes toward weight control and treatment acceptance [6,7]. Consequently, preventive efforts and therapeutic interventions must be aligned with local beliefs, socioeconomic realities, and health-system capacity. In addition, Indonesia has limited economic resources and demonstrates a relatively homogeneous dietary pattern. This pattern is characterized by high consumption of inexpensive, energy-dense staple foods such as rice, frequent intake of fried foods facilitated by abundant palm oil, and regular consumption of sugar-rich foods due to widespread sugarcane cultivation. Together, these dietary characteristics result in high intakes of carbohydrates, fats, and sugars, which are increasingly recognized as key contributors to the rising prevalence of obesity across the Indonesian archipelago.

Beyond its contribution to the increasing obesity burden, this dietary and socioeconomic context has important implications for cardiometabolic health. Obesity significantly elevates the risk of chronic diseases, including type 2 diabetes, cardiovascular disease, cancer, and metabolic syndrome, leading to higher morbidity, disability, and premature mortality [8]. A study across fourteen countries reported an obesity incidence of 24.6%, with 71.9% classified as centrally overweight, 40.7% as centrally obese, and nearly three-quarters identified as dysglycemia, collectively indicating a substantial cardiometabolic burden [9]. The Indonesia-INTERASPIRE study, a multicenter study involving 400 patients from seven centers in Indonesia (2020–2021), reported striking findings [10]. Even with optimal medical therapy, residual cardiovascular risk persists, highlighting obesity as a central and modifiable therapeutic target for cardiovascular risk reduction [10]. Comprehensive risk assessment and tailored management remain essential for improving long-term prognosis.

The aim of this review is to provide a comprehensive understanding of obesity as a major modifiable determinant of cardiovascular disease (CVD), with emphasis on its relevance to cardiovascular risk reduction in Indonesia. It addresses gaps in the existing literature by integrating mechanistic and clinical evidence on emerging obesity-directed therapeutic targets, particularly semaglutide, with contextual considerations related to cultural perceptions, socioeconomic barriers, healthcare access, and health-system capacity in resource-limited Indonesian settings. This review integrates the mechanistic pathways linking excess adiposity to cardiovascular risk with contextual factors, including cultural perceptions of body weight, economic disparities, and healthcare capacity, to inform the prioritization and implementation of evidence-based obesity management strategies in resource-limited settings, particularly Indonesia. The review further aims to present culturally sensitive and resource-oriented strategies—including lifestyle modification, pharmacologic therapy, and surgical approaches—tailored to improve cardiometabolic outcomes in Indonesian populations.

## Obesity, cardiovascular risk and comorbidities

The contribution of obesity and visceral adiposity to cardiovascular risk has long been recognized. Extensive epidemiological and clinical studies confirm that both overweight and obesity are strongly associated with increased incidence of CVD, higher morbidity, and greater all-cause and cardiovascular mortality [11-16]. This relationship is observed across diverse populations and persists even after adjusting for other risk factors [11,16]. Childhood obesity is also associated with an elevated likelihood of developing type 2 diabetes, hypertension, dyslipidemia, atherosclerosis, and subsequent CVD later in life [17].

Obesity is associated with elevated arterial pressures and increased left ventricular and left atrial filling pressures, which together contribute to the development of diastolic dysfunction [18]. Excess adiposity increases circulating blood volume and cardiac output requirements, imposing greater hemodynamic load on the left atrial and left ventricular [19]. These chronic

demands stimulate chamber dilatation and myocyte hypertrophy as compensatory responses to maintain adequate forward flow [20]. Multiple mechanistic pathways have been implicated in the increased susceptibility to atrial fibrillation observed in obesity, including increased cardiac adiposity, systemic and local inflammation, myocardial fibrosis, oxidative stress, ion-channel remodeling, and autonomic imbalance [21]. These abnormalities create both triggers and substrates for atrial fibrillation initiation and perpetuation.

Obesity also significantly increases the risk of heart failure, with a two- to six-fold higher incidence compared with individuals without obesity [22]. The association is strongest for heart failure with preserved ejection fraction (HFpEF), even after accounting for demographic, socioeconomic, and lifestyle factors [23]. Approximately one-third of individuals with heart failure are obese, and obesity is more prevalent in HFpEF than in heart failure with reduced ejection fraction (HFrEF) [22]. Large cohort and registry studies consistently showed that more than 70% of patients with HFpEF are either overweight (BMI: 25–29.9 kg/m²) or obese (BMI: ≥30 kg/m²), with some studies reporting rates up to 84% [24-27]. Obesity contributes directly to several hemodynamic and structural cardiac abnormalities—left ventricular hypertrophy, impaired myocardial relaxation, increased plasma volume, and elevated filling pressures [28]. These alterations manifest clinically as exertional dyspnea, peripheral edema, and congestion. In addition, HFpEF with obesity is often characterized by impaired augmentation of cardiac output during exercise and prominent symptoms attributable to pulmonary and systemic venous congestion [29].

Extensive experimental and clinical studies consistently demonstrated that obesity contributes to a spectrum of cardiac electrophysiological alterations, largely mediated through the expansion and biological activity of epicardial adipose tissue (EAT) [18]. Fatty infiltration from EAT can extend into the myocardium, particularly around the posterior left atrium and atrioventricular groove, separating myocardial fibers and creating anatomical conduction barriers that slow and heterogenizes atrial conduction, thereby facilitating re-entry arrhythmias [30]. In parallel, EAT secretes proinflammatory and profibrotic mediators that promote atrial fibrosis, modify ion channel expression, and disrupt intercellular electrical coupling, ultimately shortening the effective refractory period and sustaining atrial fibrillation [31]. Obesity also enhances cardiomyocyte–fibroblast electrical interactions and stretch-related signaling, which further contribute to conduction delay and arrhythmogenic substrate formation [32]. Additionally, EAT-derived factors induce ion channel remodeling, altering action potential duration and increasing susceptibility to arrhythmias [33].

Interrelated metabolic, inflammatory, and cardiac processes illustrate how excess visceral adiposity promotes the onset and progression of CVD (**Figure 1**). Visceral fat accumulation initiates a series of metabolic disturbances, including elevated blood pressure, hyperglycemia, insulin resistance, and atherogenic dyslipidemia [34]. These abnormalities arise from overactivation of the renin–angiotensin–aldosterone system (RAAS), increased sympathetic nervous stimulation, impaired glucose regulation, and a lipid profile characterized by increased triglycerides and low-density lipoprotein (LDL) cholesterol accompanied by reduced high-density lipoprotein (HDL) cholesterol [35]. Chronic inflammation originating in adipose tissue further contributes to cardiovascular pathology. Visceral adiposity promotes macrophage infiltration and release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), generating local and systemic inflammation [34]. Endothelial dysfunction emerges through reduced nitric oxide bioavailability, increased oxidative stress, and disrupted vascular integrity [36]. In parallel, oxidized LDL accumulates within the arterial intima, accelerating plaque development and fostering atherogenesis [37].

