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COMMENTARY

Maintenance of Weight Loss Is Not an Insurmountable Task

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It may come as a surprise that one of the outstanding trials presented at a major European diabetes congress investigated people without type 2 diabetes (T2D). I attended the recent 59th European Association for the Study of Diabetes (EASD) Annual Meeting in Hamburg, Germany, where the SURMOUNT-4 trial data were presented. SURMOUNT-4 explored the impact of the dual glucagon-like peptide 1 (GLP-1)-glucose-dependent insulinotropic polypeptide (GIP) agonist tirzepatide on maintenance of weight reduction and the benefits of continued therapy in patients with obesity but without T2D. The presentation of these data at this congress demonstrated an appreciation of the common underlying pathophysiologic disease processes and challenges in T2D and obesity.

In SURMOUNT-4, all participants received maximum tolerated doses of tirzepatide (10 or 15 mg) during an open-label lead-in phase of 36 weeks. Mean weight loss was 20.9% after 36 weeks. It was hypothesized that weight loss would plateau at this point.

Patients were then randomly assigned to switch to injectable placebo or continue receiving maximum tolerated doses of tirzepatide for an additional 52 weeks. At 88 weeks, the participants who continued tirzepatide achieved a further 5.5% weight loss, compared with a weight regain of 14% in the placebo group. Importantly, however, weight in the placebo group did not return to baseline even after 52 weeks. Additionally, weight loss seemed to plateau at around 70 weeks in the tirzepatide group.

Moreover, during the randomized phase of SURMOUNT-4, participants on tirzepatide had a further 4.3 cm reduction in waist circumference, compared with a 7.8 cm increase in the placebo group. Improvements in other cardiometabolic parameters, including systolic and diastolic blood pressure, A1c, and lipids, were also noted with tirzepatide.

Overall, participants receiving tirzepatide had a mean 25.3% weight loss from baseline to 88 weeks, and over half of these individuals achieved ≥ 25% weight loss. This result exceeds the 17.4% weight loss after 68 weeks seen with weekly semaglutide in the similarly designed STEP 4 trial.

The remarkable weight loss achieved in SURMOUNT-4 recalls the weight loss achieved after bariatric surgery. Notably, participants who did not continue tirzepatide still achieved a respectable mean 9.9% weight loss at trial's end.

During the maintenance phase of the study, around one quarter of individuals on tirzepatide experienced an adverse event, compared with 10.4% in the placebo group. Commonly reported adverse events included diarrhea, nausea, and vomiting. There was no imbalance in incidence of cancers, but the trial duration was too short to fully investigate this outcome. The incidence of gallbladder disease and pancreatitis did not differ between groups. These findings are consistent with the known safety profile of tirzepatide and the GLP-1 receptor agonist class in patients with obesity. Of note, the dropout rate was 14.4% in the lead-in phase and 10% in the maintenance phase, which is consistent with expectations.

Like all good studies, SURMOUNT-4 raises more questions than it answers. The fact that around 15% of the placebo group maintained around 20% weight loss at trial's end raises the possibility of intermittent treatment with tirzepatide for weight loss, and this idea was highlighted during the discussion that followed the presentation of the SURMOUNT-4 results. After an initial course of tirzepatide, could patients simply be monitored and only restarted on tirzepatide if their weight trajectory dictates this? This approach would certainly increase the cost-effectiveness of tirzepatide, which will be an inevitable barrier once it is widely available for use. Alternatively, after an initial course of course of tirzepatide, could patients be switched to a less potent, cheaper

weight loss agent, such as liraglutide, for maintenance of weight loss? Generic versions of liraglutide will be available during 2024.

We also lack hard endpoints for tirzepatide in obesity, but several ongoing studies may provide data on the impact of tirzepatide on cardiovascular outcomes (SURMOUNT-MMO), nonalcoholic steatohepatitis (SYNERGY-NASH), heart failure with preserved ejection fraction (SUMMIT), chronic kidney disease (TREASURE-CKD), and obstructive sleep apnea (SURMOUNT-OSA). Given the magnitude of weight loss with tirzepatide, I expect many of these trials to provide positive results like the recently announced positive topline results for semaglutide in the SELECT trial, which explored its impact on cardiovascular outcomes in patients with obesity. A 20% reduction in major adverse cardiovascular events was seen with weekly semaglutide in patients with overweight or obesity, established cardiovascular disease, and no history of T2D.

Finally, during the discussion, concerns were highlighted that tirzepatide may be perceived as a substitute for meaningfully changing and maintaining a healthy diet, given its efficacy and durability. It was emphasized that in addition to a revolution in weight loss therapies, society was transitioning to a new focus on diet quality, which absolutely should be adhered to alongside tirzepatide or indeed any weight loss modality. Reflecting on my past clinical experience, I am not convinced that this view will be shared by many of my patients, and it remains a key role of all healthcare professionals to reinforce the importance of a healthy and well-balanced diet.

In conclusion, obesity is a risk factor for multiple cardiometabolic conditions and is an established risk factor for 13 types of cancer; excess body fat entails an approximately 17% increased risk for cancer-specific mortality. We have a professional and moral obligation to address obesity in clinical practice, and based on the SURMOUNT-4 results, tirzepatide appears to be an invaluable addition to our armamentarium of obesity medications, alongside lifestyle interventions.

Dr Fernando is a general practitioner near Edinburgh, Scotland, with a specialist interest in diabetes; cardiovascular, renal, and metabolic diseases; and medical education.

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