Targeting the weight within

Obesity pharmacotherapy in cardiovascular disease

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Obesity is a major contributor to cardiovascular disease and mortality. New pharmacological treatments, including incretin therapies, have shown significant weight loss and cardiovascular benefits. Large trials have demonstrated that these agents reduce cardiovascular events in patients with cardiovascular disease and improve outcomes in heart failure, kidney disease and metabolic dysfunction-associated steatohepatitis. This article reviews the cardiovascular impact of weight loss and the role of therapies such as semaglutide and tirzepatide in reducing cardiovascular disease risk.

KEY POINTS

- Obesity independently increases cardiovascular mortality, and weight loss of 5 to 10% yields meaningful reductions in cardiovascular disease risk factors; weight loss of 10% and above is associated with improved cardiovascular outcomes.
- Lifestyle interventions remain foundational, but maintaining weight loss is challenging, with most patients regaining 80% of lost weight within five years.
- Glucagon-like peptide-1 receptor agonists have demonstrated significant weight loss and cardiovascular benefits in both patients with and without diabetes, including a reduction in major adverse cardiovascular events.
- Next-generation therapies are emerging, showing promise for greater weight loss and potential cardiovascular improvements, with ongoing trials evaluating long-term outcomes.

Obesity is a major public health problem that contributes both directly and indirectly to cardiovascular disease (CVD) and mortality. In 2015, obesity was estimated to have accounted for four million deaths globally, two-thirds of which were caused by CVD.[1] The management of obesity is rapidly evolving with new pharmacological treatments that have been shown to induce weight loss approachable to that achieved with weight loss surgery. Modern pharmacological agents such as glucagon- like peptide-1 (GLP-1) receptor agonists and combination glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists have also been shown to improve cardiovascular outcomes in patients with obesity.

Why is treatment of obesity important?

Obesity is a multifaceted disease that contributes directly and indirectly to atherosclerotic CVD, heart failure, atrial fibrillation and multiple CVD risk factors, including dyslipidaemia, type 2 diabetes, hypertension and sleep disorders (Figure). It is increasingly recognised that obesity leads to increased CVD mortality independent of cardiovascular risk factors.[2-11] Modest reductions in weight of 5 to 10% can produce clinically significant improvements in CVD risk factors. Moreover, the degree of benefit in reducing CVD risk factors and improving clinical outcomes increases with higher percentages of weight loss.[9,12-15]

MedicineToday FOCUS ON OBESITY 2025; 26(8 Suppl): 31-36
First published in Medicine Today 2024; 25(12): 23-29
Updated March 2026

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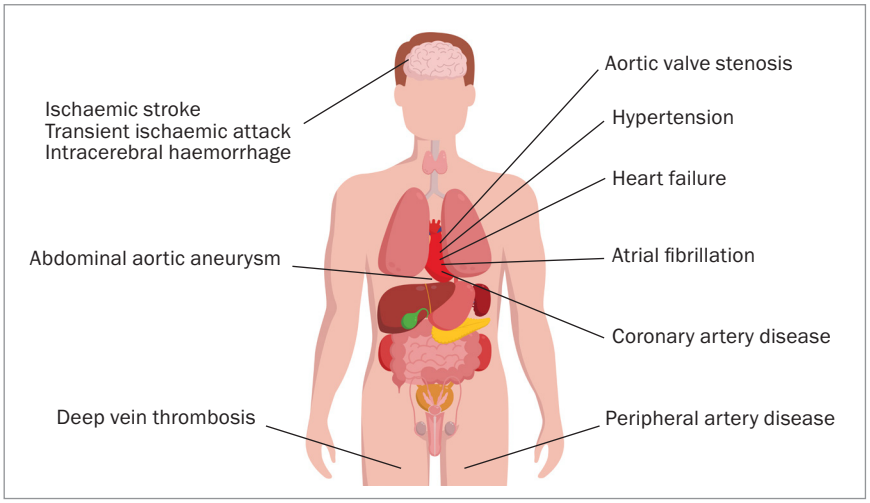

Figure. Cardiovascular diseases associated with obesity.

