Efficacy and safety of tirzepatide, liraglutide and semaglutide in patients with obesity: A Bayesian network meta-analysis of RCTs

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OBJECTIVE

- This network meta-analysis of randomised controlled trials compared the efficacy and safety of tirzepatide, semaglutide and liraglutide for weight management in patients with obesity or overweight.
- Studies were identified via a systematic literature review for patients with either obesity (BMI ≥30 kg/m^2), or overweight (BMI ≥27 kg/m^2) with ≥1 obesity-related complication, all without type 2 diabetes.

CONCLUSION

- In this network meta-analysis:
  - All tirzepatide doses demonstrated statistically improved weight reduction outcomes versus liraglutide; and comparable or statistically improved weight reduction outcomes versus semaglutide.
  - Tirzepatide demonstrated comparable or statistically improved cardiometabolic risk factors to liraglutide and semaglutide.
  - Tirzepatide demonstrated a comparable safety profile to liraglutide and semaglutide.

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METHODS

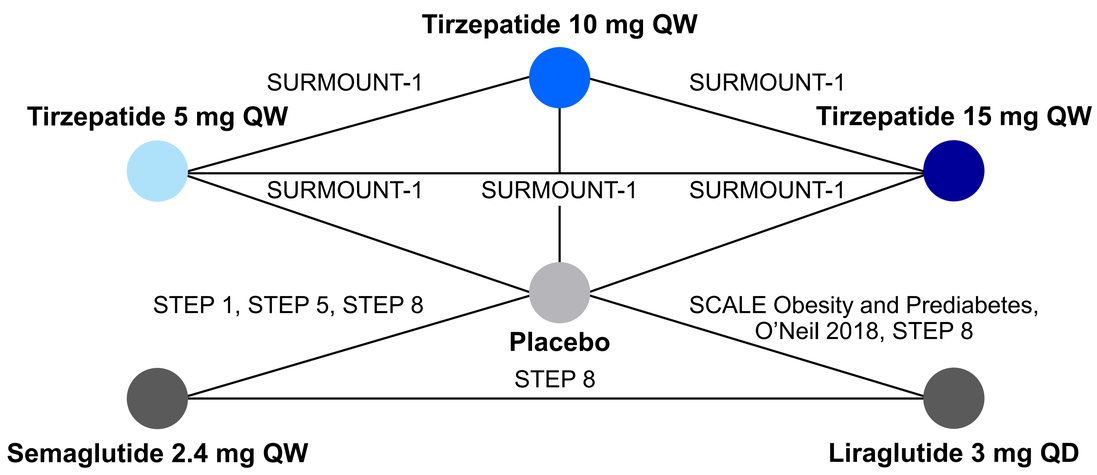
SLR Methods

- An SLR conducted in November 2023 identified 42 studies reporting on doses of tirzepatide (5/10/15 mg QW), liraglutide (3 mg QD) and semaglutide (2.4 mg QW) approved for treatment of obesity and overweight.
- Six studies identified in the SLR[1–6] were suitable to compare in an NMA:
  - Study design: blinded placebo-controlled Phase 3 RCTs; treatment adjunct to reduced-calorie diet and increased physical activity; without IBT; not maintenance studies; no focus on specific complications.
  - Patient population: patients with either obesity (BMI ≥30 kg/m^2), or overweight (BMI ≥27 kg/m^2) with ≥1 obesity-related complication, and without T2D.

