

Beyond Weight Loss: Impact of Metabolic-Bariatric Surgery on Major Adverse Cardiovascular Events in Patients with Obesity

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Abstract

Obesity is a chronic cardiometabolic disease characterized by dysfunctional expansion of adipose tissue, low-grade systemic inflammation, insulin resistance, atherogenic dyslipidemia, endothelial dysfunction, and progressive cardiovascular remodeling. These mechanisms explain its close association with major adverse cardiovascular events, including acute myocardial infarction, stroke, heart failure, and cardiovascular mortality. Metabolic-bariatric surgery is no longer considered an exclusively restrictive intervention, or one directed only toward weight loss; rather, it has become established as a strategy of physiological reprogramming capable of modifying the gut-pancreas-liver-adipose tissue axis and reducing global cardiometabolic risk. This review analyzes the pathophysiological foundations linking obesity and cardiovascular disease, the

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cardioprotective mechanisms induced by metabolic-bariatric surgery, and the available clinical evidence on the reduction of major adverse cardiovascular events. Postoperative benefits include decreased visceral adiposity, partial restoration of the adipocyte profile, increased adiponectin, reduced leptin and inflammatory mediators, improved insulin sensitivity, incretin modulation, changes in bile acids, remodeling of the gut microbiota, and partial reversal of obesity-associated vascular and cardiac alterations.

Keywords

Obesity, Metabolic-Bariatric Surgery, Major Adverse Cardiovascular Events, MACE, Gastric Bypass, Sleeve Gastrectomy, GLP-1, Cardiovascular Risk

1. Introduction

Obesity currently represents one of the leading public health problems worldwide and is recognized as a complex cardiometabolic disease associated with chronic inflammation, endocrine dysfunction, and a significant increase in cardiovascular morbidity and mortality. Its prevalence has increased steadily over recent decades, favoring the development of type 2 diabetes mellitus, arterial hypertension, dyslipidemia, and atherosclerotic cardiovascular disease; expansion of visceral adipose tissue promotes oxidative stress, endothelial dysfunction, and metabolic alterations that increase the risk of major adverse cardiovascular events [1].

From an epidemiological perspective, obesity has reached epidemic proportions globally. In 2022, more than one billion people were living with obesity, representing approximately 13% of the global population, while nearly 43% of adults had overweight or obesity. Since 1975, obesity rates have tripled, and projections estimate that by 2035 approximately 1.9 billion adults could be living with obesity, consolidating this disease as one of the main determinants of cardiovascular burden and preventable mortality in the twenty-first century. Additionally, the sustained increase in obesity in low- and middle-income countries has intensified the global impact of noncommunicable diseases, particularly type 2 diabetes mellitus and cardiovascular disease [2].

Traditionally, the therapeutic management of obesity was based on intensive lifestyle modifications and pharmacological treatment; however, the weight loss achieved through these strategies is usually modest and difficult to maintain in the long term, particularly in patients with severe obesity. In this context, metabolic-bariatric surgery has emerged as the most effective intervention for inducing substantial and sustained weight reduction, in addition to achieving significant improvement in multiple metabolic comorbidities. More importantly, several studies have shown that the benefits of surgery extend beyond simple weight loss, including improved insulin sensitivity, incretin regulation, and reduction of cardiovascular risk factors [3].

The contemporary understanding of obesity has evolved from a model centered

exclusively on caloric excess toward a complex biological paradigm involving neurohormonal, genetic, inflammatory, and gastrointestinal mechanisms. The discovery of pathways related to leptin, melanocortins, and incretin hormones such as GLP-1 enabled obesity to be understood as a chronic disease regulated by multiple metabolic circuits, and not merely as a consequence of individual behaviors. In parallel, the development of new pharmacological therapies and their integration with metabolic surgery have profoundly modified the therapeutic approach to obesity and its cardiovascular complications [4].

From a cardiovascular standpoint, obesity promotes vascular remodeling, myocardial lipotoxicity, and atherothrombotic progression through complex inflammatory and metabolic mechanisms. Visceral adipose tissue acts as an active endocrine organ capable of secreting proinflammatory adipokines and mediators related to the progression of coronary artery disease, arterial hypertension, and cardiac dysfunction. Consequently, obesity is associated with a significant increase in global cardiovascular risk and represents one of the leading determinants of preventable mortality worldwide [5].

In recent years, metabolic-bariatric surgery has ceased to be considered exclusively a weight-loss strategy and has become established as a cardiometabolic intervention capable of modifying hard clinical outcomes. Contemporary evidence suggests that procedures such as gastric bypass and sleeve gastrectomy can reduce mortality and major adverse cardiovascular events in patients with severe obesity, positioning metabolic surgery as a potentially relevant component of modern cardiovascular prevention [6].

Therefore, the objective of this review is to critically analyze the current evidence on the impact of metabolic-bariatric surgery in reducing major adverse cardiovascular events in patients with obesity, integrating pathophysiological foundations, metabolic mechanisms, and contemporary cardiovascular clinical evidence.