1. CLASSIFICATION OF OVERWEIGHT AND OBESITY ACCORDING TO BMI[24-26]*†

- **Underweight:** <18.5 kg/m^2
- **Normal:** 18.5–24.9 kg/m^2
- **Overweight:** 25.0–29.9 kg/m^2
- **Grade 1 obesity:** 30.0–34.9 kg/m^2
- **Grade 2 obesity:** 35.0–39.9 kg/m^2
- **Grade 3 or severe obesity:** ≥40.0 kg/m^2

Abbreviation: BMI = body mass index.

* BMI classifications of obesity are based on the WHO classifications.
† Country-specific cut-off points have been developed for Asian subpopulations. The WHO-suggested categories for Asian populations are as follows: ≥23 kg/m^2 for increased risk and ≥27.5 kg/m^2 for high risk.[24-26]

A systematic review and meta-analysis of randomised controlled trials evaluating weight reduction diets, with or without exercise, reported an 18% reduction in all-cause mortality over a median follow up of two years in adults with obesity.[7] Over 55% of the weighting in this meta-analysis was contributed by the Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes (LOOK AHEAD) trial, which assessed whether intensive lifestyle interventions for weight loss would reduce cardiovascular morbidity and mortality in individuals with overweight or obesity and type 2 diabetes (T2DM). The intensive lifestyle intervention group achieved greater weight loss (6.0% *vs* 3.5%) and reductions in glycated haemoglobin (HbA_{1c}) as well as in all traditional CVD risk factors, except for LDL-cholesterol. However, despite the favourable effects on CVD factors, the trial did not demonstrate a significant reduction in cardiovascular outcomes. It was therefore discontinued at a median follow up of 9.6 years following a futility analysis.[11,12]

These findings suggest that although lifestyle-based weight loss interventions confer short-term benefit, it is difficult for most patients to maintain sufficient weight loss to achieve long-term reductions in cardiovascular events. Furthermore, weight maintenance remains a challenge, with up to 80% of weight loss expected to be regained over the subsequent five years.[16]

Recent developments add momentum to the notion that larger degrees of weight loss (10–20% of body weight) may result in meaningful reductions in cardiovascular outcomes.[17,18] A post hoc analysis of LOOK AHEAD trial data found that participants who achieved at least a 10% body weight loss in the first year had a 21% lower rate of major adverse cardiac events.[17] Similar findings have been reported in analyses of subjects who underwent metabolic surgery compared with those who did not.[11,19-23] Although these findings are derived from nonrandomised cohort studies, metabolic surgery resulting in 20 to 35% total body weight loss was associated with lower rates of all-cause mortality, cardiovascular mortality, incident heart failure, myocardial infarction and stroke (p <0.001 for all comparisons).[23]

Accordingly, metabolic surgery should be considered an important adjunct to reduce CVD risk in patients with a body mass index (BMI) of 40 kg/m^2 and above, or 35 kg/m^2 and above in the presence of obesity-associated comorbidities, particularly when lifestyle and pharmacological therapy alone are insufficient.[7,23] The most widely accepted BMI classifications of obesity are listed in Box 1.[24-26]

Evidence for new pharmacological therapy

Although lifestyle interventions represent the cornerstone of weight management, sustaining long-term weight loss is challenging. The management of obesity is evolving with the advent of pharmacological agents that lead to substantial weight loss approaching that achieved with metabolic surgery.

Glucagon-like peptide-1 receptor agonists

GLP-1 is an endogenous incretin produced in the intestines following food intake. It enhances insulin secretion and suppresses glucagon release. Cardiovascular outcome studies have evaluated the safety and efficacy of GLP-1 receptor agonists in patients with T2DM, with meta-analyses reporting significant reductions in major adverse cardiovascular events (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.80–0.93) without an increased risk of severe hypoglycaemia.[27] Although these studies did not specifically enrol patients with overweight or obesity, the average BMI at baseline exceeded 30 kg/m^2. This included the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Result (LEADER) and Semaglutide and Cardiovascular Outcomes in Patients with T2DM (SUSTAIN-6) trials,

which both demonstrated that injectable GLP-1 receptor agonists (liraglutide up to 1.8 mg once daily or semaglutide up to 1.0 mg once weekly, respectively) significantly reduced the risk of major adverse cardiovascular events in patients with T2DM who were at high cardiovascular risk.[28,29]