Cardiac structural and electrical consequences represent another critical pathway linking obesity to cardiovascular risk (**Figure 1**). Increased circulating volume and elevated cardiac workload contribute to left ventricular hypertrophy and interstitial fibrosis [38]. These changes impair myocardial compliance and diastolic function, contributing to heart failure with preserved ejection fraction, a phenotype strongly associated with obesity [13]. Electrical conduction abnormalities, myocardial fibrosis, and autonomic imbalance also increase susceptibility to arrhythmias, including atrial fibrillation [19]. Collectively, these metabolic, inflammatory, vascular, and cardiac alterations converge to elevate the risk of major cardiovascular outcomes,

including coronary artery disease, myocardial infarction, ischemic and hemorrhagic stroke, heart failure, sudden cardiac death, and other major adverse cardiovascular events (MACE).

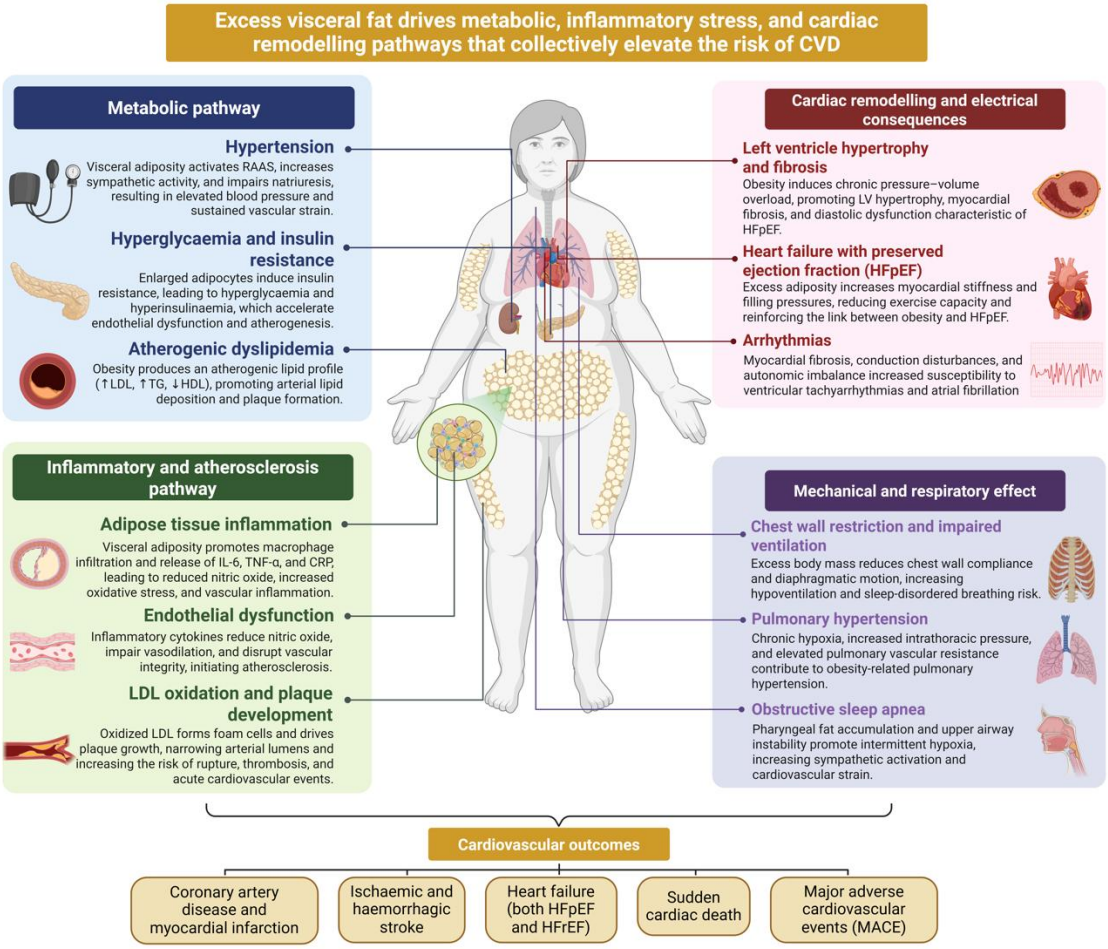



Figure 1. Mechanistic pathways through which excess visceral adiposity contributes to metabolic dysfunction, vascular inflammation, cardiac remodeling, and subsequent cardiovascular disease (CVD). CRP: C-reactive protein; HDL: high-density lipoprotein; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; IL-6: interleukin-6; LDL: low-density lipoprotein; LV: left ventricle/left ventricular; MACE: major adverse cardiovascular events; OSA: obstructive sleep apnea; RAAS: renin–angiotensin–aldosterone system; SNS: sympathetic nervous system; TG: triglycerides; TNF-α: tumor necrosis factor-α.

## Obesity and insulin resistance

Excess and ectopic adiposity, especially when accompanied by adipose tissue dysfunction, is a key driver of obesity-related complications [39]. Dysfunctional adipose tissue is marked by chronic, low-grade inflammation, increased infiltration of immune cells (notably macrophages), and altered secretion of bioactive molecules such as adipokines, cytokines, exosomes, and microRNAs [40]. This inflammatory state disrupts insulin signaling, promotes insulin resistance, and contributes to metabolic diseases like type 2 diabetes and CVD [41]. The progression from obesity-associated insulin resistance to type 2 diabetes also increases the risk of chronic complications, including diabetic peripheral neuropathy, for which early detection remains important to prevent advanced neurological impairment [42].

Adipose tissue functions as an active endocrine and metabolic organ rather than a passive lipid reservoir. Adipocytes and other resident cells—including pre-adipocytes, macrophages, endothelial cells, fibroblasts, and leukocytes—release a range of bioactive mediators, including leptin, adiponectin, lipids, and extracellular vesicles, which regulate systemic energy balance, glucose metabolism, appetite, and inflammatory pathways [43]. These circulating effectors

influence distant organs such as the liver, skeletal muscle, pancreas, and brain, shaping overall metabolic health.

During periods of energy surplus, adipose tissue stores triglycerides, which are later mobilized as fatty acids when needed [39]. In obesity, this storage capacity becomes overwhelmed, resulting in ectopic lipid deposition in organs such as the liver and skeletal muscle and further worsening metabolic dysfunction [44]. The tissue's diverse cellular composition, including stromal and immune cells, plays an important role in remodeling processes, inflammatory activation, and broader metabolic regulation [45].