2. Cardiometabolic Pathophysiology of Obesity

Obesity should be understood as a chronic disease of energetic, endocrine, and immunometabolic dysregulation. Excess adipose tissue reflects only the visible clinical manifestation of a deeper biological alteration, whose development depends on the interaction among genetic predisposition, epigenetic programming, gut microbiota, hypothalamic hunger-satiety signals, and progressive dysfunction of glucolipid metabolism. In this context, the adipocyte ceases to behave as a passive cell of energy storage and becomes an active node of endocrine, inflammatory, and vascular communication, capable of modulating insulin resistance, systemic inflammation, and cardiovascular risk [7].

Progression from excess body weight to cardiometabolic disease depends less on absolute BMI than on the distribution, quality, and functionality of adipose tissue. Visceral and ectopic adiposity have greater pathogenic relevance than subcutaneous fat because of their high lipolytic activity, proximity to the portal system,

and capacity to induce hepatic insulin resistance, atherogenic dyslipidemia, and vascular injury. This conceptual shift has given rise to the paradigm of “obesities,” in which different phenotypes express distinct degrees of inflammation, atherothrombotic risk, and cardiovascular vulnerability [8].

The central phenomenon linking obesity and cardiovascular disease is adipocyte alteration. Under conditions of nutritional overload, the hypertrophic adipocyte increases the release of free fatty acids, leptin, TNF- α , IL-6, and MCP-1, while reducing adiponectin, a molecule with anti-inflammatory, insulin-sensitizing, and vasoprotective functions. This imbalance favors NF- κ B activation, oxidative stress, mitochondrial dysfunction, and impaired insulin signaling, establishing a persistent state of low-grade metabolic inflammation [9].

At the vascular level, obesity induces endothelial injury through multiple convergent mechanisms. Expansion of visceral and perivascular adipose tissue increases the local production of inflammatory cytokines, reactive oxygen species, angiotensinogen, and vasoconstrictive mediators, thereby reducing nitric oxide bioavailability and promoting arterial stiffness, vasoconstriction, hypertension, and vascular remodeling. Perivascular adipose tissue, which under physiological conditions exerts anticontractile and homeostatic effects, loses this protective function during obesity and acquires a proinflammatory phenotype that directly contributes to endothelial dysfunction, atherosclerosis, and coronary artery disease [10].

Insulin resistance constitutes another decisive molecular axis. Excess free fatty acids and intracellular accumulation of diacylglycerols and ceramides interfere with the IRS-1/PI3K/Akt pathway, reducing peripheral glucose uptake and promoting compensatory hyperinsulinemia. This alteration is associated with increased hepatic VLDL production, hypertriglyceridemia, reduced HDL, and formation of small dense LDL particles. In this setting, indices such as the triglyceride-glucose index and markers of visceral adiposity allow approximation of integrated cardiometabolic risk, as they simultaneously capture insulin resistance, dyslipidemia, and visceral fat accumulation [11].

Abdominal obesity also has direct prognostic value for major adverse cardiovascular events. Waist circumference, as a clinical marker of visceral adiposity, identifies a high-risk phenotype that may not be adequately captured by BMI. Abdominal fat behaves as an inflammatory and atherogenic reservoir capable of promoting endothelial dysfunction, oxidative stress, low HDL, hypertriglyceridemia, and activation of prothrombotic pathways. Therefore, cardiovascular risk assessment in patients with obesity should incorporate measurements of adipose distribution and not be limited to global weight-based metrics [12].

The integration between atherogenic dyslipidemia and visceral obesity allows a better understanding of progression toward cardiovascular disease. The atherogenic index of plasma and its derivatives combined with obesity measures reflect cumulative exposure to triglycerides, low HDL, glycemic alterations, and central adiposity. This sustained exposure generates a dynamic metabolic phenotype in which diabetes amplifies cardiovascular risk through glucotoxicity, lipotoxicity,

persistent inflammation, and accelerated vascular injury. Consequently, risk does not depend only on an isolated baseline value, but on the cumulative metabolic burden over time [13].

Finally, obesity induces subcellular alterations that sustain metabolic inflammation. Autolysosomal dysfunction compromises the degradation of damaged organelles, misfolded proteins, and intracellular lipids, favoring the accumulation of dysfunctional mitochondria, endoplasmic reticulum stress, and persistent inflammatory activation. Impaired autophagy in adipose tissue, liver, skeletal muscle, pancreas, kidney, heart, and brain contributes to insulin resistance, lipotoxicity, metabolic liver disease, atherosclerosis, and myocardial dysfunction. Thus, obesity is consolidated as a systemic disease in which inflammation, metabolism, and cardiovascular injury form a pathophysiological continuum [14].

3. Metabolic-Bariatric Surgery and Cardioprotective Mechanisms

Metabolic-bariatric surgery should be defined as the set of surgical or endoluminal interventions aimed at modifying gastrointestinal anatomy and physiology to treat obesity and its metabolic complications, not only through mechanical restriction or caloric malabsorption, but through systemic reprogramming of the gut-pancreas-liver-adipose tissue axis. The term “metabolic” has progressively replaced the classical notion of “bariatric” surgery because its therapeutic effects include remission or improvement of type 2 diabetes mellitus, reduction of insulin resistance, modification of incretin signaling, changes in bile acids, remodeling of the gut microbiota, and attenuation of systemic inflammation. In this sense, procedures such as Roux-en-Y gastric bypass and sleeve gastrectomy should not be interpreted only as techniques that reduce gastric capacity, but as interventions capable of altering intestinal nutrient exposure, modifying enteroendocrine signals, and activating metabolic circuits with potential impact on cardiovascular risk [15].