NMA Methods

- For the six studies[1–6] deemed suitable for the NMA, a heterogeneity assessment by visual inspection of the baseline clinical characteristics deemed these studies to be suitably homogenous to compare without population-adjustment.
- Bayesian random-effects NMAs compared efficacy and safety endpoints at the respective study timepoints from Week 52 to 72. Pooling of different timepoints was deemed suitable given the plateau in weight reduction after Week 52,[1–5] and as a previous comparison of GLP-1 RAs showed no sensitivity of the result to the timepoint differences.[7]

Figure 1: NMA Network Diagram



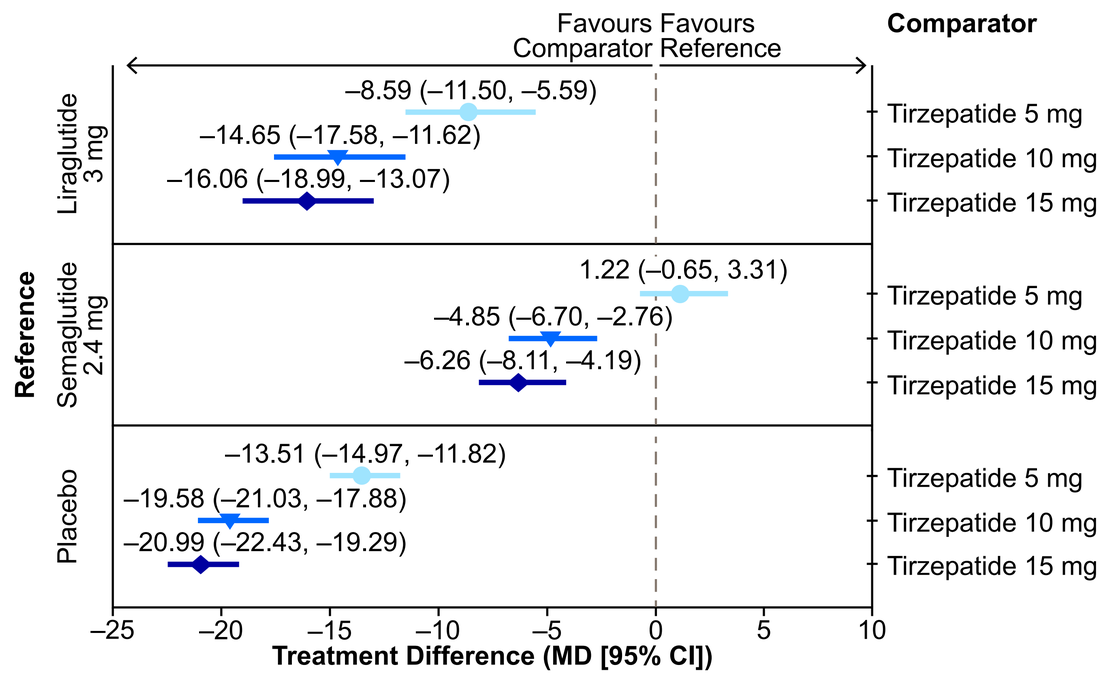
Nodes indicate treatments, and lines indicate studies. Not all studies were included in analysis for every outcome due to data availability. Analyses for efficacy endpoints were performed for the efficacy estimand or equivalent: all participants who remained on the randomised medication without rescue medication. Analyses for safety endpoints were performed for the safety analysis set or equivalent: all participants who took ≥1 dose of randomised medication, regardless of adherence or use of rescue medication.

BACKGROUND

- Tirzepatide, liraglutide, and semaglutide are nutrient-stimulated hormone based therapies approved for the treatment of obesity and overweight in several regions.
- Liraglutide and semaglutide are GLP-1 RAs, and tirzepatide is a GIP and GLP-1 RA.
- In obesity and overweight management, no published RCTs compare tirzepatide versus semaglutide or liraglutide, and available indirect comparisons do not exclusively focus on these three treatments. Therefore, an SLR and NMA were conducted to compare tirzepatide, semaglutide and liraglutide following key methodological guidelines.[8–12]

KEY RESULT: WEIGHT REDUCTION (kg)

Figure 2: All tirzepatide doses showed statistical improvements in weight reduction (kg) vs liraglutide and placebo, and tirzepatide 10 and 15 mg showed statistical improvements vs semaglutide



Forest plot of NMA results for each tirzepatide dose versus each comparator. Points indicate the estimated mean difference; error bars indicate the 95% CrI.

