Tirzepatide SURMOUNTs semaglutide for weight loss

In people with obesity but not diabetes, tirzepatide demonstrated increased weight loss and greater reduction in waist circumference compared with semaglutide in SURMOUNT-5, a head-to-head, open-label study presented at the European Congress on Obesity 2025 and published in the *New England Journal of Medicine*. The mean percentage change in weight at week 72 of treatment was –20.2% with tirzepatide and –13.7% with semaglutide, while the mean change in waist circumference was –18.4 cm versus –13.0 cm. Overall, 19.7% of people in the tirzepatide group had a reduction in body weight of at least 30%, compared to 6.9% in those treated with semaglutide. The study enrolled a diverse pool of participants, including 19% Black African American and 26% Hispanic or Latino. Weight loss in females was greater than in males, a reversal of findings observed with lifestyle changes alone. The trial was not blinded since original drug packs were used, but the findings are consistent with previous blinded studies of the two drugs. Tirzepatide is a single molecule which activates both the GIP and GLP-1 receptors, producing overlapping and non-overlapping actions alike, and the authors postulate that the effects on the GIP receptors on adipose tissue cells may have contributed to the greater weight reduction achieved with tirzepatide.

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SURMOUNT-5 is a Phase 3b, open-label, randomised controlled trial and the first published head-to-head comparison of the GIP/GLP-1 receptor agonist tirzepatide and the GLP-1 receptor agonist semaglutide for weight loss in adults living with obesity but without diabetes. In the present report, presented at the European Congress on Obesity (ECO) 2025 and published in the *New England Journal of Medicine*, 751 participants with obesity were randomized 1:1 to subcutaneous tirzepatide or semaglutide once weekly, titrated to the maximum tolerated dose (10 mg or 15 mg with tirzepatide, or 1.7–2.4 mg with semaglutide), along with a behaviour support programme, for 72 weeks (Aronne et al, 2025).

The primary endpoint was the percentage weight change from baseline to week 72, and secondary endpoints included changes in waist circumference and achievement of weight reductions of at least 10%, 15%, 20% and 25%.

The mean age of the study participants was 44.7 years, 64.7% were female and 76% were White. Mean baseline weight was 113 kg (106 kg in women and 126 kg in men), mean BMI was 39.4 kg/m^2 and mean waist circumference 118 cm.

The trial was not blinded since original drug packs and information for both semaglutide and tirzepatide were used. However, the results of the study demonstrate findings consistent with those from blinded studies of the two drugs.

The results

The mean percentage change in weight was –20.2% (95% CI –21.4 to –19.1%) with tirzepatide and –13.7% (95% CI –14.9 to –12.6%) with semaglutide. Twice as many people in the tirzepatide arm of the study lost at least 25% of weight compared to those in the semaglutide arm (31.6% vs 16.1%).

The mean change in waist circumference was –18.4 cm with tirzepatide and –13.0 cm with semaglutide. This 5.4 cm difference is clinically relevant, as a previous pooled study identified that each 5 cm increase in waist circumference predicted a 9% increased mortality in women and a 7% increased mortality in men (Cerhan et al, 2014).

In weight loss studies without the use of drugs or bariatric metabolic surgery, men typically lose more weight than women, but with GLP-1 and GIP/GLP-1 receptor agonists women lose

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more weight than men, and there is as yet no explanation for this reversal. This was postulated to explain the slightly lower degree of weight loss observed in this study compared with other studies of these drugs for weight loss, as there was a higher proportion of men enrolled in this study.

Improvements in additional cardiometabolic parameters, including systolic and diastolic blood pressure, glycaemia, fasting insulin and triglycerides, occurred proportionately with greater weight loss in both treatment arms, and since more people in the tirzepatide treated group achieved the higher categories of weight loss at 72 weeks, tirzepatide was associated with greater improvement in these cardiometabolic parameters. There were no significant changes in LDL or non-HDL cholesterol levels with either treatment.