From an anatomic-functional perspective, the main metabolic-bariatric techniques induce differentiated physiological effects. Roux-en-Y gastric bypass combines the creation of a small gastric pouch with diversion of alimentary transit toward the jejunum, substantially modifying early contact among nutrients, bile, and intestinal mucosa. Sleeve gastrectomy reduces gastric volume through longitudinal gastric resection, but also alters hormonal signals related to satiety, gastric emptying, and intestinal peptide secretion. Adjustable gastric banding, historically relevant, exerts a predominantly restrictive effect, but has shown lower metabolic and weight-loss efficacy compared with modern techniques. In contemporary comparative trials, gastric bypass and sleeve gastrectomy have demonstrated superiority over gastric banding in weight loss and quality of life, consolidating their role as central procedures in the surgical management of severe obesity [16].

Roux-en-Y gastric bypass represents one of the most complete models of metabolic surgery because it integrates gastric restriction, duodenal exclusion, accelerated nutrient transit toward the distal intestine, and profound changes in enter-

hepatic signaling. Unlike a purely mechanical intervention, RYGB modifies the postprandial kinetics of glucose, lipids, intestinal peptides, and bile acids, generating a new metabolic environment. The introduction of laparoscopic and robotic platforms has allowed standardization of the technique, improved surgical precision, and expanded applicability in patients with severe obesity or complex anatomy. Although technical aspects are important for perioperative safety, their pathophysiological relevance lies in the fact that the resulting gastrointestinal reconstruction generates sustained reorganization of nutritional flows and hormonal signals that condition the magnitude of subsequent metabolic effects [17].

The expansion of less invasive procedures, such as endoscopic sleeve gastropasty, has broadened the therapeutic spectrum for patients with obesity who are not ideal candidates for conventional surgery or who require bridging strategies. This technique reduces gastric volume through endoscopic suturing without surgical resection, slowing gastric emptying, increasing satiety, and producing clinically relevant weight loss. Although its metabolic and cardiovascular impact appears lower than that of classical surgical procedures, its conceptual interest lies in demonstrating that anatomical modification of the stomach can induce effects on appetite, intake, glycemia, and metabolic profile without requiring major intestinal diversion. Therefore, endoluminal techniques help clarify that the metabolic benefit of these interventions does not depend on a single mechanism, but on the combination of reduced intake, gastric signals, satiety, and neurohormonal adaptation [18]. Unlike gastric bypass and surgical sleeve gastrectomy, endoluminal interventions still have limited direct evidence regarding MACE reduction; therefore, their inclusion in this review should be interpreted mainly from a mechanistic, metabolic, and weight-loss perspective, and not as equivalent to the cardiovascular support available for classical surgical procedures.

One of the most important axes of postoperative cardioprotection is endocrine remodeling of adipose tissue, muscle, and liver. After metabolic-bariatric surgery, there is progressive modification of the adipokine, myokine, and hepatokine profile, favoring a less inflammatory, more insulin-sensitive, and metabolically efficient state. Adiponectin usually increases, whereas leptin and proinflammatory mediators such as IL-1, IL-6, and IL-8 decrease, reducing the chronic inflammatory signaling characteristic of obesity. At the muscular level, metabolic improvement may be related to changes in myokines associated with insulin resistance, whereas the liver adjusts the secretion of hepatokines linked to lipid oxidation, insulin sensitivity, and energy homeostasis. This interorgan reorganization allows metabolic surgery to be interpreted as a systemic endocrine intervention that partially restores communication among dysfunctional metabolic organs [19].

Clinical evidence confirms that metabolic surgery favorably modifies the inflammatory and metabolic profile in patients with obesity. After procedures such as sleeve gastrectomy and gastric bypass, increases in adiponectin, reductions in leptin, decreases in glucose, total cholesterol, LDL cholesterol, triglycerides, and high-sensitivity C-reactive protein, together with increases in HDL cholesterol,

have been observed. These changes are especially relevant because they connect the reduction of visceral adipose tissue with partial reversal of the atherogenic phenotype. Reduced leptin may decrease sympathetic activation and vascular inflammation, while increased adiponectin promotes fatty acid oxidation, insulin sensitivity, and endothelial protection. Thus, postoperative improvement does not correspond only to lower body weight, but to a biochemical reconfiguration that reduces the inflammatory, glucotoxic, and lipotoxic burden associated with cardiovascular risk [20].

The incretin system constitutes another essential component of the metabolic effects following surgery. Accelerated nutrient delivery to the distal intestine increases secretion of GLP-1, peptide YY, and oxyntomodulin, mediators that regulate satiety, insulin secretion, gastric emptying, energy expenditure, and hepatic metabolism. The relevance of this axis has been reinforced by experimental studies demonstrating that dual GLP-1/glucagon agonists can partially reproduce the metabolic effects of surgery through controlled lipolysis of white adipose tissue, increased adiponectin, elevated FGF21, activation of brown adipose tissue, induction of adipocyte “beiging,” and increased energy expenditure. This phenomenon suggests that metabolic surgery acts as a physiological modulator of hormonal networks capable of reorganizing energy flow among adipose tissue, pancreas, and liver [21].

