

Cardiovascular benefits of obesity therapies: an overview of obesity medicines and metabolic bariatric surgery

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ABSTRACT

Obesity is an independent driver of cardiovascular disease (CVD), mediated through adverse haemodynamic loading, insulin resistance, systemic inflammation, endothelial dysfunction and prothrombotic pathways. Contemporary obesity therapies show cardiovascular (CV) benefits beyond improvements in traditional risk factors. Across large CV outcome trials, glucagon-like peptide 1 receptor agonists consistently reduce three-point major adverse CV events (MACE) in patients with overweight, obesity and established CVD with and without diabetes. In obesity-related heart failure of preserved ejection fraction, semaglutide and tirzepatide improve symptoms and functional capacity and reduce worsening heart failure events, while effects on CV mortality remain uncertain. In contrast, evidence for metabolic bariatric surgery is dominated by large observational cohorts and meta-analyses, which are associated with durable weight loss and lower observed rates of MACE, heart failure and all-cause mortality compared with non-surgical care, though causal inference is constrained by residual confounding. Data support that sustained weight loss of at least 10% is more likely to translate into CVD event reduction, alongside other organ specific mechanisms that impact CV health independent from weight reduction. Obesity treatments offer a safe and effective method to lose weight with varying CV benefits, with current evidence still in early stages to establish robust clinical recommendations.

INTRODUCTION

Obesity is a major, independent risk factor for cardiovascular disease (CVD), associated with increased incidence of coronary artery disease, heart failure, stroke and cardiac death, beyond its effects on traditional risk factors such as hypertension, dyslipidaemia and diabetes.^{1–3} Excess adiposity in individuals with obesity induces a chronic low-grade inflammatory state, characterised by increased secretion of pro-inflammatory adipokines and cytokines, which promotes a pro-thrombotic milieu and drives the development of insulin resistance. These pathophysiological changes likely contribute to adverse cardiac remodelling and endothelial dysfunction, thereby accelerating the progression of atherosclerosis and myocardial dysfunction.^{4,5} In this review, we examine how metabolic bariatric surgery (MBS) and obesity medicines, particularly glucagon-like peptide 1 receptor agonists (GLP-1 RAs), might help mitigate residual cardiovascular (CV) risk, not only by reducing adipose tissue which brings an array of CV benefits, but by explaining the mechanistic pathways that are involved in the reduction

of classic CV risk factors and their contribution in reducing residual risk in these patients.

METHODOLOGY

We conducted a structured literature search in PubMed/MEDLINE, Embase and the Cochrane Library from January 2015 to December 2025 to identify relevant studies on obesity, bariatric surgery, GLP-1 analogues, CV outcomes and heart failure. Randomised controlled trials (RCTs) with CV outcomes, systematic reviews and meta-analyses were included. Separate searches identified relevant large cohort studies for MBS and comparative studies between MBS and GLP-1 therapies. For GLP-1 analogues, 284 studies were identified, yielding 51 RCTs comprising 45 092 participants. For MBS, 139 studies were screened with four RCTs and matched cohort analyses totalling 323 922 participants. For comparative studies, a total of 86 studies were screened, yielding one meta-analysis and eight observational studies.

Treatment of obesity and CV outcomes

Obesity is a major driver of CVD,^{1–3} and the assumption that body weight alone might mitigate the risks is still a debated question. Observational data, particularly in older adults, indicate that weight loss, especially when it is unintentional, is associated with increased all-cause mortality and higher cancer-specific, CVD and non-cancer, non-CVD mortality.⁶ Randomised trial data reinforce the notion that weight reduction alone does not directly guarantee CV benefit when it comes to major CV events. The Look AHEAD trial (Action for Health in Diabetes)⁷ enrolled approximately 5000 adults with type 2 diabetes and obesity and followed participants for a median of 10 years. Intensive lifestyle intervention resulted in significant improvements in CV risk factors, including blood pressure, glycaemic control and renal function, as well as secondary benefits such as reduced prevalence of obstructive sleep apnoea, decreased hepatic steatosis and enhanced physical mobility.⁷ These improvements did not translate into a reduction in major adverse CV events (MACEs) in the primary intention-to-treat analysis. However, a post hoc analysis of this trial⁸ showed that individuals achieving at least 10% weight loss in the first year experienced a statistically significant reduction in the incidence of MACE.⁸ Similarly, the SCOUT trial⁹ randomised over 10 000 high-risk individuals to sibutramine or placebo. Only modest weight loss was observed in this study, and it was associated



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with an increased risk of non-fatal CV events and mortality, particularly among those with minimal weight loss. However, while the sibutramine group experienced an increased risk of non-fatal CV events and mortality than the placebo group, when sibutramine or lifestyle changes produced greater weight loss, this was associated with overall less risk of CV events in both groups as published in a post hoc analysis.¹⁰ These findings suggest that, although lifestyle and pharmacological weight loss interventions improve CV risk factors, current randomised trials have not consistently demonstrated a reduction in MACE, and benefits may be limited to individuals achieving substantial and sustained weight loss.^{7–10}

Comparatively, other major weight loss intervention trials, such as the DiRECT UK,¹¹ have shown that 5–10% weight loss improves CV risk factors, but only larger and sustained weight losses of more than 10% were associated with lower rates of events in high-risk populations.¹² This has also been observed in MBS studies, where weight loss of at least 10% was required to achieve lower rates of MACE as shown in a large matched-cohort study of patients with obesity and type 2 diabetes.¹³ No RCTs have directly established this threshold, but the available observational evidence provides a consistent signal for the 10% cut-off in the surgical population.¹⁴ In summary, more than 10% sustained weight loss is required for a meaningful decrease of MACE together with durable weight loss; smaller weight losses improve risk factors but do not consistently reduce events.^{12–14}

From recent studies on GLP-1 RAs, a post hoc analysis from the SELECT trial,¹⁵ a randomised placebo-controlled trial with over 17 000 adults and a composite endpoint of three-point MACE, to test if semaglutide reduced CV events in people with body mass index (BMI) >27 kg/m² and existing CVD, but not diabetes. This prespecified study¹⁶ showed that CV benefits of semaglutide were independent of baseline adiposity, that early weight loss did not predict CV benefit, and that waist circumference reduction explained only a proportion of the observed benefit on MACE.¹⁶ Collectively, these findings suggest that to reduce CV events when treating patients with obesity, strategies beyond lifestyle and weight loss are required. The following sections explore contemporary obesity treatments, principally MBS and recent obesity pharmacotherapy, which appear to potentially reduce MACE through weight loss and other organ-specific weight-independent mechanisms.

MBS and CV outcomes

MBS is associated with favourable CV profiles via multiple mechanistic pathways, mainly through anatomical changes from procedures such as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy. Both induce rapid improvements in insulin secretion and glycaemic control mediated by altered entero-endocrine hormone pathways, notably increased GLP-1 and Peptide Tyrosine (PYY), decreased ghrelin, enhanced bile acid signalling and favourable shifts in the gut microbiome.^{12 17} Mechanistically, improvements are mediated both by sustained weight loss and by organ-specific effects, such as insulin sensitivity, blood pressure, gut-kidney axis, lipid profiles, hepatic mediation and systemic inflammation.^{12 17 18} Favourable CV outcomes have been reported in observational studies across diverse populations, including those with and without diabetes, with results being more pronounced in patients with pre-existing CVD or diabetes, see [table 1](#).

