

The Upcoming Weekly Tides (Semaglutide vs. Tirzepatide) against Obesity: STEP or SURPASS?

Han Na Jung^{1,2}, Chang Hee Jung^{1,2,*}

¹Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul; ²Asan Diabetes Center, Asan Medical Center, Seoul, Korea

The rapidly increasing prevalence of obesity and obesity-associated morbidity is causing an ever-increasing global burden. Beyond lifestyle modifications, pharmacological approaches to losing body weight to achieve a decrease in cardiometabolic complications are in the spotlight. Pre-existing anti-obesity medications (AOMs) approved for long-term prescription use showed a weight reduction of around 5% more than placebo. In contrast to the modest efficacy of pre-existing AOMs, two newly developed, weekly-administered injectable drugs, semaglutide and tirzepatide, exhibited outstanding weight-loss effects in a series of multinational randomized phase III trials. Considering that these two peptides are the most promising candidates for the upcoming battle in the anti-obesity market, comparison of their efficacy and safety is essential. This review summarizes the body weight reduction efficacy, glycemic control, and safety of semaglutide up to a 2.4-mg dose and tirzepatide up to a 15-mg dose, focusing on the Semaglutide Treatment Effect in People with Obesity (STEP) 2, SURPASS-1, and SURPASS-2 trials, the subjects of which were all patients with type 2 diabetes mellitus.

Key words: Obesity, Semaglutide, Tirzepatide

Received February 23, 2022
Reviewed March 15, 2022
Accepted March 15, 2022

*Corresponding author
Chang Hee Jung

 <https://orcid.org/0000-0003-4043-2396>

Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-1418
Fax: +82-2-3010-6962
E-mail: chjung0204@gmail.com

INTRODUCTION

The global prevalence of obesity has rapidly tripled since 1975, regardless of gender, age, and nation.^{1,2} In 2016, the worldwide proportions of overweight and obese adults were approximately 39% and 13%, reaching 1.9 billion and 650 million, respectively.¹ Beyond its literal meaning of excess body weight, obesity is considered to be a serious disease associated with numerous non-communicable disorders such as type 2 diabetes mellitus (T2DM), hypertension, myocardial infarction, stroke, fatty liver disease, dementia, osteoarthritis, depression, and several cancers.^{3,4}

The U.S. Food and Drug Administration (FDA) approved pharmacotherapy for obesity with concomitant dietary and physical lifestyle modifications in subjects with a body mass index (BMI) of at least 30 kg/m² or 27 kg/m² in conjunction with any of the fol-

lowing obesity-related comorbidities: T2DM, hypertension, or dyslipidemia.⁵⁻⁹ The 2020 Korean Society for the Study of Obesity recommends anti-obesity medication (AOM) for the failure to reduce weight after lifestyle interventions in individuals with a BMI of at least 25 kg/m².¹⁰

The market for AOM is facing a new phase with the introduction of two highly effective peptides, semaglutide and tirzepatide. Semaglutide Treatment Effect in People with Obesity (STEP) phase III trials found a substantial weight reduction with semaglutide 2.4 mg given once weekly in both diabetic and non-diabetic obese patients.¹¹⁻¹⁴ The SURPASS trials validated the weight-losing effect of weekly tirzepatide up to a 15-mg dose only in T2DM patients;¹⁵⁻¹⁸ a phase III tirzepatide study restricted to non-diabetic participants, SURMOUNT-1, is still ongoing. Although tirzepatide demonstrated its superiority in reducing weight at doses of 5 mg,

10 mg, and 15 mg compared to semaglutide at 1 mg in SURPASS-2,¹⁶ a comparison of tirzepatide with semaglutide at a dose of 2.4 mg has yet to be performed.

This review aims to discuss the weight-loss efficacy, as well as the glycemic control and safety, of semaglutide and tirzepatide. To compare the two drugs within equivalent subjects, we focused on the STEP 2, SURPASS-1, and SURPASS-2 trials. STEP 2 was the only study of semaglutide 2.4 mg to target obese T2DM subjects, and no tirzepatide trial targeting non-diabetic obese subjects has been concluded.