Bile acids and the gut microbiota constitute a second layer of metabolic signaling induced by surgery. After gastric bypass or sleeve gastrectomy, changes in intestinal transit and luminal exposure alter the bile acid pool, which functions not only as detergents for lipid absorption, but also as endocrine molecules capable of activating FXR and TGR5 receptors. Activation of these pathways regulates gluconeogenesis, insulin sensitivity, GLP-1 secretion, lipid metabolism, and hepatic inflammation. Simultaneously, surgery modifies the composition of the gut microbiota, favoring a less dysbiotic ecosystem that may be more efficient in producing metabolites associated with metabolic homeostasis. Together, the bile acid-microbiota-nuclear receptor axis helps explain why surgery may generate durable metabolic benefits even after weight loss stabilizes.

The effect of metabolic surgery on microbiota is particularly relevant because obesity is associated with intestinal dysbiosis, low-grade inflammation, metabolic endotoxemia, insulin resistance, and dyslipidemia. After gastric bypass, several studies describe increased microbial diversity, enrichment of beneficial bacteria, and partial reversal of the dysbiotic profile induced by a Western diet. This microbial remodeling may reduce lipopolysaccharide translocation, attenuate systemic immune activation, and improve intestinal metabolic signaling. From a cardiometabolic standpoint, restoration of the microbiota-host axis represents a plausible mechanism to explain reduced systemic inflammation, better glycemic control, and improved lipid profile after surgery, all of which are involved in reducing atherothrombotic risk [15] [22].

The cardiovascular translation of these metabolic changes is particularly evident in the phenotype of obesity-associated heart failure with preserved ejection

fraction. Severe obesity induces plasma volume expansion, increased preload, left ventricular hypertrophy, increased epicardial fat, diastolic dysfunction, and mechanical cardiac restriction. By inducing sustained weight loss and reduction of visceral and epicardial adiposity, metabolic surgery may decrease left ventricular mass, improve myocardial compliance, and reduce filling pressures. These effects are not purely hemodynamic, as reduced systemic inflammation, decreased myocardial lipotoxicity, and improved insulin sensitivity also participate. Therefore, metabolic surgery offers a therapeutic model to study the extent to which obesity-induced cardiac remodeling is reversible [23].

The coronary microvasculature constitutes another potentially modifiable pathophysiological target. In patients with obesity, coronary microvascular dysfunction may appear even in the absence of obstructive coronary artery disease and is associated with reduced coronary flow reserve, systemic inflammation, insulin resistance, and impaired endothelium-dependent vasodilation. Positron emission tomography studies have shown that coronary flow reserve discriminates the risk of death, infarction, or hospitalization for heart failure better than BMI alone. This finding is fundamental because it reinforces the concept that cardiovascular risk in obesity is not explained only by weight, but by functional vascular injury. Consequently, interventions capable of reducing inflammation, improving metabolic profile, and restoring endothelial function—such as metabolic surgery—could affect residual microvascular risk [24].

Body composition also modulates cardiovascular response in obesity. The coexistence of obesity with low muscle mass or sarcopenia increases metabolic vulnerability and is associated with greater risk of coronary microvascular dysfunction and cardiovascular events, particularly hospitalization for heart failure. This point is relevant for metabolic surgery because weight loss should not be interpreted only as reduction of total fat mass, but as qualitative modification of body composition. Preferential reduction of visceral adiposity and preservation of muscle mass may be determinants for maximizing cardiovascular benefit. Therefore, postoperative follow-up should integrate nutrition, physical activity, muscle preservation, and cardiometabolic assessment, avoiding weight loss at the expense of functional deterioration [25].

4. Reduction of Major Adverse Cardiovascular Events after Metabolic-Bariatric Surgery

Major adverse cardiovascular events, or MACE, constitute a composite outcome used to capture the clinically relevant burden of cardiovascular disease in longitudinal studies. Although their definition varies across investigations, they usually include acute myocardial infarction, stroke, cardiovascular death, and, in some bariatric studies, hospitalization for heart failure or all-cause mortality. This heterogeneity requires that each result be interpreted according to the exact composition of the endpoint, follow-up time, and baseline risk profile of the cohort. In the context of metabolic-bariatric surgery, the relevance of MACE lies in its ability

to evaluate whether the intervention modifies hard outcomes and not only intermediate biomarkers. In a systematic review and meta-analysis of patients with obesity and cardiovascular disease, bariatric surgery was associated with lower odds of MACE compared with no surgery, with a pooled OR of 0.49 and an adjusted hazard ratio of 0.57, suggesting a clinically significant cardioprotective effect despite heterogeneity among included studies [26].

5. Strengths and Limits of Postoperative Cardiovascular Evidence

Although the association between metabolic-bariatric surgery and lower incidence of MACE is consistent across multiple cohorts, its interpretation must recognize the inherent limitations of observational evidence. Confounding by indication represents a central source of bias, since patients selected for surgery often differ from nonoperated patients in age, obesity trajectory, access to the health care system, frailty, adherence, comorbidity burden, and probability of receiving multidisciplinary follow-up. Similarly, procedure selection is not random: gastric bypass, sleeve gastrectomy, gastric banding, and endoluminal techniques are indicated according to different clinical profiles, including diabetes, gastroesophageal reflux, nutritional risk, obesity severity, surgical anatomy, and perioperative risk, which may modify both the probability of exposure and baseline cardiovascular event risk.