CV outcomes derive primarily from large cohort studies and meta-analyses, which report consistent associations with lower rates of MACE, myocardial infarction, stroke, HF and all-cause

mortality in patients undergoing bariatric surgery compared with non-surgical care, with more supporting evidence in favour of RYGB versus other metabolic surgical methods,^{19 20} with HRs for MACE and CV death typically ranging from 0.4 to 0.6 compared with non-surgical controls (refer to [table 1](#)). However, data are notably observational, which is subject to confounding and selection bias, limiting causal inference. RCTs with CV endpoints remain limited, and further research is needed to delineate weight-independent mechanisms and compare surgery to newer pharmacotherapies.

Obesity medications and CV outcomes in patients with and without type 2 diabetes

GLP-1RAs exert central anorectic effects via hypothalamic pathways and peripheral actions including potentiation of glucose-dependent insulin secretion, delayed gastric emptying and suppression of glucagon release, resulting in improved glycaemic control, lipid metabolism and attenuation of systemic inflammation.²¹ These pleiotropic effects contribute to the overall improvement in cardiometabolic risk profiles observed with GLP-1 RA therapy¹² (see [table 2](#)). GLP-1RAs and related co-agonists have demonstrated substantial efficacy in weight reduction across phase three trials. In 2025, Cochrane published three systematic reviews across semaglutide, liraglutide and tirzepatide. Resulting in a moderate-to-high confidence for weight loss versus placebo.^{22–24} These findings are also corroborated by a 2025 systematic review and meta-analysis which reported a mean placebo-adjusted weight reduction of 10.6% at 12–18 months for GLP-1RAs, with greater effects observed in adherent patients and with a longer duration of therapy.²⁵

GLP-1RAs have also shown CV benefits in patients with obesity, type 2 diabetes and high CV risk. Large RCTs show relative reductions of 10–15% in three-point MACE endpoints, as shown in [table 3](#). Reductions in all-cause mortality, as well as composite kidney outcomes, particularly in high-risk populations, have also been reported.^{26 27}

In a 2023 and subsequent 2025 systematic review and meta-analyses, Ussher *et al* and Galli *et al*, respectively,^{28 29} found that these agents reduce MACE as well as heart failure and acute kidney injury. Both authors agree that the CV benefits appear early after initiation and are not solely attributable to weight loss or glycaemic improvement, suggesting additional mechanisms such as improved endothelial function, modulation of atherosclerotic plaque stability and reductions in blood pressure and epicardial fat.^{12 28 29}

The SELECT trial extended the paradigm to individuals with BMI >27 kg/m² with established CVD but no diabetes, demonstrating that once-weekly semaglutide 2.4 mg reduced three-point MACE by 20%, all-cause mortality and heart failure hospitalisations over a mean follow-up of 3.3 years.^{15 16} These results suggest considering the use of GLP-1 RAs for CV risk reduction in people with obesity and established CVD.^{16 28 29}

Obesity and heart failure with preserved ejection fraction: impact of MBS and GLP-1 therapy

Obesity is a major aetiological factor for heart failure with preserved ejection fraction (HFpEF), acting through both indirect pathways such as hypertension, diabetes mellitus, sleep apnoea and chronic kidney disease and direct effects including systemic inflammation, adverse cardiac remodelling, epicardial adiposity and diastolic dysfunction. Central adiposity is present in over 80% of patients with established HFpEF and is strongly correlated with disease severity and haemodynamic

Table 1 Observational cohorts (≥ 5000 total; surgery vs non-surgery; clinical CV endpoints) and meta-analyses