Chronic, low-grade inflammation arising from adipose tissue represents a key pathway connecting obesity to insulin resistance and broader metabolic impairment [46]. As adipose tissue enlarges, it becomes increasingly populated by immune cells, particularly pro-inflammatory macrophages, which release cytokines such as TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1) [47]. These mediators interfere with insulin signaling in adipose tissue, liver, and muscle through activation of stress-related pathways that impair insulin receptor substrate activity, resulting in diminished glucose uptake and utilization [48]. This inflammatory environment also increases the release of free fatty acids and other bioactive lipids, further aggravating insulin resistance and driving ectopic fat accumulation in non-adipose organs, thereby amplifying metabolic dysfunction [49]. As insulin resistance progresses, pancreatic β-cells initially compensate by increasing insulin secretion; however, sustained metabolic stress eventually leads to β-cell failure, persistent hyperglycemia, and the development of type 2 diabetes [37]. The associated abnormalities commonly include dyslipidemia, hypertension, and additional disturbances in glucose regulation [50].

Insulin resistance disrupts central mechanisms that govern appetite and energy balance, particularly within the hypothalamus [51]. Under physiological conditions, insulin and leptin interact with hypothalamic neurons to reduce appetite and facilitate energy expenditure [51]. In obesity and insulin-resistant states, chronic inflammatory activity and endoplasmic reticulum stress impair these signaling pathways, producing central resistance to insulin and leptin [52]. This alteration promotes hyperphagia and accelerates weight gain. Molecular mediators such as suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B)—upregulated during inflammation and cellular stress—serve as negative regulators of insulin signaling and contribute to diminished hypothalamic responsiveness [53]. Concurrent shifts in neuropeptide profiles, characterized by increased neuropeptide Y/agouti-related peptide (NPY/AgRP) and reduced pro-opiomelanocortin activity, further destabilize appetite control [52,54].

Progressive obesity and advancing insulin resistance diminish adipose tissue's capacity to safely store surplus energy [53]. Hypertrophic, dysfunctional adipocytes lose sensitivity to insulin's antilipolytic action, resulting in excessive release of free fatty acids into the circulation [54]. Surplus lipids accumulate in non-adipose organs such as the liver, skeletal muscle, and pancreas, generating ectopic fat deposition and lipotoxic injury that further impairs insulin signaling [55]. Chronic low-grade inflammation, oxidative stress, and mitochondrial dysfunction within adipose tissue intensify this process and contribute to systemic insulin resistance as well as broader metabolic complications [56].

## Obesity and atherosclerosis

Atherosclerosis develops through a sequence of lipid-driven and inflammation-mediated events that begin with the infiltration and modification of LDL within the vascular intima [57]. Oxidized LDL is readily taken up by intimal macrophages through scavenger receptors, leading to the formation of foam cells and fatty streaks as the earliest detectable lesions [58]. Continued lipid accumulation and macrophage activation promote the evolution of these fatty streaks into atheromatous plaques that may progress toward unstable, rupture-prone lesions capable of precipitating thrombosis [59]. Obesity further accelerates this trajectory by creating a chronic pro-inflammatory and oxidative milieu that enhances LDL oxidation and amplifies macrophage lipid uptake [60]. Concurrent endothelial dysfunction—driven by reduced nitric oxide bioavailability, oxidative stress, and cytokine activity—increases leukocyte adhesion, facilitates lipid penetration into the intima, and promotes maladaptive vascular remodeling [61]. These

combined processes expedite the transition from early lipid deposition to advanced atherothrombotic disease in both large vessels and the microvasculature [62].

Extensive studies indicate that abdominal adiposity, particularly visceral fat, exerts a stronger influence on the initiation and progression of atherosclerotic injury than generalized obesity [63-65]. Autopsy and imaging studies consistently demonstrated that abdominal panniculus thickness and visceral adipose tissue are closely associated with the extent and severity of coronary and carotid atherosclerotic lesions, independent of BMI, with more pronounced effects observed in young men and in individuals with elevated visceral-to-subcutaneous fat ratios [63,64,66]. Ectopic fat depots such as perivascular, epicardial, and visceral adipose tissue further amplify vascular injury through the release of adipocytokines including leptin, resistin, TNF-α, visfatin, and IL-6 [67-69]. These mediators act through paracrine and vasocrine mechanisms to impair endothelial function, increase oxidative stress, intensify vascular inflammation, and drive maladaptive remodeling [68]. The vasa vasorum may facilitate the diffusion or transport of these signaling molecules, thereby accelerating local atherogenic processes and enhancing plaque vulnerability [69]. Imaging and biomarker studies support the close association between the inflammatory activity of these ectopic depots and the development of unstable plaques as well as adverse cardiovascular outcomes [64-66].

Obesity induces a pro-inflammatory and oxidative milieu that alters perivascular adipose tissue (PVAT), marked by increased circulating IL-6, greater lipid peroxidation, upregulation of inflammatory genes such as IL-6 and interleukin-1 beta (IL-1β), reduced adipocyte size and lipid content, and disrupted adipokine secretion [70,71]. Although declines in PVAT adiponectin have been reported, some investigations suggest compensatory elevations under oxidative stress, underscoring the complex, depot-specific regulation of this anti-inflammatory adipokine [72,73]. These structural and functional shifts diminish PVAT's vasoprotective and vasorelaxant properties, thereby facilitating vascular dysfunction and atherogenesis [74]. Advances in cardiovascular imaging, particularly coronary computed tomography angiography, now permit non-invasive characterization of PVAT inflammation through the perivascular fat attenuation index, which reflects the transition from lipid-dense to more aqueous adipose tissue during inflammatory activation [71,72]. Higher, less negative attenuation values denote greater local vascular inflammation and have been consistently associated with unstable coronary plaques, increased risk of MACEs, and measurable response to anti-inflammatory treatment [74-76].

## Obesity and hypertension

Obesity—particularly excess visceral adiposity—accounts for approximately 65–75% of primary hypertension cases and drives blood pressure elevation through several well-defined mechanisms [77,78]. RAAS overactivation arises when visceral and perirenal fat exert direct mechanical compression on the kidneys, triggering renin release, increasing angiotensin II and aldosterone concentrations, and enhancing sodium retention and plasma volume expansion; adipocytes also synthesize angiotensinogen and other RAAS components, further intensifying this pathway [35,38,79,80]. Sympathetic nervous system overactivity is another hallmark of obesity-related hypertension, characterized by heightened renal and skeletal muscle sympathetic drive in response to hyperleptinemia, insulin resistance, and impaired baroreceptor and chemoreceptor reflex sensitivity, resulting in increased heart rate, augmented renal sodium reabsorption, and secondary RAAS stimulation [80]. Adipokine and inflammatory dysregulation, including elevated leptin, reduced adiponectin, and increased IL-6, promotes endothelial dysfunction, oxidative stress, vascular stiffness, and structural remodeling while simultaneously reinforcing sympathetic nervous system and RAAS activation [38]. Insulin resistance and hyperinsulinemia further enhance renal sodium retention and sympathetic activity, although the absence of hypertension in some individuals with severe insulin resistance underscores a more complex interaction [78]. Chronic visceral adiposity also induces renal and cardiac structural alterations, including kidney compression, increased tubular sodium reabsorption, and progressive target-organ injury, contributing to more treatment-resistant hypertension [38]. At the population level, blood pressure shows strong associations with BMI, visceral fat mass, and fat distribution, with visceral or trunk fat exerting the most pronounced independent effect, whereas lean mass

contributes modestly to blood pressure elevation and peripheral (leg) fat demonstrates weaker associations or potential protective effects [81,82].

