비만약물치료의 최신 지견

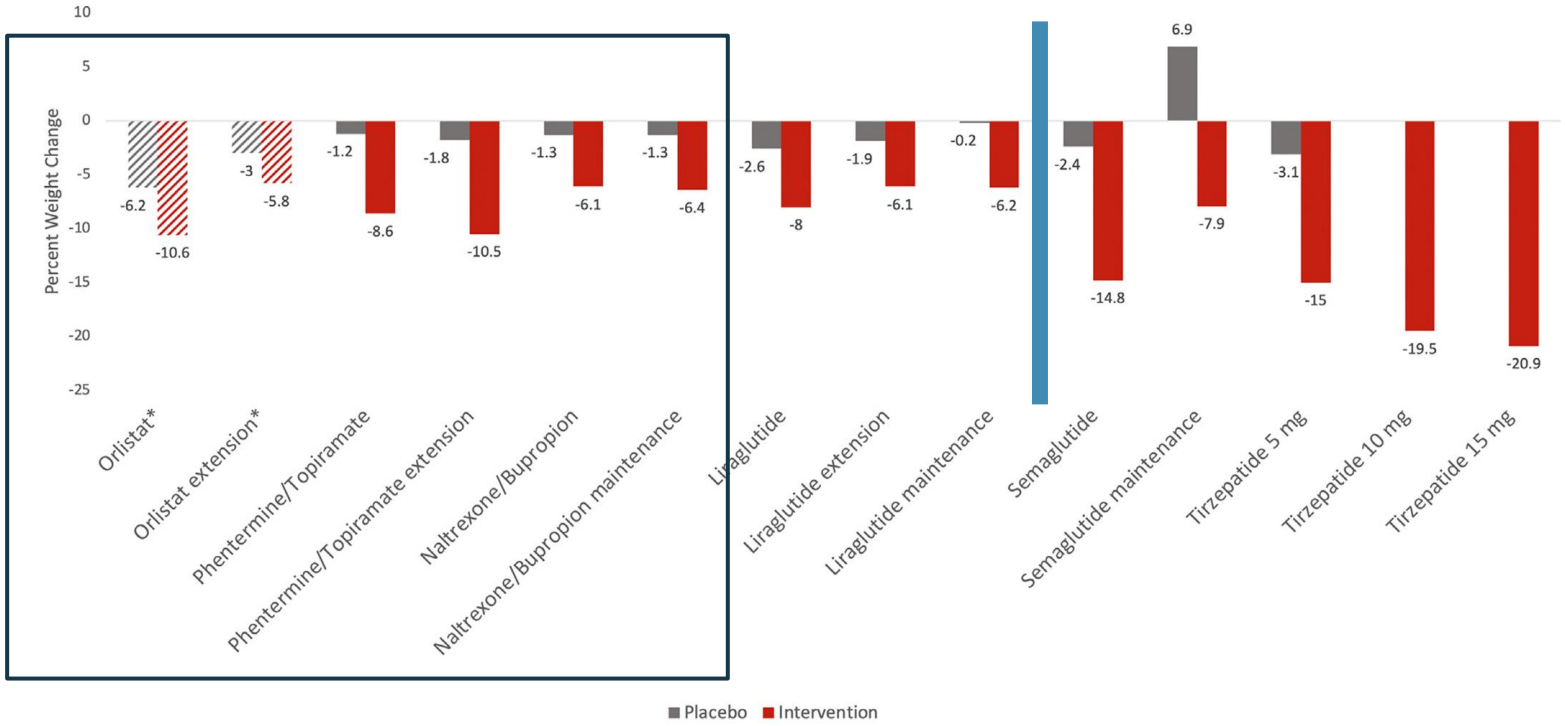
- GLP-1 기반 치료제를 중심으로 -

고려대학교 안암병원 가정의학과

비만체중조절센터

김양현

미국 및 국내 승인 비만 약물 효과 비교



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체중 감량 정도 별 약제 비교

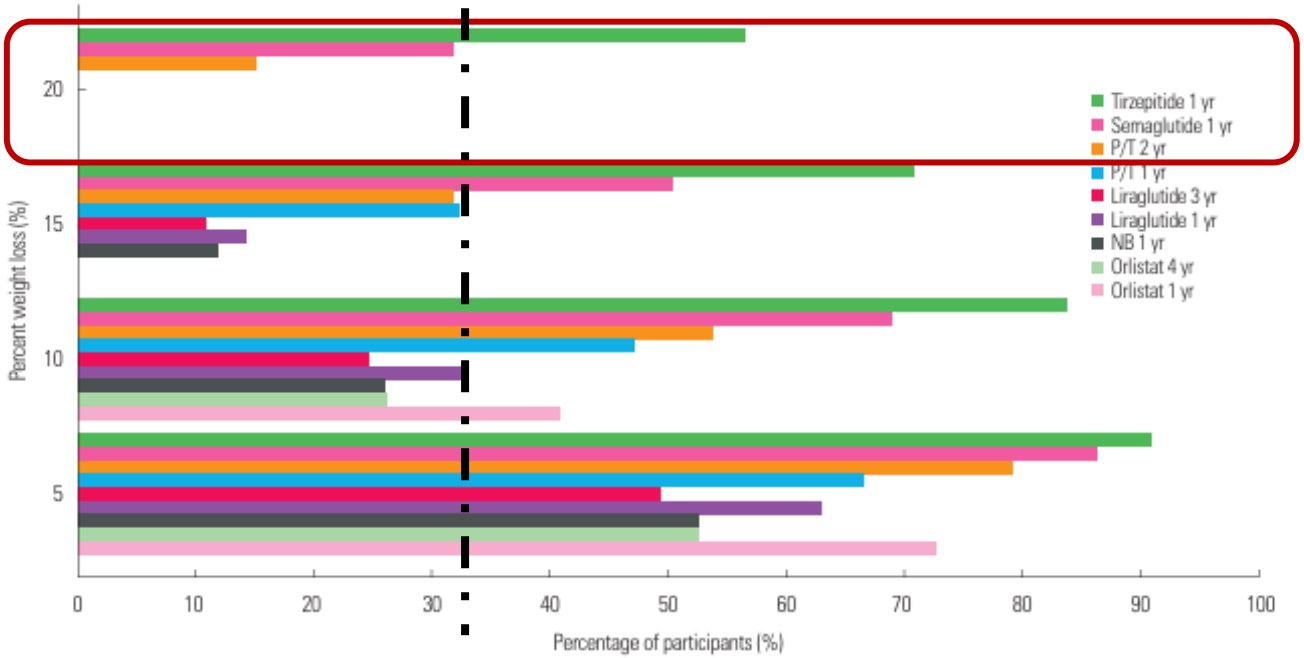

Figure 3. The percentage of participants achieving ≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20% weight loss for each medication. Data were extracted from the following trials: XENical in the Prevention of Diabetes in Obese Subjects (XENDOS; orlistat),[8] Contrave Obesity Research I (COR-I; naltrexone/bupropion [NB] extended-release [ER]),[23] Satiety and Clinical Adiposity-Liraglutide (SCALE) Obesity and Prediabetes and its extension (liraglutide 3.0 mg),[37,40] EQUIP (phentermine/topiramate [P/T] ER 1 year),[49] SEQUEL (P/T ER 2 years),[31] Semaglutide Treatment Effect in People with obesity (STEP) 1 (semaglutide 2.4 mg),[13] and SURMOUNT-1 (tirzepatide 15 mg).[48]

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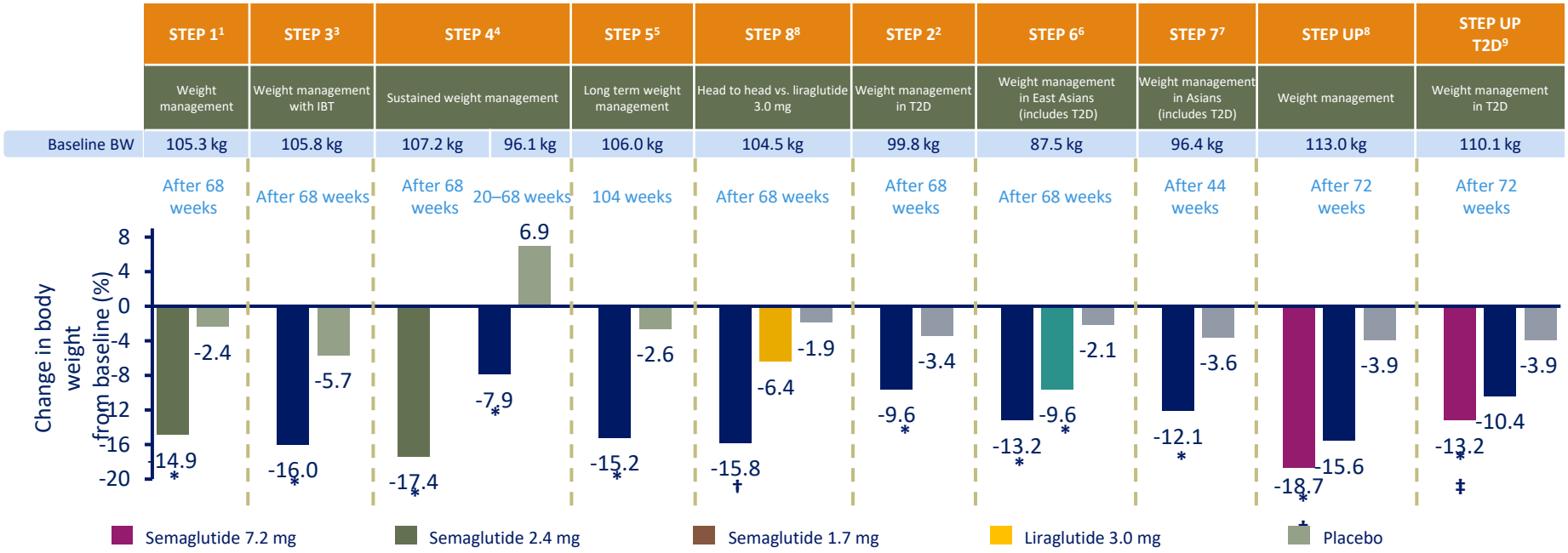
새로운 비만약의 등장
(위고비, Semaglutide)

Before Semaglutide (BS) vs. After Semaglutide (AS)

새로운 GLP-1R agonist: 위고비

1달마다 용량 증가,
1주일에 1번 투여,
0.25mg에서 2.4mg까지

위고비를 이용한 체중 감소 연구 (STEP trials)



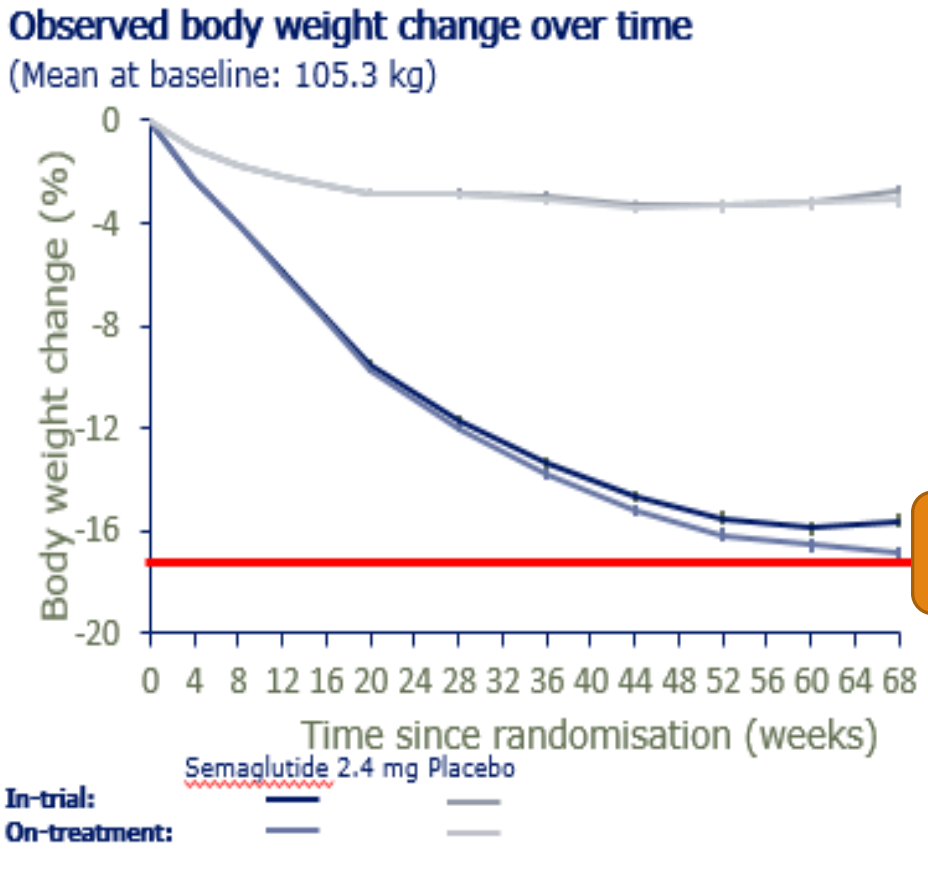
Treatment policy estimand: Evaluates the treatment effect regardless of trial product discontinuation and use of rescue intervention**