Study (Journal)	Total N	CV outcomes	CV effect	Reference
Sonaiya <i>et al</i> , Maryland Health Review Commission database (<i>Journal of Surgical Research</i>)	222 700	All-cause mortality, new-onset HF, MI and ischaemic stroke	Association between bariatric surgery and improvement in long-term CV outcomes and association with lower rates of all-cause mortality.	Sonaiya S, Long-Term Cardiovascular Disease Outcomes Following Bariatric Surgery. <i>J Surg Res.</i> 2024;304:225–231.
Mentias <i>et al</i> , Medicare matched cohort (<i>JACC</i>)	189 770	In-hospital mortality; 30-day mortality; 4-year risk of HF, MI, stroke	Lower in-hospital and 30-day mortality with relative reductions in 4-year risk of incident HF, MI, stroke and all-cause mortality 35–55%.	Mentias A, Long-Term Cardiovascular Outcomes After Bariatric Surgery in the Medicare Population. <i>J Am Coll Cardiol.</i> 2022;79(15):1429–1437.
William <i>et al</i> , Ischemic stroke risk cohort (<i>Surgery for Obesity and related Diseases</i>)	113 028	Ischaemic stroke incidence	Associated with a lower observed incidence of ischaemic stroke, with OR: 0.5 at 1 year and 0.8 at 5 years, indicating marked early risk reduction that persisted.	Williams MD, The effect of bariatric surgery on ischaemic stroke risk. <i>Surg Obes Relat Dis.</i> 2021 (12):1949–1955.
Moussa <i>et al</i> UK CPRD nationwide nested cohort (<i>European Heart Journal</i>)	7402	Composite fatal/non-fatal MI and ischaemic stroke; plus, HF and mortality	59% lower risk of composite fatal/non-fatal MI or ischaemic stroke (adjusted HR 0.41), 60% lower risk of incident HF (HR 0.40) and 75% lower all-cause mortality (HR 0.25) over a median of 4 years.	Moussa O, <i>et al</i> Effect of bariatric surgery on long-term cardiovascular outcomes: a nationwide nested cohort study. <i>Eur Heart J.</i> 2020;41(28):2660–2667. ²⁷
Aminian <i>et al</i> , Cleveland Clinic cohort (<i>JAMA</i>)	13 722	Incident MACE + mortality (metabolic surgery vs usual care)	40% lower risk of incident MACE, 40% lower all-cause mortality compared with usual care (adjusted HRs 0.6).	Aminian A, <i>et al</i> Association of Metabolic Surgery With Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes and Obesity. <i>JAMA.</i> 2019;322(13):1271–1282.
Stenberg <i>et al</i> , nationwide matched cohort in hypertension (<i>PLOS Medicine</i>)	38 062	MACE, ACS, cerebrovascular event, fatal CV event, sudden death) + all-cause mortality	Associated with a lower observed incidence of associated with a lower MACE and lower all-cause mortality compared with matched controls, with relative risk reductions in the 25–35% range for composite CV endpoints.	Stenberg E, <i>et al</i> . Association between metabolic surgery and cardiovascular outcome in patients with hypertension: A nationwide matched cohort study. <i>PLoS Med.</i> 2020;17(9):e1003307.
Persson <i>et al</i> , Sweden registry cohort (<i>Journal of Cardiac Failure</i>)	47 859	Heart failure (hospital admission for HF)	Associated with a lower observed incidence of HF hospitalisation compared with non-surgical obesity controls, 80% relative risk of incident HF.	Persson CE, <i>et al</i> Risk of Heart Failure in Obese Patients with and Without Bariatric Surgery in Sweden - A Registry-Based Study. <i>J Card Fail.</i> 2017;23(7):530–537.
Bouchard <i>et al</i> , Quebec population-level matched cohort (<i>Obesity Surgery</i>)	9047	Composite MACE: coronary artery events, HF, cerebrovascular events, all-cause mortality	Lower risk of composite MACE and all-cause mortality, with relative risk reductions that remained robust after multivariable adjustment.	Bouchard, P <i>et al</i> . Long-term Impact of Bariatric Surgery on Major Adverse Cardiovascular Events in Patients with Obesity, Diabetes and Hypertension: A Population-level Study. <i>OBES SURG</i> 32, 771–778 (2022).
Elsaid <i>et al</i> , Surgery compared with non-surgical management (<i>JAMA Network Open</i>)	86 964	Cardiovascular events + all-cause mortality (study-level composite CV outcomes)	Associated with a lower observed incidence of associated with a lower composite CV events and all-cause mortality compared with non-surgical, largest absolute and relative risk reductions observed in those with more advanced liver disease.	Elsaid MI, <i>et al</i> Association of Bariatric Surgery with Cardiovascular Outcomes in Adults with Severe Obesity and Nonalcoholic Fatty Liver Disease. <i>JAMA Netw Open.</i> 2022;5(10): e2235003.
Aminian <i>et al</i> , weight-loss 'dose' after metabolic surgery (<i>Annals of Surgery</i>)	7201	MACE + all-cause mortality (risk reductions by achieved weight-loss category)	Reduced risk at 10% total body weight loss and continued to improve up to 20–25%, after which additional benefit plateaued.	Aminian A, <i>et al</i> How Much Weight Loss is Required for Cardiovascular Benefits? Insights From a Metabolic Surgery Matched-cohort Study. <i>Ann Surg.</i> 2020 ;272(4):639–645.
Kostanjsek <i>et al</i> , nationwide propensity-matched cohort (<i>International Journal of Cardiology</i>)	6104	Incident HF + mortality	Associated with a lower observed incidence of associated with a lower HF and reduced all-cause mortality compared with non-surgical obesity care. Benefits persisting after adjustment for baseline CV risk factors.	Kostanjsek L, <i>et al</i> Bariatric Surgery and Incident Heart Failure: a Propensity Score Matched Nationwide Cohort Study. <i>Int J Cardiol.</i> 2023 May 1; 378:42–47.
Meta-analysis*				
Syn NL <i>et al</i> , Matched cohort and prospective controlled studies (<i>Lancet</i>)	174 772	Long term survival in adults with and without diabetes after MBS	Association with lower rates of association with lower hazard rate of death of 49.2% (95% CI 46.3 to 51.9, $p < 0.0001$) and median life expectancy was 6.1 years (95% CI 5.2 to 6.9) longer than usual care.	Syn NL, <i>et al</i> Association of metabolic-bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies. <i>Lancet.</i> 2021 May 15;397 (10287):1830–1841.
Tang <i>et al</i> , 21 population-based cohort studies (<i>Surgery for Obesity and related Diseases</i>)	2 857 016	MACE, MI, stroke, CV death, all-cause death	Lower risks of MACE, MI, stroke, CV death and all-cause mortality compared with non-surgical obesity management; relative risk estimates indicating 30–60% reductions in major CV outcomes.	Tang B, <i>et al</i> Effect of bariatric surgery on long-term cardiovascular outcomes: a systematic review and meta-analysis of population-based cohort studies. <i>Surg Obes Relat Dis.</i> 2022(8):1074–1086.
van Veldhuisen <i>et al</i> , 39 cohort studies (<i>European Heart Journal</i>)	Not stated	All-cause and CV mortality, AF, HF, MI, stroke	Relative risk reductions in all-cause and CV mortality, HF, MI and stroke vs non-surgical care, with effects particularly pronounced in individuals with obesity and type 2 diabetes.	van Veldhuisen SL, <i>et al</i> Bariatric surgery and cardiovascular disease: a systematic review and meta-analysis. <i>Eur Heart J.</i> 2022;43(20):1955–1969. ³⁸
Cui <i>et al</i> , 40 matched cohort studies (<i>International Journal of Surgery</i>)	Not stated	MACE + components (including HF, MI, stroke) and CV mortality	Significantly lower risk of MACE including HF, MI and stroke, and CV mortality after bariatric surgery compared with medical/lifestyle management.	Cui B, <i>et al</i> Disease-specific mortality and major adverse cardiovascular events after bariatric surgery: a meta-analysis of age, sex and BMI-matched cohort studies. <i>Int J Surg.</i> 2023 Mar 1;109(3):389–400.

Continued

Table 1 Continued

Study (Journal)	Total N	CV outcomes	CV effect	Reference
Wiggins <i>et al</i> 18 studies (<i>PLoS Medicine</i>)	1 539 904	Long-term mortality and incidence of new onset obesity-related disease	Associated with lower rates of association with lower rates of all-cause mortality and incidence of obesity-related disease in patients with obesity for the whole operated population.	Wiggins T, <i>et al</i> Association of bariatric surgery with all-cause mortality and incidence of obesity-related disease at a population level: A systematic review and meta-analysis. <i>PLoS Med.</i> 2020;17(7).

*Duplicated studies in the meta-analyses.
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; RR, relative risk.

compromise.^{30–32} The American College of Cardiology highlights that obesity drives concentric left ventricular remodelling, right ventricular dilatation and increased epicardial fat, resulting in pericardial restraint and impaired ventricular interdependence.³³ Therefore, the assumption that by treating the disease of obesity in patients with HFpEF should confer an improvement is still a complex assumption. This is driven mainly by challenges in distinguishing between the disease of obesity and HFpEF, due to overlapping clinical symptoms, pathophysiology and cardiac and functional abnormalities. Both conditions commonly present with exercise intolerance, dyspnoea and fluid retention and share similar findings on physical examination and ultrasound imaging, such as left ventricular hypertrophy, increased plasma volume and abnormal diastolic filling dynamics. Also, biomarkers such as natriuretic peptides may be less elevated in patients with

obesity and HFpEF.^{30–34} Diagnostic ambiguity is compounded by the fact that a substantial proportion of individuals with obesity may have unrecognised mild HFpEF, and standard diagnostic criteria may not reliably distinguish between obesity-related cardiac dysfunction and true HFpEF.^{30–33–34} Overall, this impacts the ability to diagnose and manage these chronic conditions early and hinders the application of standardised criteria and hard endpoints in RCTs for research purposes.