The Semaglutide Treatment Effect in People with obesity (STEP) series of clinical trials evaluated semaglutide up to 2.4 mg once weekly in people with obesity. The STEP 1 trial showed that from baseline to week 68, the mean change in body weight in subjects without diabetes was –14.9% in the semaglutide group compared with –2.4% with placebo ($p < 0.001$).[30] The STEP 5 trial reported sustained weight loss with semaglutide out to 104 weeks.[31]

The Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes (SELECT) trial was the first randomised, placebo-controlled cardiovascular outcome trial evaluating semaglutide in patients without diabetes who had overweight or obesity.[32] A total of 17,604 patients aged 45 years or older with pre-existing CVD and a BMI of 27 kg/m^2 and above (but without diabetes) were randomised to subcutaneous semaglutide once weekly (titrated up to 2.4 mg) or placebo. At a mean follow up of 39.8 months, semaglutide significantly reduced the incidence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke (6.5% *vs* 8.0%, HR 0.80, 95% CI 0.72–0.90). Patients receiving semaglutide also experienced greater improvements in a variety of secondary endpoints, including reductions in body weight, HbA_{1c} level, systolic and diastolic blood pressure and high-sensitivity C-reactive protein and lipid levels.[32]

Although the reduction in cardiovascular events may be mediated through weight loss and improvements in traditional CVD risk factors (e.g. lipid levels, glycaemia, blood pressure), the early separation of event curves between the semaglutide and placebo groups even before substantial weight loss occurred suggests additional direct cardioprotective effects. This may involve modulation of inflammatory and prothrombotic pathways or other pleiotropic mechanisms.

Recent studies also report beneficial effects of semaglutide beyond cardiovascular risk reduction. At a target dose of 2.4 mg once weekly (which is TGA approved for chronic weight management), semaglutide led to significant weight loss, improved quality of life and increased six-minute walk distance in patients with obesity and heart failure with preserved or mildly reduced ejection fraction, with or without T2DM.[33,34] Notably, weight reduction in these trials was associated with reductions in NT pro B-type natriuretic peptide, suggesting beneficial effects on myocardial remodelling.

Semaglutide (aiming for a target dose of 1.0 mg weekly), which is TGA approved for T2DM) was also found to reduce the risk of clinically important kidney outcomes in patients with T2DM and chronic kidney disease (defined by either estimated glomerular filtration rate [eGFR] 50 to 70 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio >300 and <5000; or eGFR 25 to <50 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio of >100 and <5000). The primary outcome – a composite of kidney failure (dialysis, transplantation or an eGFR of <15 mL/min/1.73 m^2), at least 50% reduction in eGFR from baseline or death from kidney-associated or cardiovascular causes – was 24% lower in the semaglutide group (HR 0.76, 95% CI 0.66–0.88) at a median follow up of 3.4 years. Similar results were observed for a composite of the kidney-specific components of the primary outcome (HR 0.79, 95% CI 0.66–0.94) and for death from cardiovascular causes (HR 0.71, 95% CI 0.56–0.89). Major cardiovascular events were also reduced by 18% (HR 0.82, 95% CI 0.68–0.98).[35]

The recent phase 3 Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis (ESSENCE) trial showed that semaglutide 2.4 mg once weekly improved liver histology in patients with metabolic dysfunction-associated steatohepatitis with moderate or advanced liver fibrosis. Resolution of steatohepatitis and fibrosis reduction occurred in 32.7% of semaglutide-treated patients versus 16.1% in the placebo group (estimated difference 16.5 percentage points, 95% CI 10.2–22.8).[36] Results from the Semaglutide and Walking Capacity in People with Symptomatic Peripheral Artery Disease and T2DM (STRIDE) trial also found that semaglutide 1.0 mg once weekly is associated with an increase in walking distance in individuals with symptomatic peripheral artery disease and T2DM.[37]

Given the promising results of semaglutide 2.4 mg, the phase 3b STEP-UP trial compared intensified semaglutide 7.2 mg with semaglutide 2.4 mg in adult patients with a BMI of 30 kg/m^2 and above, without diabetes. This showed that semaglutide 7.2 mg led to a mean weight loss of 18.7%, outperforming the 2.4 mg dose (–15.6%) at 72 weeks. Furthermore, semaglutide 7.2 mg was associated with a greater likelihood of achieving body weight reduction of at least 25%, compared with semaglutide 2.4 mg (OR 2.4, 95% 1.6–3.5).[38]