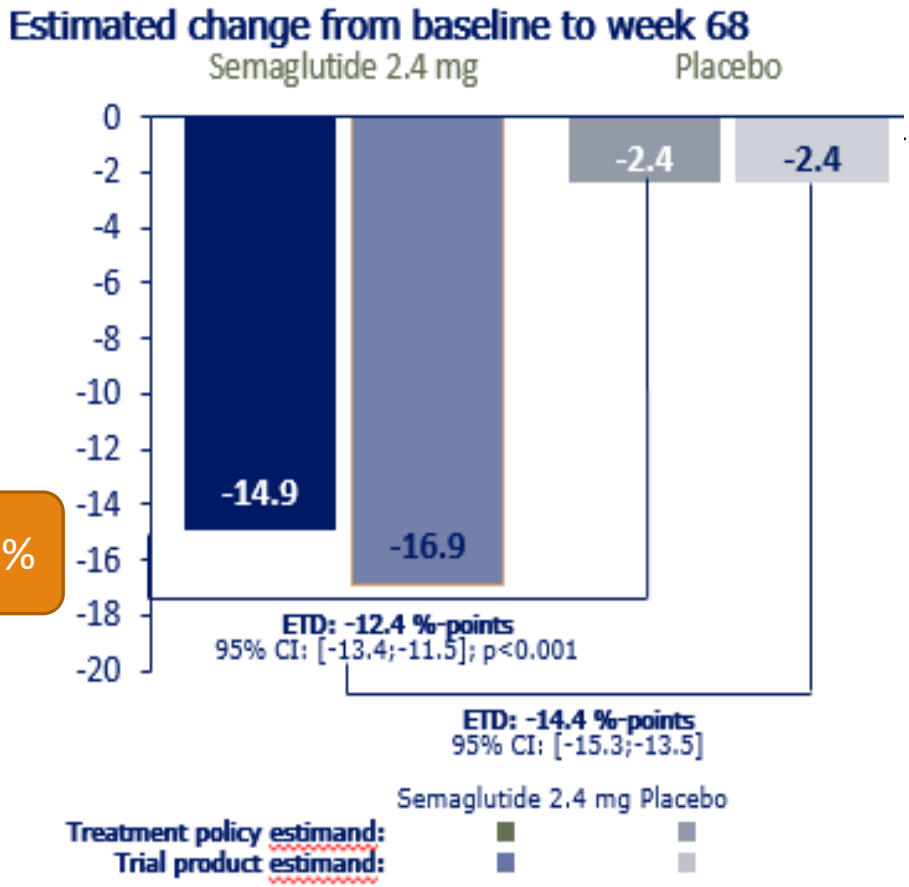
Semaglutide 2.4 mg (Wegovy®)'s maintain dose is 2.4 mg. Semaglutide 7.2 mg is not approved for obesity treatment by MFDS Korea.

**Statistically significant vs placebo. †Statistically significant vs. liraglutide 3.0 mg; ‡Statistically significant vs semaglutide 2.4 mg (exploratory for STEP UP T2D); ** other AOM or bariatric surgery*
BW, body weight; IBT, intensive behavioural therapy.
1. Wilding et al. N Engl J Med 2021; doi:10.1056/NEJMoa2032183; 2. Davies et al. Lancet, 2021; doi.org/10.1016/S0140-6736(21)00213-0: 3. Wadden et al. JAMA. doi:10.1001/jama.2021.1831;
4. Rubino et al. JAMA. 2021 Apr 13;325(14):1414-1425. doi: 10.1001/jama.2021.3224. 5. Garvey et al. Nat Med 28, 2083–2091 (2022); 6. Kadowaki et al. The Lancet Diabetes & Endocrinology 2022.;
7. Mu, Y., et al. The Lancet Diabetes & Endocrinology, 2024. 12(3): p. 184-195 8. Rubino et al. JAMA 2022; 327(2): 138-150; 8. Wharton S et al. Presented at the American Diabetes Association (ADA) 85th Scientific Sessions, June 20–23, 2025, Chicago, IL, USA: 6521-LB; 9. Lingvay I et al. Presented at the American Diabetes Association (ADA) 85th Scientific Sessions, June 20–23, 2025, Chicago, IL, USA: 1978-LB.

체중 변화

STEP 1

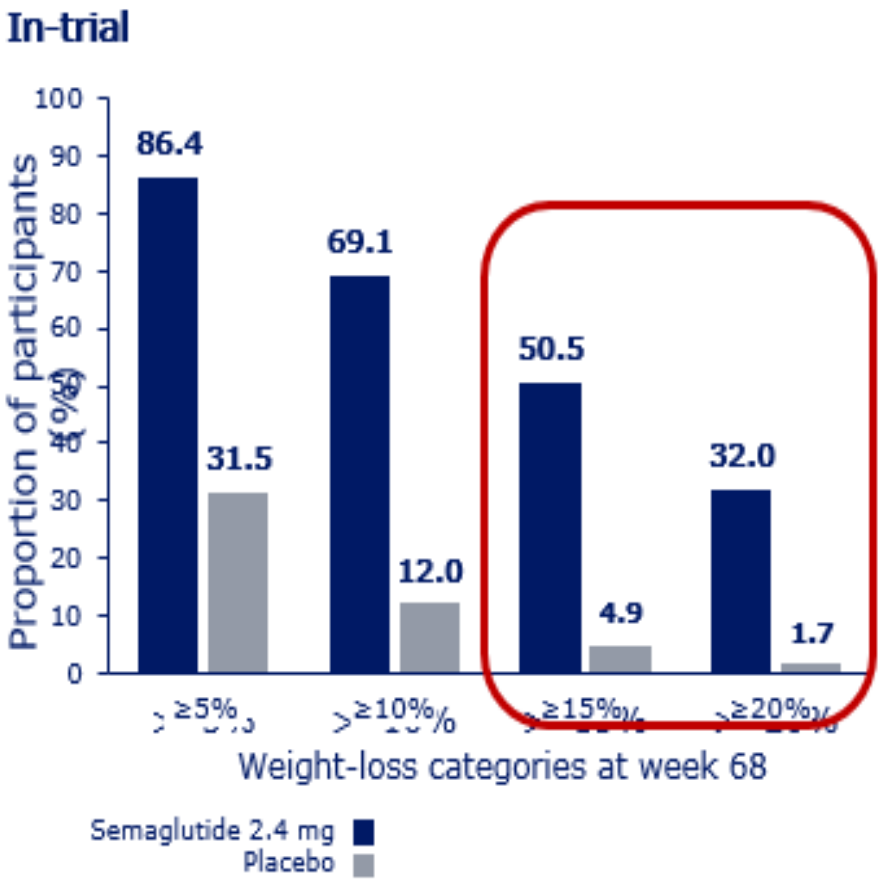


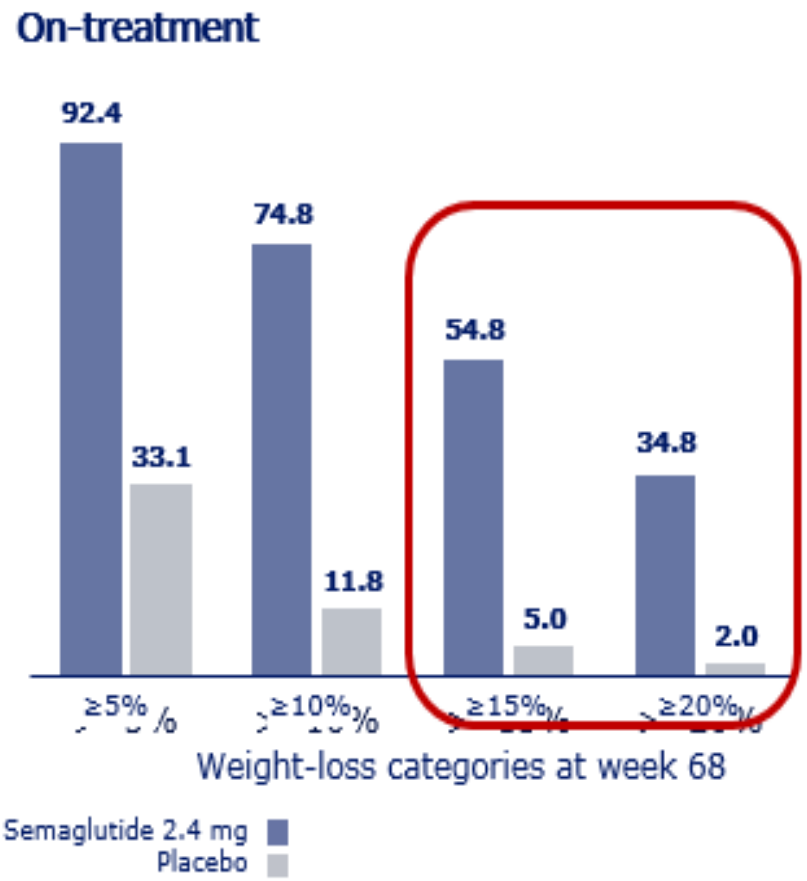


Error bars are +/- standard error of the mean.
CI, confidence interval; ETD, estimated treatment difference.
Wilding et al. N Engl J Med 2021;384:989-1002;

대표 체중 변화 연구

STEP 1

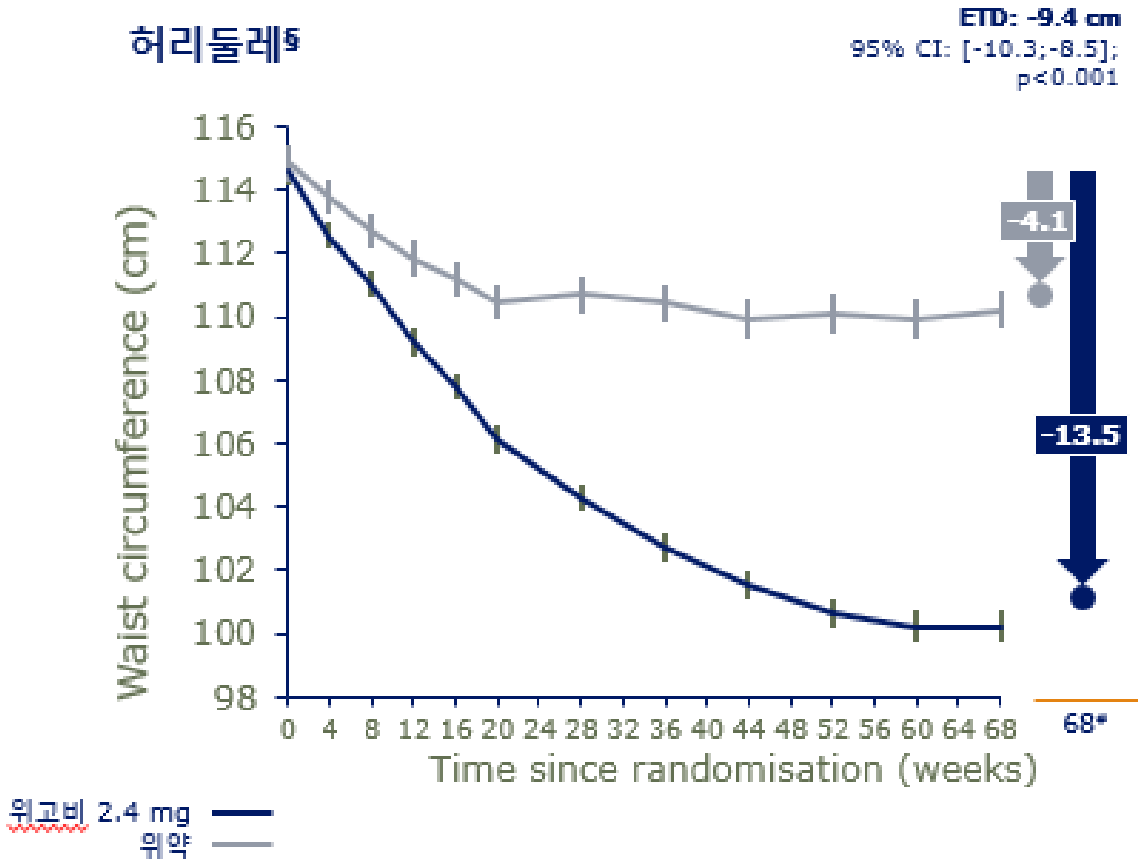




§ Proportions are based on observed data.
Wilding et al. N Engl J Med 2021;384:989-1002.

