Systolic Blood Pressure Reduction with Tirzepatide across the SURPASS Program: A Mediation Analysis Using Weight Loss as a Factor

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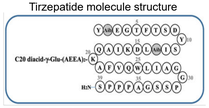
OBJECTIVE

To evaluate weight loss dependent (WL-D) and weight loss independent (WL-IND) effects of tirzepatide on systolic blood pressure (SBP) reductions across the 5 SURPASS studies.

BACKGROUND

- Tirzepatide is a once weekly GIP/GLP-1 receptor agonist, approved in the US for treatment of people with type 2 diabetes (T2D).
- In Phase 3 clinical trials, tirzepatide produced substantial reductions in HbA1c (-1.9 to -2.6%), and body weight (-6.6 to -13.9%) over 40 to 52 weeks, enabling many people with T2D to achieve normalization of glucose control. [1-5]
- Across the SURPASS 1-5 clinical studies, tirzepatide 5, 10 and 15 mg also demonstrated clinically significant improvements in systolic blood pressure (SBP) (-2.8 to -12.6 mm Hg) over 40 to 52 weeks.[1-5]

Tirzepatide molecule structure

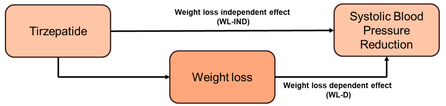


Shading indicates non-coded amino acids.

[1]Rosenstock et al. Lancet 2021;398(10295):143-155. [2]Frias et al. N Eng J Med 2021;385(6):503-515. [3]Ludvik et al. Lancet 2021;398(10300):583-589. [4]Del Prato et al. Lancet 2021; 398(10313): 1811–24. [5]Dahl et al. JAMA 2022;327(6):534-545.

METHODS

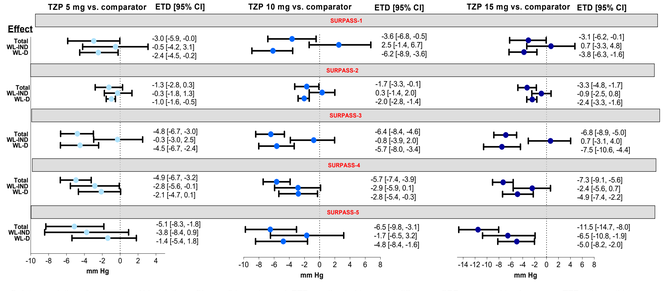
- Post-hoc mediation analyses were conducted to evaluate weight loss dependent (WL-D) and weight loss independent (WL-IND) effects of tirzepatide on SBP reductions across 5 SURPASS studies.



- WL-D and WL-IND effects on SBP at Week 40 were estimated using product method for mediation analysis, which included the interaction between treatment and weight change, with the baseline variable for SBP, use of anti-hypertensive drug, country and HbA1c category ([≤8.0%, >8.0%] for SURPASS-5, [≤8.5%, >8.5%] for other studies) as covariates in the model.
- Safety population (all randomly assigned patients who took at least 1 dose of study drug) of each study was used in this analysis which included data regardless of adherence to study drug or initiation of new glucose lowering agents.

KEY RESULTS

Weight loss dependent (WL-D) and Weight loss independent (WL-IND) effects of tirzepatide on systolic blood pressure (SBP) across SURPASS 1-5 studies



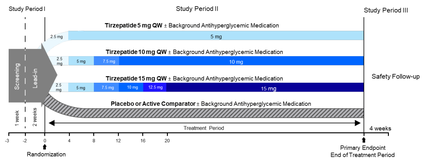
Safety population of each study. Abbreviations: CI = confidence interval; ETD = estimated treatment difference; SBP = systolic blood pressure; TZP = tirzepatide; WL-D = weight loss dependent; WL-IND = weight loss independent.