Therefore, even studies using matching, propensity score weighting, or multi-variable adjustment may retain residual confounding, bias related to the nonsurgical comparator, survival bias, temporal biases, and variability in cardiovascular outcome coding. From a causal inference perspective, these studies should be interpreted as approximations to a hypothetical target trial, not as complete substitutes for randomization; moreover, the available randomized trials in bariatric surgery have primarily been designed to evaluate weight loss, quality of life, surgical safety, and metabolic outcomes, rather than adjudicated MACE as a primary cardiovascular endpoint. Consequently, current evidence supports a robust and biologically plausible cardioprotective association, but the exact magnitude of the causal effect on MACE should be considered dependent on study design, comparator, baseline population, and procedure evaluated [27]–[29].

An initial approach to postoperative cardiovascular benefit comes from studies evaluating early reduction in cardiometabolic risk using predictive scores. In a prospective cohort of patients with morbid obesity, bariatric surgery produced a mean weight loss of 35.8 kg at six months and a significant reduction in calculated risk of diabetes and cardiovascular events. Although this study did not measure observed MACE, it showed that the intervention modifies early components that feed atherothrombotic risk, including weight, metabolic profile, and cardiovascular risk scores. The decrease in the “Progetto Cuore” score from 2.0 to 0.8 suggests that early postoperative changes may anticipate a later reduction in clinical events, especially when sustained over time [30].

Direct evidence of cardiovascular event reduction began to consolidate with long-term follow-up cohorts. In a matched cohort of patients undergoing Roux-en-Y gastric bypass, compared with nonoperated controls, a significant reduction was observed in major cardiovascular events composed of myocardial infarction, stroke, and congestive heart failure during follow-up of up to 12 years. The adjusted model confirmed lower risk of severe cardiovascular events in the surgical group, with an HR of 0.58. In addition, the specific reduction in heart failure suggests that surgery not only attenuates coronary atherosclerosis, but also modifies hemodynamic, inflammatory, and metabolic determinants involved in ventricular remodeling and clinical congestion [31].

The impact of surgery on MACE was also evaluated in a historical cohort of patients with class II-III obesity treated at Mayo Clinic. The study compared patients undergoing gastric bypass within the first year of evaluation with nonsurgical medical management, using as the primary endpoint a composite of all-cause mortality, stroke, hospitalization for heart failure, and acute myocardial infarction. Early surgery was associated with lower risk of MACE, with an adjusted HR of 0.62, and lower all-cause mortality, with an adjusted HR of 0.51. This observation is important because it suggests that the timing of intervention may influence the degree of cardiovascular protection before cumulative vascular and myocardial injury becomes irreversible [32].

In patients with type 2 diabetes mellitus and severe obesity, event reduction is particularly relevant because of the high baseline risk burden. In a population-based matched cohort from Ontario, Canada, including patients with diabetes and BMI ≥ 35 kg/m², bariatric surgery was associated with a 47% reduction in all-cause mortality, 68% reduction in cardiovascular mortality, and 34% reduction in composite cardiac events. A reduction in nonfatal renal events was also observed, reinforcing the concept that metabolic surgery modifies systemic vascular risk and not only coronary risk. These data support the concept of multiorgan intervention, especially in patients with diabetes and severe obesity, in whom reduction of glucotoxicity, lipotoxicity, and inflammation may translate into lower macrovascular and microvascular injury [33].

The cardiovascular benefit appears to extend to populations with advanced metabolic liver disease. In the SPLENDOR study, conducted in patients with obesity and biopsy-confirmed fibrotic nonalcoholic steatohepatitis, bariatric surgery was associated with a marked reduction in major liver outcomes and MACE. At 10 years, the cumulative incidence of MACE was 8.5% in the surgical group versus 15.7% in the nonsurgical group, with an adjusted HR of 0.30. This result is particularly important because it integrates the hepato-cardiovascular axis: fibrotic steatohepatitis represents a phenotype of systemic metabolic inflammation, insulin resistance, and atherogenic dyslipidemia, such that its postoperative improvement may be accompanied by simultaneous reduction in cardiovascular events [34].

In patients with arterial hypertension and morbid obesity, a matched Swedish nationwide cohort showed that metabolic surgery was associated with lower risk

of MACE compared with nonoperated controls. The endpoint included acute coronary syndrome, cerebrovascular event, fatal cardiovascular event, or sudden unwitnessed death. After adjustment for duration of hypertension, comorbidities, and education, the surgical group had an adjusted HR of 0.73 for MACE and an HR of 0.52 for acute coronary syndrome. These findings suggest that postoperative benefit does not depend only on weight loss, but also on improvements in blood pressure, vascular stiffness, insulin sensitivity, dyslipidemia, and inflammatory burden, mechanisms closely related to atherosclerotic progression [35].

Asian evidence also provides relevant data on estimated cardiovascular risk reduction. In a multicenter study of patients undergoing one-anastomosis gastric bypass or single-anastomosis duodenojejunal bypass with sleeve gastrectomy, both procedures showed sustained improvements in weight, diabetes, hypertension, and dyslipidemia at three years. Using regional predictive models, a significant reduction was observed in 10-year risk of MACE and stroke, along with decreased risk of atherosclerotic cardiovascular disease. Although this study used projected risk and not adjudicated events as the primary outcome, it offers valuable information on procedures less represented in Western literature and underscores the need to validate risk models in diverse populations [36].