Oral GLP-1 receptor agonists are also under development. A phase 3 trial found that high-dose oral semaglutide (50 mg) produced a 12.7% placebo-adjusted weight loss at week 68, comparable to subcutaneous semaglutide in patients without diabetes.[39] Lower-dose oral semaglutide 25 mg has also shown substantial benefit, with an estimated mean weight reduction of –13.6% at 64 weeks.[40] The Semaglutide Cardiovascular Outcomes Trial (SOUL) trial evaluated the cardiovascular efficacy of oral semaglutide (up to 14 mg) in patients with T2DM (HbA_{1c} 6.5–10.0%) and established atherosclerotic CVD, chronic kidney disease (eGFR <60 mL/min/1.73 m^2), or both. The study demonstrated that oral semaglutide was associated with a lower risk of major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal

stroke; HR 0.86, 95% CI 0.77–0.96), particularly nonfatal myocardial infarction (HR 0.74, 95% CI 0.61–0.89). However, a significant effect on major kidney outcomes was not observed (HR 0.91, 95% CI 0.80–1.05). Serious adverse event rates were comparable with placebo, although gastrointestinal events were slightly more frequent in the semaglutide group versus placebo (5.0% *vs* 4.4%).[41]

Orforglipron, an oral small-molecule, nonpeptide GLP-1 receptor agonist, has also demonstrated weight loss comparable to injectable GLP-1 receptor agonists.[42] A phase 3 trial including adults with T2DM receiving orforglipron daily (3 mg, 12 mg or 36 mg) showed significant placebo-adjusted reductions in HbA_{1c} (–1.07%) and weight loss (–5.9%) at the highest dose.[43] In a phase 3 trial including patients with obesity (excluding T2DM), the highest dose group achieved a mean weight reduction of 11.2% by week 72. Notably, 18.4% of participants achieved 20% or greater total body weight loss.[44] There are ongoing studies evaluating the efficacy of orforglipron on weight loss and cardiovascular outcomes (clinical trial number NCT05803421; Table).

Ecnoglutide is a novel GLP-1 receptor agonist designed with cyclic adenosine monophosphate (cAMP)-biased signalling. By preferentially promoting cAMP-mediated intracellular pathways, thought to be central to insulin secretion and appetite regulation, this receptor bias may enhance metabolic efficacy while potentially reducing the activation of alternative signalling cascades associated with receptor desensitisation or adverse effects (although the clinical relevance of this remains to be fully established). In a phase 3 trial involving adults with overweight or obesity (BMI ≥28 kg/m², or ≥24 kg/m² with at least one weight-related comorbidity) without diabetes, treatment with 2.4 mg ecnoglutide produced a mean body weight reduction of 13.2% at 40 weeks. Additionally, 77% of participants achieved at least a 5% reduction in body weight.[45]

At the time of this publication, both subcutaneous liraglutide and semaglutide (2.4 mg weekly dose) are TGA approved for chronic weight management in Australia. This includes adults with an initial BMI of 30 kg/m² and above, or 27 to 29.9 kg/m² with at least one weight-associated comorbidity (e.g hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes or T2DM).

Combination incretin therapies

Next-generation pharmacological treatments for obesity include combinations of GLP-1 receptor agonists with other enteropancreatic hormones (such as GIP, glucagon and amylin). These combinations may enhance weight loss and cardiometabolic outcomes beyond those achieved with GLP-1 receptor agonist monotherapy.

Glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide receptor agonists

Tirzepatide is a once-weekly, subcutaneous injectable peptide with dual agonist activity at both GLP-1 and GIP receptors. GIP activation appears to act synergistically with GLP-1 receptor activation, enabling greater weight reduction than GLP-1 receptor agonism alone.[46]

In patients with T2DM, the Tirzepatide versus Semaglutide once weekly in patients with T2DM (SURPASS-2) trial compared tirzepatide with semaglutide 1 mg (both as add-on therapies to metformin) and found tirzepatide was either noninferior or superior at all doses (5 mg, 10 mg 15 mg), for both HbA_{1c} reduction and weight loss at 40 weeks. The 15 mg dose led to a mean HbA_{1c} reduction of 2.3% and a mean weight loss of 11 kg.[47]

