First head-to-head study in people living with obesity shows tirzepatide results in around 50% more weight loss than semaglutide

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A new head-to-head study of tirzepatide versus semaglutide for weight loss in people living with obesity, but not diabetes, shows that over 72 weeks tirzepatide results in an average weight loss of 20.2%, 47% higher than the 13.7% average weight loss for semaglutide. The study, presented at this year's European Congress on Obesity in Malaga, Spain (11-14 May) and published in *NEJM*, is by Dr Louis J Aronne, Comprehensive Weight Control Center, Weill Cornell Medicine, New York, New York, USA, and colleagues.

While both tirzepatide and semaglutide are highly effective obesity management medications, this new study is the first to test, in a head-to-head study the efficacy and safety of tirzepatide compared with semaglutide in adults with obesity but without type 2 diabetes. The study is sponsored by Eli Lilly & Company, the manufacturer of tirzepatide.

In this phase 3b open-label, randomised, controlled trial, 751 adult participants with obesity, but without type 2 diabetes, in a 1:1 ratio received tirzepatide maximum tolerated dose (10mg or 15mg) or semaglutide maximum tolerated dose (1.7mg or 2.4mg) subcutaneously once weekly for 72 weeks. The mean age of the participants was 44.7 years; most were female (64.7%) and White (76.1%); mean body weight was 113.0 kg, mean BMI was 39.4 kg/m^2, and mean waist circumference was 118.3 cm. Average reported duration of obesity was 16 years; and 50% had obesity-related multimorbidity (at least 2 obesity-related complications).

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

Key inclusion criteria for this trial included being aged 18 years or older, a body-mass index (BMI) of 30 kg/m^2 or more, or a BMI of 27 kg/m^2 or more and at least one prespecified obesity-related complication (hypertension, dyslipidemia, obstructive sleep apnea (OSA), or cardiovascular disease), and experiencing at least one unsuccessful dietary effort for weight reduction. Key exclusion criteria included diagnosis of diabetes, prior or planned surgical treatment for obesity, or if within 90 days before screening they had received treatment with a medication for weight reduction or a GLP-1 receptor agonist, or a change in body weight of more than 5 kg.

The mean percentage change in weight at week 72 was −20.2% (with tirzepatide and -13.7% with semaglutide – thus 47% higher for tirzepatide. The mean decrease in waist circumference was −18.4 cm with tirzepatide and -13.0 cm with semaglutide – thus 42% higher for tirzepatide. Participants treated with tirzepatide were 30%, 60%, 80% and twice as likely to achieve the weight reduction targets of 10%, 15%, 20%, and 25%, respectively, compared to semaglutide. The most common adverse events for both study treatments were gastrointestinal, and most were mild to moderate in severity, occurring primarily during dose escalation.

Weight reduction was around 6% less in males than females for both treatments and is believed to explain the slightly lower weight reduction in the current trial compared with previous trials. The current trial had a higher proportion of males at 35%, especially compared to the STEP non-diabetes trials, which included 19-26% males. The current findings align with results reported for the SURMOUNT and STEP programs as well as recent real-world evidence demonstrating higher weight reduction with tirzepatide than semaglutide.

Dr Aronne explains: "Tirzepatide, while a single molecule, pharmacologically activates two metabolic receptors, GIP and GLP-1, which have both overlapping and non-overlapping

expression and function. This dual agonism of tirzepatide may contribute to the higher weight reduction observed in the current study compared to semaglutide, a mono-agonist."

The results show that as weight reduction increased there were greater improvements in cardiometabolic risk factors, including blood pressure, and blood fat and sugar levels, with both treatments consistent with previous reports. The authors explain that, while some patients will not necessarily require the higher magnitudes of weight reduction to see clinical benefits **(Q OK?)**, overall, these findings support the clinical relevance of the current study as the majority of participants receiving tirzepatide (65%) were able to achieve at least 15% weight loss versus 40% for semaglutide; **and nearly a third (32%)** achieved at least 25% weight reductions with tirzepatide compared to 16% with semaglutide.

They further explain that the additional 5.4 cm extra reduction in waist circumference with tirzepatide compared with semaglutide is also clinically relevant. Each 5 cm increase in waist circumference predicts a 7% increase in mortality for men and 9% for women. Aligned with these data, guidelines have emphasized the importance of treating patients with abdominal obesity and aiming for a reduction of at least 4 cm.

The trial has certain strengths and limitations. One strength is the diversity of the participants as 19% reported race as Black-African American and 26% reported ethnicity Hispanic or Latino, representative of the populations in the USA living with obesity. The trial's approach of using the maximum tolerated dose for both treatments addresses a potentially more meaningful real-world question, compared to a fixed dose approach. However, a limitation is that the trial was not blinded, **meaning participants knew which drug and the dose they were receiving. However,** the authors explain the consistency of the current findings with previously blinded trials supports their generalisability.

Dr Aronne concludes: "Our study shows that treatment with tirzepatide was superior to semaglutide with respect to reduction in body weight and waist circumference."

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This press reléase is based on abstract 474 at the European Congress on Obesity in Malaga, Spain, 11-14 May. The study is published in NEJM at the embargo time stated above. As the full paper is provided, the abstract is not provided.

Dr Aronne will present the key findings in an embargoed press conference at the European Congress on Obesity at 1200H noon Malaga time on Sunday 11 May, in room 20 at the Congress. A video recording of the press conference will be circulated under embargo shortly after this.

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