SEMAGLUTIDE

Semaglutide is an analog with 94% homology to human glucagon-like peptide-1 (GLP-1).¹⁹ Three major structural modifications to native GLP-1, including two amino acid substitutions and one acylation, improve its resistance to dipeptidyl peptidase-4 (DPP-4) cleavage and its affinity for albumin.¹⁹ Unlike the short half-life of one to two minutes for human GLP-1, which is rapidly inactivated by DPP-4, the half-life of semaglutide is 165 to 184 hours.^{19,20} This longer duration enables weekly administration. Semaglutide engages in glucose-dependent insulin secretion and glucagon suppression, a feature of GLP-1 receptor agonists.²¹⁻²³ The

primary mechanism of weight loss by semaglutide is thought to be reduced energy consumption via interference with food preference, inhibition of appetite, and intensification of satiety. Semaglutide also has a minimal effect on energy expenditure and gastric emptying.²⁴⁻²⁶

In a randomized, double-blinded, phase II trial involving non-diabetic adults with a BMI of at least 30 kg/m², the mean weight loss at week 52 was 13.8% for 0.4 mg semaglutide given once daily. This is equivalent to 2.8 mg weekly and was compared to a 7.8% loss for liraglutide therapy or 2.3% loss for placebo.²⁷ STEP was a global phase III study that defined the weight-loss efficacy of semaglutide 2.4 mg once per week. Six STEP trials have been completed, four of which have been published so far.¹¹⁻¹⁴ The substantial weight reduction of semaglutide 2.4 mg weekly demonstrated in the STEP trials resulted in FDA approval for semaglutide as a long-term AOM adjunct to calorie restriction and physical activity.⁹

STEP 2 was a randomized, double-blind trial with a 1:1:1 random allocation to semaglutide 2.4 mg, semaglutide 1.0 mg, and placebo groups (Table 1).¹² A double-dummy design was used in which all subjects were administered two injections weekly of semaglutide plus a placebo or two placebos. From 12 countries, 1,210 adult patients with T2DM, a BMI of at least 27 kg/m², and a glycosylated hemoglobin (HbA1c) of 7%–10% were recruited. The mean

Table 1. Study outlines of STEP 2, SURPASS-1, and SURPASS-2

Variable	STEP 2 ¹² (n=1,210)	SURPASS-1 ¹⁵ (n=478)	SURPASS-2 ¹⁶ (n=1,879)
Study arm	Placebo vs. Semaglutide 1, 2.4 mg	Placebo vs. Tirzepatide 5, 10, 15 mg	Semaglutide 1 mg vs. Tirzepatide 5, 10, 15 mg
Study duration (wk)	68	40	40
Baseline characteristics			
Age (yr)	55±11	54.1±11.9	56.6±10.4
Male (%)	49.1	51.7	47.0
Duration of diabetes (yr)	8.0±6.1	4.7±5.4	8.6±6.5
Body weight (kg)	99.8±21.5	85.9±19.8	93.7±21.9
BMI (kg/m ²)	35.7±6.3	31.9±6.6	34.2±6.9
HbA1c (%)	8.1±0.8	7.9±0.9	8.3±1.0
FPG (mg/dL*)	155.0±41.4	153.6±39.8	172.9±51.5
Blood pressure (mmHg)			
Systolic	130±14	127.6±14.1	130.6±13.8
Diastolic	80±9	79.4±8.8	79.2±9.0
eGFR (mL/min/1.73 m ²)	93.3±22.4	94.1±19.7	96.0±17.1

Values are presented as mean ± standard deviation unless otherwise indicated.

*FPG levels presented only in mmol/L were converted to mg/dL by multiplying 18.018.

STEP, Semaglutide Treatment Effect in People with Obesity; BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate.

age and BMI were 55 years and 35.7 kg/m², respectively, with men accounting for 49.1% of participants (Table 1). The participants were required to be on a steady dose of up to three oral antidiabetics (OAD) including metformin, sulfonylureas, sodium-glucose co-transporter-2 inhibitors, or thiazolidinediones for a minimum of 90 days prior to screening. In addition to counseling on diet and physical activity, weekly injections of the allocated drugs were sustained for 68 weeks followed by an off-drug period of 7 weeks. Titration increases from a starting dose of 0.25 mg occurred every 4 weeks, requiring 16 weeks to achieve the final 2.4-mg dose. The sulfonylurea doses were approximately halved at the start of treatment in accordance with a decision by the researcher.

TIRZEPATIDE

Tirzepatide is a dual receptor agonist of the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 and is therefore referred to as a “twincretin.”^{28,29} Tirzepatide is a 39 amino acid-long synthetic peptide, the structure of which is based on that of the native GIP.²⁸ A 20-carbon fatty diacid moiety of tirzepatide increases its half-life to 5 days, allowing for once-weekly injection.²⁸ Animal models of obesity and diabetes have demonstrated that GIP and GLP-1 co-administration has synergistic effects in lowering body weight, food consumption, and fat mass.²⁹

The phase II trial of weekly tirzepatide 1 mg, 5 mg, 10 mg, and 15 mg for 26 weeks in patients with T2DM exhibited a dose-dependent weight reduction of 0.9 kg, 4.8 kg, 8.7 kg, and 11.3 kg, respectively, compared to 0.4 kg for placebo or 2.7 kg for dulaglutide 1.5 mg.³⁰ SURPASS was a randomized, phase III trial that aimed to determine the efficacy of tirzepatide in patients with T2DM in terms of both glycemic control and weight reduction. Referring to the findings of the phase II study, doses of 5 mg, 10 mg, and 15 mg every week were assessed in this series of studies. Six global and two Japanese SURPASS studies were concluded, and four global programs have been published.¹⁵⁻¹⁸