허리 둘레의 변화

STEP 1

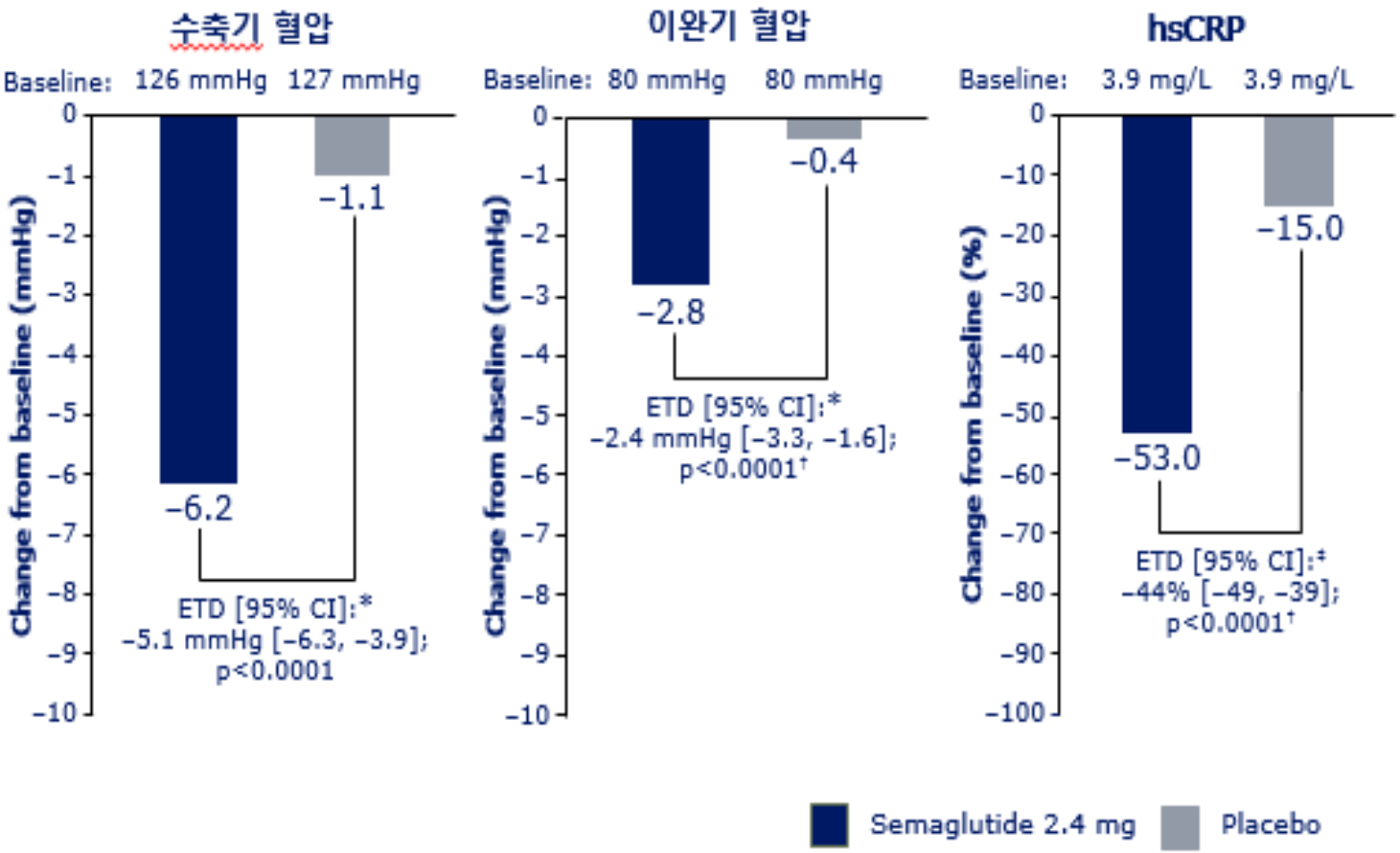


5.3인치 감소

§ Means are based on observed data from the in-trial period and the ETD is for the treatment policy estimand. Error bars are +/- standard error of the mean.
BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference.
Wilding et al. N Engl J Med 2021;384:989-1002.

심혈관 위험인자의 변화

STEP 1

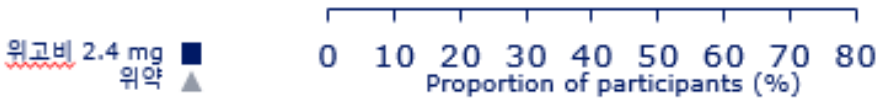


**Expressed as estimated absolute difference between groups. †Not adjusted for multiplicity. ‡Expressed as estimated relative percentage difference between groups.*
Data are for the in-trial period and the treatment policy estimand.
CI, confidence interval; CV, cardiovascular; ETD, estimated treatment difference; hsCRP, high-sensitivity C-reactive protein.
Garvey et al. Presented at the European and International Congress on Obesity (ECO) virtual meeting. May 10–13, 2021.

흔한 부작용(≥10%)

STEP 1

Preferred term	위고비 2.4 mg (N=1306)				위약 (N=655)			
	N	(%)	E	R	N	(%)	E	R
오심	577	44.2	1068	62.6	114	17.4	146	17.6
설사	412	31.5	766	44.9	104	15.9	138	16.6
구토	324	24.8	636	37.3	43	6.6	52	6.3
변비	306	23.4	390	22.9	62	9.5	73	8.8
비인후염	281	21.5	480	28.1	133	20.3	216	26.0
두통	198	15.2	387	22.7	80	12.2	104	12.5
소화불량	135	10.3	179	10.5	23	3.5	30	3.6
복통	130	10.0	175	10.3	36	5.5	41	4.9
상기도감염	114	8.7	158	9.3	80	12.2	116	14.0



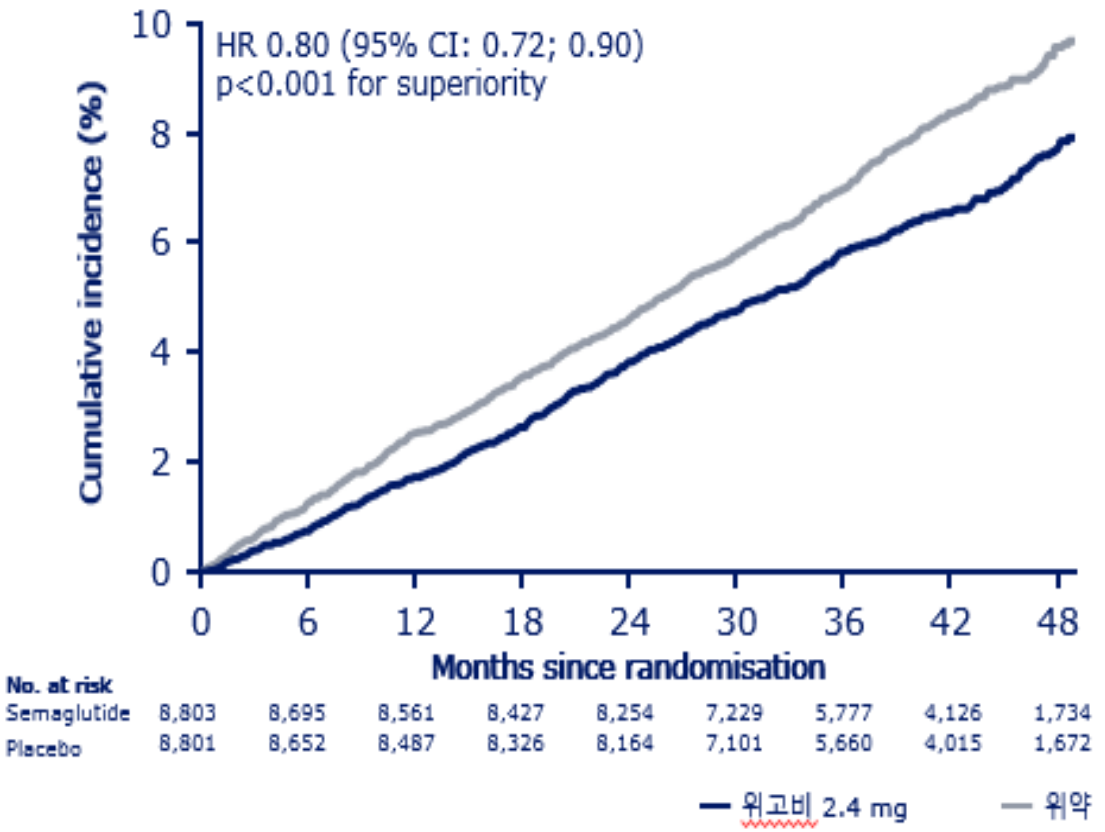
위장관계 부작용

오심, 설사, 구토, 변비

Data are for the on-treatment observation period.
E, number of events; N, number of participants with event(s); R, events per 100 patient years of exposure; %, proportion of participants with event(s).
Wilding et al. N Engl J Med 2021;384:989-1002.

심혈관 질환 감소 효과

SELECT



20%
MACE 감소*

위고비2.4 mg 는
주요심혈관위험을 **20% 감소**
in people with obesity and established CVD, without T2D[1,2]

All three components (death from CV causes, non-fatal MI and non-fatal stroke) contributed to MACE risk reduction

Mean follow-up time was 39.8 months

Cumulative incidence (using the Aalen–Johansen method) of the composite MACE primary endpoint. The HR was estimated using a Cox proportional hazards regression model. The proportion of participants with MACE was 6.5% with semaglutide 2.4 mg and 8.0% with placebo. MACE was defined as death from CV causes, non-fatal myocardial infarction, or non-fatal stroke.

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.

1. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563; 2. Novo Nordisk A/S. Company announcement, 8 August 2023. Available at: https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=166301. Accessed October 2023.

