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Important New Evidence Service

In partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch® Rapid Update 2 – July 2025

RCT finds tirzepatide is associated with greater weight loss than semaglutide in people with obesity

The manufacturer of tirzepatide has conducted an open-label randomised controlled trial to compare the efficacy and safety of tirzepatide with semaglutide in adults with obesity (BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 and at least one prespecified obesity-related complication) but without diabetes. At 72 weeks, the mean percentage decrease in weight was significantly greater with tirzepatide than with semaglutide (20% *vs.* 14%, p < 0.001). Gastrointestinal events were the most common adverse events leading to treatment discontinuation (3% and 6% of participants in the tirzepatide and semaglutide groups, respectively). Injection-site reactions were more common with tirzepatide than with semaglutide (9% *vs*. <1%).

Reference: Aronne LJ, , Horn DB, Le Roux CW *et al.* Tirzepatide as Compared with Semaglutide for the Treatment of Obesity *N Engl J Med*. May 11, 2025. DOI: 10.1056/NEJMoa2416394

What do we know already?

- Obesity is usually defined as having a body mass index (BMI) of 30 or above; a BMI of between 25 and 30 is classified as 'overweight'. It has been estimated that 28% of adults in England and 32% of adults in Scotland are obese. A further 36% and 34% of adults in England and Scotland, respectively, are overweight but not obese. Obesity is associated with an increased risk of developing (or exacerbation of) a number of chronic diseases and conditions including type 2 diabetes and cardiovascular disease.
- Tirzepatide (Mounjaro) is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist. NICE recommends it as an option for managing obesity alongside a reduced calorie diet and increased physical activity in adults, only if they have an initial BMI ≥ 35 kg/m^2 and at least one weight-related comorbidity. Lower BMI thresholds (usually reduced by 2.5 kg/m^2) should be used for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds. NHS England is implementing a phased rollout of tirzepatide for weight management to ensure safe and effective delivery and manage workload.
- Semaglutide (Wegovy) is a GLP-1 receptor agonist. NICE recommends it as an option for weight management, alongside a reduced-calorie diet and increased physical activity in adults, only if it is used for a maximum of two years, and within a specialist weight management service. Patients are eligible for treatment with semaglutide if they have at least one weight-related comorbidity, and either a BMI ≥ 35 kg/m^2 or a BMI of 30 to 34.9 kg/m^2 if they meet the criteria for referral to a specialist weight management service. Lower BMI thresholds (usually reduced by 2.5 kg/m^2) should be used for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds.

What does this evidence add?

- The SURMOUNT-5 trial Is the first head-to-head RCT to compare tirzepatide with semaglutide in people with obesity but not diabetes. As noted by the authors, the findings align with the results reported for a recent cohort study that also found greater weight reduction with tirzepatide than with semaglutide.
- Weight loss was approximately 6% lower in men than in women for both treatments, and the authors suggest this may account for the slightly reduced weight loss observed in the current trial compared with earlier studies. This trial included a higher proportion of male participants (35%), compared with the STEP trials where only 19 to 26% of participants were men.
- The author of an accompanying editorial notes that whether the differential weight loss according to sex was due to the stimulation of the GLP-1 receptor, a mechanism both drugs share, is unclear, but the finding raises a question about the body constituents involved in weight loss and why these may vary according to sex.

Study details

Participants:

- This multicentre, open-label RCT recruited adults aged ≥ 18 years with a BMI ≥ 30 or a BMI ≥ 27 and at least one prespecified obesity related complication (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease). Eligible participants also reported at least one unsuccessful dietary effort for weight reduction.
- Key exclusion criteria included a diagnosis of diabetes, previous or planned surgical treatment for obesity, treatment with a medication for weight reduction or a GLP-1 receptor agonist within 90 days before screening, or a change in body weight of more than 5 kg within 90 days before screening.
- In total, 751 people were randomised across 32 study sites in the US and Puerto Rico. The mean age of the participants was 44.7 years, and the majority (64.7%) were women and white (76.1%). The mean body weight was 113 kg, the mean BMI was 39.4, and the mean waist circumference 118cm. The average reported duration of obesity was 16 years and 50% of the participants had at least two obesity-related complications.

Intervention and Comparison:

- Patients were randomised via an interactive web-response system, to receive either the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or the maximum tolerated dose of semaglutide (1.7 mg or 2.4 mg) subcutaneously once weekly for 72 weeks. Randomisation was stratified according to baseline BMI (<35 or ≥35), sex, and prediabetes status as determined from laboratory tests performed at screening after the participants had fasted. Baseline characteristics were reported to be similar between the groups.
- All participants received counselling on nutrition and physical activity.

Outcomes and results:

- The primary end point was the percent change in weight from baseline to week 72. Key secondary end points included weight reductions of at least 10%, 15%, 20%, and 25% and a change in waist circumference from baseline to week 72.
- At 72 weeks, the mean percentage decrease in weight was significantly greater with tirzepatide than with semaglutide (20.2%, 95% confidence interval [CI] 19.1 to 21.4 with tirzepatide and 13.7%, 95% CI 12.6 to 14.9 with semaglutide, p < 0.001).
- More participants treated with tirzepatide than those treated with semaglutide had reductions in body weight of at least 10%, 15%, 20%, and 25% from baseline (p<0.001). Participants treated with tirzepatide were 1.3, 1.6, 1.8, and 2.0 times more likely than participants treated with semaglutide to have weight reductions of at least 10%, 15%, 20%, and 25%, respectively.
- A total of 19.7% of the participants in the tirzepatide group had a reduction in body weight of at least 30% (an exploratory end point) as compared with 6.9% of those in the semaglutide group, which indicated that the likelihood of meeting this weight-reduction target with tirzepatide was 2.8 times as high as that with semaglutide.
- Tirzepatide was superior to semaglutide with respect to reduction in waist circumference. The least-squares mean change in waist circumference from baseline to week 72 was -18.4 cm with tirzepatide (95% CI -19.6 to -17.2) and -13.0 cm with semaglutide (95% CI -14.3 to -11.7), p < 0.001).
- Systolic blood pressure improved in both groups (least-squares mean reduction 10.2 mm Hg with tirzepatide and 7.7 mmHg with semaglutide). Diastolic blood pressure also improved in both treatment groups.
- Overall, 76.7% of the participants in the tirzepatide group and 79.0% of those in the semaglutide group reported at least one adverse event that occurred or worsened during the treatment period. The most frequently reported adverse events were gastrointestinal (e.g. nausea, constipation, diarrhea, and vomiting). Most gastrointestinal adverse events were mild to moderate in severity. Injection site reactions were more common with tirzepatide than with semaglutide (8.6% *vs.* 0.3%).
- The trial treatment was discontinued because of adverse events by 6.1% of the participants in the tirzepatide group and 8.0% of those in the semaglutide group.
- Serious adverse events were reported by 31 participants (4.1%) overall, with a similar occurrence in the tirzepatide group (4.8%) and the semaglutide group (3.5%). One adjudication-confirmed case of pancreatitis was reported in the semaglutide group. No adjudication-confirmed major cardiovascular events, deaths, cases of medullary thyroid cancer, or cases of pancreatic cancer were reported.

Level of evidence: Level 1 (good quality patient-orientated evidence) according to the SORT criteria.

Study funding: Eli Lilly (manufacturer of tirzepatide)