Alterations in BMI and body composition exert a clear, dose-dependent influence on blood pressure throughout the lifespan. Large population studies demonstrated that the rise in blood pressure begins at approximately the 25$^{th}$ BMI percentile—well within the normal weight range—in both children and adults [83,84]. Each incremental increase in BMI or waist circumference confers a progressively higher risk of hypertension, a pattern consistently observed across demographic, ethnic, and socioeconomic groups [85]. Central adiposity, particularly visceral fat, significantly magnifies this association, and individuals with both elevated BMI and increased waist circumference had a synergistically greater elevation in blood pressure. Weight reduction produces quantifiable and clinically meaningful improvements in blood pressure [83]. Meta-analyses of randomized controlled trials indicate that each kilogram of weight loss lowers systolic blood pressure by about 1.05 mmHg and diastolic pressure by roughly 0.92 mmHg [86]. Greater degrees of weight loss yield proportionately larger benefits [87]. For example, a reduction of 5 kg is typically associated with a 4.4–6.7 mmHg decrease in systolic pressure and a 3.6–5.1 mmHg decrease in diastolic pressure [88]. These effects are evident across age groups and tend to be more pronounced in individuals with higher baseline BMI or central adiposity.

In healthy individuals, acute elevations in insulin increase sympathetic nervous system activity yet concurrently elicit peripheral vasodilation through augmented β-adrenergic vasodilatory responses and reduced α-adrenergic vasoconstriction [89]. This dual action lowers peripheral vascular resistance and maintains stable blood pressure, with hemodynamic support shifting toward increased cardiac output rather than heightened vascular resistance [90]. As metabolic status changes, chronic hyperinsulinemia and insulin resistance progressively attenuate insulin's vasodilatory effects [90]. In obesity, sustained sympathetic activation—driven by persistent hyperinsulinemia and inflammatory signaling—elevates peripheral vascular resistance and contributes to hypertension, forming a self-reinforcing cycle in which sympathetic overactivity further diminishes insulin sensitivity and amplifies sympathetic nervous system drive [91,92]. Evidence from sympathetic blockade studies showed partial restoration of insulin-mediated vasodilation in obesity, underscoring the central role of sympathetic activation in this impairment [91,93]. Neural pathways involving leptin and the melanocortin-4 receptor within the hypothalamus are key mediators of obesity-related sympathetic activation [94]. Elevated leptin concentrations in obesity stimulate these circuits and increase blood pressure, even as metabolic actions such as appetite suppression become ineffective, a pattern termed selective leptin resistance [93]. Insights from monogenic obesity syndromes—such as leptin deficiency and MC4R gene mutations—demonstrated that severe obesity can occur without hypertension or sympathetic overactivation when central leptin–melanocortin signaling is disrupted, highlighting the specificity of these pathways in obesity-induced blood pressure elevation [52].

## Management strategies to reduce cardiovascular risk in obesity

### Lifestyle modification: Dietary approach, exercise and behavioral therapy

Dietary modification and physical activity remain the cornerstone strategies for preventing and managing obesity, insulin resistance, and obesity-related hypertension. Studies showed that weight reduction achieved through a combination of structured exercise and moderate caloric restriction can significantly reduce inflammatory markers, improve insulin sensitivity, elevate adiponectin concentrations, and enhance responsiveness to antihypertensive therapy [95-97]. In overweight and obese populations, this combined approach consistently reduces systemic inflammatory markers, including C-reactive protein, IL-6, and TNF-α, with larger effects observed when weight loss reaches approximately 5–10% [95,97]. Compared with caloric restriction alone, the addition of exercise leads to greater improvements in insulin sensitivity, glycemic control, and blood pressure, reflecting favorable effects on both metabolic and vascular regulation [98]. The response of adiponectin appears more variable; exercise or caloric restriction can increase adiponectin in certain populations, but consistent elevations are more likely when weight loss exceeds 10%, whereas smaller reductions often yield neutral results [99].

Dietary interventions exert clinically meaningful effects on dyslipidemia and overall cardiometabolic risk across diverse populations [100]. Mediterranean and plant-based dietary patterns consistently lower LDL cholesterol and total cholesterol, often reduce triglycerides, preserve or modestly increase HDL cholesterol, and improve the apolipoprotein B/apolipoprotein A1 ratio, thereby conferring broad cardiometabolic benefit [100,101]. The Dietary Approaches to Stop Hypertension (DASH) diet similarly reduces LDL cholesterol, total cholesterol, and very-low-density lipoprotein (VLDL) cholesterol, with demonstrated efficacy in overweight, obese, diabetic, and mixed dyslipidemia populations [102]. Vegetarian and vegan diets, particularly in type 2 diabetes, achieve substantial reductions in LDL cholesterol compared with other dietary patterns [101]. Moderate low-carbohydrate diets that maintain adequate fiber intake improve total cholesterol, triglycerides, HDL cholesterol, and apolipoprotein B, and generally outperform very low-carbohydrate regimens except for triglyceride reduction, which is more pronounced with greater carbohydrate restriction [103]. High-fiber diets, especially those rich in viscous fibers, lower total and LDL cholesterol by approximately 5–10%, enhance lipid-lowering pharmacotherapy effects, and improve insulin sensitivity and inflammatory status [104]. In addition, plant sterols or stanols at doses of approximately 2 g/day reduce LDL cholesterol by around 10%, with modest triglyceride lowering, particularly in individuals with elevated baseline triglyceride concentrations [101]. The Mediterranean diet, endorsed by recent updates from the European Society of Cardiology and the European Atherosclerosis Society (ESC/EAS), is recommended for cardiovascular prevention [8]. This dietary pattern emphasizes vegetables, fruits, nuts, whole grains, cereals, and extra-virgin olive oil, encourages moderate intake of fish and poultry, and limits sweets, red meat, and dairy products [8].

