Title: Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

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Journal title: New England Journal of Medicine

Date, issue, pages of publication: 5 August 2021, 385:503-515

Digital object identifier: 10.1056/NEJMoa2107519

Introduction & Aims

This international, randomised, open-label, phase-3, non-inferiority trial studied the efficacy and safety of tirzepatide and semaglutide once weekly in patients with type 2 diabetes.

Methods

1879 patients were randomised into 1:1:1:1: ratio to receive tirzepatide 5mg, 10mg, 15mg or semaglutide 1mg over 40 weeks. Inclusion criteria: Patient who has T2DM inadequately controlled with metformin of at least 1.5g/day, with HbA1c between 53 - 91 mmol/mol and BMI of $\geq$25. The primary and secondary endpoint for efficacy were the change in HbA1c and body weight from baseline to week 40 respectively.

Results

The reduction in HbA1c with tirzepatide 5mg, 10mg and 15 mg were -2.5%, -2.24%, and -2.3 % respectively, as compared to -1.86% with semaglutide (Estimated treatment difference P=0.02, P<0.001 and P<0.001 respectively). The mean reduction in body weight at 40 weeks were -7.6kg, -9.3kg and -11.2kg respectively, as compared to -0.57kg with semaglutide (P<0.001). There was a similar percentage of patients reporting any adverse event across the groups, with gastrointestinal symptoms being the most common.

Conclusion

The author concludes that Tirzepatide showed non-inferiority and superiority to semaglutide.

Strength

This trial has a large sample size of patients with similar baseline characteristics who completed the trial. The endpoints chosen were also crucial and clear. The trial also had

incorporated the application of estimand based on the newly released ICH E9(R1) for estimands and sensitivity analysis, allowing the accuracy of interpretation of result following consideration of intercurrent events.

Limitations

There were limited data on the co-morbidities of participants (apart from the presence of albuminuria) and the use of other therapies in T2DM management. The length of the trial was also modest, considering dose escalation was required for all study groups. Last but not least, there was a higher number of documented deaths in the tirzepatide group (4 in each group versus 1 in the semaglutide group) which would certainly impact the overall safety profile of the medication for drug approval.

Applicability/Future direction

Despite proven efficacy in HbA1c and body weight reduction in T2DM, there is certainly a need to consider the cardiovascular protection profile before its release into the market. As such, there is an ongoing trial comparing the cardiovascular outcomes of tirzepatide with dulaglutide (SURPASS-CVOT study). Given the high prevalence of obesity and T2DM in Ireland, the introduction of a drug that could tackle both obesity and diabetes will help reduce the health-economic burdens.