In patients with overweight or obesity without diabetes, the Tirzepatide Once Weekly for the Treatment of Obesity (SURMOUNT-1) trial showed that tirzepatide 15 mg weekly led to a mean body weight reduction of 20.9% after 72 weeks of treatment, compared with 3.1% with placebo.[48] In the Tirzepatide as Compared with Semaglutide for the Treatment of Obesity (SURMOUNT-5) trial in adult participants with obesity but without T2DM, tirzepatide (10 mg or 15 mg) achieved greater weight loss compared with semaglutide (1.7 mg or 2.4 mg weekly dose): –20.2% (95% CI –21.4 to –19.1) *versus* –13.7% (95% CI –14.9 to –12.6) at week 72. Tirzepatide was also associated with greater reductions in waist circumference and higher rates of achieving at least 25% weight loss.[49]

Tirzepatide has also been shown to improve cardiovascular outcomes. The recently published randomised controlled Study of Tirzepatide Compared with Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes (SURPASS-CVOT) demonstrated that tirzepatide (up to 15 mg) was noninferior to dulaglutide (1.5 mg) in reducing major adverse cardiovascular events (death from cardiovascular causes, myocardial infarction or stroke) in patients with T2DM and atherosclerotic CVD. Although tirzepatide did not meet the criterion for superiority to dulaglutide with respect to the primary endpoint, a prespecified subgroup analysis suggested a possible lower incidence of death from any cause and of death from noncardiovascular causes in the tirzepatide group than in the dulaglutide group.[50] A Study of Tirzepatide on the Reduction on Morbidity and Mortality in Adults with Obesity (SURMOUNT- MMO) is due for completion in 2027 (clinical trial number NCT05556512).

In the Study of Tirzepatide in Participants with Heart Failure with Preserved Ejection Fraction with Obesity (SUMMIT) trial, tirzepatide significantly reduced the risk of death from cardiovascular causes or worsening heart failure events in patients with heart failure with preserved ejection fraction (ejection fraction 50% and above) and obesity (BMI 30 kg/m²), compared with placebo (HR 0.62; 95% CI 0.41–0.95). Tirzepatide was also associated with an improved quality of life.[51]

TABLE. SELECTED ONGOING RANDOMISED CONTROLLED CV OUTCOME TRIALS EVALUATING PHARMACOLOGICAL INTERVENTIONS TO ACHIEVE WEIGHT LOSS IN PATIENTS WITH OVERWEIGHT OR OBESITY

Ongoing cardiovascular outcome trials	Study population	Intervention	Primary outcome	Estimated study completion date
GLP-1 receptor agonist				
A study of Daily Oral Orforglipron (LY3502970) Compared with Insulin Glargine in Patients with Overweight at Increased Cardiovascular Risk (ACHIEVE-4) (clinical trial number NCT05803421)	N = 2620; key inclusion criteria: adults age ≥18 years, BMI ≥25 kg/m^2, T2DM (HbA_{1c} ≥7.0% without sulfonylurea, or ≥7.5 to ≤10.5% with sulfonylurea), stable on 1 to 3 oral antihyperglycaemic drugs for least 90 days, have increased risk for CV events, stable weight (±5%) for at least 90 days	Escalated doses of orforglipron once daily *vs* subcutaneous insulin glargine once daily	Time to first occurrence of any MACE (MI, stroke, hospitalisation for unstable angina or CV death)	March 2026
GLP-1/GIP receptor agonist (tirzepatide)				
A Study of Tirzepatide on the Reduction on Morbidity and Mortality in Adults with Obesity (SURMOUNT-MMO) (clinical trial number NCT05556512)	N = 15,374; key inclusion criteria: adults age ≥40 years with established CVD, BMI ≥27 kg/m^2	Tirzepatide once-weekly subcutaneous injection *vs* placebo	Time to first occurrence of any component of composite (all-cause death, nonfatal MI, nonfatal stroke, coronary revascularisation or heart failure events)	October 2027
Combined GLP-1 receptor agonist/amylin analogues (cagrilintide/semaglutide)				
A Research Study to see the effects of CagriSema in People Living with Diseases in the Heart and Blood vessels (REDEFINE 3) (clinical trial number NCT05669755)	N = 7000; key inclusion criteria: adults age ≥55 years, BMI ≥25 kg/m^2, established CVD	Cagrilintide 2.4 mg and semaglutide 2.4 mg *vs* placebo	Time to first occurrence of MACE (composite endpoint of CV death, nonfatal MI, nonfatal stroke)	October 2027
Glucagon and GLP-1 receptor dual agonist (survodutide)				
A Study to Test the Effect of Survodutide (BI 456906) on Cardiovascular Safety in People with Overweight and Obesity (SYNCHRONIZE-CVOT) (clinical trial number NCT06077864)	N = 4935; key inclusion criteria: adults age ≥18 years, BMI ≥25 kg/m^2 with established CVD and/or at least two weight-related complications or risk factors for CVD	Survodutide once-weekly subcutaneous injection *vs* placebo	Time to first occurrence of any of the adjudicated components of the composite endpoint: CV death, nonfatal MI, nonfatal stroke, ischaemic coronary revascularisation or heart failure events	June 2026