MBS, including RYGB and sleeve gastrectomy, has been associated with significant improvements in cardiac structure and function relevant to HFpEF.^{35–36} Surgical weight loss leads to reverse left ventricular remodelling, improved diastolic function and reductions in left ventricular mass index, with these benefits most strongly linked to reductions in visceral and epicardial fat rather than subcutaneous fat or total body weight alone.^{35–37}

Table 2 Main mechanisms of GLP-1 receptor agonists and metabolic bariatric surgery in cardiovascular risk reduction

Mechanism	GLP-1 receptor agonists	Metabolic bariatric surgery
Glycaemia control	Improvements in HbA1c. Mechanisms: glucose-dependent increases in insulin secretion and decreases in glucagon, delayed gastric emptying and improvements in β -cell function and hepatic insulin sensitivity. Importantly, glycaemia benefits are evident early in treatment, before major weight loss. ^{28–29} Central effects via hypothalamic GLP-1 receptors to improve adipocyte mass regulation, and peripheral effects by stimulating pancreatic β -cell insulin secretion, inhibiting glucagon release, gastric emptying and promoting natriuresis and vasodilation. ^{12–21}	Strong and durable improvement or remission of type 2 diabetes; the probability and durability of remission are strongly related to the magnitude and maintenance of weight loss. Improvement in fasting and postprandial glycaemia within days to weeks after RYGB or sleeve gastrectomy, before significant weight loss occurs. ^{12–18–37} Mechanism: postsurgery patients show threefold \uparrow endogenous GLP-1. Improved glycaemia early and partly independent of weight loss. With >25% weight loss, glycaemic improvements become more weight-dependent, potentially masking independent effects. ^{12–14–17–18} Stimulate hepatic glucagon receptors, contributing to improved hepatic steatosis and metabolic dysfunction-associated steatohepatitis. ^{12–14–17–18}
Blood pressure haemodynamics	Modest but consistent reductions in SBP 3–11 mm Hg; STEP and SURMOUNT trials (see table 3), with BP reductions scaling partly with weight and visceral fat loss (see table 3 for references). Mechanisms: GLP-1 receptors in the kidney and vasculature promote natriuresis, improved endothelial function, reduced arterial stiffness and lower sympathetic tone. BP lowering is observed in patients with modest weight loss and occurs early in treatment, reflecting a combination of haemodynamic and weight-mediated effect. ^{12–21}	Large and durable reductions in SBP and DBP with higher rates of antihypertensive discontinuation compared with usual care. ⁵⁰ Mechanisms: strongly associated with overall adiposity reduction and improved insulin sensitivity, but RYGB is also associated with increased urinary sodium excretion and a possible gut-kidney natriuretic signal beyond restrictive procedures such as gastric banding. ^{14–37–50}
Lipid profile	Modest reductions in triglycerides and LDL and mild increases in HDL. Mechanism: partly mediated by weight loss and improved insulin sensitivity ¹² (see table 3 for SELECT trial).	Consistently improves lipid profile, especially HDL. Increases of HDL \uparrow . ³⁷ Swedish Obese Subjects study: HDL \uparrow 24–48%, independent of BMI changes. ⁵⁰ Mechanisms: \uparrow reverse cholesterol transport, \uparrow apo A-I production, altered bile acid metabolism, gut microbiota shifts. ¹²
Anti-inflammatory/endothelial function	Significantly reduce hs-CRP, 40–60%, IL-6, TNF- α and oxidative stress markers across obesity and type 2 diabetes trials (STEP, SCALE trials, see table 3). Mechanisms: GLP-1 receptors in immune cells, endothelium and myocardium mediate direct anti-inflammatory and anti-oxidative actions, with improved endothelial function, reduced arterial stiffness and increased nitric oxide bioavailability demonstrated in experimental studies ^{28–37} (see table 3 for SELECT trial).	Rapid reductions in CRP and other inflammatory markers detectable soon after surgery before major weight loss. Mechanisms: Before maximal weight loss is achieved, implicating changes in incretins, bile acids, gut microbiota and insulin sensitivity. ^{12–37–50}
Reduced adiposity/reduced body weight	Large reductions in visceral and ectopic fat with improvements in waist circumference and fat mass indices. Mechanism: adiposity changes are primarily mediated by weight loss itself, with no clear evidence of sustained adiposity change in the absence of weight loss (see references table 3).	Reductions in visceral and ectopic fat that are more durable over \geq 10–15 years (procedure-dependent). Mechanisms: early postoperative catabolic phase with transient energy expenditure changes and gut-brain adaptation before weight nadir may contribute to a new 'defended' weight set-point through altered gut-brain signalling and bile-acid pathways. These adaptations are expressed as sustained reductions in adiposity, ¹² see cohort studies in table 1.

AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; ETD, estimated treatment difference; GLP, glucagon-like peptide; HbA1c, haemoglobin A1c; HDL, high density lipoprotein cholesterol; HF, heart failure; HFpEF, heart failure of preserved ejection fraction; hs-CRP, highly sensitive C-reactive protein; IL, interleukin; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LDL, low density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; 6MWD, 6-minute walk distance; RR, relative risk; RYGB, Roux-en-Y gastric bypass; SBP, systolic blood pressure; TNF, tissue necrotic factor.

Table 3 Cardiovascular outcomes from randomised controlled trials with GLP-1 RAs

Trial	Total N	Population	CV outcomes	CV effect	Reference
LEADER (<i>New England Journal of Medicine</i>)	9340	T2D with high CV risk	Three-point MACE	Liraglutide versus placebo 13% lower three-point MACE (HR 0.87)	Marso SP <i>et al</i> Liraglutide and cardiovascular outcomes in type 2 diabetes. <i>N Engl J Med.</i> 2016;375(4):311–322.
SUSTAIN-6 (<i>New England Journal of Medicine</i>)	3297	T2D with high CV risk	Three-point MACE	Semaglutide versus placebo 26% lower three-point MACE (HR 0.74)	Marso SP <i>et al</i> Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. <i>N Engl J Med.</i> 2016;375(19):1834–1844.
EXSCEL (<i>New England Journal of Medicine</i>)	14 752	T2D with or without established CVD	Three-point MACE	Exenatide versus placebo 9% lower three-point MACE; not statistically superior (HR 0.91)	Holman RR <i>et al</i> Effects of once weekly exenatide on cardiovascular outcomes in type 2 diabetes. <i>N Engl J Med.</i> 2017;377(13):1228–1239.
HARMONY Outcomes (<i>Lancet</i>)	9463	T2D with established CVD	Three-point MACE	Albiglutide versus placebo 22% lower three-point MACE (HR 0.78)	Hernandez AF <i>et al</i> Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease. <i>Lancet.</i> 2018; 392 (10157):1519–1529.
REWIND (<i>Lancet</i>)	9901	T2D with established CVD or CV risk factors	Three-point MACE	Dulaglutide versus placebo 12% lower three-point MACE (HR 0.88)	Gerstein HC <i>et al</i> Dulaglutide and cardiovascular outcomes in type 2 diabetes: a double-blind, randomised placebo-controlled trial. <i>Lancet.</i> 2019;394 (10193):121–130.
AMPLITUDE-O (<i>New England Journal of Medicine</i>)	4076	T2D with established CVD or CKD	Three-point MACE+renal composite	Efpeglenatide versus placebo. 27% lower three-point MACE (HR 0.73; 95% CI 0.58 to 0.92) 32% lower renal composite (HR 0.68)	Gerstein HC <i>et al</i> Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. <i>N Engl J Med.</i> 2021;385(10):896–907.
STEP-HFpEF (<i>New England Journal of Medicine</i>)	529	Obesity-related HFpEF	KCCQ-CSS change at 52-week body weight change at 52-week hierarchical composite	Semaglutide versus placebo Improved function and weight loss versus placebo. KCCQ-CSS change +16.6 versus +8.7; ETD+7.8 Body weight diff –13.3% versus –2.6%; ETD –10.7% Hierarchical composite win ratio 1.72	Kosiborod MN <i>et al</i> Semaglutide in patients with heart failure with preserved ejection fraction and obesity. <i>N Engl J Med.</i> 2023; 389:1069–1084.
STEP-HFpEF DM (<i>Lancet Diabetes Endocrinology</i>)	616	Obesity-related HFpEF+T2D	KCCQ-CSS change at 52-week body weight change at 52-week hierarchical composite	Semaglutide versus placebo Improved function and weight loss versus placebo ETD+7.3 KCCQ-CSS points KCCQ-CSS change+13.7 versus +6.4; ETD+7.3 Body weight changes –9.8% versus –3.4%; ETD –6.4%	Davies MJ <i>et al</i> Semaglutide in obesity-related heart failure with preserved ejection fraction and type 2 diabetes across baseline HbA1c levels: a prespecified analysis of heart failure and metabolic outcomes from a randomised, placebo-controlled trial. <i>Lancet Diab Endocrinol.</i> 2025;13(3):196–209.
SELECT (<i>New England Journal of Medicine</i>)	17 604	Overweight/obesity+established CVD; no diabetes	Three-point MACE Key secondary: all-cause death	Semaglutide versus placebo 20% lower three-point MACE (HR 0.80) 19% lower all-cause death (HR 0.81)	Lincoff AM <i>et al</i> ; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. <i>N Engl J Med.</i> 2023; 389(24):2221–2232.
SOUL (<i>New England Journal of Medicine</i>)	9650	T2DM and ASCVD, CKD, or both	Three-point MACE in patients with T2DM and ASCVD, chronic kidney disease (CKD) or both	Oral semaglutide ->lower risk of three-point MACE vs placebo +beneficial risk-benefit profile of oral semaglutide in patients with T2DM and established ASCVD and/or CKD	McGuire <i>et al</i> , for the SOUL Study Group. Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes. <i>N Engl J Med</i> 2025.
SUMMIT (<i>New England Journal of Medicine</i>)	731	HFpEF+obesity with / without T2D	CV death or worsening HF event KCCQ-CSS and 6MWD at 52 weeks	Tirzepatide versus placebo 38% lower primary composite (HR 0.62) Improved KCCQ-CSS, ETD+6.9 points and 6MWD ETD+18.3 m	Packer M <i>et al</i> Tirzepatide for heart failure with preserved ejection fraction and obesity. <i>N Engl J Med.</i> 2025; 392:427–437.
SURPASS-CVOT (<i>New England Journal of Medicine</i>)	13 299	T2D+ASCVD	Three-point MACE	Tirzepatide versus dulaglutide. Non-inferior versus dulaglutide. Not statistically superior (p=0.09)	Nicholls SJ <i>et al</i> Cardiovascular outcomes with tirzepatide vs dulaglutide. <i>N Engl J Med.</i> 2025; 393:2409–2420.