SURPASS-1 was a double-blind, placebo-controlled trial distributing the subjects equally among weekly tirzepatide 5 mg, 10 mg, and 15 mg, and placebo groups (Table 1).¹⁵ The participants were 478 adult patients with T2DM who had an HbA1c level of 7%–9.5%, a BMI of at least 23 kg/m², no prior experience with injectable drugs,

and no history of OAD use within the preceding 3 months. The mean age and BMI of the included subjects were 54.1 years and 31.9 kg/m², respectively (Table 1). The treatment period was 40 weeks and was continued for an additional 4 weeks for continued safety monitoring. The initial dose was 2.5 mg, followed by the gradual addition of 2.5 mg at 4-week intervals. Consequently, target doses of 5 mg, 10 mg, and 15 mg were reached after 4, 12, and 20 weeks, respectively. This gradual dosing titration was selected based on the findings that nearly a quarter of participants allocated to the tirzepatide 15 mg group discontinued the treatment due to gastrointestinal adverse events.^{30,31}

SURPASS-2 was an active-controlled trial in which subjects were randomized 1:1:1:1 to once-weekly tirzepatide 5 mg, 10 mg, or 15 mg and semaglutide 1 mg groups (Table 1).¹⁶ Contrary to the double-blind design of STEP 2 or SURPASS-1,^{12,15} SURPASS-2 employed an open-label setting due to different devices and dose adjustment schedules. This study involved 1,879 adult patients with T2DM, BMI of ≥ 25 kg/m², and HbA1c of 7%–10.5% despite taking at least a 1,500-mg dose of metformin. For the 3 months prior to study initiation, treatment with metformin was the only therapeutic measure allowed. Mean participant age was 56.6 years old and their BMI was 34.2 kg/m² on average (Table 1). SURPASS-2 complied with SURPASS-1’s study duration and dose increment regimen for tirzepatide.¹⁵ Dose titration for semaglutide was achieved as in STEP 2 up to 1 mg.¹²

BODY WEIGHT REDUCTION

In STEP 2, 68-week treatment with semaglutide at a dose of 2.4 mg reduced the absolute body weight by 9.7 kg, which corresponded to a 9.6% decrease from baseline (Fig. 1).¹² The estimated treatment difference (ETD) of semaglutide 2.4 mg was 2.7% and 6.2% compared to semaglutide 1.0 mg and placebo, respectively.¹² SURPASS-1 revealed that tirzepatide 15 mg at week 40 displayed 9.5 kg of absolute weight loss with a 10.1% greater decrease than placebo.¹⁵ Injection of tirzepatide at 15 mg for the same duration lowered the body weight by 13.1% in SURPASS-2 with an ETD of 6.4% compared to semaglutide 1 mg treatment.¹⁶

Fig. 2 shows the target body weight loss of 5%, 10%, and 15% from baseline. The proportion of patients who attained at least a