Abbreviations: BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; HbA_{1c} = glycated haemoglobin; MACE = major adverse cardiovascular event; MI = myocardial infarction; T2DM = type 2 diabetes mellitus.

The Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity (SURMOUNT-OSA) trial reported that tirzepatide (10 mg or 15 mg) significantly reduced the apnoea–hypopnea index in people with moderate to severe obstructive sleep apnoea and obesity. Among participants using positive airway pressure, the apnoea–hypopnea index was reduced by up to 29.3 events per hour (95% CI –29.6 to –17.9), a 58.7% change from baseline, compared with a 5.3 events per hour (3.0%) reduction with placebo.[52] Tirzepatide also improved sleep-associated patient-reported outcomes.[52]

Since September 2024, subcutaneous tirzepatide has been TGA approved for the treatment of overweight and obesity. Eligible adults include those with an initial BMI of 30 kg/m^2 and above, or 27 to 29.9 kg/m^2 in the presence of at least one weight-associated comorbidity. It is also approved for the treatment of obstructive sleep apnoea in adults living with obesity.

In contrast to tirzepatide, maridebart cafraglutide is a long-acting peptide–antibody conjugate that combines GLP-1 agonism with GIP antagonism. In a phase 2 trial, once-monthly dosing produced significant weight loss at 52 weeks: –12.3% to –16.2% in patients with obesity without diabetes (*vs* –2.5% with placebo), and –8.4% to –12.3% in those with obesity and type 2 diabetes (*vs* –1.7% with placebo).[53]

Novel 'triple-G' agonists

Retatrutide is a novel, once-weekly injectable agent that acts on GIP, GLP-1 and glucagon receptors, and has shown promise in clinical trials for significant weight loss. In a phase 2 trial involving people with obesity, the 12 mg weekly dose of retatrutide resulted in a placebo-adjusted mean weight reduction of 22.1% after 48 weeks of treatment.[54] The phase 3 randomised controlled Study of Retatrutide in Participants with Obesity and Cardiovascular Disease (TRIUMPH-3) seeks to determine the percentage change from baseline in body weight in patients with BMI ≥35 kg/m^2 and established CVD (clinical trial number NCT05882045; Table).

2. CONSIDERATIONS FOR HEALTHCARE PRACTITIONERS MANAGING CVD IN PATIENTS WHO HAVE OVERWEIGHT OR OBESITY

- Ask permission to discuss the patient's weight in a nonjudgmental manner
- Recognise that obesity is a chronic disease that requires ongoing management and monitoring from medical and other allied healthcare professionals
- Discuss the impact of weight on health outcomes and quality of life, and the benefits of weight reduction
- Classify obesity according to BMI (with measurement of waist circumference)
- Take a history regarding current eating patterns and physical activity
- Consider underlying contributors to weight gain, including pharmacotherapy (e.g. insulin, sulfonylureas, beta blockers, antidepressants, corticosteroids, contraceptives) and metabolic conditions (e.g. hypothyroidism)
- Evaluate and manage other CVD risk factors according to guidelines
- Screen for psychological conditions (e.g. depression), obesity-associated complications and consider the contribution of cardiac disease to exercise intolerance (e.g. heart failure)
- Discuss lifestyle approaches (e.g. dietary, exercise) to weight reduction and set realistic goals, which may involve referral to allied healthcare professionals (e.g. dietician, exercise physiologist, clinical psychologist)
- Discuss pharmacological approaches to weight reduction considering limitations associated with reimbursement and supply
- Consider referral to appropriate specialists for consideration of metabolic surgery in patients with a BMI of 40 kg/m^2 or more or 35 kg/m^2 or more with obesity-associated comorbidities despite lifestyle and pharmacological therapy

Abbreviations: BMI = body mass index; CVD = cardiovascular disease.