In Indonesia, the implementation of evidence-based dietary interventions should be adapted to local food preferences, cultural practices, and socioeconomic conditions. Rather than directly adopting Western dietary models, the underlying principles of cardiometabolic risk reduction may be incorporated into traditional Indonesian dietary patterns. Given the widespread consumption of white rice as a dietary staple, portion control and partial substitution with higher-fiber alternatives, such as brown rice or other locally available whole grains, may help improve dietary quality and glycemic regulation. Similarly, reducing the frequency of fried food consumption, limiting repeatedly heated cooking oil, and moderating the use of palm oil may contribute to lower saturated fat intake and improved lipid profiles. Reducing added sugar from sweetened beverages, traditional desserts, and processed foods is also important for limiting excessive energy intake. Greater consumption of locally available vegetables, fruits, legumes, tempeh, tofu, and fish should be encouraged as affordable sources of dietary fiber, plant-based protein, and essential nutrients. These culturally adapted dietary strategies, combined with portion control, regular physical activity, and behavioral support, may provide feasible and sustainable approaches to obesity management and cardiovascular risk reduction in resource-limited Indonesian settings.

Beyond nutrition, regular physical activity produces great improvements in adiposity, fat mobilization, and metabolic risk that often surpass the effects of caloric restriction alone. Acute aerobic exercise increases adipose tissue blood flow and stimulates lipolysis through catecholamine-mediated β-adrenergic pathways and natriuretic peptide signaling, facilitating the release of fatty acids for uptake by skeletal muscle; this response increases in parallel with exercise intensity and metabolic demand [105]. Long-duration exercise performed at approximately 45–70% of maximal oxygen consumption ($VO_2$max) significantly enhances whole-body lipid oxidation and increases adipose tissue lipoprotein lipase activity, supporting greater fat utilization in the post-exercise period [105,106]. At the molecular level, acute and short-term exercise downregulates adipose gene expression involved in lipid uptake and lipogenesis and modulates circadian clock genes, consistent with a transition toward healthier adipose tissue function [106]. In addition, both resistance and aerobic training can promote browning of white adipose tissue and increase thermogenic activity, effects that may occur even in the absence of significant weight loss [104,107].

Resistance training improves muscle strength, lean mass, and bone density and provides important metabolic benefits [108]. Low muscle mass is associated with increased risks of obesity, insulin resistance, and type 2 diabetes; therefore, resistance exercise represents an

effective strategy to lower metabolic risk [108,109]. In individuals with overweight or obesity, supervised resistance training programs significantly reduce body fat (approximately 1–5 kg) and body fat percentage, with the greatest effects observed when resistance training is combined with caloric restriction, while resistance training alone produces modest fat loss but yields the largest gains in lean mass (approximately 0.8 kg compared with no training) [109]. Network meta-analyses demonstrated that exercise combined with energy restriction is superior to diet alone for reducing fat mass and preserving muscle across age groups, with resistance training or combined aerobic–resistance programs ranking highest, and moderate-to-low intensity resistance training with caloric restriction being particularly effective for reducing fat while minimizing lean mass loss [110,111]. Typical effective programs use mixed aerobic and resistance training at moderate–vigorous intensity, performed three to four times per week for 12–24 weeks, resulting in reductions in body weight, BMI, waist circumference, visceral adiposity, and improvements in cardiometabolic markers compared with non-exercise controls [109,111].

## Pharmacological approach in obesity: Incretin analogues

Obesity is characterized by dysregulation of appetite within subcortical brain regions and by counter-regulatory mechanisms that promote weight regain following caloric restriction [112]. Advances in anti-obesity pharmacotherapy have introduced therapeutic strategies capable of addressing the maladaptive physiological and hormonal disturbances underlying this condition [113,114]. Glucagon-like peptide-1 receptor agonist (GLP-1RA), such as semaglutide, is a class of incretin analogues. It reduces postprandial glucose levels and supports weight reduction by enhancing satiety, decreasing food intake, and delaying gastric emptying [115]. Glucagon-like peptide-1 (GLP-1) is a 30-amino-acid peptide hormone primarily synthesized by intestinal L cells, with additional production occurring in specific central and autonomic neurons and, to a lesser extent, within the endocrine pancreas [116]. Nutrient ingestion markedly enhances GLP-1 release, and subsequent receptor activation augments glucose-dependent insulin secretion [116]. Oral glucose administration induces a 71% greater insulinotropic response than intravenous delivery at equivalent glucose concentrations—a phenomenon known as the incretin effect—attributed largely to the combined actions of GLP-1 and gastric inhibitory polypeptide [115,116]. GLP-1RA such as semaglutide reproduce the effects of endogenous GLP-1 with prolonged half-life [117]. This improves glycemic control, induces clinically significant weight loss, and modifies multiple cardiometabolic pathways implicated in coronary artery disease, heart failure, and stroke [118].

GLP-1 receptors are expressed in pancreatic β-cells and α-cells, hypothalamic and brainstem nuclei involved in appetite and autonomic control, vagal afferents, cardiomyocytes, endothelial cells, and several peripheral tissues including liver, adipose tissue, and skeletal muscle [119]. Semaglutide engages these receptors and activates cAMP–protein kinase A and other downstream pathways that enhance insulin gene transcription, promote insulin exocytosis, and modulate cellular survival [115]. Because insulinotropic effects are glucose-dependent, semaglutide enhances insulin secretion predominantly in the postprandial and hyperglycemic range, with minimal risk of hypoglycemia in the absence of concomitant insulin or sulfonylureas [115]. Simultaneously, semaglutide suppresses inappropriate glucagon secretion via actions on pancreatic α-cells, further lowering hepatic glucose output (**Figure 2**) [115].

Semaglutide, with structural modifications that prolong half-life for once-weekly use, produces even greater weight loss, with the Semaglutide Treatment Effect in People with Obesity (STEP) trials consistently demonstrating reductions of 15–17% of baseline weight accompanied by improvements in waist circumference, triglycerides, LDL cholesterol, HDL cholesterol, blood pressure, and inflammatory markers such as high-sensitivity C-reactive protein [120,121]. Higher-dose semaglutide has demonstrated additional weight-loss efficacy. In the STEP UP phase 3b trial, once-weekly semaglutide 7.2 mg achieved a mean body-weight reduction of 18.7% at 72 weeks, compared with 15.6% for semaglutide 2.4 mg and 3.9% for placebo, based on the treatment policy estimand [122]. The estimated treatment difference between the 7.2 mg and 2.4 mg doses was −3.1 percentage points (95% confidence interval (CI): −4.7 to −1.6; $p<0.001$). The higher weight reduction of approximately 21% reported under the trial product estimand reflects a different analytical approach and should not be directly combined with treatment policy estimates [122]. Among participants receiving 7.2 mg, 47.7% achieved at least 20% weight loss

and 31.2% achieved at least 25% weight loss. In the STEP-HFpEF trial, among patients with BMI ≥30 kg/m² and HFpEF (EF≥45%), semaglutide-associated weight loss was accompanied by improvements in symptoms and functional capacity [123].