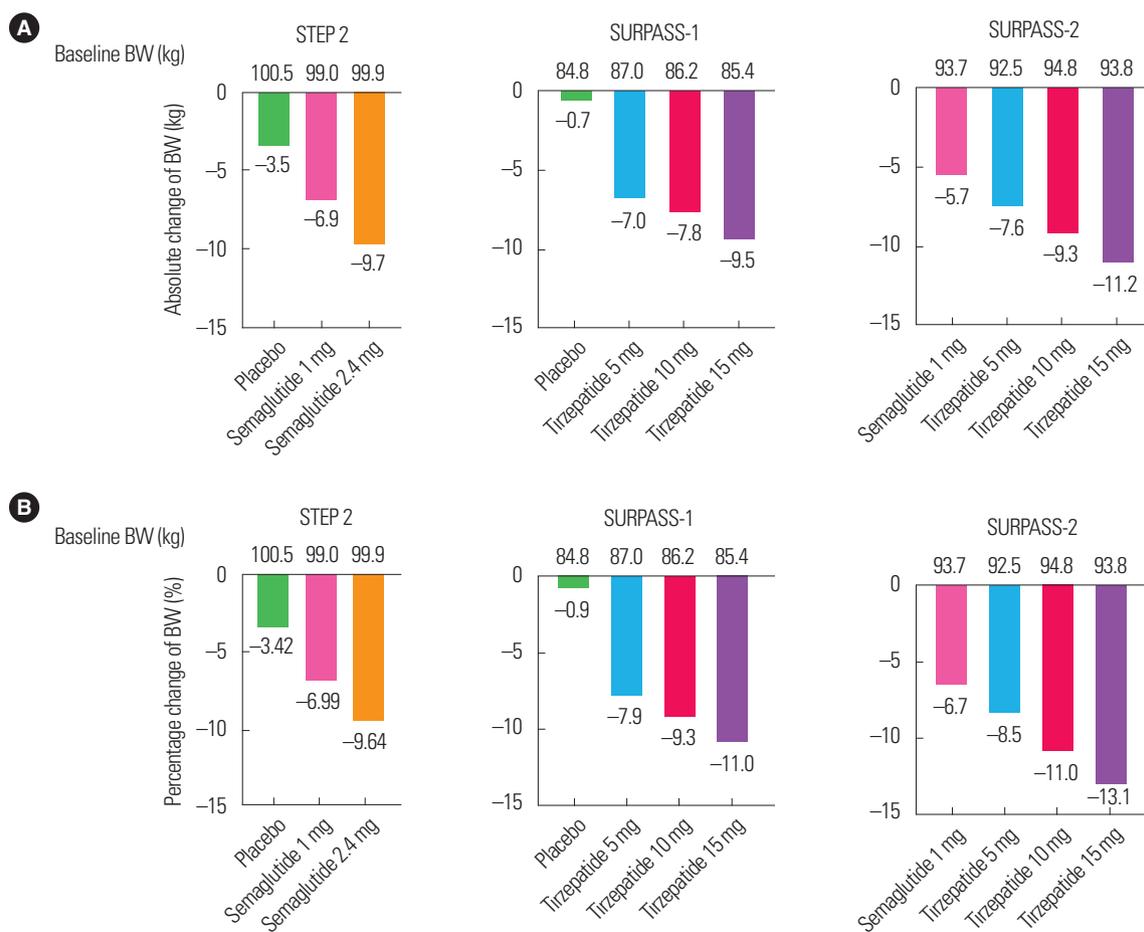


Figure 1. Comparison of the mean change in body weight (BW) in Semaglutide Treatment Effect in People with Obesity (STEP) 2, SURPASS-1, and SURPASS-2. (A) Absolute change of BW (kg) from baseline. (B) Percentage change of BW (%) from baseline.

5% weight reduction with semaglutide 2.4 mg was 69% over the 68 weeks of STEP 2, which was higher than either semaglutide 1.0 mg or placebo.¹² All doses of tirzepatide for the 40-week duration of SURPASS-1 produced even larger differences from placebo than did semaglutide 2.4 mg in STEP 2.^{12,15} Treatment with semaglutide 2.4 mg in STEP 2 and tirzepatide 15 mg in SURPASS-1 showed similar percentages of 46%–47% and 26%–27% for those who reached at least 10% and 15% weight loss, respectively.^{12,15} In SURPASS-2, tirzepatide also displayed a dose-dependent increase in target achievement, with a 15-mg dose attaining 57% and 36% for HbA1c targets of 10% and 15%, respectively.¹⁶

As of 2021, five AOMs have been authorized for long-term administration in the United States: orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide 3.0 mg, and semaglutide 2.4 mg,⁵⁻⁹ of which four, excluding semaglutide, have been approved in Ko-

rea.³² With the exception of the recently authorized semaglutide, these actively prescribed AOMs generally result in 3%–7% greater weight loss than placebo.³² The weight-losing effects of semaglutide 2.4 mg and tirzepatide 15 mg are highly significant in light of this. While reducing 5% of baseline weight is conventionally regarded as clinically significant,³³ a greater amount of weight loss influences different organs to varying extents.³⁴ Moderate weight loss of 5 to 10% ameliorates cardiovascular risk factors such as hyperglycemia, hypertension, or dyslipidemia;³⁴ and 70% to 80% of patients treated with semaglutide 2.4 mg and tirzepatide 15 mg reached this goal (Fig. 2). A greater weight loss of up to 10% is associated with improvements in obstructive sleep apnea or non-alcoholic steatohepatitis, and a 15% loss is associated with T2DM remission and mortality reduction.³⁴ Approximately half and one-quarter of patients treated with semaglutide 2.4 mg or tirzepatide 15 mg experienced