SUMMARY/CONCLUSION

- Across the 5 multinational SURPASS clinical studies, there was a clinically meaningful difference in change from baseline in systolic blood pressure between tirzepatide and comparators at week 40
  - Tirzepatide 5 mg: -1.3 to -5.1 mmHg
  - Tirzepatide 10 mg: -1.7 to -6.5 mmHg
  - Tirzepatide 15 mg: -3.1 to -11.5 mmHg
- Overall, the majority of systolic blood pressure reduction with tirzepatide was mediated by weight loss
- In the SURPASS-4 study where patients with established cardiovascular disease were enrolled, weight loss independent effects explained 33% to 57% of difference in systolic blood pressure change between tirzepatide and insulin glargine groups.
- In the SURPASS-5 study where patients had longest duration of diabetes, weight loss independent effects explained 26% to 73% of difference in systolic blood pressure change between tirzepatide and placebo groups.
- The ongoing SURPASS-CVOT study will provide more evidence on clinical relevance of blood pressure reduction with tirzepatide.

Overall, tirzepatide-induced systolic blood pressure reduction was primarily mediated through weight loss, with different degrees of contributions from weight loss independent effects across the different SURPASS trials.

SURPASS 1-5 STUDY DESIGNS



	Sample Size, Randomization ratio, Background glucose-lowering therapy	Comparator	Primary end point
SURPASS-1	(N=478) 1:1:1:1 None	Placebo QW	Week 40
SURPASS-2	(N= 1879) 1:1:1:1 + Metformin	Semaglutide 1 mg QW	Week 40
SURPASS-3	(N=1444) 1:1:1:1 + Metformin ± SGLT-2i	Titrated Insulin Degludec QD	Week 52
SURPASS-4	(N=2002) 1:1:1:3 ± Metformin ± SU ± SGLT-2i	Titrated Insulin Glargine QD	Week 52
SURPASS-5	(N=475) 1:1:1:1 + Titrated Insulin Glargine ± Metformin	Placebo QW	Week 40

Abbreviations: N = population size; QD = once-daily; QW =once-weekly; SGLT-2i = sodium-glucose co-transporter 2 inhibitors; SU = Sulfonylurea

BASELINE DEMOGRAPHICS AND CHARACTERISTICS

Data Pooled across All Treatment Arms

(All Randomized Participants who administered at least 1 dose of study drug)

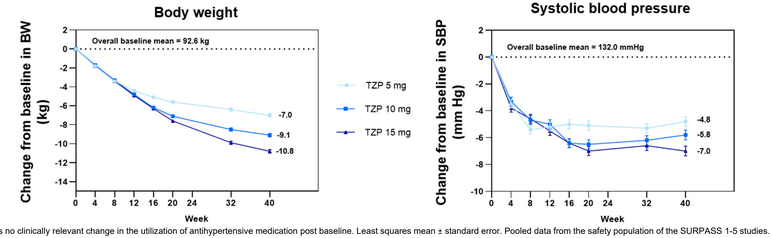
	SURPASS-1 (N=478)	SURPASS-2 (N=1878)	SURPASS-3 (N=1437)	SURPASS-4 (N=1995)	SURPASS-5 (N=475)
Age (years)	54.1 ± 11.9	56.6 ± 10.4	57.4 ± 10.0	63.6 ± 8.6	60.6 ± 9.9
Sex – male (n, %)	247 (51.7)	882 (47.0)	802 (55.8)	1246 (62.5)	264 (55.6)
Duration of diabetes (years)	4.7 ± 5.4	8.6 ± 6.5	8.4 ± 6.2	11.8 ± 7.5	13.3 ± 7.3
CVD (%)*	5	8	13	87	18
HbA1c (%)	7.9 ± 0.9	8.3 ± 1.0	8.2 ± 0.9	8.5 ± 0.9	8.3 ± 0.9
BMI (kg/m^2)	31.9 ± 6.6	34.2 ± 6.9	33.5 ± 6.1	32.6 ± 5.5	33.4 ± 6.1
Weight (kg)	85.9 ± 19.8	93.7 ± 21.9	94.3 ± 20.1	90.3 ± 18.7	95.2 ± 21.6
SBP (mm Hg)	127.6 ± 14.1	130.6 ± 13.8	131.5 ± 13.3	134.4 ± 15.4	137.9 ± 15.7
DBP (mm Hg)	79.4 ± 8.8	79.2 ± 9.0	79.2 ± 8.9	78.4 ± 9.4	80.7 ± 10.8
Antihypertensive medication use (%)*	47	64	70	94	75
eGFR (mL/min/1.73m^2)	94.1 ± 19.7	96.0 ± 17.1	94.1 ± 17.0	81.3 ± 21.1	85.5 ± 17.8