The Lancet Diabetes & Endocrinology
Volume 13, Issue 10, October 2025, Pages 838-847

Articles

Once-weekly semaglutide 2·4 mg in an Asian population with obesity, defined as BMI ≥25 kg/m^2, in South Korea and Thailand (STEP 11): a randomised, double-blind, placebo-controlled, phase 3 trial

Prof Soo Lim MD [a], Supawan Buranapin MD [b], Xiaolei Bao PhD [c], María Quiroga MD [d], Prof Kyung Hee Park PhD [e], Prof Jee-Hyun Kang PhD [f], Anders Rasmussen Rinnov PhD [d], Arisara Suwanagool MD [g]

Methods

STEP 11 was a 44-week, randomised, double-blind, placebo-controlled, phase 3 trial conducted at 12 clinical sites in **South Korea** and Thailand. Adults (aged ≥18 years in Thailand and ≥19 years in South Korea) **with obesity (BMI ≥25 kg/m²)** of Asian descent, without diabetes

	Semaglutide 2·4 mg (n=101)	Placebo (n=49)	Total (N=150)
Age, years	41 (10)	37 (11)	39 (11)
Sex			
Female	78 (77%)	33 (67%)	111 (74%)
Male	23 (23%)	16 (33%)	39 (26%)
Country of residence			
South Korea	57 (56%)	28 (57%)	85 (57%)
Thailand	44 (44%)	21 (43%)	65 (43%)
Asian race	101 (100%)	49 (100%)	150 (100%)
Bodyweight, kg	82·1 (16·9)	87·4 (20·0)	83·8 (18·1)
BMI, kg/m²	30·8 (4·4)	32·3 (6·4)	31·3 (5·2)
BMI category			
25 to <27 kg/m²	19 (19%)	4 (8%)	23 (15%)
27 to <30 kg/m²	26 (26%)	19 (39%)	45 (30%)
30 to <35 kg/m²	43 (43%)	13 (27%)	56 (37%)
35 to <40 kg/m²	8 (8%)	9 (18%)	17 (11%)
≥40 kg/m²	5 (5%)	4 (8%)	9 (6%)
Waist circumference, cm	96·6 (10·7)	101·1 (14·8)	98·1 (12·3)
≥85 cm in women*	64/78 (82%)	28/33 (85%)	92/111 (83%)
≥90 cm in men*	22/23 (96%)	15/16 (94%)	37/39 (95%)

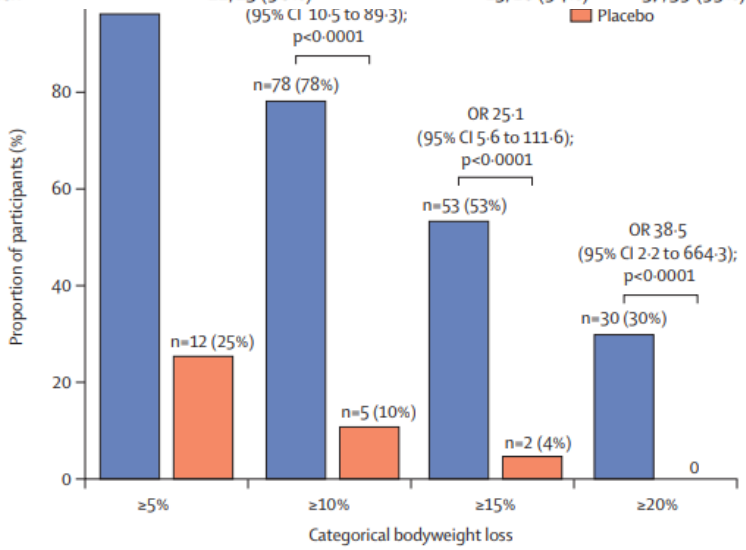
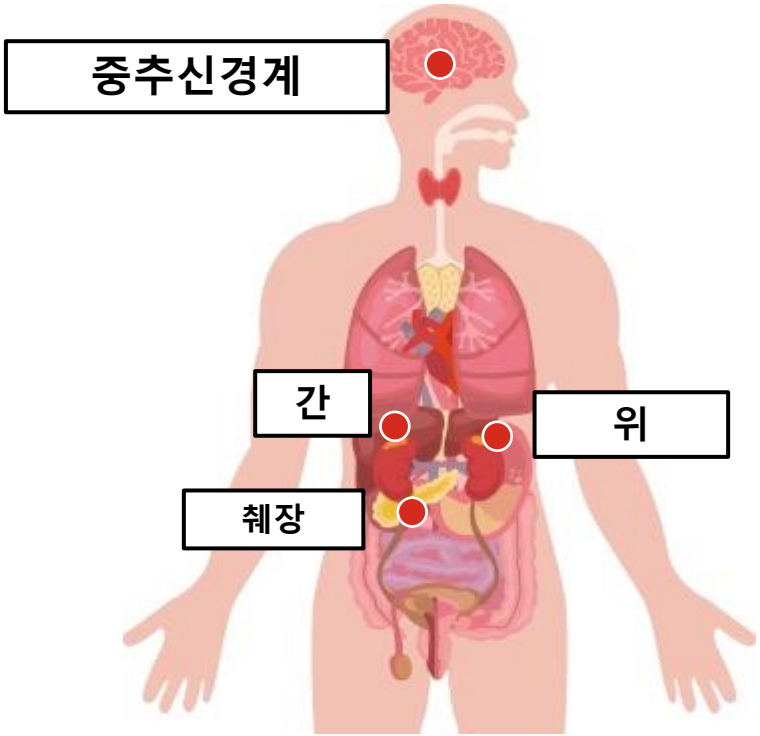


Figure 2: **Bodyweight variables from baseline to week 44**

마운자로
(Tirzepatide : GLP-1 R agonist + GIP)



중추신경계[1]
- ↓ 식욕
- ↓ 음식 섭취

간[2]
- ↓ 간 내 지방 감소

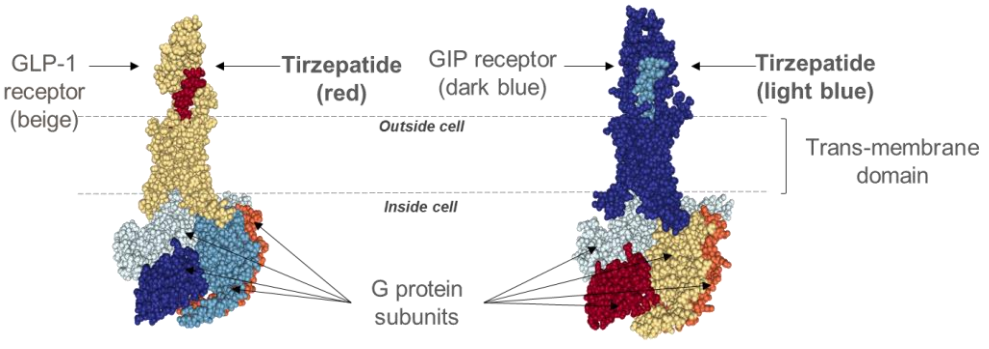
위[3]
- ↓ 위 배출

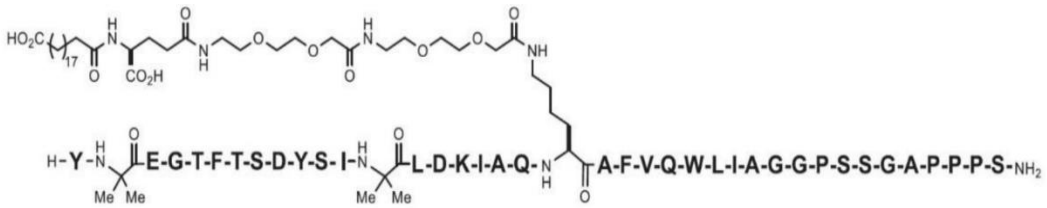
전신 작용[4]
- ↑ 인슐린 민감도

1. Heise T, et al. Oral presentation at: *ADA 2022*. Abstract 338-OR. 2. Gastaldelli A, et al. *Lancet Diabetes Endocrinol*. 2022;10(6):393-406. 3. Heise T, et al. *Lancet Diabetes Endocrinol*. 2022;10(6):418-429. 4. Samms RJ, et al. *Trends Endocrinol Metab*. 2020;31(6):410-421.

Tirzepatide: Molecular Structure and Properties

- Tirzepatide is a long-acting GIP receptor and GLP-1 receptor agonist[1]
- It is an amino acid sequence including a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life[1]
- Mean half-life of approximately **5 days** (116.7 h), enabling once-weekly dosing[1]
- Its plasma concentrations in patients with renal and hepatic impairment do not differ from those in healthy people[2]

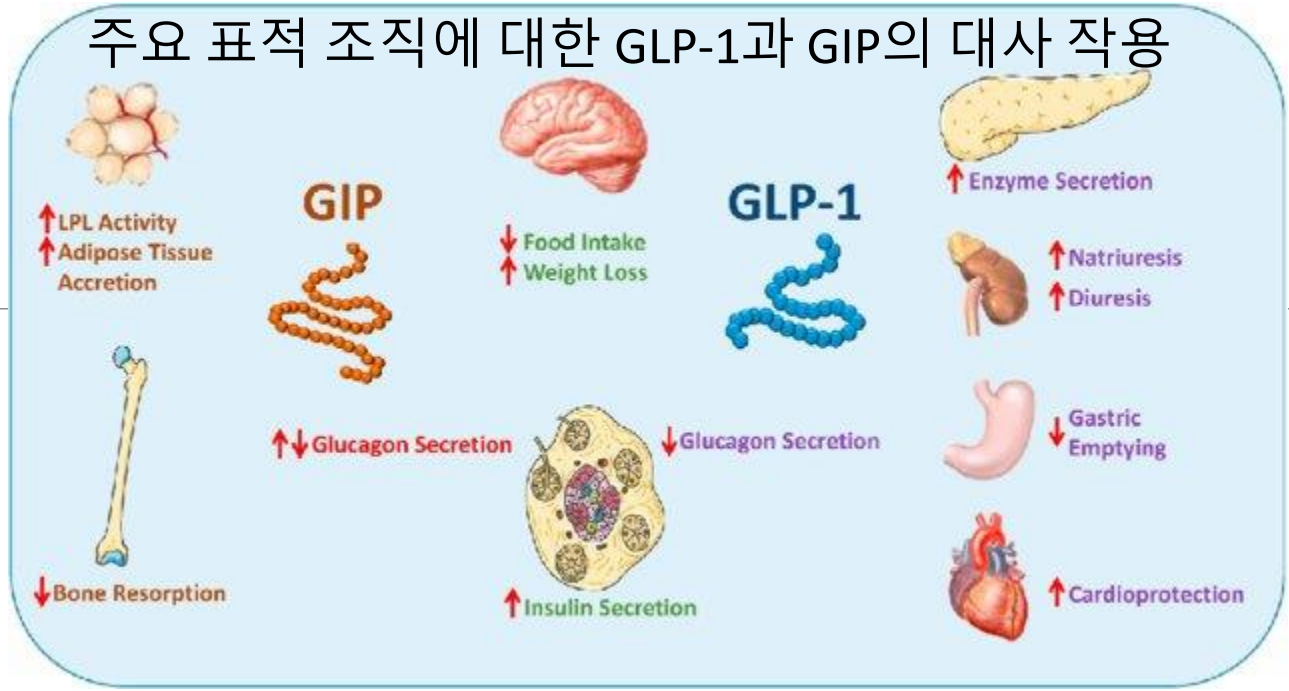


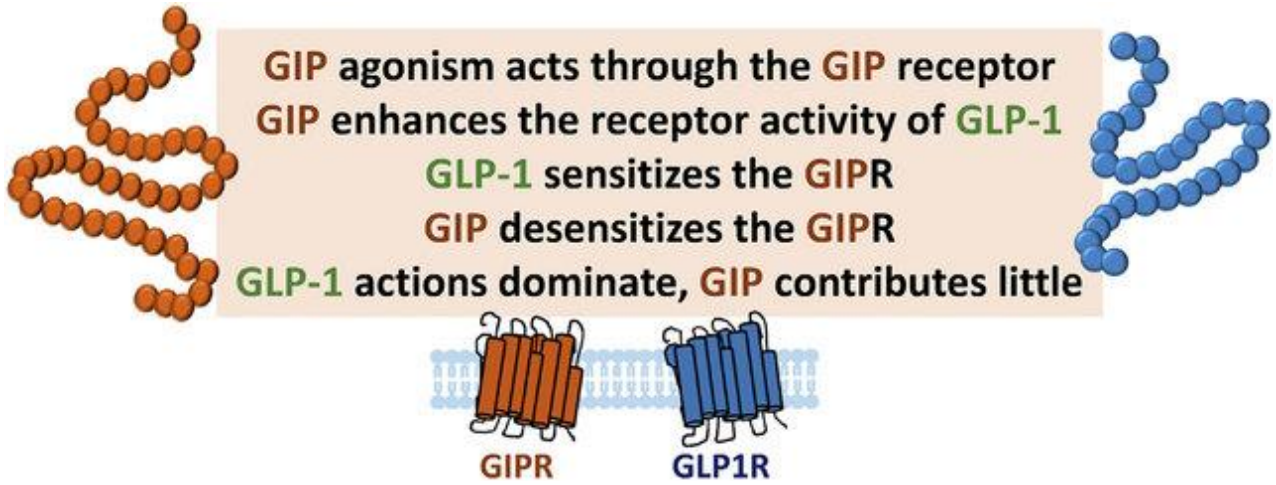


GIP=Glucose-Dependent Insulinotropic Polypeptide; GIPR=Glucose-Dependent Insulinotropic Polypeptide Receptor; GLP-1R=Glucagon-Like Peptide-1 Receptor.