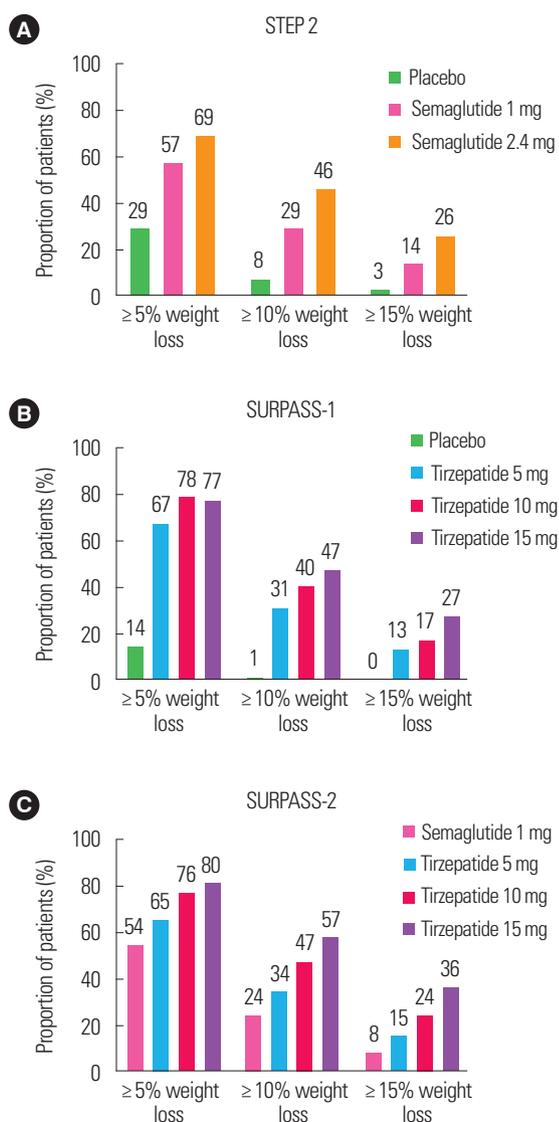


Figure 2. Comparison of the proportion of patients (%) reaching weight loss targets of 5%, 10%, and 15% in Semaglutide Treatment Effect in People with Obesity (STEP) 2 (A), SURPASS-1 (B), and SURPASS-2 (C).

body weight losses of at least 10% and 15%, respectively (Fig. 2).

Achieving a healthy body composition rather than merely losing weight is the ultimate goal of AOMs. The risk of comorbidities, including T2DM, cardiovascular disease, dyslipidemia, and atherosclerosis, is independently correlated with visceral fat mass that is inadequately distinguished by BMI or total body fat.³⁵⁻³⁷ Sub-population analysis in STEP 1, which involved only non-diabetic obese patients, revealed that weekly semaglutide 2.4 mg eliminated 6.99 kg and 0.27 kg more total and visceral fat mass, respectively, than placebo as measured by dual emission X-ray absorptiometry.¹¹ Sema-

glutide 2.4 mg also increased the relative percentage of lean body mass to total body mass.¹¹ However, the effects of semaglutide 2.4 mg or tirzepatide 15 mg on body composition of diabetic patients have not been examined in STEP 2 or the SURPASS series. Further investigation into the change in body composition and the corresponding complications of obesity is required.

GLYCEMIC CONTROL

Contrary to the dose-dependent increment in the extent of weight loss observed in STEP 2, SURPASS-1, and SURPASS-2, each increment of semaglutide 1 mg to 2.4 mg and tirzepatide 5 mg to 15 mg added only a slight improvement in glycemic control (Fig. 3).^{12,15,16} In STEP 2, the difference in the HbA1c change at week 68 was -0.1% between semaglutide 1 mg and 2.4 mg. Both doses lowered HbA1c by more than 1% compared to placebo.¹² Tirzepatide 15 mg reduced HbA1c by 2.1% and 2.3% in SURPASS-1 and SURPASS-2, respectively.^{15,16} These differences were only 0.2% to 0.3% greater than that of the 5-mg dose.^{15,16}

STEP 2 participants who reached an HbA1c level below 7% accounted for 78.5% of all patients with semaglutide 2.4 mg in contrast to 26.5% with placebo.¹² The same HbA1c target was attained in a higher percentage of patients by tirzepatide 15 mg in SURPASS-1 (88% for tirzepatide 15 mg vs. 19% for placebo) and SURPASS-2 (92% for tirzepatide 15 mg).^{15,16} Semaglutide 2.4 mg in STEP 2 achieved the lower HbA1c goal of at least 6.5% in 67.5% of subjects,¹² while tirzepatide 15 mg in SURPASS-1 and SURPASS-2 achieved this goal in 86% and 87% of subjects, respectively.^{15,16}

Hypoglycemic events defined as blood glucose levels less than 56 mg/dL were reported in 5.7% of patients on semaglutide 2.4 mg and 3% on placebo in STEP 2.¹² Episodes of glucose below 70 mg/dL occurred in 6.6% of cases with tirzepatide 15 mg in contrast to only 0.9% with placebo in SURPASS-1.¹⁵ However, in SURPASS-2 an overall low rate of hypoglycemia was displayed despite the low glucose level (less than 54 mg/dL) for confirming hypoglycemia (1.7% for tirzepatide 15 mg vs. 0.4% for semaglutide 1 mg).¹⁶