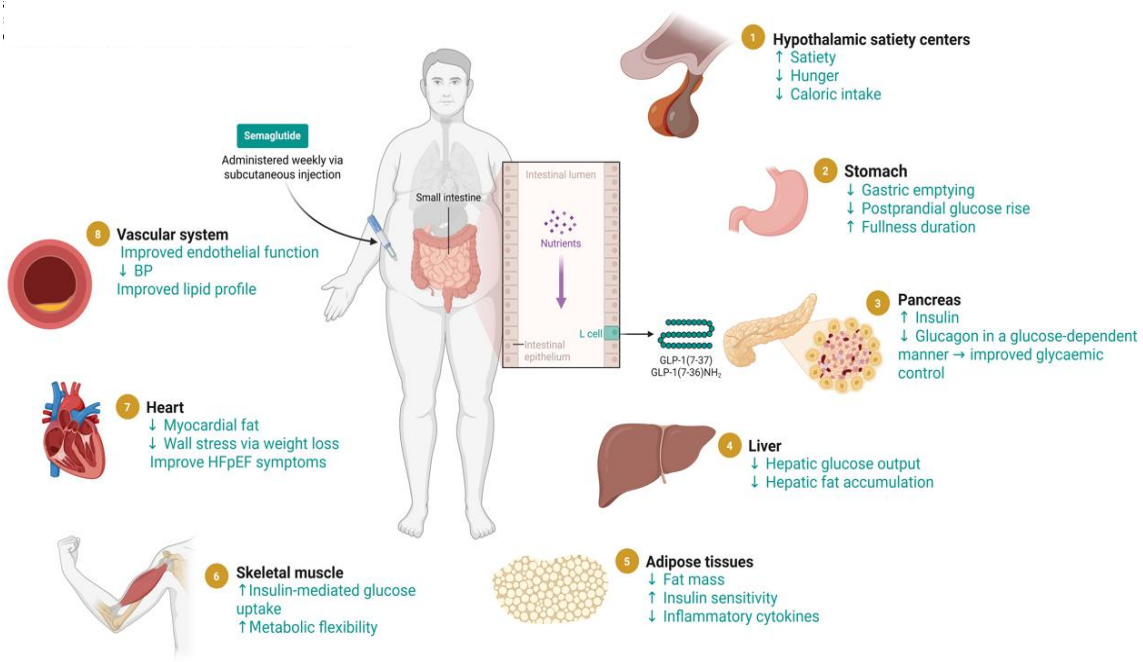



Figure 2. Multisystem mechanisms by which semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), reduces cardiovascular disease (CVD) risk. BP: blood pressure; GLP-1RA: glucagon-like peptide-1 receptor agonist; HFpEF: heart failure with preserved ejection fraction.

Importantly, semaglutide has now been shown to reduce MACE in individuals with overweight or obesity without type 2 diabetes in the SELECT trial, establishing the first dedicated evidence supporting cardiovascular event reduction through pharmacological weight loss therapy [124]. The SELECT trial [124], a large randomized controlled trial, enrolled 17,604 participants with BMI ≥27 kg/m², established cardiovascular disease, and no diabetes. Once-weekly subcutaneous semaglutide 2.4 mg, administered over a median follow-up of 39.8±9.4 months, reduced the risk of the composite primary endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by 20% (hazard ratio=0.80; 95%CI: 0.72–0.90) [124]. The benefit emerged early after treatment initiation and was consistent across cardiovascular outcomes and prespecified subgroups. Semaglutide also significantly reduced body weight and waist circumference, reinforcing its metabolic benefit [124]. Notably, this trial provided direct evidence that pharmacological weight reduction with semaglutide can improve cardiovascular outcomes in individuals with overweight or obesity without diabetes. The mean weight loss was greater than that typically reported with other non-surgical interventions, and post hoc analyses suggested that the cardiovascular benefit was greatest among those achieving at least 10% loss of baseline body weight [124]. Real-world evidence from the STEER study further supports the potential cardiovascular advantage of semaglutide in patients with overweight or obesity and established atherosclerotic cardiovascular disease [125]. However, these findings should be interpreted cautiously because the study was observational, relied on administrative claims data, and had a relatively short follow-up period, leaving potential residual confounding and uncertainty regarding long-term cardiovascular outcomes. In a large retrospective observational cohort using US claims data, semaglutide was associated with significantly lower risks of revised 3-point MACE and revised 5-point MACE compared with tirzepatide, 29% (hazard ratio: 0.71; $p$=0.046) and 22% (hazard ratio: 0.78; $p$=0.040), respectively [125].

The summaries of detailed mechanisms by which semaglutide reduces CVD risk are presented in **Figure 2**. Semaglutide may confer cardiovascular protection through both weight-dependent and weight-independent mechanisms (**Figure 2**). In addition to improving glycemic control and reducing conventional cardiovascular risk factors, weight loss induced by

semaglutide may decrease ectopic fat depots, including perivascular and epicardial adipose tissue, which contribute to endothelial dysfunction, myocardial impairment, and a pro-inflammatory, prothrombotic state (**Figure 2**). In resource-limited settings such as Indonesia, where bariatric surgery is not widely accessible and dual GIP/GLP-1RAs may be unavailable, once-weekly semaglutide may offer a practical and effective option for achieving clinically meaningful weight loss and reducing obesity-related cardiovascular risk [125].

Semaglutide exerts integrated effects across central nervous, gastrointestinal, metabolic, and cardiovascular systems (**Figure 3**). Activation of hypothalamic satiety centers reduces hunger and caloric intake, leading to weight loss and lower autonomic drive, thereby decreasing blood pressure and cardiac stress [119]. Delayed gastric emptying attenuates postprandial glycemic excursions and enhances fullness [126]. Pancreatic actions improve glucose homeostasis through increased insulin secretion and reduced glucagon release [127]. In peripheral tissues, enhanced skeletal muscle glucose uptake and improved insulin sensitivity in adipose tissue reduce metabolic stress, visceral adiposity, and systemic inflammation [34]. Hepatic effects include reduced triglyceride synthesis and lower hepatic glucose output [128]. Vascular benefits encompass reductions in blood pressure, LDL cholesterol, and triglycerides, with concurrent increases in HDL cholesterol and improved endothelial function [129]. Collectively, these pathways converge on the heart to reduce afterload, myocardial stress, adverse left ventricular remodeling, HFpEF risk, and MACE.