1. Coskun T, et al. *Mol Metab*. 2018;18:3-14. 2. Urva S, et al. *Diabetes*. 2020;69(1):Abstract 971-P.

주요 표적 조직에 대한 GLP-1과 GIP의 대사 작용



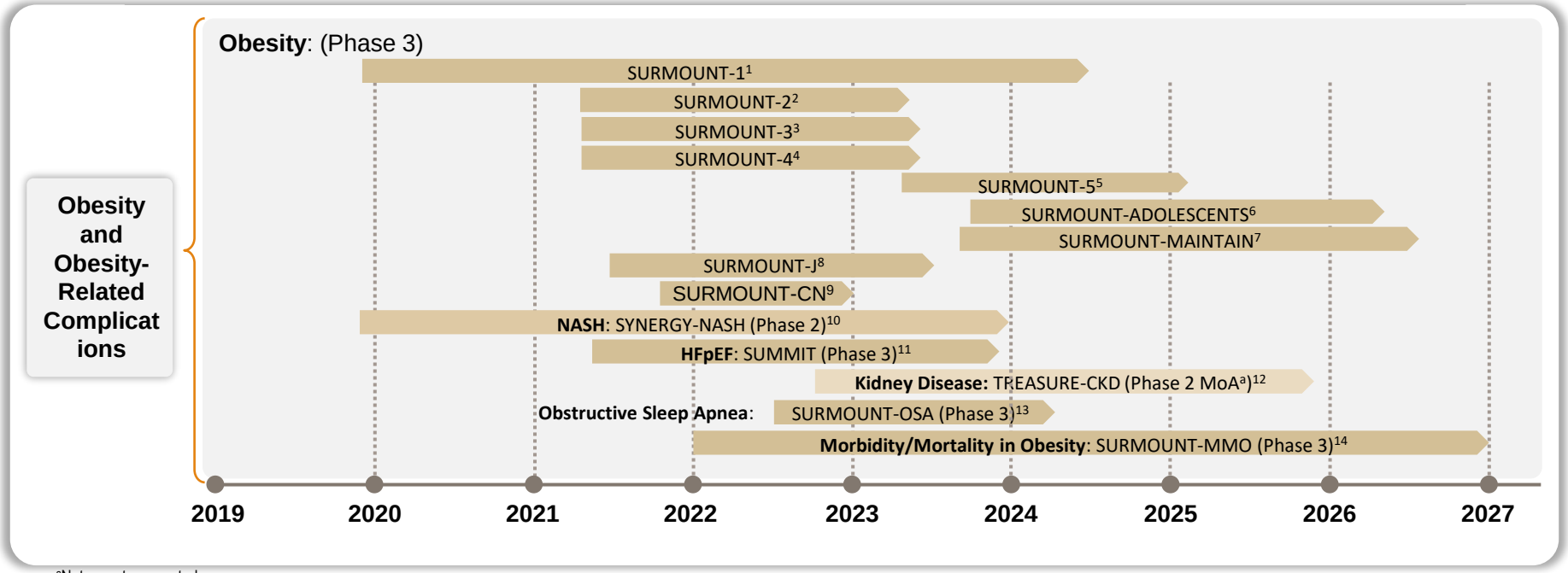


대사 장애 치료를 위한 GIP와 GLP-1 상호작용의 가능한 메커니즘

Molecular Metabolism, 2021-04-01, Volume 46, Article 101090

Tirzepatide Clinical Development Program

For Obesity and Obesity-Related Complications



[a]Not an outcomes study.

CKD=Chronic Kidney Disease; HFpEF=Heart Failure With Preserved Ejection Fraction; MMO=Morbidity/Mortality in Obesity; MoA=Mechanism of Action; NASH=Non-Alcoholic Steatohepatitis; OSA=Obstructive Sleep Apnea.

1. https://clinicaltrials.gov/ct2/show/NCT04184622 (Accessed November 12, 2023). 2. https://clinicaltrials.gov/ct2/show/NCT04657003 (Accessed November 12, 2023). 3. https://clinicaltrials.gov/ct2/show/NCT04657016 (Accessed November 12, 2023). 4. https://clinicaltrials.gov/ct2/show/NCT04660643 (Accessed November 12, 2023). 5. https://classic.clinicaltrials.gov/ct2/show/NCT05822830 (Accessed November 12, 2023). 6. https://classic.clinicaltrials.gov/ct2/show/NCT06047548 (Accessed November 12, 2023). 7. https://classic.clinicaltrials.gov/ct2/show/NCT06075667 (Accessed November 12, 2023). 8. https://www.clinicaltrials.gov/ct2/show/NCT04844918 (Accessed November 12, 2023). 9. https://www.clinicaltrials.gov/ct2/show/NCT05024032 (Accessed November 12, 2023). 10. https://clinicaltrials.gov/ct2/show/NCT04166773 (Accessed November 12, 2023). 11. https://clinicaltrials.gov/ct2/show/NCT04847557 (Accessed November 12, 2023). 12. https://clinicaltrials.gov/ct2/show/NCT05536804 (Accessed November 12, 2023). 13. https://clinicaltrials.gov/ct2/show/NCT05412004 (Accessed November 12, 2023). 14. https://clinicaltrials.gov/ct2/show/NCT05556512 (Accessed November 12, 2023).

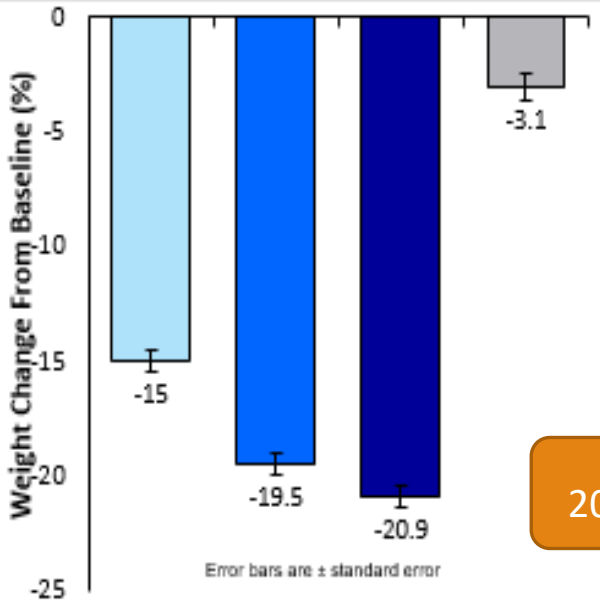
Tirzepatide의 체중 감소 효과

- **15mg 용량에서 약 21% 정도의 체중감소**

Treatment-Regimen Estimand

Tirzepatide 5 mg Tirzepatide 10 mg

	TZP 5 mg vs PBO*	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	-11.9 (-13.4, -10.4)	-16.4 (-17.9, -14.8)	-17.8 (-19.3, -16.3)
P value		<.001	

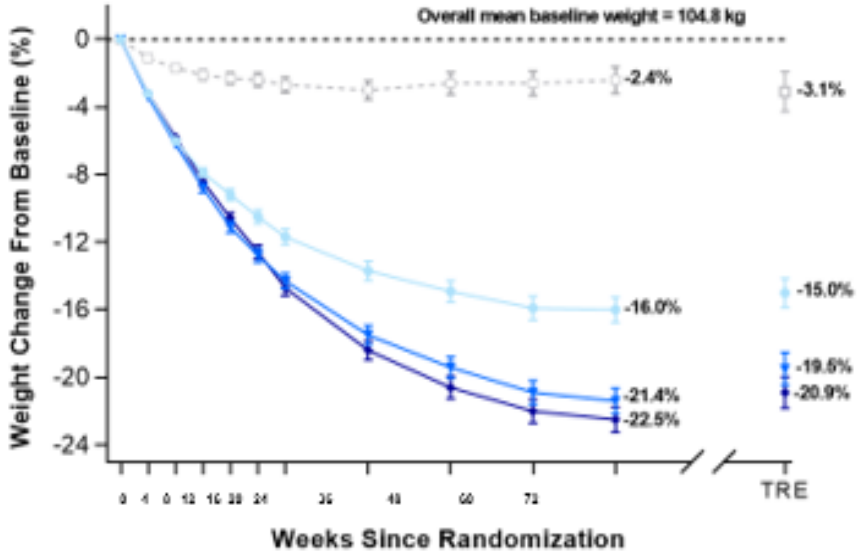


20% 감소

Efficacy Estimand

Tirzepatide 15 mg Placebo

	TZP 5 mg vs PBO*	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	-13.5 (-14.6 to -12.5)	-18.9 (-20.0, -17.8)	-20.1 (-21.2, -19.0)
P value		<.001	



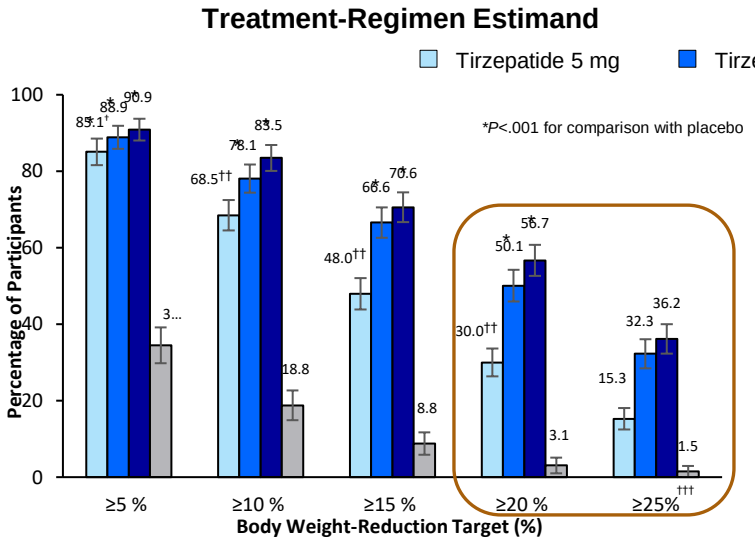
*Change in body weight in the TZP 5 mg group was not a coprimary endpoint and was analyzed as a key secondary endpoint
CI = Confidence Interval; ETD = Estimated Treatment Difference; TRE = Treatment-Regimen Estimand; TZP = Tirzepatide; PBO = Placebo.
Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

Note: Data derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand; week 72 estimates for the treatment-regimen estimand are also shown; Error bars are ± standard error

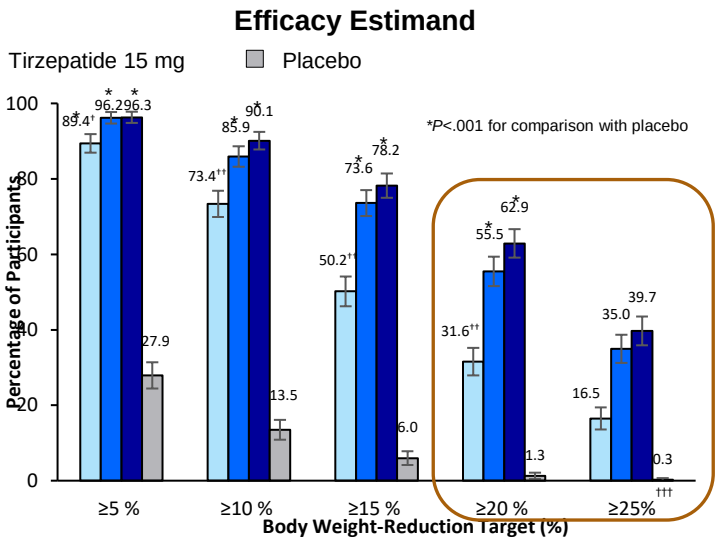
SURMOUNT-1

Percentage of Participants Achieving Body Weight Reductions Targets

- **Significantly greater proportion of participants on tirzepatide treatment achieved body weight reductions of ≥5%, ≥10%, ≥15%, and ≥20% from baseline than placebo**
- **36.2% of patients achieved pre-specified exploratory endpoint of ≥25% body weight reduction with tirzepatide 15 mg**



Note: The percentage was calculated with the use of Rubin's rules by combining the percentages of patients who met the target in imputed data sets. Missing value at week 72 was imputed using MMRM if missing was solely due to COVID-19 and using multiple imputation if missing was not due to COVID-19
Least-squares means are presented for both estimands, unless otherwise noted. Error bars indicate the 95% confidence interval



Note: The percentage of participants achieving weight loss targets was obtained by dividing the number of participants reaching respective goals at week 72 by the number of participants with baseline value and at least one non-missing postbaseline value. Missing value at week 72 was predicted from MMRM analysis. Logistic regression analysis was used for all comparisons to placebo

† The change in body weight in the tirzepatide 5-mg arm for ≥5% was analyzed as a key secondary end point; †† These were analyzed as additional secondary endpoints and not controlled for type 1 error. Hypothesis testing not conducted/*P*-value not shown
††† Participants with weight reduction ≥25% is an exploratory endpoint and not controlled for type 1 error; therefore, *P* values are not shown.