Steatotic liver disease offers another scenario in which surgery appears to modify extrahepatic outcomes. In a TriNetX analysis of patients with steatotic liver disease, metabolic-bariatric surgery was associated with lower risk of major liver events, MACE, major renal events, obesity-related cancers, and all-cause mortality during a mean follow-up of 4.1 years. The HR for MACE was 0.52 and the HR for all-cause mortality was 0.49, with benefits observed in women, patients with diabetes, BMI >50 kg/m², and independently of surgery type. These data reinforce the hypothesis that surgery acts on a shared inflammatory-metabolic risk network involving the liver, kidney, vascular system, and myocardium [37].

Nevertheless, the magnitude of cardiovascular benefit may be modulated by specific comorbidities. In patients undergoing adjustable gastric banding, the presence of obstructive sleep apnea was associated with higher incidence of cardiovascular events despite similar weight loss. Patients with sleep apnea had higher cardiovascular event rates than those without sleep apnea, and sleep apnea remained an independent predictor of events, with an HR of 6.92. Moreover, CPAP use was associated with fewer events compared with untreated sleep apnea. This finding suggests that surgery does not completely neutralize all pathophysiological risk axes and that postoperative optimization of sleep apnea, hypertension, diabetes, and dyslipidemia remains essential [38].

Unlike classical cardiovascular pharmacology, randomized evidence in bariatric surgery has rarely been designed or powered for MACE as a primary endpoint. The SLEEVEPASS trial compared laparoscopic sleeve gastrectomy with Roux-en-Y gastric bypass with seven-year follow-up, primarily evaluating weight loss, quality of life, and morbidity. Gastric bypass produced greater excess weight

loss than sleeve gastrectomy, whereas quality of life was similar and overall morbidity did not differ significantly. Although this trial does not directly answer the MACE question, it is fundamental because it demonstrates differential durability of procedures and provides a randomized methodological basis for interpreting later surgical comparisons oriented toward cardiovascular outcomes [39].

Comparative observational studies have complemented the limited randomized evidence. In a national Medicare database, geographic variation in the adoption of sleeve gastrectomy after insurance coverage enabled the use of an instrumental variable approach to compare sleeve gastrectomy and gastric bypass. At one year, sleeve gastrectomy was associated with lower mortality, complications, emergency department visits, hospitalizations, and reinterventions compared with bypass, although the study was not oriented toward long-term major cardiovascular events. This type of analysis is relevant because it shows that comparisons between techniques must balance perioperative safety, sustained metabolic efficacy, and late cardiovascular outcomes, avoiding interpretation of a procedure as superior solely because of its lower initial risk [40].

6. Clinical Phenotypes with the Strongest Cardiovascular Support

The most consistent cardiovascular evidence is concentrated in patients with severe obesity and high baseline cardiometabolic burden, especially those with type 2 diabetes mellitus, arterial hypertension, steatohepatitis or metabolic dysfunction-associated steatotic liver disease, marked visceral adiposity, and high global cardiovascular risk. In these groups, metabolic-bariatric surgery acts on several simultaneous determinants of vascular injury—insulin resistance, atherogenic dyslipidemia, blood pressure, systemic inflammation, hepatic dysfunction, and cardiac remodeling—making it biologically plausible that sustained weight reduction translates into lower incidence of MACE and mortality.

In contrast, generalization of these benefits remains more uncertain in patients with less severe obesity, low baseline cardiovascular risk, absence of major metabolic comorbidities, advanced age with frailty, high surgical risk, advanced non-stabilized cardiovascular disease, or exposure to interventions with less evidence for hard outcomes, such as endoluminal techniques. Similarly, extrapolation to comparisons against modern GLP-1 agonists should be prudent, because many available studies evaluated earlier pharmacological generations and do not always capture the magnitude of weight loss or cardiometabolic benefit of contemporary incretin therapies. Therefore, the clinical applicability of MACE reduction should be interpreted according to baseline risk, metabolic phenotype, selected procedure, feasibility of long-term follow-up, and availability of effective pharmacological alternatives [41]–[43].

7. Gastric Bypass versus Sleeve Gastrectomy

Direct comparison of MACE between gastric bypass and sleeve gastrectomy has

gained relevance because sleeve gastrectomy has become the most frequently performed procedure worldwide. In a Swiss population-based cohort weighted by inverse probability, gastric bypass was associated with lower risk of four-point MACE—acute myocardial infarction, ischemic stroke, hospitalization for heart failure, and all-cause mortality—compared with sleeve gastrectomy during a median follow-up of 5.1 years. The primary endpoint occurred in 1.9% of the bypass group and 3.0% of the sleeve group, with an HR of 0.75, a difference driven mainly by fewer acute myocardial infarctions. However, bypass also showed greater post-operative complexity, which requires technical selection to be individualized according to cardiovascular risk, reflux, diabetes, nutritional profile, and surgical risk [44].