Semaglutide produces clinically meaningful reductions in body weight through central appetite suppression, delayed gastric emptying, and improved postprandial glucose regulation (**Figure 3**) [130]. These effects are accompanied by enhanced insulin secretion, reduced glucagon release, and improved glycemic control [128]. Downstream metabolic responses include improved hepatic insulin sensitivity, reduced hepatic fat accumulation, greater skeletal muscle glucose uptake, and modest reductions in inflammatory cytokines within adipose tissue [128,129]. Collectively, these pathways translate into improvements in blood pressure, lipid profile, endothelial function, and overall vascular health [128-130]. In the hypothalamic satiety centers, semaglutide enhances satiety, reduces hunger, and lowers caloric intake, leading to sustained weight loss (**Figure 3**) [127]. In the stomach, semaglutide slows gastric emptying, blunts postprandial glucose excursions, and prolongs fullness [126]. Dual agonists produce similar gastrointestinal effects through wider incretin signaling [131-134]. At the pancreatic level, semaglutide increases glucose-dependent insulin secretion and suppresses glucagon, thereby improving glycemic control [119,135]. Dual agonists amplify these effects through additive stimulation of both GLP-1 and GIP receptors [131-133].

Within adipose tissue, semaglutide reduces fat mass, improves insulin sensitivity, and lowers inflammatory cytokine levels [117]. Dual agonists enhance these effects with greater increases in fat oxidation and larger reductions in ectopic fat in the liver, myocardium, and skeletal muscle, contributing to meaningful reductions in systemic inflammation [118]. In the liver, semaglutide lowers hepatic glucose output and decreases fat accumulation, while dual agonists further improve hepatic steatosis and hepatic insulin sensitivity [128]. Skeletal muscle responses include improved glucose uptake and enhanced metabolic flexibility with semaglutide [129].

The vascular system benefits from improved endothelial function, reduced inflammation, lower blood pressure, and more favorable lipid profiles [136]. These changes are more marked in dual agonists [131,132]. At the cardiac level, semaglutide reduces myocardial fat, lowers wall stress through weight loss, and alleviates HFpEF-related symptoms, although further studies were needed to confirm it [123]. Dual agonists show further improvement in functional capacity, symptomatic status, and biomarkers such as NT-proBNP [137]. Detailed central and peripheral mechanisms of how semaglutide and GIP/GLP-1RA induce metabolic improvement and cardiovascular protection are presented and summarized in **Figure 3**.

Semaglutide stimulates insulin secretion and suppresses glucagon release in a glucose-dependent manner [126]. Semaglutide has received approval for chronic weight management in adults with obesity or overweight complicated by at least one weight-related comorbidity such as hypertension, type 2 diabetes, or hyperlipidemia, and to reduce the risk of MACE in adults with established cardiovascular disease and either obesity or overweight [137]. Summaries of cardiometabolic and cardiovascular effects of semaglutide are presented in **Table 1**.

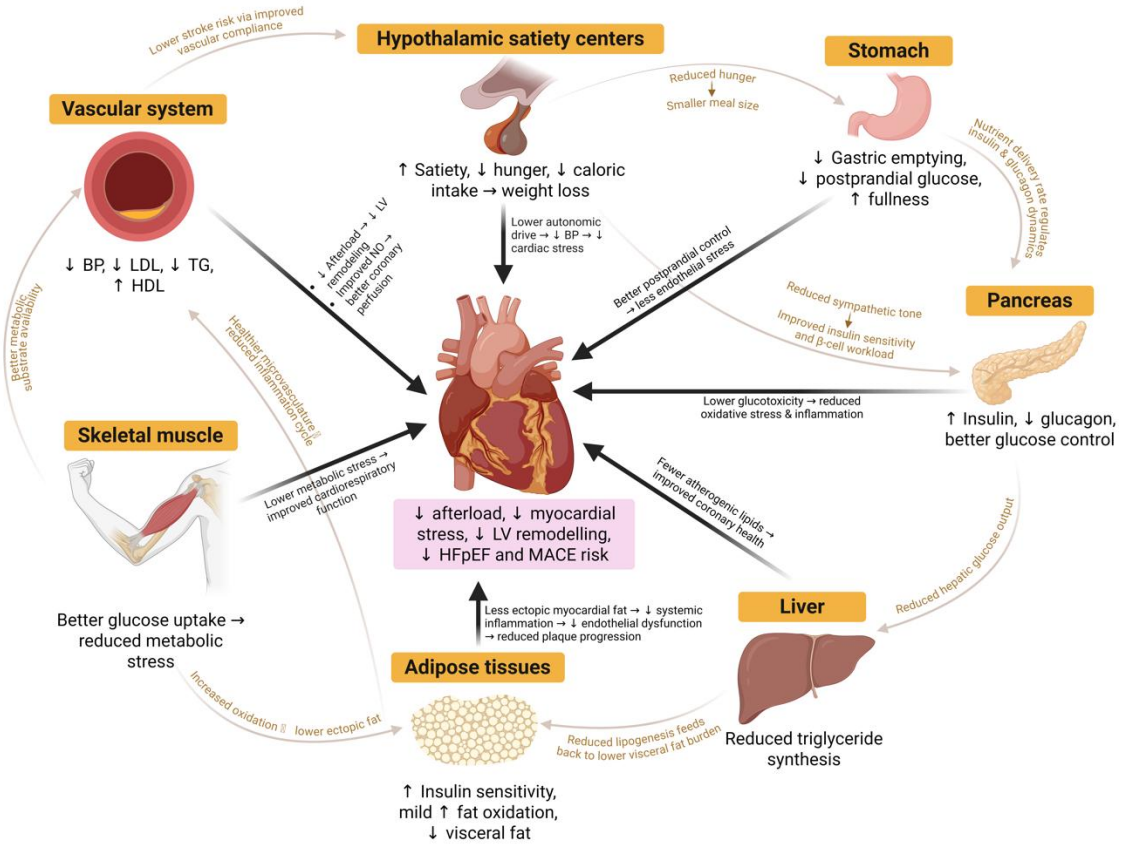



Figure 3. Central and peripheral mechanisms by semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), produce metabolic improvement and cardiovascular protection. BP: blood pressure; GLP-1RA: glucagon-like peptide-1 receptor agonist; HDL: high-density lipoprotein; HFpEF: heart failure with preserved ejection fraction; LDL: low-density lipoprotein; MACE: major adverse cardiovascular events.

Subcutaneous semaglutide (2.4 mg weekly) is an established pharmacologic option. More recent evidence from the published phase 3b STEP UP trial demonstrated that once-weekly semaglutide 7.2 mg achieved significantly greater body-weight reduction than the 2.4 mg dose over 72 weeks, further supporting the efficacy of higher-dose semaglutide for weight management [122]. To accommodate individuals reluctant to initiate injectable therapy, an oral formulation of semaglutide has been developed using an absorption enhancer that facilitates gastric mucosal uptake [138]. Oral semaglutide is administered in the morning with water at least 30 minutes before food to ensure optimal absorption [139]. PIONEER program has demonstrated significant reductions in HbA1c and modest weight loss with the 14 mg oral formulation in individuals with type 2 diabetes [139].