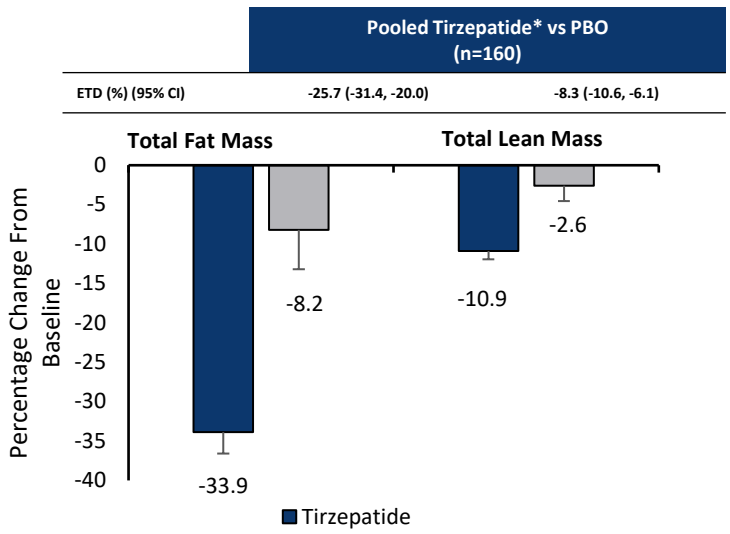
COVID-19=Coronavirus Disease 2019; MMRM = Mixed-model or Repeated-measures.

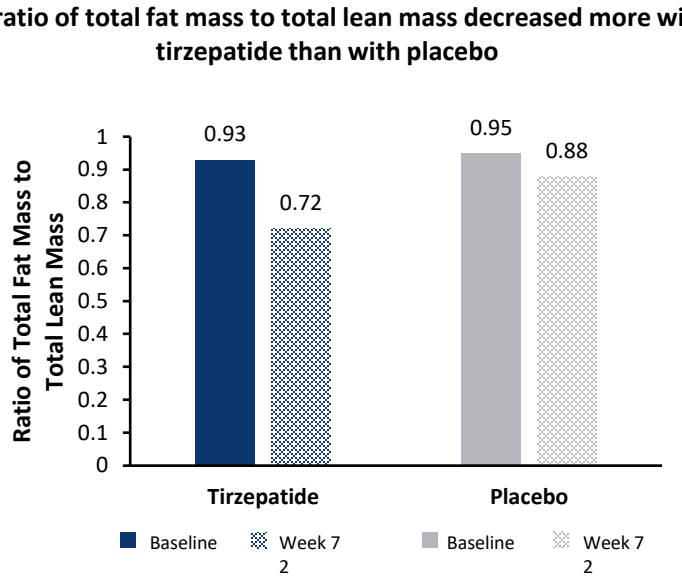
Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

Change in Body Composition

Efficacy Estimand

Treatment with tirzepatide was associated with greater improvements than placebo in total fat mass and total lean mass





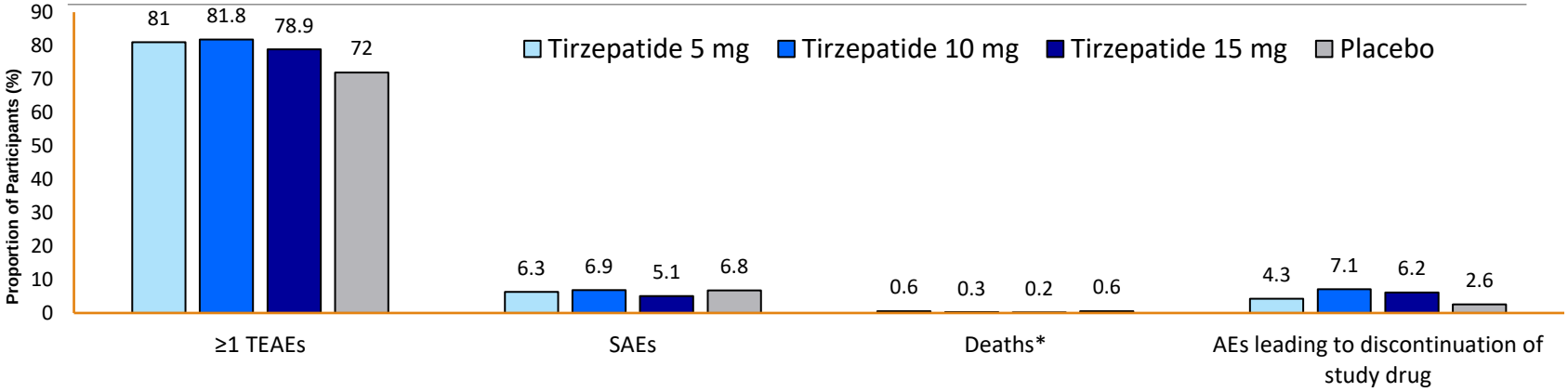
Note: Pooled tirzepatide refers to pooled tirzepatide 5 mg, 10 mg, and 15 mg groups, unless otherwise indicated.
The percentage change in total body fat mass from baseline to week 72 was assessed in a subset of participants who underwent dual-energy X-ray absorptiometry (enrolled n=255; completers with both baseline and week 72 DXA n=160).

CI = Confidence Interval; ETD = Estimated Treatment Difference; PBO = Placebo.

Jastreboff AM, et al. *New Engl. J. Med.* 2022; doi: 10.1056/NEJMoa2206038 (Online ahead of print).

SURMOUNT-1

Overview of Adverse Events



	Tirzepatide 5 mg (N=630)	Tirzepatide 10 mg (N=636)	Tirzepatide 15 mg (N=630)	Placebo (N=643)
Adverse events leading to discontinuation of study drug n (%)	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)
Nausea n (%)	6 (1.0)	7 (1.1)	12 (1.9)	2 (0.3)
Diarrhea n (%)	2 (0.3)	5 (0.8)	3 (0.5)	0
Abdominal pain n (%)	0	2 (0.3)	3 (0.5)	0
Vomiting n (%)	0	4 (0.6)	0	0
Discontinuation of study drug due to gastrointestinal events (%)	1.9	4.4	4.1	0.5

*All deaths were adjudicated by an external committee of physicians; n=4, 2, 1, 4 in tirzepatide 5 mg, 10 mg, 15 mg, and placebo groups, respectively. Three deaths in TZP arms were related to COVID-19 and also included as SAEs.

AE = Adverse Event; SAE = Serious Adverse Event; TEAE = Treatment-emergent Adverse Event; TZP = Tirzepatide.

Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

ORIGINAL ARTICLE

Tirzepatide as Compared with Semaglutide for the Treatment of Obesity

Authors: Louis J. Aronne, M.D., Deborah Bade Horn, D.O., Carel W. le Roux, M.D., Ph.D., Wayne Ho, M.D., Beverly L. Falcon, Ph.D., Elisa Gomez Valderas, M.Sc., Sagar Das, M.Sc., Clare J. Lee, M.D., M.H.S., Leonard C. Glass, M.D., Cagri Senyucel, M.D., Ph.D., and Julia P. Dunn, M.D., for the SURMOUNT-5 Trial Investigators* Author Info & Affiliations

Published May 11, 2025 | DOI: 10.1056/NEJMoa2416394 | Copyright © 2025

Tirzepatide Tops Semaglutide for Weight Loss: SURMOUNT-5

Tirzepatide slashed weight by 20%, leading researchers to call this a new "golden age" for weight-loss therapies.

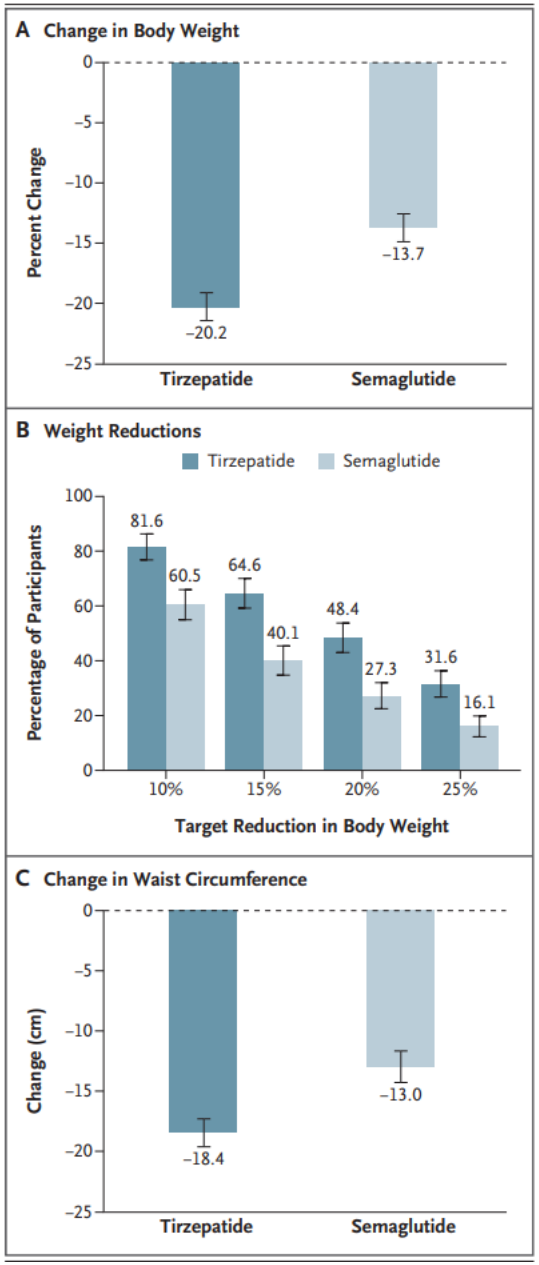
by Michael O'Riordan | MAY 12, 2025

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Tirzepatide (N=374)	Semaglutide (N=376)	Total (N=750)
Age — yr	45.0±12.9	44.4±12.7	44.7±12.8
Age categories — no. (%)			
<65 yr	342 (91.4)	349 (92.8)	691 (92.1)
≥65 yr	32 (8.6)	27 (7.2)	59 (7.9)
Female sex — no. (%)	242 (64.7)	243 (64.6)	485 (64.7)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	6 (1.6)	0	6 (0.8)
Asian	11 (2.9)	7 (1.9)	18 (2.4)
Black	77 (20.6)	67 (17.8)	144 (19.2)
White	276 (73.8)	295 (78.5)	571 (76.1)
Multiple	4 (1.1)	7 (1.9)	11 (1.5)
Hispanic or Latino	93 (24.9)	103 (27.4)	196 (26.1)
Prediabetes at randomization — no. (%)	215 (57.5)	210 (55.9)	425 (56.7)
Duration of obesity — yr	16.4±11.6	14.7±11.0	15.6±11.3
Body weight — kg	112.7±24.8	113.4±26.3	113.0±25.6
Body-mass index‡	39.4±7.4	39.4±7.7	39.4±7.6
Waist circumference — cm	117.7±16.1	118.8±17.6	118.3±16.9
Body-mass index category — no. (%)‡			
<35	115 (30.7)	118 (31.4)	233 (31.1)
≥35	259 (69.3)	258 (68.6)	517 (68.9)
Participants with multiple obesity-related complications — no. (%)§	187 (50.0)	189 (50.3)	376 (50.1)

* Plus–minus values are means ±SD.
† Race or ethnic group was reported by the participants.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Participants were considered to have multiple obesity-related complications if they had two or more complications related to obesity, including a history of conditions reported at screening.