AF, atrial fibrillation; aHR, adjusted HR; AMPLITUDE-O trial, Effect of Efpeglenatide on Cardiovascular Outcomes in Type 2 Diabetes; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; ETD, estimated treatment difference; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HARMONY trial, Health outcomes and Rate of Management for Once-weekly Albiglutide; HF, heart failure; HFpEF, heart failure of preserved ejection fraction; IHD, ischaemic heart disease; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical summary score; LEADER trial, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular outcome Results; MACE, major adverse cardiovascular event; MAKE, major adverse kidney event; MBS, metabolic bariatric surgery; MI, myocardial infarction; 6MWD, 6-minute walk distance; REWIND trial, Researching cardiovascular events with Weekly Dulaglutide in Diabetes; RR, relative risk; RYGB, Roux-en-Y gastric bypass; SELECT trial, Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity; SG, sleeve gastrectomy; SOS, Swedish obesity surgery; SOUL trial, Semaglutide cardiovascular outcomes trial; STEP-HFpEF DM, Semaglutide Treatment Effect in People with obesity and HFpEF and Type 2 Diabetes Mellitus; STEP-HFpEF trial, Semaglutide Treatment Effect in People with obesity and HFpEF; SUMMIT trial, Study of Tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction and Obesity; SURPASS-CVOT trial, Cardiovascular outcomes trial investigating the effects of tirzepatide on major adverse cardiovascular events; SUSTAIN-6 trial, Evaluate Cardiovascular and Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes 6; T2D, type 2 diabetes; T2DM, type 2 diabetes mellitus.

Observational studies and meta-analyses show a marked association with lower rates of incidence and hospitalisation for heart failure, including HFpEF, and improved New York Heart

Association (NYHA) class and ejection fraction in patients with established heart failure.^{38 39} The American Heart Association notes that bariatric surgery improves CV risk factors and cardiac

function in patients with obesity and heart failure, though RCTs in HFpEF populations are lacking. In summary, MBS is associated with lower observed rates of HFpEF-related events and with favourable changes in cardiac structure and function in patients with obesity. These effects are supported by cohort studies, meta-analyses and consensus guidelines from the American College of Cardiology and American Heart Association,^{33 37} while RCTs are awaited to establish causality.

GLP-1 RAs, especially semaglutide and tirzepatide, have shown weight loss effects in patients with obesity-related HFpEF. The three main pivotal trials, STEP-HFpEF, STEP-HFpEF DM and SUMMIT, produced improvements in heart failure symptoms, functional capacity and quality of life, see [table 3](#). The American College of Cardiology and European Journal of Heart Failure Expert Consensus Document highlights that weight loss with GLP-1RAs in HFpEF is linked to improved NYHA class, reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP) and lower systemic inflammation.^{30 31 33 40–42} Although these pivotal trials are still in early stages and longer-term with larger population trials are required to establish more robust associations, the CV outcomes indicate that GLP-1RA therapies on patients with obesity-driven HFpEF reduce heart failure events with no differences shown in mortality ([table 3](#)). Meta-analyses confirm these benefits, with HRs for heart failure hospitalisation ranging from 0.57 to 0.68, and improvements in KCCQ scores and 6 min walk distance,^{30 31 40–44} with effects on CV death remaining non-significant, and all-cause mortality not consistently observed.^{43 44}

In summary, tirzepatide and semaglutide improve symptoms, functional status and indicate a potential reduction of heart failure events in patients with HFpEF and obesity, but do not significantly reduce CV or all-cause mortality in these patients. These findings are supported by RCTs and meta-analyses, although more RCTs with larger numbers and longer follow-ups are required to help recognise this therapy as a Class IA recommendation in future guidelines.

Comparative studies between MBS and GLP-1 therapy with CV outcomes

Across the current literature, true head-to-head comparisons of MBS versus GLP-1 RAs therapies on hard CV outcomes are dominated by observational, registry and claims database analyses. No randomised CV outcome trials directly comparing these strategies currently exist. These comparative cohorts, as described in [table 4](#), evaluate all-cause mortality, MACE and incident HF, with most studies reporting associations favouring MBS over GLP-1 RAs for mortality and CV events. However, interpretation is limited by lack of causal inference, confounding by indication and selection, such as surgical eligibility, access to care and baseline metabolic risk. Also confounding by misclassification with drug dose, duration, adherence, switching and heterogeneity between GLP-1 agents. A key criticism of these comparative studies is the temporal mismatch between interventions. Many comparative datasets reflect earlier GLP-1 RAs with liraglutide predominance that do not compare to newer high-potency GLP-1 agents, while the only two studies incorporating agents such as tirzepatide and semaglutide yielded the reverse of this apparent advantage of surgery, Ibrahim *et al* and Wu *et al*, TriNetX-based recent studies reflected in [table 4](#).