Results

Weight Reduction

- Versus liraglutide, tirzepatide 5, 10 and 15 mg demonstrated statistically improved total weight reduction (kg), total weight reduction (%), and odds of ≥5/10/15/20% weight reduction.
- Versus semaglutide, tirzepatide 10 and 15 mg demonstrated statistically improved total weight reduction (kg) and odds of ≥20% weight reduction.

Cardiometabolic Risk Factors

- Versus liraglutide, all tirzepatide doses demonstrated statistically improved reductions in waist circumference, triglycerides and DBP.
- Versus semaglutide, tirzepatide 10 and 15 mg demonstrated statistically improved reductions in waist circumference, and tirzepatide 15 mg demonstrated a statistically improved reduction in triglycerides.
- Glycaemic parameters (HbA1c, FPG), other lipids (total cholesterol, LDL, HDL) and blood pressure (SBP, DBP) were comparable to liraglutide and semaglutide, although mostly numerically improved for tirzepatide 10 and 15 mg.

Safety

- Tirzepatide 5 mg demonstrated comparable odds of safety outcomes (nausea, discontinuations due to AEs, GI AEs) to liraglutide and semaglutide, although numerically improved.
- Tirzepatide 10 and 15 mg demonstrated comparable odds of safety outcomes to liraglutide and semaglutide, although mostly numerically improved versus liraglutide, and mostly numerically worsened versus semaglutide.