DOI: 10.1056/NEJMoa2416394



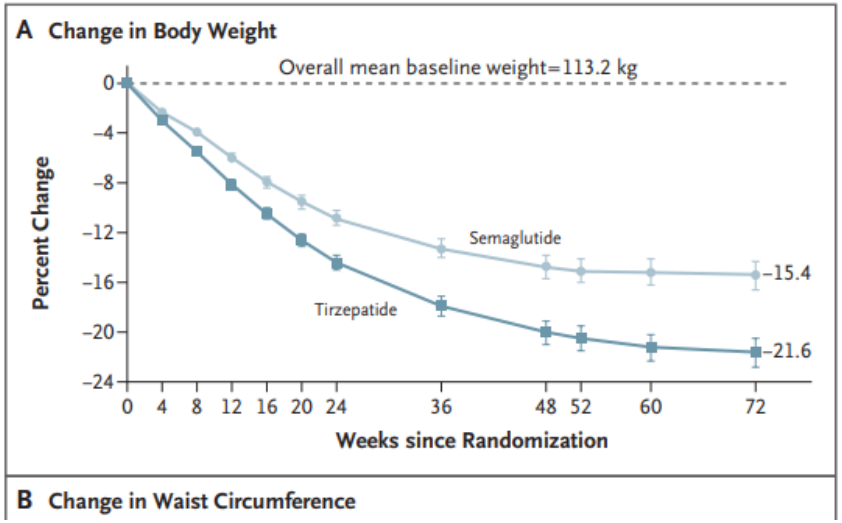


Table 2. Primary and Secondary End Points for the Modified Treatment-Regimen Estimand.

End Point	Tirzepatide (N=374)	Semaglutide (N=376)	Treatment Difference or Relative Risk (95% CI)*
Primary end point			
Least-squares mean percent change in body weight (95% CI)	−20.2 (−21.4 to −19.1)	−13.7 (−14.9 to −12.6)	−6.5 (−8.1 to −4.9)
Key secondary end points			
Least-squares mean change in waist circumference — cm	−18.4 (−19.6 to −17.2)	−13.0 (−14.3 to −11.7)	−5.4 (−7.1 to −3.6)
Weight reduction of ≥10% — no. (%)†	304 (81.6)	227 (60.5)	1.3 (1.2 to 1.5)
Weight reduction of ≥15% — no. (%)†	241 (64.6)	151 (40.1)	1.6 (1.4 to 1.9)
Weight reduction of ≥20% — no. (%)†	181 (48.4)	103 (27.3)	1.8 (1.5 to 2.2)
Weight reduction of ≥25% — no. (%)†	118 (31.6)	60 (16.1)	2.0 (1.5 to 2.6)
Additional secondary end points‡			
Weight reduction of ≥30% — no. (%)†	74 (19.7)	26 (6.9)	2.8 (1.9 to 4.3)
Least-squares mean change in body weight — kg	−22.8 (−24.1 to −21.5)	−15.0 (−16.3 to −13.7)	−7.9 (−9.7 to −6.0)
Least-squares mean change in body-mass index	−8.0 (−8.5 to −7.5)	−5.3 (−5.8 to −4.8)	−2.7 (−3.3 to −2.0)

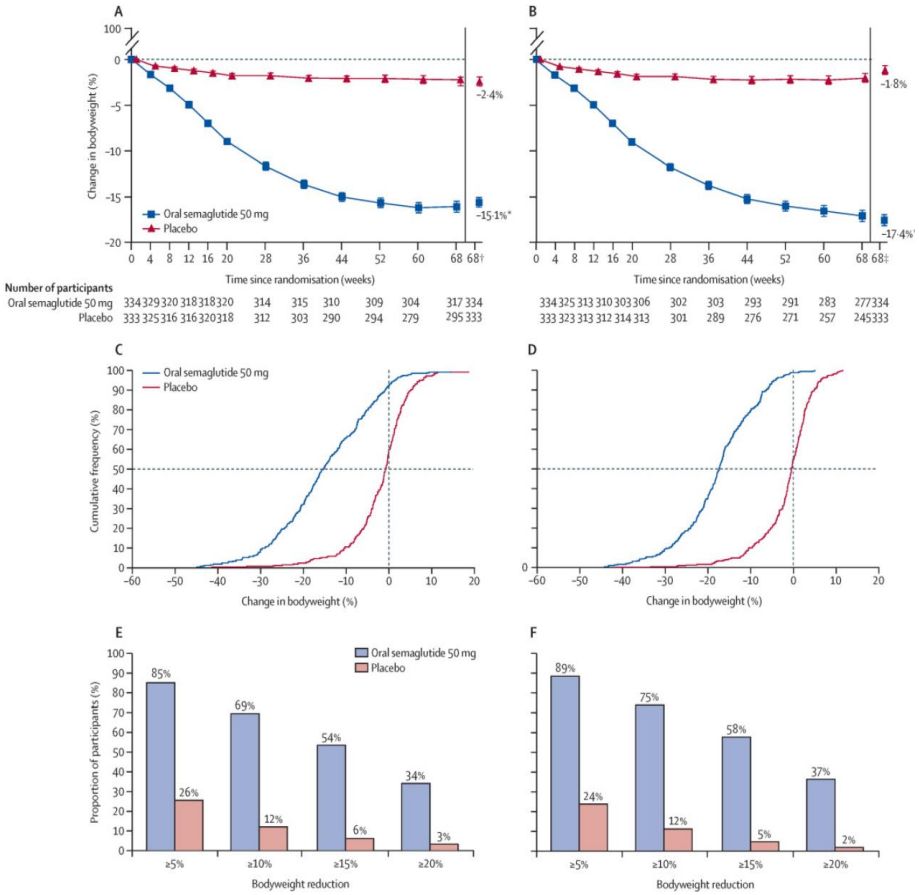
* Values are shown as the estimated percentage-point treatment difference between groups with the exception of the weight-reduction categories of at least 10%, 15%, 20%, 25%, and 30%, which are shown as the relative risk. Relative risk was calculated with the use of G-computation methods[16] on the basis of logistic regression. P<0.001 for all primary and key secondary end points.

† The number and percentage were calculated according to imputed data. The number was calculated by averaging the number of participants who achieved the target weight reduction across imputed data sets and then rounding to the integer; the percentage was calculated by combining the percentage of participants who achieved the target weight reduction in imputed data sets with the use of Rubin's rule.

‡ The confidence intervals for the additional secondary end points have not been adjusted for multiplicity and should not be used to make inferences.

DOI: 10.1056/NEJMoa2416394

GLP-1 경구용 제제의 효과는? (oral semaglutide)



- **임상 3상 연구, 667명 대상 (평균 50세)**
- **용량 (50mg) :** 3mg으로 시작 4주마다 7mg, 14mg, 25mg으로 증량, 16주차 최대 50mg(유지 용량)까지 증량
- **평균 체중: 105.4kg**
- **평균 BMI : 37.5kg/m²**
- **68주 후 체중 15.1% 감소**
- **68주 후 15% 이상 체중 감량자: 54%**
- **68주 후 BMI 5.6 감소 (비만 1단계 낮춤)**
- **68주 후 허리둘레 13.0cm 감소**

Lancet 2023; 402: 705–19

GLP-1 경구용 제제의 효과는? (oral tirzepatide)

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity

Wharton S et al. DOI: 10.1056/NEJMoa2302392

CLINICAL PROBLEM

For patients with obesity or overweight, clinical guidelines now recommend treatment with weight-management medications. Trials of injectable glucagon-like peptide-1 (GLP-1) receptor agonists have shown long-term efficacy for weight loss in this patient population. However, the injectable formulation is a disincentive for some patients. Easy-to-use, oral alternatives to currently approved injectable GLP-1 receptor agonists are of interest.

CLINICAL TRIAL

Design: A phase 2, multicenter, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of orforglipron, an oral nonpeptide GLP-1 receptor agonist, for weight reduction in adults with obesity, or with overweight plus at least one weight-related health condition, and without diabetes.

Intervention: 272 adults 18 to 75 years of age with a body-mass index (BMI) of ≥30, or with a BMI of 27 to <30 plus at least one weight-related coexisting condition (hypertension, dyslipidemia, cardiovascular disease, or obstructive sleep apnea), were assigned to receive one of four doses of orforglipron (12 mg, 24 mg, 36 mg, or 45 mg) or placebo once daily for 36 weeks. The primary end point was the percentage change from baseline in body weight at week 26.

RESULTS

Efficacy: At week 26, patients receiving orforglipron had lost approximately 9% to 13% of their body weight, whereas patients receiving placebo had lost 2%.

Safety: Gastrointestinal adverse events — including nausea, vomiting, constipation, and diarrhea — occurred more often with orforglipron than with placebo and were most commonly mild to moderate in severity.

LIMITATIONS AND REMAINING QUESTIONS

- The number of participants in each trial group was relatively small.
- The trial duration was relatively short.
- Most participants were White, which limits generalizability to other racial or ethnic groups.

Links: Full Article | NEJM Quick Take | Editorial

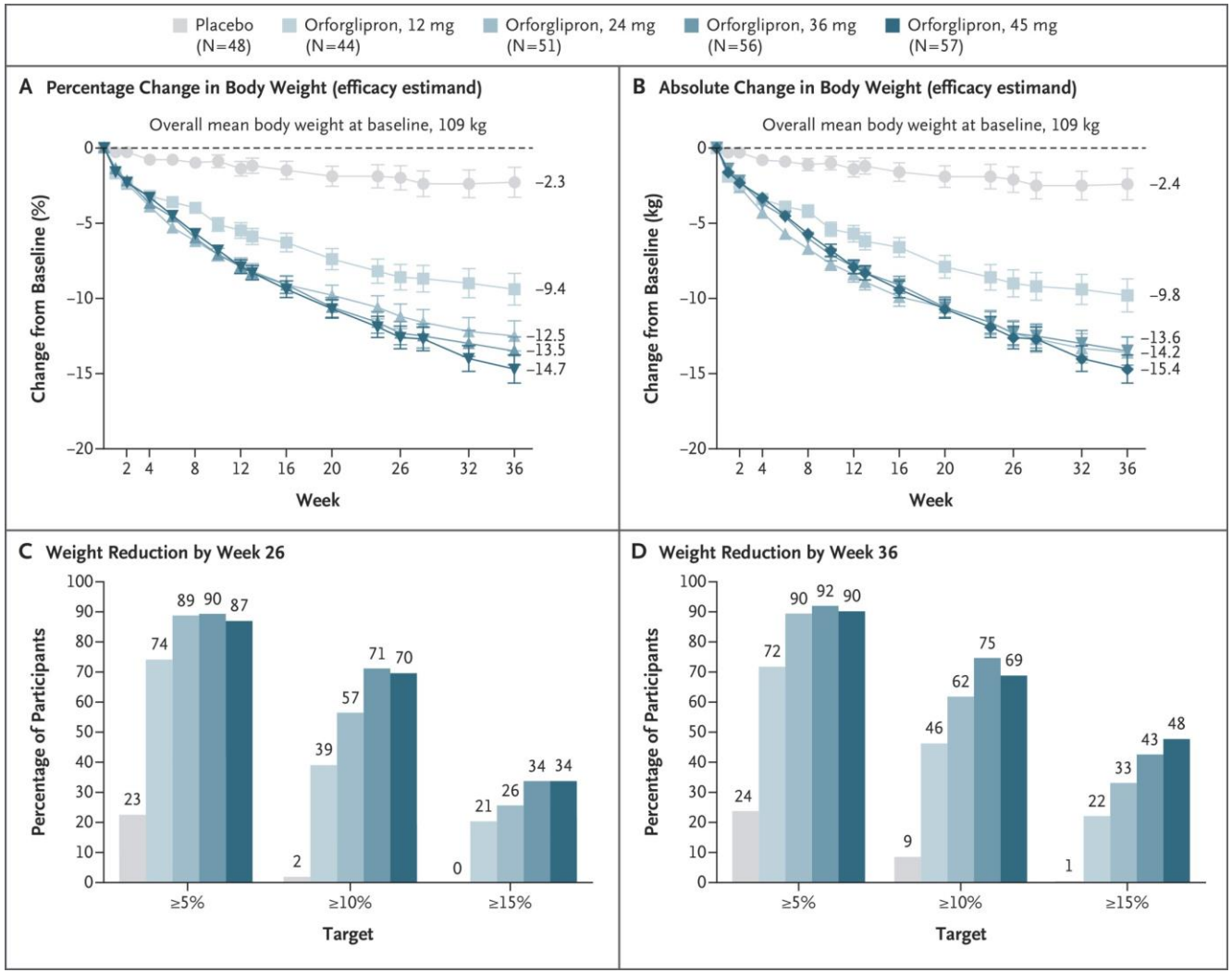
CONCLUSIONS

In patients with obesity or overweight, daily treatment with the oral GLP-1 receptor agonist orforglipron was associated with weight reduction and had a safety profile similar to that of injectable GLP-1 receptor agonists.