A meta-analysis of multiple randomized trials reported greater weight reduction with GLP-1RAs (-17.36 to -2.49 kg) than with control treatments (-6.2 to +0.43 kg), with higher doses yielding more pronounced effects [140]. Rapid dose escalation of semaglutide has been associated with further increases in weight-loss magnitude in individuals with and without diabetes [140]. In addition to supporting weight loss, semaglutide reduces cardiometabolic risk by lowering blood pressure, improving lipid concentrations, and mitigating components of metabolic syndrome. Meta-analytic data indicated significant reductions in systolic and diastolic blood pressure with GLP-1RAs, particularly with accelerated dose-titration protocols (**Table 1**) [140].

Table 1. Cardiometabolic and cardiovascular effects of semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA)

| Feature | Detailed explanation |
|---|---|
| Primary receptor target | Glucagon-like peptide-1 receptor (GLP-1R) only |
| Origin mimicked | Intestinal L-cell glucagon-like peptide-1 (GLP-1) |
| Insulin secretion | ↑ Insulin (glucose-dependent) |

| Feature | Detailed explanation |
|---|---|
| Glucagon secretion | ↓ Glucagon |
| Central appetite regulation | ↑ Satiety, ↓ hunger, ↓ intake |
| Gastric emptying | ↓ Gastric emptying |
| Fat oxidation | Modest increase via weight loss |
| Insulin sensitivity | Improved (secondary to weight loss, GLP-1 action) |
| Ectopic fat (liver, myocardium, muscle) | Reduction, mainly via weight loss |
| Typical weight loss | ~10–17% (semaglutide 2.4 mg) |
| Lipids and blood pressure | ↓ triglycerides, ↓ low-density lipoprotein, ↑ high-density lipoprotein |
| HFpEF outcomes | Semaglutide: improved symptoms, 6MWD, NT-proBNP |
| Hard cardiovascular outcomes in obesity without type 2 diabetes | Semaglutide: ↓ MACE |
| Summary | Potent weight loss and cardiometabolic benefit via GLP-1R |

HFpEF: heart failure with preserved ejection fraction; MACE: major adverse cardiovascular events; NT-proBNP: N-terminal pro–B-type natriuretic peptide; 6MWD: six-minute walk distance

### Surgical approach in obesity

Metabolic bariatric surgery (MBS) remains the most effective long-term intervention for managing clinical obesity and reducing severe obesity–related comorbidities and mortality [141]. Modern pharmacotherapies using incretin-based agents, including semaglutide, have demonstrated substantial short- and intermediate-term weight-loss efficacy, yet surgical intervention continues to provide greater durability [112]. In addition to the two most commonly performed procedures—sleeve gastrectomy and Roux-en-Y gastric bypass—multiple other MBS techniques exist, with considerable variation in practice patterns across regions [112,141].

Guideline recommendations for bariatric surgery are generally based on BMI criteria in combination with adiposity-related complications [112]. According to the updated 2022 guidelines jointly issued by the American Society for Metabolic and Bariatric Surgery (ASMBS) and the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO), MBS is recommended for individuals with a body mass index (BMI) ≥35 kg/m², regardless of the presence or severity of obesity-related comorbidities [112]. MBS is also recommended for patients with type 2 diabetes and BMI ≥30 kg/m² and should be considered for individuals with BMI 30–34.9 kg/m² who fail to achieve substantial or sustained weight reduction or improvement in obesity-related comorbidities through nonsurgical interventions [112]. Importantly, the guidelines recognize that Asian populations develop obesity-related metabolic complications at lower BMI thresholds, suggesting that MBS eligibility should be evaluated using population-specific criteria. For Indonesia and other resource-limited settings, implementation of these recommendations should also consider surgical expertise, healthcare infrastructure, affordability, and access to long-term postoperative follow-up.

Bariatric surgery can profoundly improve health outcomes in individuals with obesity, and thorough preoperative evaluation has traditionally been emphasized to optimize postoperative success. Although substantial weight loss is commonly achieved, approximately 20–30% of individuals undergoing sleeve gastrectomy or Roux-en-Y gastric bypass do not reach the expected degree of weight reduction [142,143]. To the best of our knowledge, no validated method is currently available to reliably predict which candidates will experience the most favorable outcomes.

## Implementation challenges and priorities in resource-limited settings

Despite the established efficacy of semaglutide in obesity management and cardiovascular risk reduction, its implementation in resource-limited settings presents substantial economic and healthcare challenges. The 2025 World Health Organization (WHO) guideline conditionally recommends GLP-1 therapies for long-term obesity management, while emphasizing concerns regarding affordability, health-system preparedness, treatment sustainability, and equitable access [144]. In Indonesia, the potential implementation of semaglutide should consider medication costs, insurance coverage, availability and continuity of supply, and the capacity of healthcare facilities to support long-term treatment and monitoring. Given competing healthcare priorities and constrained resources, treatment prioritization may be necessary, particularly for

eligible patients with established cardiovascular disease or substantial cardiometabolic risk who are expected to derive meaningful clinical benefits. Strengthening primary healthcare services to support patient selection, treatment monitoring, adverse-event management, and long-term adherence is also essential. Strategies such as negotiated pricing, pooled procurement, and tiered pricing may improve affordability and accessibility. The integration of emerging pharmacological therapies, including semaglutide, into obesity management should consider clinical benefits, affordability, accessibility, and long-term treatment sustainability, alongside continued investment in scalable population-level cardiovascular prevention strategies, including dietary improvement, physical activity promotion, and management of conventional cardiovascular risk factors. Context-specific cost-effectiveness and budget-impact evaluations are therefore needed to guide equitable access, appropriate resource allocation, and sustainable implementation within resource-limited healthcare systems.

# Conclusion

Semaglutide represents a major advancement in obesity management, demonstrating substantial weight reduction, improvements in cardiometabolic risk factors, and significant reductions in major adverse cardiovascular events among patients with overweight or obesity and established cardiovascular disease, including those without diabetes. These benefits support its role as an important therapeutic option for obesity management and cardiovascular risk reduction. However, translating this evidence into clinical practice in resource-limited settings, particularly Indonesia, requires careful consideration of affordability, equitable access, treatment availability, long-term adherence, safety monitoring, and healthcare system capacity. Implementation strategies should prioritize eligible patients with the greatest anticipated clinical benefit while integrating semaglutide into comprehensive obesity management that includes culturally appropriate lifestyle interventions and cardiovascular risk factor control. Further research on cost-effectiveness, long-term sustainability, and real-world outcomes in Indonesian populations is warranted to inform equitable and evidence-based treatment strategies.

### Ethics approval

Not required.

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### Competing interests

The authors disclose that Novo Nordisk provided financial support for the preparation of this manuscript. The funding relationship constitutes a potential competing interest given that semaglutide is a product manufactured by Novo Nordisk. The authors declare no other competing interests.

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### Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

### Declaration of artificial intelligence use

Authors declare that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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