SAFETY

Participants who experienced any adverse events accounted for

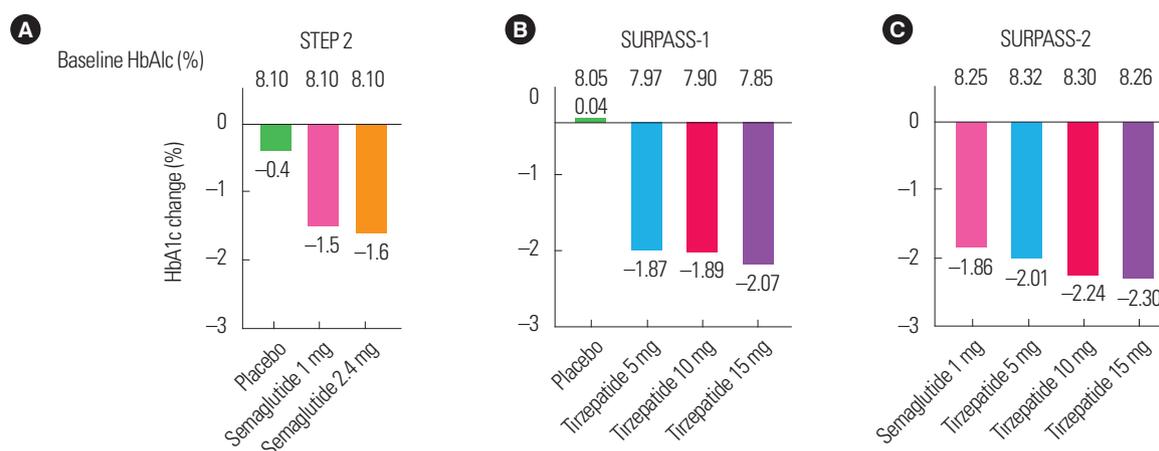


Figure 3. Comparison of the mean change in glycosylated hemoglobin (HbA1c; %) from baseline in Semaglutide Treatment Effect in People with Obesity (STEP) 2 (A), SURPASS-1 (B), and SURPASS-2 (C).

Table 2. Summary of adverse events in STEP 2, SURPASS-1, and SURPASS-2

Variable	Placebo	Semaglutide 1 mg	Semaglutide 2.4 mg	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
All AEs (%)	66.1*–76.9 [†]	64.2 [‡] –81.8 [‡]	87.6 [‡]	63.6 [†] –68.6*	66.9*–68.7 [‡]	63.6*–68.9 [‡]
Serious AE (%)	2.6*–9.2 [†]	2.8 [‡] –7.7 [†]	9.9 [‡]	4.1*–7.0 [‡]	1.7*–5.3 [‡]	0.8*–5.7 [‡]
All GI AEs (%)	19.1*–34.3 [†]	41.2 [‡] –57.5 [‡]	63.5 [‡]	38.0*–40.0 [‡]	41.3*–46.1 [‡]	41.3*–44.9 [‡]
Nausea	6.1*–9.2 [†]	17.9 [‡] –32.1 [†]	33.7 [‡]	11.6*–17.4 [‡]	13.2*–19.2 [‡]	18.2*–22.1 [†]
Vomiting	1.7*–2.7 [†]	8.3 [‡] –13.4 [†]	21.8 [‡]	3.3*–5.7 [‡]	2.5*–8.5 [‡]	5.8*–9.8 [‡]
Discontinuation due to AE (%)	2.6*–3.5 [†]	4.1 [‡] –5.0 [†]	6.2 [‡]	3.3*–6.0 [‡]	5.0*–8.5 [‡]	6.6*–8.5 [‡]

*Derived from SURPASS-1; [†]Derived from STEP 2; [‡]Derived from SURPASS-2. STEP, Semaglutide Treatment Effect in People with Obesity; AE, adverse event; GI, gastrointestinal.

87.6% with semaglutide 2.4 mg, 81.8% with semaglutide 1 mg, and 76.9% with placebo in STEP 2.¹² The proportion of any adverse events for tirzepatide 15 mg was 63.6% compared to 66.1% for placebo in SURPASS-1.¹⁵ In SURPASS-2, 68.9% and 64.2% of patients with tirzepatide 15 mg and semaglutide 1 mg, respectively, reported any adverse events.¹⁶ In all trials, gastrointestinal events were the most common adverse events. These were mostly tolerable and occurred temporarily in the early phases of the trials.^{12,15,16} The composite gastrointestinal events and nausea occurred more frequently with semaglutide 2.4 mg and tirzepatide 15 mg compared to placebo (proportion of all gastrointestinal events and nausea, 63.5% and 33.7%, respectively, for semaglutide 2.4 mg vs. 34.3% and 9.2%, respectively, for placebo in STEP 2; and 41.3% and 18.2%, respectively, for tirzepatide 15 mg vs. 19.1% and 6.1%, respectively, for placebo in SURPASS-1).^{12,15} Those treated with tirzepatide 15 mg reported more gastrointestinal and nausea events than those treated with semaglutide 1 mg (44.9% and 22.1%, respectively, for tirzepatide