Glucagon-like peptide-1 receptor agonist and amylin analogue combinations

Amylin is co-secreted with insulin from the pancreas and contributes to postprandial satiety regulation, delays gastric emptying and inhibits glucagon secretion. Cagrilintide is a long-acting amylin analogue that, when combined with the GLP-1 receptor agonist semaglutide, has demonstrated synergistic effects. In a phase 3 trial (REDEFINE-2) of adults with T2DM and a BMI of 27 kg/m^2 and above, combining the GLP-1 receptor agonist semaglutide with the long-acting amylin analogue cagrilintide resulted in greater weight loss than placebo at 68 weeks (–13.7% *vs* –3.4%). In addition, 73.5% of participants receiving the combination achieved an HbA_{1c} level of 6.5% or less, compared with 15.9% in the placebo group.[55] The phase 3 REDEFINE-3 trial will further assess the impact of cagrilinitide/semaglutide on major adverse cardiovascular events in people with obesity (with or without T2DM) and established CVD (clinical trial number NCT05669755; Table). Amycretin, a novel unimolecular peptide agonist of GLP-1, amylin and calcitonin receptors, has demonstrated 24% weight loss (60 mg dose) at 36 weeks in a phase 1b/2a study and offers a promising oral formulation.[56]

Glucagon and glucagon-like peptide-1 dual agonist

Survodutide is a dual GLP-1 and glucagon receptor agonist. In a phase 2 randomised controlled trial involving adults without diabetes and with a BMI of 27 kg/m^2 and above, survodutide administered once weekly for 46 weeks led to dose-dependent weight loss. The 4.8 mg dose produced a placebo-adjusted weight reduction of 12.1%.[57] Phase 3 trials – A Study to Test Whether Survodutide Helps People with Overweight or Obesity Who do Not Have (SYNCHRONISE-1; in people without diabetes) and Have Diabetes (SYNCHRONISE-2; in people with diabetes) – are ongoing to assess the efficacy and durability of weight loss with 3.6 and 6 mg doses over 76 weeks (clinical trial numbers NCT06066515 and NCT06066528). The SYNCHRONISE-CVOT trial will evaluate the cardiovascular safety of survodutide in participants with overweight or obesity and established CVD, chronic kidney disease or cardiovascular risk factors (clinical trial number NCT06077864; Table).

Mazdutide, which has been studied predominantly in Chinese populations, is also a dual GLP-1 and glucagon receptor agonist. In a phase 3 trial involving adults with overweight or obesity, treatment with once-weekly 6 mg mazdutide resulted in a mean percentage reduction in body weight of –12.55% by 32 weeks.[58]

Conclusion

Obesity should be recognised as both an independent CVD risk factor and a chronic disease in its own right. An evolving body of evidence shows that weight reduction improves health outcomes beyond its effect on intermediary CVD risk factors. Lifestyle interventions remain the cornerstone of obesity management, and typically involve a multidisciplinary approach with GPs, cardiologists, endocrinologists and allied health professionals. Although addressing obesity can be challenging, all healthcare professionals should discuss a patient's weight in a sensitive, nonjudgemental manner (Box 2). If lifestyle measures alone are insufficient, pharmacotherapy should be considered. Available options include GLP-1 receptor agonists such as semaglutide (2.4 mg weekly dose) and the dual GLP-1/GIP receptor agonist tirzepatide. Cardiovascular outcome trials evaluating novel agents that target multiple pathways – including combinations of GLP-1 agonism, GIP agonism, glucagon receptor agonism and amylin analogues – are ongoing and will help define the next generation of obesity treatments. MT

COMPETING INTERESTS: Dr Sun: None. Professor Atherton has received travel sponsorship and/or honoraria or consultancy payments (made to his employer) from or undertaken clinical trials sponsored by Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Novo Nordisk.

MedicineToday FOCUS ON OBESITY 2025; 26(8 Suppl): 31-36
First published in Medicine Today 2024; 25(12): 23-29
Updated August 2025

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