Overall, across multiple large contemporary observational cohorts, MBS has been associated with lower rates of MACE and all-cause mortality compared with GLP-1 RA therapy in adults with obesity and type 2 diabetes. However, emerging data with newer agents show a more heterogeneous picture, underscoring

the need for randomised trials that align exposure definitions and adjudicate CV endpoints in the era of newer, more potent GLP-1 medications.

Main mechanisms of GLP-1 RAs and MBS in CV risk reduction

MBS improves CV health through several mechanisms. The most prominent is sustained weight loss which impacts together with other organ mechanisms, glycaemic control, blood pressure, lipid profiles and resolution of obstructive sleep apnoea, all of which are major CV risk factors. Additionally, MBS induces rapid changes in gut hormone secretion (notably increased endogenous GLP-1), bile acid metabolism and the gut microbiome, resulting in enhanced insulin sensitivity and reduced systemic inflammation. These changes are associated with improvements in endothelial function and cardiac remodelling and may plausibly relate to atherosclerotic risk modification.^{14 17 38 39 45 46} However, direct causal effects on atherosclerosis regression have not been established.

GLP-1 RA therapies improve CV health both via weight-dependent effects and organ-specific mechanisms. GLP-1RAs promote weight loss by suppressing appetite and reducing food intake through central nervous system pathways. They also enhance glucose-dependent insulin secretion, suppress glucagon, delay gastric emptying and improve insulin sensitivity, leading to better glycaemic control and reductions in blood pressure and postprandial lipids. GLP-1 receptors are expressed in the heart and vasculature, allowing for direct anti-inflammatory, anti-atherosclerotic and endothelial-protective effects;^{12 21 28 29} refer to [table 2](#).

Safety, durability and accessibility of GLP-1 RAs and MBS

GLP-1 RAs have a generally favourable safety profile in individuals with obesity, in whom semaglutide and tirzepatide have been evaluated in contemporary randomised trials. Their tolerability profile is dominated by gastrointestinal adverse effects (nausea, vomiting, diarrhoea/constipation), which are typically dose-dependent and can be mitigated with gradual titration and anticipatory counselling.^{22–24} Across large CV outcome trial populations, GLP-1 RAs have not been associated with excess CV mortality, while maintaining an acceptable serious adverse event profile. In a meta-analysis of 21 placebo-controlled randomised trials with n=99 599; mean follow-up 2.4 years, GLP-1RA therapy reduced serious adverse events (RR 0.91) and was associated with lower risks of myocardial infarction (RR 0.85), heart failure (RR 0.85), acute kidney failure (RR 0.91) and infections (RR 0.90), while increasing gastrointestinal disorders (RR 1.63) and gallbladder disorders (RR 1.26); no significant differences were observed for stroke, pancreatitis or cancer.²⁹

Durability with GLP-1 RAs across trials shows that benefits are largely maintained on-treatment, and major weight regain occurs after withdrawal over 2 years, supporting the view that obesity pharmacotherapy requires chronic use,^{15 16 47} refer to [table 5](#). Recent evidence quantifies the durability limitation of GLP-1 RA after discontinuation, as shown in a recent systematic review and meta-analysis of 37 studies with more than 9000 adults, evaluating outcomes after cessation of GLP-1 agents, West *et al*,⁴⁷ reporting a consistent pattern of rapid weight regain accompanied by progressive attenuation and reversal of improvements in cardiometabolic risk factors like glycaemia, blood pressure and lipids. Supporting caution against short-term prescribing of these agents in the absence of structured, lifestyle and longitudinal maintenance strategies. These results should not be surprising as obesity is a chronic disease that will relapse if treatment is

Table 4 Cardiovascular outcomes from comparative observational studies between metabolic bariatric surgery and GLP-1 RAs

Study	Total N	Population	CV outcomes	CV effect	References
Gasoyan <i>et al</i>	3932	Adults with T2DM and obesity; MBS: RYGB 61.3% SG 38.7% or GLP-1RA: liraglutide: 65.4% Dulaglutide: 48.6% Exenatide: 32.5% Semaglutide: 26.5% (overlap due to switch)	All-cause mortality; incident MACE; nephropathy; retinopathy (time-to-event)	MBS associated lower: All-cause mortality: HR 0.68 MACE aHR 0.65 Nephropathy aHR 0.53 Retinopathy aHR 0.46	Gasoyan <i>et al</i> Macrovascular and microvascular outcomes of metabolic surgery vs GLP-1 in patients with diabetes and obesity. <i>Nat Med.</i> 2025 doi: 10.1038/s41591-025-03893-3.
Wolff Sagy <i>et al</i>	4410	Adults with obesity and T2DM; no prior CHF, IHD or stroke; MBS: laparoscopic banding, RYGB, SG versus GLP-1RA: liraglutide, dulaglutide, exenatide, lixisenatide, semaglutide	Primary incidence of CHF in adults with obesity +T2DM without prior IHD, stroke or CHF	MBS associated: reduction in primary incidence of CHF aHR 0.43	Wolff <i>et al</i> Effectiveness of bariatric metabolic surgery vs glucagon-like peptide-1 receptor agonists for prevention of congestive heart failure. <i>Nat Med.</i> 2024 doi: 10.1038/s41591-024-03052-0.
Dicker <i>et al</i>	6070	Adults with obesity and diabetes; no known CVD; MBS: 54% SG 46% RYGB or GLP-1RA: exenatide 63.4% Liraglutide 23.0% dulaglutide 13.6%	All-cause mortality; MACE stratified by diabetes duration (≤ 10 years vs > 10 years)	MBS associated: reduced mortality versus GLP-1RAs, mediated via greater weight loss	Dicker D <i>et al</i> Bariatric Metabolic Surgery vs Glucagon-Like Peptide-1 Receptor Agonists and Mortality. <i>JAMA Netw Open.</i> 2024. doi:10.1001/jamanetworkopen.2024.15392.
Stenberg <i>et al</i>	4078	Adults primary MBS: (RYGB and SG) matched with patients with GLP-1: liraglutide 78%, semaglutide 13%, dulaglutide 9%	MACE; microvascular complications (retinopathy, nephropathy, neuropathy/leg ulcers); safety outcomes: alcohol/substance abuse, self-harm, fractures	MBS lower risk: MACE HR 0.75 Retinopathy HR 0.88 Nephropathy HR 0.72 Neuropathy/leg ulcers HR 0.82 MBS higher risk: Alcohol/substance abuse HR 2.56 Self-harm HR 1.41 Fractures HR 1.86	Stenberg E <i>et al</i> Cardiovascular and diabetes outcomes among patients with obesity and type 2 diabetes after metabolic bariatric surgery or glucagon-like peptide 1 receptor agonist treatment. <i>Br J Surg.</i> 2024 doi: 10.1093/bjs/znae221.
Stenberg <i>et al</i>	4322	Adults with T2DM and severe obesity. MBS: 80.9% RYGB, 19.1% SG in Sweden 2007–2019 SOS Registry versus group with T2DM+GLP-1 RA: liraglutide 81.7%, dulaglutide 9.9%, exenatide 6.0%, lixisenatide 1.6%	All-cause mortality; MACE	MBS lower risk: MACE or all-cause mortality HR 0.76	Stenberg E <i>et al</i> Major adverse cardiovascular events among patients with type-2 diabetes, a nationwide cohort study comparing primary metabolic and bariatric surgery to GLP-1 receptor agonist treatment. <i>Int J Obes (Lond).</i> 2023. doi: 10.1038/s41366-023-01254-z.
Ibrahim <i>et al</i> TriNetX network	5494	Adults ≥ 18 years with HFpEF and obesity (BMI > 30 kg/m ²). GLP-1 RAs (semaglutide or tirzepatide) and those who underwent bariatric surgery not specified	Acute HF events and all-cause hospitalisations All-cause death, myocardial infarction, stroke and follow-up BMI	Semaglutide or tirzepatide associated: Lower incidence of acute HF events HR 0.78 All-cause death HR 0.71 All-cause hospitalisations HR 0.62 No differences in rates of MI HR 0.99 and stroke HR 0.87	Ibrahim R <i>et al</i> Glucagon-Like Peptide-1 Receptor Agonists vs Bariatric Surgery in Patients with Obesity and Heart Failure with Preserved Ejection Fraction. <i>J Am Heart Assoc.</i> 2025 doi: 10.1161/JAHA.125.044577.
Maan <i>et al</i> TriNetX network	76 395	Adults with BMI ≥ 35 kg/m ² ; underwent MBS not stated or received GLP-1 not stated ≥ 2 years	Cardiovascular disease. A composite of incident HF, CAD and cerebrovascular disease	MBS associated: Lower hazard of CVD: HR 0.54 Incident HF: HR 0.45 CAD: HR 0.54 Cerebrovascular disease HR 0.64 MBS versus GLP-1 therapy	Maan S <i>et al</i> Metabolic and bariatric surgery vs glucagon-like peptide-1 receptor agonist therapy: A comparison of cardiovascular outcomes in patients with obesity. <i>Am J Surg.</i> 2025 doi: 10.1016/j.amjsurg.2025.116242.
Wu <i>et al</i> TriNetX network	84 884	Adults with BMI ≥ 30 kg/m ² Patients initiating tirzepatide treatment were compared with those undergoing MBS not specified	All-cause mortality, MACE and MAKE	Tirzepatide associated: Lower all-cause mortality HR 0.31 Lower MACE HR 0.74 Lower MAKE HR 0.37	Wu <i>et al</i> Tirzepatide vs bariatric metabolic surgery. <i>Diabetes Obesity & Metabolism</i> (2025), DOI: 10.1111/dom.16353.
Meta-analysis					
Cordova <i>et al</i> Systematic review and meta-analysis	39 569	Long-term outcomes of MBS versus GLP-1RA therapy (not specified) in adults with obesity	Mortality, MACE or HF	MBS associated: 43% lower risk of mortality HR 0.57, 35% lower MACE risk HR 0.65 55% lower risk of heart failure HR 0.45	Cordova F <i>et al</i> Cardiovascular outcomes and mortality of bariatric surgery vs glucagon-like peptide-1 receptor agonists: a systematic review and meta-analysis. <i>Surg Obes Relat Dis.</i> 2025 Dec doi: 10.1016/j.soard.2025.11.024.