15 mg vs. 41.2% and 17.9%, respectively, for semaglutide 1 mg in SURPASS-2).¹⁶ Additionally, the premature discontinuation rate due to adverse events was higher with semaglutide 2.4 mg and tirzepatide 15 mg than with placebo (6.2% vs. 3.5% in STEP 2, and 6.6% vs. 2.6% in SURPASS-1).^{12,15} In SURPASS-2, patients treated with tirzepatide 15 mg experienced approximately twice as many adverse events leading to early termination as those treated with semaglutide 1 mg (8.5% vs. 4.1%).¹⁶ Table 2 summarizes the safety profile of all treatments in STEP 2, SURPASS-1, and SURPASS-2.

STEP VS. SURPASS

A randomized trial capable of directly comparing semaglutide and tirzepatide is currently difficult to conceive; and the heterogeneous study designs among STEP 2, SURPASS-1, and SURPASS-2 make any indirect comparisons complicated despite all three being restricted to diabetic patients. STEP 2 and SURPASS-1 adopted a

double-blind design, but SURPASS-2 used an open-label system.^{12,15,16} Semaglutide treatment for 68 weeks in STEP 2 allowed for 52 weeks on a full dose of 2.4 mg after stepwise up-titration.¹² However, tirzepatide at a 15-mg dose was administered for only 20 weeks, an inadequate duration to attain a plateau for weight reduction in SURPASS-1 and SURPASS-2.^{15,16}

Two types of estimands were introduced in all trials: a policy-oriented estimand averaging all assigned subjects and a product-oriented estimand encompassing patients who adhered to medication during the trial without rescue therapy. The former was the main estimand used to evaluate efficacy in STEP 2 and SURPASS-2 except for percentage change of body weight in SURPASS-2,^{12,16} while the latter estimand was chiefly used in SURPASS-1.¹⁵ A consistent estimand used in all of the trials may have resulted in different findings.

The differences in the baseline characteristics of the participants also needs to be scrutinized. Patients in SURPASS-1 tended to be in better condition than those in STEP 2 or SURPASS-2, with a shorter duration of T2DM, lower average body weight, lower mean HbA1c level, and lower fasting plasma glucose level (Table 1). Moreover, the antidiabetics used prior to study inclusion were dissimilar. STEP 2 permitted combinations of a maximum of three OADs; none were allowed in SURPASS-1, and only metformin was allowed in SURPASS-2 within 3 months of enrollment.^{15,16}

The implications of these heterogeneities are difficult to pinpoint. Nonetheless, comparisons of semaglutide and tirzepatide under similar settings is inevitable considering the upcoming battle for supremacy in the anti-obesity treatment market.

CONCLUSION

Despite recognition of the severe medical and socioeconomic burden of obesity, the weight-loss effects of pre-existing AOMs are insufficient to overcome obesity-associated complications. The recently introduced peptides semaglutide and tirzepatide can be administered once weekly and have demonstrated substantially improved weight-losing effects within a tolerable safety margin in a series of STEP and SURPASS trials. These highly effective medications enable a considerable proportion of their users to achieve sufficient weight loss to alleviate obesity-associated metabolic diseases.

This review summarized the efficacy and safety of semaglutide and tirzepatide based on the STEP 2, SURPASS-1, and SURPASS-2 trials, all of which were conducted with T2DM subjects. Considering the dissimilar backgrounds and methods of these studies, a direct comparison of the two medications is still required. Also, further investigation into their effects on body composition, cardio-metabolic comorbidities, as well as their cost-effectiveness, will allow for personalized utilization.

CONFLICTS OF INTEREST

Chang Hee Jung is an Associate Editor. However, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. Otherwise, no other potential conflicts of interest relevant to this article were reported.

ACKNOWLEDGMENTS

The authors are grateful for the contributions of Wordvice (www.wordvice.com) for the English language review. This review was funded by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, grant number NRF- 2020R1A2C1101977, to CHJ. These funding sources had no roles in the writing of the article or the decision to submit the article for publication. HNJ has no funding to declare for this work.

AUTHOR CONTRIBUTIONS

Study concept and design: CHJ; analysis and interpretation of data: all authors; drafting of the manuscript: HNJ; critical revision of the manuscript: CHJ.