The need for revisional surgery after sleeve gastrectomy also influences comparative assessment of procedures. A surgical meta-analysis compared conversion to Roux-en-Y gastric bypass versus one-anastomosis gastric bypass after failed sleeve gastrectomy due to insufficient weight loss, weight regain, or gastroesophageal reflux. No significant differences were found in excess weight loss between procedures, but postoperative reflux was higher with one-anastomosis gastric bypass, while operative time was shorter. Although the study did not evaluate MACE, it provides a clinically relevant element: technical choice has metabolic, gastrointestinal, and safety consequences that may condition adherence, need for reintervention, and stability of long-term cardiometabolic benefit [45].

8. Balance between Cardiovascular Benefit and Long-Term Risks

The cardiovascular benefit of metabolic-bariatric surgery must be interpreted within an individualized benefit-risk relationship. Although contemporary peri-operative mortality is low and the safety of laparoscopic procedures has improved substantially, the intervention is not free from early complications such as bleeding, leak, infection, thromboembolism, hospital readmission, or need for reintervention. In addition, the risk profile varies according to technique: gastric bypass may be associated with greater anatomic complexity, malabsorption, marginal ulcer, internal obstruction, or nutritional deficiencies, whereas sleeve gastrectomy may have lower initial complexity but a higher risk of persistent gastroesophageal reflux or need for conversion in selected patients.

In the long term, potential cardiovascular protection is sustained only if weight loss and metabolic improvement are accompanied by structured follow-up. Post-operative surveillance should include assessment of iron, vitamin B12, folate, vitamin D, calcium, protein intake, body composition, bone health, gastrointestinal symptoms, adherence to supplementation, and control of cardiometabolic comorbidities. Therefore, metabolic-bariatric surgery should not be presented as an isolated intervention, but as the beginning of a longitudinal strategy combining appropriate procedure selection, complication prevention, nutritional support, muscle mass preservation, and multidisciplinary follow-up to maximize cardio-

vascular benefit and reduce avoidable risks [46]-[48].

9. Bariatric Surgery versus GLP-1 Receptor Agonists

The comparison between metabolic surgery and GLP-1 receptor agonists constitutes one of the most current questions in the cardiometabolic field. In a matched Swedish nationwide cohort of patients with type 2 diabetes and severe obesity, metabolic-bariatric surgery was compared with treatment using first-generation GLP-1 agonists. During follow-up, the eight-year cumulative incidence of MACE or all-cause mortality was lower in the surgical group, with an HR of 0.76, and the risk of nonfatal MACE was also lower, with an HR of 0.68. These results suggest that, in patients with severe obesity and diabetes, surgery may provide superior cardiovascular protection compared with early incretin pharmacotherapy, although interpretation should consider differences in treatment intensity, adherence, and availability of newer drugs such as semaglutide or tirzepatide [49].

An Israeli cohort of adults with obesity and diabetes without known cardiovascular disease compared metabolic surgery versus GLP-1 agonists in primary prevention. In patients with diabetes duration ≤ 10 years, surgery was associated with lower all-cause mortality compared with GLP-1RA, with an HR of 0.38; however, this association lost significance when weight loss was incorporated into the model, suggesting that the survival effect was largely mediated by greater weight reduction. In contrast, no significant differences in nonfatal MACE were observed between groups. This finding introduces a more nuanced interpretation: surgery may outperform GLP-1RA in mortality in selected subgroups, but superiority for nonfatal MACE is not uniform and may depend on diabetes duration, magnitude of weight loss, and pharmacological generation used [50].

Quantitative synthesis of comparative studies also favors surgery for hard outcomes, although with limitations. A meta-analysis that included four observational studies and approximately 247,000 patients showed that metabolic surgery was associated with lower risk of MACE compared with GLP-1RA, with an RR of 0.71, and lower all-cause mortality, with an RR of 0.75. Interpretation should be prudent because the available evidence comes from nonrandomized studies, with potential confounding by indication, differences in pharmacological adherence, and variability in GLP-1RA generations used. Even so, the effect size suggests that surgery remains a reference intervention for patients with severe obesity and high cardiometabolic risk [51].

Indirect comparisons among surgery, pharmacotherapy, and lifestyle interventions show that surgery offers the greatest overall efficacy for weight loss and multiple cardiovascular risk factors, although at the cost of higher risk of serious adverse events in some procedures. A systematic review and network meta-analysis of randomized clinical trials found that bariatric surgery was the most potent modality for weight reduction and cardiometabolic improvement, while semaglutide emerged as a highly effective pharmacological alternative, with effects comparable to bypass and sleeve gastrectomy in several intermediate domains and lower risk

of serious adverse events. This evidence does not replace direct MACE studies, but helps position semaglutide as a real therapeutic competitor and surgery as a preferred strategy when maximum metabolic durability is sought [52].

In class II obesity, the economic comparison between semaglutide and endoscopic sleeve gastropasty adds another therapeutic dimension. A five-year Markov model found that endoscopic gastropasty was more cost-effective than semaglutide, with greater sustained weight loss and lower total costs. The endoscopic intervention added 0.06 QALYs and reduced costs by 33,583 dollars compared with semaglutide; additionally, the annual price of semaglutide would need to decrease from 13,618 to 3,591 dollars to achieve nondominance. Although this analysis does not evaluate MACE, it highlights that the choice between drugs and procedures should integrate efficacy, treatment duration, adherence, accumulated costs, and health system sustainability [53].