aHR, adjusted HR; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IHD, ischaemic heart disease; MACE, major adverse cardiovascular event; MAKE, major adverse kidney event; MBS, metabolic bariatric surgery; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; SOS, Swedish obesity surgery; T2DM, type 2 diabetes mellitus.

stopped, in the same way we do not expect interventions for other chronic diseases such as diabetes, hypertension or dyslipidaemia to work when treatment is stopped.

MBS is also an effective and generally safe obesity treatment with structured perioperative and long-term follow-up. A large meta-analysis (164 studies; 1 617 566 patients) reported very low

perioperative mortality (30-day mortality 0.08%) with acceptable complication (17%) and reoperation rates (7%). Long-term outcomes consistently demonstrate durable weight loss and metabolic benefit, with RYGB cohorts maintaining substantial weight reduction for 10–12 years, although some weight regain in a subset of patients.^{18 46} Procedure choice influences both

Table 5 Evidence, outcomes, strengths and limitations—GLP-1 RAs versus metabolic bariatric surgery

Dimensions	GLP-1 receptor agonists	Metabolic bariatric surgery
Evidence hierarchy	Multiple RCTs and CVOTs → stronger causal inference. Multiple large RCT CVOTs: LEADER, REWIND, SUSTAIN-6, SELECT; smaller populations in SUMMIT, STEP-HFpEF for HF outcomes (see table 3)	Extensive observational data: large cohorts, propensity-matched studies, non-randomised analyses. Limited number of randomised trials (see table 1).
Consistency	Highly consistent across RCTs (see table 3)	Highly consistent across large cohorts, especially in T2DM (see table 1).
Causality	Causal relationship established via RCTs	Associative; RCT evidence lacking.
Effect on MACE	Consistent ranges from 12–26% relative risk reduction in MACE in T2DM; 20% reduction in obesity without diabetes; 19% reduction in patients without diabetes but with established CVD in SELECT	Observational studies show ranges from 30–60% RRR in MACE (including cardiovascular death), mostly in T2DM patients.
Mortality outcome	Not specifically emphasised beyond MACE reductions	Associated with reduced all-cause mortality and increased life expectancy (particularly in obesity and T2DM).
Populations studied	Trials largely in high/very high-risk populations	Particularly pronounced benefits in obesity+T2DM; broad observational cohorts across the risk spectrum.
Follow-up and durability	RCT follow-up generally ≤5 years Weight regains after 2-year discontinuation and gradual increase of glycaemia, BP and lipids	Long-term (10–20 years) observational follow-up. Gradual weight regain after nadir over >7 years on. Gradual increase in glycaemia, BP and lipids.
Safety of treatments	GLP-1 RAs reduced serious adverse events (–9%), MI (–15%), acute kidney failure (–9%), HF (–15%) and infections (–10%) Increased gastrointestinal (+63%) and gallbladder (+26%) disorders No differences in stroke, pancreatitis or cancer between groups	1 RCT: mortality rate within 30 days was 0.08% mortality rate after 30 days was 0.31%. The complication rate was 17% and the reoperation rate was 7%. RYGB: more effective in weight loss but associated with more complications. Adjustable GB: lower mortality and complication rates; but higher reoperation rates+weight loss was less substantial than GB. SG: comparable with gastric bypass.
Design strengths	Randomisation, strong causal inference for on-treatment effect; mechanisms and benefits consistent across studies	Real-world, large sample sizes; consistent effect sizes across many analyses.
Key limitations	Shorter follow-up: high/very high-risk populations dominate trials → limited generalisability to lower-risk groups	No RCTs with MACE as primary endpoint; residual confounding and selection bias; procedure heterogeneity (eg, bypass vs sleeve) may yield variable cardiovascular outcomes.

CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; GB, gastric banding; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; LEADER trial, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular outcome Results; MACE, major adverse cardiovascular events; MI, myocardial infarction; RCT, randomised controlled trial; REWIND trial, Researching cardiovascular events with Weekly Dulaglutide in Diabetes; RRR, relative risk reduction; RYGB, Roux-en-Y gastric bypass; SELECT trial, Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity; SG, sleeve gastrectomy; STEP HFpEF trial, Semaglutide Treatment Effect in People with obesity and HFpEF; SUMMIT trial, Study of Tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction and Obesity; SUSTAIN-6 trial, Evaluate Cardiovascular and Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes 6; T2DM, type 2 diabetes mellitus.

the magnitude of weight loss and the risk profile, including nutritional deficiencies and procedure-specific complications, supporting individualised decision-making and multidisciplinary follow-up^{12 18} (see table 5).