REFERENCES

1. World Health Organization. Obesity and overweight. Geneva: World Health Organization; 2021.
2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 popula-

- tion-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* 2017;390:2627-42.
3. Ortega FB, Lavie CJ, Blair SN. Obesity and cardiovascular disease. *Circ Res* 2016;118:1752-70.
 4. Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol* 2019;15:288-98.
 5. U.S. Food and Drug Administration. Highlights of prescribing information: Xenical. Silver Spring (MA): U.S. Food and Drug Administration; 2012.
 6. U.S. Food and Drug Administration. Highlights of prescribing information: Qsymia. Silver Spring (MA): U.S. Food and Drug Administration; 2020.
 7. U.S. Food and Drug Administration. Highlights of prescribing information: Contrave. Silver Spring (MA): U.S. Food and Drug Administration; 2020.
 8. U.S. Food and Drug Administration. Highlights of prescribing information: Saxenda. Silver Spring (MA): U.S. Food and Drug Administration; 2018.
 9. U.S. Food and Drug Administration. Highlights of prescribing information: Wegovy. Silver Spring (MA): U.S. Food and Drug Administration; 2021.
 10. Kim BY, Kang SM, Kang JH, Kang SY, Kim KK, Kim KB, et al. 2020 Korean Society for the Study of Obesity guidelines for the management of obesity in Korea. *J Obes Metab Syndr* 2021;30:81-92.
 11. Wilding JP, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021;384:989.
 12. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021;397:971-84.
 13. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA* 2021;325:1403-13.
 14. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA* 2021;325:1414-25.
 15. Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Fernández Landó L, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet* 2021;398:143-55.
 16. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;385:503-15.
 17. Ludvik B, Giorgino F, Jódar E, Frias JP, Fernández Landó L, Brown K, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet* 2021;398:583-98.
 18. Del Prato S, Kahn SE, Pavo I, Weerakkody GJ, Yang Z, Doupis J, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet* 2021;398:1811-24.
 19. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem* 2015;58:7370-80.
 20. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev* 2007;87:1409-39.
 21. Meloni AR, DeYoung MB, Lowe C, Parkes DG. GLP-1 receptor activated insulin secretion from pancreatic β -cells: mechanism and glucose dependence. *Diabetes Obes Metab* 2013;15:15-27.
 22. Ahrén B, Masmiquel L, Kumar H, Sargin M, Karsbøl JD, Jacobsen SH, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol* 2017;5:341-54.
 23. Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, et al. Efficacy and safety of once-weekly semaglutide

- versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care* 2018;41:258-66.
24. Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. *Diabetes Obes Metab* 2017;19:1242-51.
 25. Gabery S, Salinas CG, Paulsen SJ, Ahnfelt-Rønne J, Alanentalo T, Baquero AF, et al. Semaglutide lowers body weight in rodents via distributed neural pathways. *JCI Insight* 2020;5:e133429.
 26. Friedrichsen M, Breitschaft A, Tadayon S, Wizert A, Skovgaard D. The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. *Diabetes Obes Metab* 2021;23:754-62.
 27. O'Neil PM, Birkenfeld AL, McGowan B, Mosenzon O, Pedersen SD, Wharton S, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet* 2018;392:637-49.
 28. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. *Mol Metab* 2018;18:3-14.
 29. Finan B, Ma T, Ottaway N, Müller TD, Habegger KM, Hepner KM, et al. Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. *Sci Transl Med* 2013;5:209ra151.
 30. Frias JP, Nauck MA, Van J, Kutner ME, Cui X, Benson C, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet* 2018;392:2180-93.
 31. Frias JP, Nauck MA, Van J, Benson C, Bray R, Cui X, et al. Efficacy and tolerability of tirzepatide, a dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes: a 12-week, randomized, double-blind, placebo-controlled study to evaluate different dose-escalation regimens. *Diabetes Obes Metab* 2020;22:938-46.
 32. Kim BY, Kang SM, Kang JH, Kim KK, Kim B, Kim SJ, et al. Current long-term pharmacotherapies for the management of obesity. *J Obes Metab Syndr* 2020;29:99-109.
 33. Williamson DA, Bray GA, Ryan DH. Is 5% weight loss a satisfactory criterion to define clinically significant weight loss? *Obesity (Silver Spring)* 2015;23:2319-20.
 34. Ryan DH, Yockey SR. Weight loss and improvement in comorbidity: differences at 5%, 10%, 15%, and over. *Curr Obes Rep* 2017;6:187-94.
 35. Neeland IJ, Turer AT, Ayers CR, Powell-Wiley TM, Vega GL, Farzaneh-Far R, et al. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. *JAMA* 2012;308:1150-9.
 36. Neeland IJ, Turer AT, Ayers CR, Berry JD, Rohatgi A, Das SR, et al. Body fat distribution and incident cardiovascular disease in obese adults. *J Am Coll Cardiol* 2015;65:2150-1.
 37. Neeland IJ, Ayers CR, Rohatgi AK, Turer AT, Berry JD, Das SR, et al. Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults. *Obesity (Silver Spring)* 2013;21:E439-47.