Contemporary comparison of costs and weight loss between metabolic surgery and GLP-1RA in insurance databases also favors surgery in patients with class II-III obesity. In a U.S. cohort, metabolic surgery was associated with greater weight loss at two years than GLP-1RA and with lower accumulated costs, driven by sustained pharmaceutical expenditure in the GLP-1RA group. Total weight loss was 28.3% with surgery versus 10.3% with GLP-1RA, and total two-year costs were lower for surgery. Although the study does not evaluate cardiovascular events, the magnitude of weight reduction and economic burden supports the hypothesis that surgery retains a central role in severe obesity, particularly when a profound and sustained metabolic effect is required [54].

10. Complementary Use of GLP-1RA around Surgery

The relationship between GLP-1RA and surgery should not be framed solely as therapeutic competition. In the randomized BARI-OPTIMISE trial, liraglutide 3.0 mg was evaluated in patients with insufficient weight response after metabolic surgery and suboptimal GLP-1 response. During the 24 weeks, liraglutide produced significantly greater weight reduction than placebo, without serious adverse events or treatment-related deaths. This result suggests that GLP-1RA may function as an adjuvant strategy in patients with insufficient weight loss or incomplete hormonal response after bypass or sleeve gastrectomy, reinforcing a sequential and personalized model in which surgery and pharmacotherapy are integrated to sustain cardiometabolic benefit [55].

In real-world clinical practice, GLP-1 agonists also appear useful for treating weight regain after bariatric surgery. In a retrospective cohort, patients treated with liraglutide or semaglutide after weight regain lost a median of 10.5 kg at 12 months, equivalent to a loss of 99.3% of regained weight. BMI reduction was greater with semaglutide than with liraglutide, and adverse events were mild and transient. These data support the use of GLP-1RA as metabolic rescue therapy, especially when weight regain threatens to reactivate hypertension, diabetes, dyslipidemia, and residual cardiovascular risk [56].

The safety of GLP-1RA after surgery is also relevant for therapeutic integration. In a retrospective cohort of patients initiating anti-obesity medications after bypass or sleeve gastrectomy, GLP-1RA use was not associated with a higher likelihood of adverse events compared with non-GLP-1RA drugs. This observation is important because many postsurgical patients have modified gastrointestinal anatomy, nutritional risk, and digestive symptoms, factors that could limit pharmacological tolerance. The available evidence suggests that, with appropriate selection and clinical follow-up, GLP-1RA can be safely incorporated into postoperative strategies for weight maintenance and cardiometabolic control [57].

Finally, preoperative use of GLP-1RA is emerging as a bridging strategy before bariatric surgery. In a cohort of patients operated between 2018 and 2023, GLP-1RA use before surgery increased markedly, reflecting the contemporary therapeutic shift in obesity. This approach could improve glycemic control, reduce preoperative weight, facilitate the surgical technique, and decrease perioperative risk in selected patients; however, prospective studies are still required to determine whether preoperative incretin therapy modifies cardiovascular outcomes, surgical complications, or long-term weight loss. For now, the evidence positions GLP-1RA and surgery as potentially complementary tools within a stepwise strategy of cardiometabolic risk reduction [58].

11. Conclusions

Contemporary evidence supports the view that metabolic-bariatric surgery represents far more than a weight-loss strategy. Its clinical impact derives from a profound reconfiguration of systemic metabolism, in which reduction of visceral adiposity, attenuation of chronic inflammation, improvement in insulin sensitivity, incretin modulation, changes in bile acids, partial restoration of the gut microbiota, and reversal of obesity-associated vascular and cardiac alterations converge. This pathophysiological integration explains why its benefits may translate into reduction of hard cardiovascular outcomes and not only improvement in intermediate markers.

Available cohort studies, population-based analyses, and meta-analyses consistently show an association between metabolic-bariatric surgery and lower incidence of major adverse cardiovascular events, cardiovascular mortality, heart failure, and coronary events, especially in patients with severe obesity and high metabolic risk. Roux-en-Y gastric bypass appears to offer cardiovascular advantages over sleeve gastrectomy in some cohorts, although at the cost of greater technical complexity and potential complication burden; therefore, procedure selection should be individualized according to cardiometabolic profile, surgical risk, presence of diabetes, gastroesophageal reflux, body composition, and need for metabolic durability. Nevertheless, causal inference regarding MACE reduction should remain cautious, given that most evidence comes from observational studies, whereas available randomized trials have focused mainly on weight loss, quality of life, and metabolic outcomes, rather than adjudicated cardiovascular events as a primary end-

point.

The emergence of GLP-1 receptor agonists has transformed obesity treatment and requires rethinking the place of surgery within a modern therapeutic strategy. However, comparative data suggest that surgery retains a central role in patients with severe obesity, type 2 diabetes mellitus, or elevated cardiovascular risk, while GLP-1RA emerge as complementary tools for preoperative optimization, treatment of insufficient weight response, or management of postoperative weight regain.

Consequently, metabolic-bariatric surgery should be understood as an integral cardiometabolic intervention capable of modifying the natural history of obesity and its cardiovascular complications. Its appropriate implementation requires individualized selection, multidisciplinary follow-up, and articulation with contemporary pharmacological therapies, with the ultimate goal of reducing cardiovascular burden, improving survival, and preserving long-term metabolic health.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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