From a health systems perspective, both modalities face major access barriers. Surgical access is often limited by specialist capacity, geographic distribution of accredited centres and waiting

lists, whereas GLP-1 RA access is frequently constrained by drug acquisition cost, supply and heterogeneous reimbursement policies that can undermine initiation and long-term adherence.

DISCUSSION

This review aimed to stimulate a nuanced discussion on obesity therapies that not only induce weight loss but also reduce CV

	Metabolic bariatric surgery (MBS)	GLP-1 receptor agonists (GLP-1 RA)	Comparative real-world (MBS vs GLP-1 RA)
Evidence	Multiple Observational cohorts + meta-analyses	Multiple randomised CVOTs + HFpEF trials Meta-analyses	Comparative observational cohorts (claims/EHR; incl. TriNetX)
Design strengths	Long follow-up (10-20 years) Hard clinical endpoints Consistent direction	Randomisation → causal inference Adjudicated outcomes (CVOTs) Early on-treatment benefit	Large real-world samples Target-trial possible if strong causal predesign
Key limitations	Residual confounding/selection Procedure heterogeneity Peri-op risk; Some weight regain	Follow-up usually ≤5 years High/very-high-risk populations Stopping therapy → weight regain	Confounding by indication Exposure misclassification No randomised head-to-head CVOT
CV outcomes	Observed ↓ MACE, HF and mortality vs non-surgical care (HRs often 0.4-0.6)	↓ 3-point MACE (T2DM: 12–26%) SELECT: 20% ↓ MACE + ↓ death HFpEF: symptoms/function ↑ ↓ worsening HF; mortality uncertain	Most studies favour MBS for MACE/mortality (7/9 studies) Newer agents show mixed results
Future	Strong long-term signal, causal attribution limited → need contemporary RCTs	Best causal evidence for MACE Durability depends on adherence Benefits partly weight-independent	Hypothesis-generating; interpret cautiously → urgent head-to-head trials

CVOT, cardiovascular outcomes trial; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse cardiovascular events; RCT, randomised controlled trial; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy. Figure produced by IVT

Figure 1 Current evidence in cardiovascular outcomes with obesity treatments.

events. We recognise that this remains a contentious area for several reasons. First, the evidence base for MBS is largely observational even though the field benefits arise from long-term follow-up. Obesity medicines are supported by high-quality randomised trials, but these are comparatively of short duration. There is a clear need for further rigorous studies to inform clinical guidelines with level 1 evidence, to address persisting uncertainties for both surgical and pharmacological approaches, in separate and combination trials. Second, our intention was not to advocate for surgery or pharmacotherapy, nor to assert that combined therapy is universally superior or inferior, but rather to frame a conceptual model of how these modalities might be used individually or together in a risk-stratified manner. In this context, the application of a ‘treat-to-target’ paradigm in obesity is still in early stages.⁴⁸ This dilemma parallels hypertension or dyslipidaemia management, where treatment targets (eg, systolic blood pressure or low density lipoprotein-cholesterol thresholds) are defined by levels associated with reduced CV risk rather than by the proportion of patients who can practically attain them. In obesity, however, robust data linking specific degrees of weight loss or adiposity reduction to hard CV endpoints are only beginning to emerge, and current proposals about optimal targets remain theoretical compared with the well-established evidence base for glycaemic, lipid and blood pressure targets. These weight-loss magnitudes should be interpreted as observational associations rather than prescriptive targets and should not be understood as mandatory thresholds for individual patients. These considerations are particularly relevant when translating the available evidence into day-to-day clinical decision-making. In routine cardiology practice, treatment decisions are influenced not only by efficacy and safety but also by real world access. Referrals for MBS may be constrained by specialist availability, institutional capacity, geographic distribution of accredited centres and waiting times. Conversely, the use of GLP-1 based therapies is often shaped by drug cost, reimbursement policies and long-term affordability, which may affect initiation and treatment durability.⁴⁷ Awareness of these practical constraints is important when counselling patients and individualising cardiometabolic risk-reduction strategies.

We also acknowledge that some organ-specific benefits both from bariatric surgery and pharmacotherapy may occur independent of weight loss, but disentangling the relative contributions of weight reduction versus hormonal and organ-specific mechanisms is challenging, although emerging data are showing cardiometabolic changes before weight loss is achieved and more studies are helping support the idea that strategies for weight loss and CV protection could be managed with current available obesity treatments.

Finally, how likely patients will require either or combined surgical and pharmacological therapy will depend heavily on how future ‘low risk’ adiposity or cardiometabolic targets are defined. If relatively modest targets are shown to confer substantial risk reduction, the proportion needing combination therapy may remain small; conversely, if very low adiposity thresholds are required, a larger subset may benefit from combined approaches. It is also conceivable that, if the CV benefits of GLP-1-based therapies prove to be largely tissue-specific and not contingent on further reductions in adipocyte mass, the incremental CV advantage of adding surgery to GLP-1 therapy (or vice versa) could be limited.⁴⁹ These questions can only be resolved through carefully designed mechanistic studies and long-term outcome trials, which will be essential to define the role and magnitude of surgical and/or pharmacological strategies in routine obesity and CV risk management. Therefore, current clinical decisions must

rely on shared decision-making in the absence of robust comparative evidence and defined cardiometabolic targets.

CONCLUSIONS

This review synthesises current evidence indicating that MBS is associated with favourable CV outcomes and GLP-1 RAs meaningfully attenuate CV risk in patients with obesity through pleiotropic endocrine, metabolic and haemodynamic effects across multiple organ systems. Given that obesity is an independent driver of CVD, risk reduction appears to be mediated in part by weight loss, with available data suggesting that durable reductions of at least 10% seem to help translate into improvements in clinically relevant decreases in MACE. Importantly, both MBS and GLP-1 RAs may also confer CV protection via hormonal, inflammatory, organ-specific mechanisms, although the magnitude and relative contribution of these pathways remain incompletely defined, as shown in [table 5](#).

The evidentiary base for GLP-1 RAs and MBS differs in both hierarchy and duration of follow-up. GLP-1 RAs have demonstrated reductions in MACE across multiple large, randomised CV outcome trials, supporting a stronger causal inference for on-treatment benefit; however, follow-up is typically limited to fewer than 5 years, and the long-term durability of benefit remains contingent on sustained pharmacotherapy adherence. In contrast, MBS is supported primarily by large observational cohorts and meta-analyses that consistently associate surgery with substantial reductions in MACE and all-cause mortality, with follow-up extending 10–20 years ([figure 1](#)). Yet, in the absence of large, randomised trials, causal attribution remains constrained. As summarised in [table 4](#), most large comparative observational studies favour MBS for long-term CV and mortality outcomes, whereas findings comparing newer, more potent pharmacotherapies show a more variable pattern; nevertheless, residual confounding, confounding by indication and selection bias limit the interpretability of both assumptions. Well-designed randomised trials comparing contemporary GLP-1 based agents with MBS, using adjudicated CV endpoints and long-term follow-up, are needed to address these evidence gaps.

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