Data are mean ± SD, unless otherwise indicated. *Data presented for all randomized patients and for CVD includes history of myocardial infarction, coronary revascularization, hospitalization for unstable angina or heart failure, stroke or transient ischemic attack, peripheral arterial disease, lower extremity arterial revascularization, carotid revascularization, or documented coronary artery disease

Abbreviations: BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; N = population size; n = sample size; SBP = systolic blood pressure; SD = standard deviation.

CHANGE IN BODY WEIGHT AND SYSTOLIC BLOOD PRESSURE OVER TIME

Data Pooled across the SURPASS 1-5 Trials



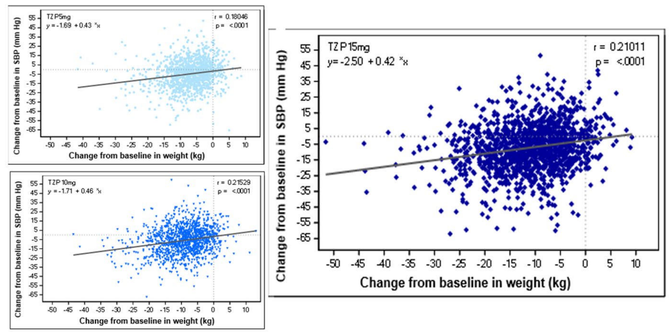
There was no clinically relevant change in the utilization of antihypertensive medication post baseline. Least squares mean ± standard error. Pooled data from the safety population of the SURPASS 1-5 studies. Analysis based on MMRM model. BW = body weight; MMRM = mixed-model repeated measures; SBP = systolic blood pressure; TZP = tirzepatide.

SAFETY RESULTS

- Treatment with tirzepatide resulted in a mean increase in heart rate of 1 to 4, 2 to 4, and 3 to 6 beats per minute (bpm) for 5-, 10- and 15-mg groups, respectively, at primary end point (Week 40 for SURPASS-1, 2, and 5; Week 52 for SURPASS-3 and 4). For the 2 placebo-controlled studies, heart rate increased by 0-2 bpm on average. Treatment with semaglutide 1 mg, insulin degludec, and insulin glargine resulted in mean heart rate increases of 4, 1, and 1 bpm, respectively.
- In a meta-analyses conducted across seven Phase 2 and 3 clinical studies, tirzepatide demonstrated cardiovascular (CV) safety when compared with pooled comparators with the hazard ratio of 0.80 (95% CI: 0.57-1.11) for major cardiovascular events (MACE-4) which included death due to CV cause, myocardial infarction, stroke, and hospitalization for unstable angina.[6]

[6]Sattar et al. Nature Medicine 2022;28,591–598

CORRELATION BETWEEN CHANGE IN BODY WEIGHT AND SYSTOLIC BLOOD PRESSURE AT WEEK 40



Safety population of SURPASS 1-5 pooled.
Abbreviations: SBP = systolic blood pressure; TZP = tirzepatide

ClinicalTrial.gov Identifiers: NCT03954834, NCT03987919, NCT03882970, NCT03730662, NCT04039503

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