As expected, the most common adverse events were gastrointestinal, and these occurred at a similar rate across both treatment groups. Most were mild to moderate in severity and, as in other studies and with real-world use of these drugs, were more common early, during dose titration. Discontinuation rates due to adverse events were low, at 1.6% in both groups, and no unexpected adverse drug reactions were reported. There were more injection site reactions in those using tirzepatide than semaglutide, and many of these were clustered in individual participants, with 14 people reporting more than five injection site reactions. These were not severe enough to warrant drug discontinuation.

Alopecia was reported in around 6% of both treatment arms. Losing weight by any method may cause alopecia, and the more rapidly the weight is lost, the greater the risk of hair loss.

Discussion

Asked about whether tirzepatide should now be the first-choice drug for weight loss in a press conference at ECO 2025, lead study author Dr Louis Aronne, Director of the Comprehensive Weight Control Center at Weill Cornell Medicine, New York, highlighted that both tirzepatide and semaglutide are very effective for weight loss in conjunction with behaviour change support, and that clinicians should individualise the choice of drug offered based on need. In those with Class 1 obesity (BMI 30 to <35 kg/m^2), Dr Aronne suggested that the weight loss achievable with semaglutide is likely to be more than enough to achieve BMIs in the overweight or indeed normal range, whereas people with higher BMIs are likely to benefit from the increased weight loss associated with tirzepatide.

The SELECT cardiovascular outcomes trial of semaglutide demonstrated a reduction in major adverse cardiovascular events with semaglutide in people with established cardiovascular disease (Lincoff et al, 2023), while the SURMOUNT-MMO study of morbidity and mortality outcomes with tirzepatide in people with obesity but not type 2 diabetes is ongoing, so this will influence treatment choice.

Tirzepatide is licensed for use in those with obstructive sleep apnoea in the US, based on evidence from the SURMOUNT-OSA study (Malhotra et al, 2024), and semaglutide is licensed for use in adolescents in the US and other countries, and this will also influence drug choice.

Adverse events with both drugs were low, as were discontinuations for adverse events; nonetheless, Dr Aronne reminded clinicians that the study was designed to titrate people to the maximal tolerated dose; therefore, titrations likely occurred as frequently as possible and faster than would happen in real-world practice.

Implications for practice

Following the funding variation for the NICE Technology Appraisal for tirzepatide, ICBs across England are planning implementation of primary care prescribing of the incretin drugs for weight loss in those with BMI ≥40 kg/m^2 plus comorbidities, so SURMOUNT-5 adds to our knowledge base of the important benefits achievable with 72 weeks' use of these drugs.

In Wales, prescribing of injectable weight loss drugs is to remain via specialist weight management clinics at present, pending further discussions. As a result, variation in availability and capacity of such services in different Health Boards across Wales is likely to result in inequitable access to these drugs for weight loss, and it is hoped that this will be remedied as soon as possible, however achieved.

Many presentations and publications of data from ECO 2025 support the importance of measuring waist circumference at all ages, including in children, as a surrogate measure of visceral fat and to calculate waist:height ratio (WHtR) as a measure of fat distribution in the body. Although measurement of WHtR is recommended by NICE (2025) in its NG246 guideline, this is still not common in practice. Encouraging people to measure and monitor their waist circumference not only provides useful information about cardiometabolic risk but can also provide motivation, as waist circumference may decrease more rapidly than BMI with weight loss and is easy and cheap to monitor at home. ■

Aronne LJ, Bade Horn D, le Roux CW et al (2025) Tirzepatide as compared with semaglutide for the treatment of obesity. *N Engl J Med* 11 May [Epub ahead of print]. https://doi.org/10.1056/NEJMoa2416394

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Practice points

1. Both semaglutide and tirzepatide have significant effects on weight loss, in conjunction with behaviour change support.
2. Tirzepatide might be considered the first-choice drug in people with higher BMIs due to its greater weight-reducing effects.
3. Waist circumference should be routinely measured, both as a surrogate measure of visceral fat and to calculate waist:height ratio.
4. Measuring waist circumference can also be motivational for the individual, as it usually decreases rapidly with weight loss.

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