Table 1: NMA results of tirzepatide versus comparators

	Outcome [Measure]	Tirzepatide 5 mg		Tirzepatide 10 mg		Tirzepatide 15 mg	
		Liraglutide	Semaglutide	Liraglutide	Semaglutide	Liraglutide	Semaglutide
Weight Reduction	CfB weight (kg) [MD]	–8.59 (–11.50, –5.59)	1.22 (–0.65, 3.31)	–14.65 (–17.58, –11.62)	–4.85 (–6.70, –2.76)	–16.06 (–18.99, –13.07)	–6.26 (–8.11, –4.19)
	CfB weight (%) [MD]	–7.52 (–11.27, –0.07)	1.57 (–1.76, 8.78)	–12.86 (–16.53, –5.14)	–3.78 (–6.99, 3.66)	–13.95 (–17.61, –6.14)	–4.86 (–8.07, 2.67)
	≥5% weight reduction [OR]	3.74 (1.29, 10.97)	0.84 (0.28, 2.32)	11.48 (3.80, 34.82)	2.57 (0.83, 7.49)	11.82 (3.92, 35.88)	2.64 (0.85, 7.75)
	≥10% weight reduction [OR]	4.54 (1.47, 14.46)	0.79 (0.27, 2.43)	10.04 (3.25, 32.19)	1.75 (0.59, 5.38)	15.18 (4.83, 48.97)	2.64 (0.87, 8.24)
	≥15% weight reduction [OR]	3.82 (1.15, 11.51)	0.61 (0.20, 1.71)	10.59 (3.17, 32.13)	1.69 (0.55, 4.77)	13.64 (4.05, 41.55)	2.18 (0.71, 6.12)
	≥20% weight reduction [OR]	14.65 (3.50, 59.74)	1.43 (0.40, 5.05)	39.54 (9.45, 161.66)	3.87 (1.10, 13.47)	53.50 (12.80, 218.72)	5.24 (1.48, 18.44)
Cardiometabolic Risk Factors	CfB waist circ. (cm) [MD]	–7.02 (–10.03, –3.74)	–0.04 (–1.87, 2.41)	–11.79 (–14.83, –8.49)	–4.81 (–6.63, –2.36)	–12.30 (–15.32, –9.04)	–5.32 (–7.14, –2.86)
	CfB HbA1c (%) [MD]	–0.15 (–4.35, 4.09)	0.03 (–3.68, 3.84)	–0.24 (–4.40, 4.00)	–0.06 (–3.76, 3.72)	–0.26 (–4.48, 4.00)	–0.08 (–3.82, 3.77)
	CfB FPG (mg/dL) [MD]	–1.02 (–4.37, 2.74)	1.05 (–1.20, 4.21)	–3.00 (–6.34, 0.81)	–0.92 (–3.16, 2.29)	–3.90 (–7.28, –0.13)	–1.83 (–4.09, 1.37)
	CfB triglycerides (%) [MD]	–8.41 (–16.08, –0.66)	–0.42 (–5.17, 4.64)	–10.99 (–18.56, –3.18)	–2.98 (–7.70, 2.12)	–15.44 (–23.02, –7.70)	–7.47 (–12.17, –2.43)
	CfB LDL (%) [MD]	–4.73 (–15.41, 9.41)	2.13 (–7.52, 14.39)	–5.95 (–16.43, 8.51)	0.92 (–8.50, 13.37)	–7.82 (–18.17, 7.01)	–0.95 (–10.10, 11.93)
	CfB HDL (%) [MD]	2.39 (–11.85, 13.80)	3.93 (–9.49, 13.84)	3.87 (–10.66, 15.16)	5.43 (–8.34, 15.16)	3.50 (–10.97, 14.78)	5.05 (–8.56, 14.77)
	CfB total chol. (%) [MD]	–4.21 (–14.86, 9.91)	1.99 (–8.07, 14.22)	–4.88 (–15.52, 9.37)	1.33 (–8.71, 13.71)	–6.53 (–16.94, 7.96)	–0.35 (–10.01, 12.30)
	CfB SBP (mmHg) [MD]	1.09 (–2.77, 5.33)	0.52 (–1.74, 4.05)	–0.27 (–4.12, 3.99)	–0.86 (–3.09, 2.72)	0.51 (–3.37, 4.72)	–0.08 (–2.33, 3.47)
	CfB DBP (mmHg) [MD]	–3.71 (–6.40, –0.85)	–1.59 (–3.26, 0.53)	–4.19 (–6.89, –1.33)	–2.08 (–3.75, 0.02)	–3.10 (–5.79, –0.26)	–0.99 (–2.66, 1.10)
Safety	Total GI AEs [OR]	0.70 (0.29, 1.66)	0.84 (0.34, 1.81)	0.87 (0.36, 2.07)	1.04 (0.42, 2.25)	0.81 (0.33, 1.94)	0.97 (0.39, 2.10)
	Nausea AEs [OR]	0.79 (0.41, 1.49)	0.77 (0.38, 1.47)	1.21 (0.63, 2.28)	1.18 (0.59, 2.25)	1.08 (0.56, 2.04)	1.06 (0.52, 2.02)
	Disc. due to AEs [OR]	0.49 (0.14, 1.53)	0.94 (0.29, 3.69)	0.83 (0.24, 2.54)	1.60 (0.51, 6.25)	0.72 (0.21, 2.21)	1.38 (0.44, 5.38)

Dark green: tirzepatide performed statistically better vs comparator; light green: tirzepatide performed numerically better vs comparator; light red: tirzepatide performed numerically worse vs comparator. Normal dist. for continuous outcomes, binomial dist. for binomial outcomes.

Abbreviations: AE: adverse event; **BMI:** body mass index; **CfB:** change from baseline; **CrI:** credible interval; **DBP:** diastolic blood pressure; **FPG:** fasting plasma glucose; **GI:** gastrointestinal; **GIP:** glucose-dependent insulinotropic polypeptide; **GLP-1:** glucagon-like peptide 1; **HbA1c:** glycated haemoglobin; **HDL:** high-density lipoprotein; **IBT:** intensive behavioral therapy; **LDL:** low-density lipoprotein; **MD:** mean difference; **NMA:** network meta-analysis; **OR:** odds ratio; **QD:** once daily; **QW:** once weekly; **RA:** receptor agonist; **RCT:** randomised controlled trial; **SBP:** systolic blood pressure; **SLR:** systematic literature review; **T2D:** type 2 diabetes.

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