- 임상 2상 연구, 272명 대상 (18-75세)
- 4개 용량 (12, 24, 36, 45mg)
- 평균 체중: 108.7kg
- 평균 BMI : 37.9kg/m^2
- 36주 후 체중 14.7% 감소
- 36주 후 15% 이상 체중 감량자: 48%
- 36주 후 BMI 5.5 감소 (비만 1단계 낮춤)
- 36주 후 허리둘레 13.6cm 감소

N Engl J Med 2023;389:877-888

Change in Body Weight with Daily Oral Orforglipron versus Placebo.



N Engl J Med 2023;389:877-888

GLP-1 기반 체중 감량 시 고려할 점

- 체중 감량 이후 체중 유지 전략

- 10% 정도 감량 이후에는 체중 감량 늦추기 위해 배고픔이 증가

- 기존의 약물에 반응이 있는 사람 vs 그렇지 않은 사람

- 고비용 vs 저비용

Table 3. Studies of weight regain after GLP-1 agonist or dual GLP-1/GIP agonist discontinuation.

GLP-1 Agonist Used	Period of Agonist Treatment	Observed Weight Loss (%)	Weight Regain After Withdrawal (%)	References
Semaglutide	68 weeks 68 weeks	17.3 7.9	11.6 6.9	[244] [224]
Liraglutide	56 weeks	6.2 (after 6% loss on low-calorie diet alone)	1.9	[131]
Tirzepatide (GLP-1/GIP dual agonist)	36 weeks	20.9%	14	[243]

Abbreviations: GLP-1—glucagon-like peptide-1; GIP—glucose-dependent insulinotropic polypeptide.

J. Clin. Endocrinol. Metab. 2011, 96, E1512–E1516.

Obesity 2014 , 22 , 2563–2569.

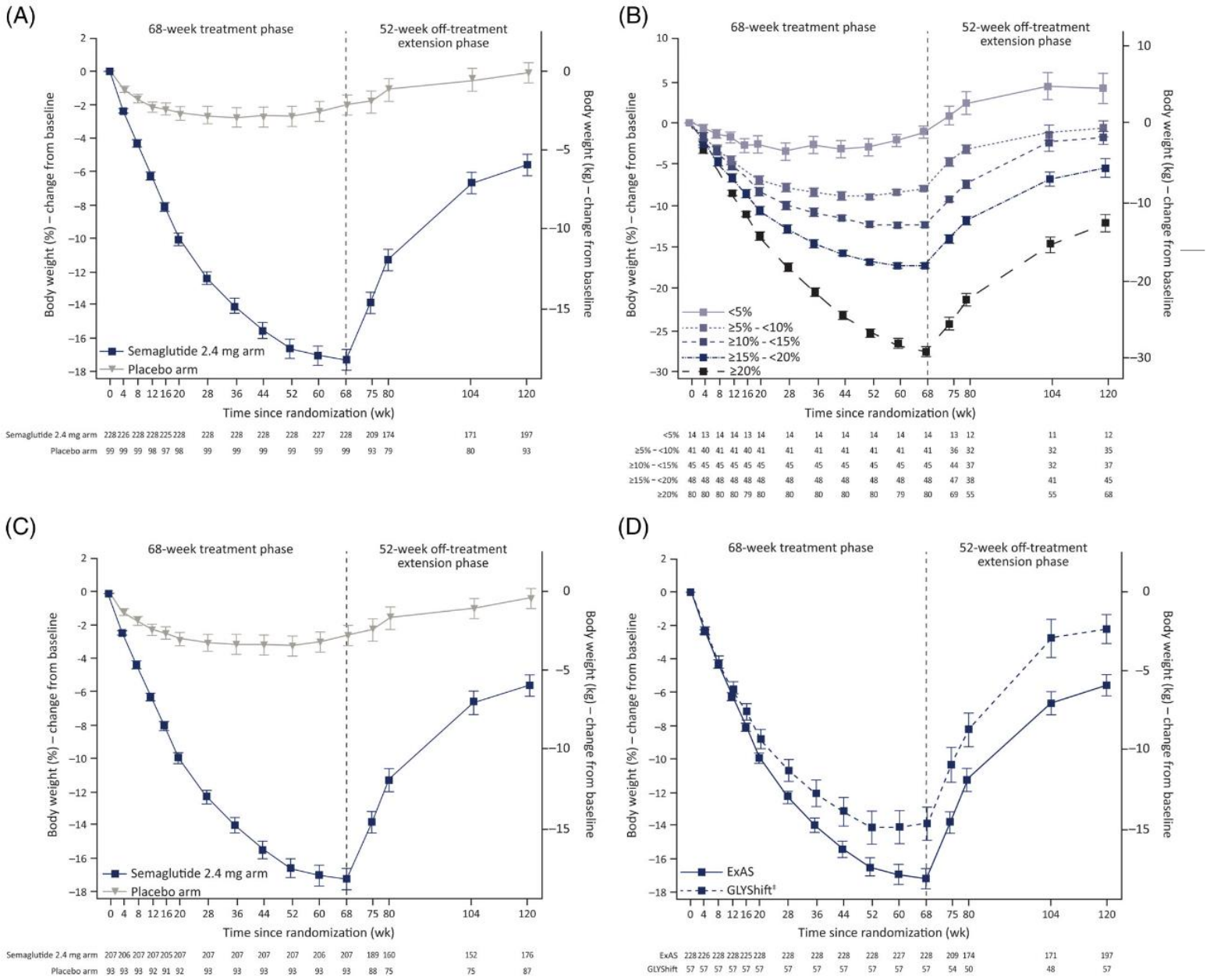
Biomolecules 2025, 15, 408

시간 경과에 따른 GLP-1a 의 효과

Table 2. GLP-1 agonist intervention and observed effects over time.

Duration of Intervention with GLP-1 Agonist (in Months)	Observed Beneficial Effects	References
BaselineStarting dose	Body adjustment, appetite reduction, decreased caloric intake	[234]
1-3 monthsStep-up dose	Weight loss, improvement in insulin sensitivity, reduction in HbA1c	[121,122,158]
3-6 monthsStep-up dose	Continued improvement in blood sugar levels, most effective weight loss, reduced risk for cardiovascular events	[121,158,224,225]
6-12 monthsStable dose	Weight loss plateau, improvement in HbA1c, further decrease in cardiovascular events	[123,158]
Beyond 12 monthsStable dose	Well-controlled HbA1c, prevention of long-term diabetes complications, weight loss maintained	[123,124,132,158]

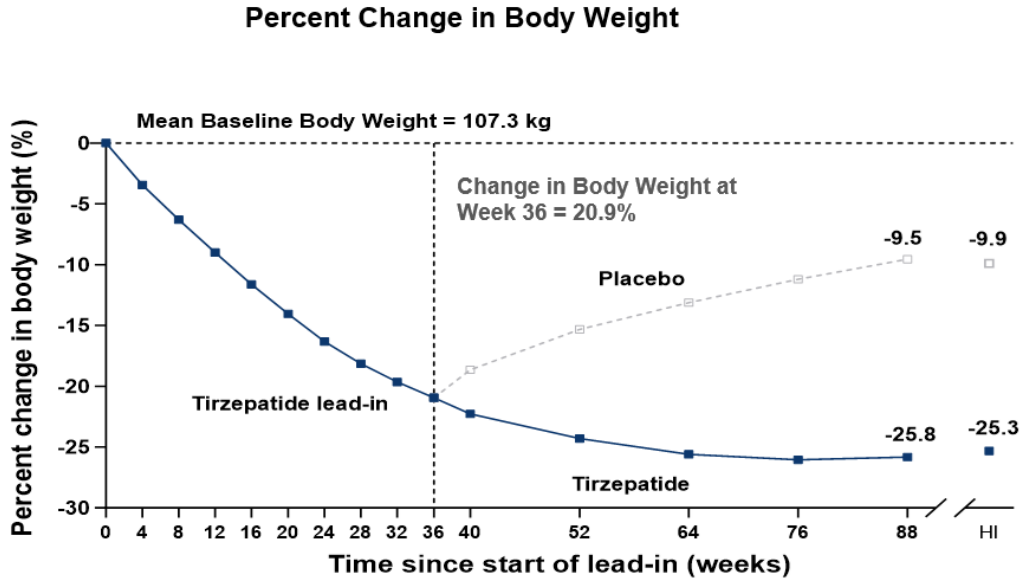
Abbreviations: GLP-1—glucagon-like peptide-1; HbA1c—hemoglobin A1c.



Diabetes Obes Metab. 2022;24:1553–1564.

SURMOUNT-4

Change in Body Weight from Week 0 to Week 88



Treatment group	Number of participants at each time point									
Tirzepatide lead-in	670	666	669	668	667	667	669	663	659	670
Tirzepatide						335	333	328	317	310
Placebo	310		335							
	289		335			335	330	317	303	292

Notes=Data are observed mean values; The dashed vertical line at week 36 represents the randomization time point; Analysis of covariance with hybrid imputation least square means at week 88 are also shown on the right; The number of participants shown denote those contributing to the mean.
H=Hybrid Imputation;
Aronne LJ, et al. JAMA. 2023;doi:10.1001/jama.2023.24945 (Ahead of print).

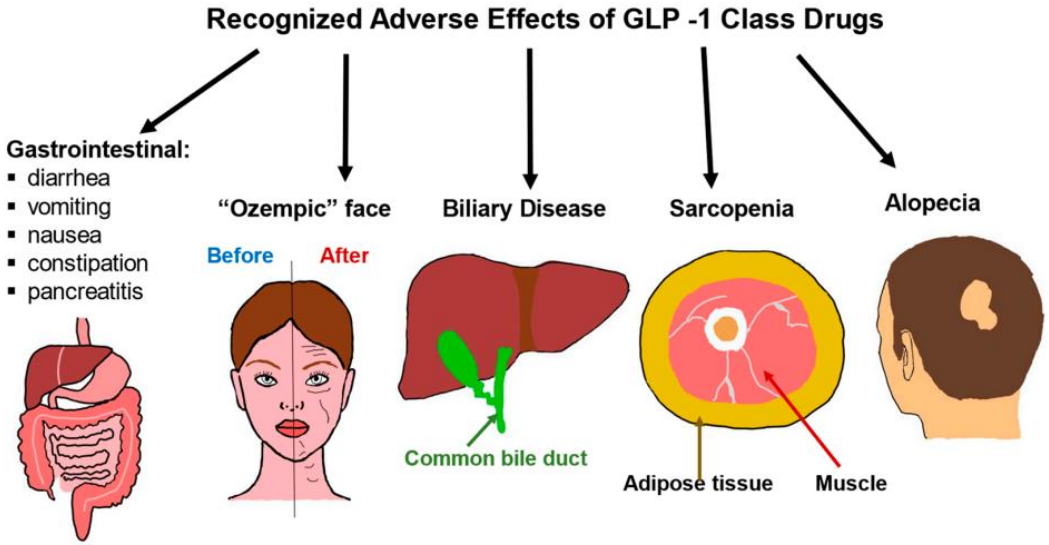


Figure 2. Adverse effects of GLP-1 class drugs. Gastrointestinal issues are common, ranging from nausea and diarrhea to rarer and more severe consequences such as pancreatitis. Rapid weight loss due to the use of GLP-1 drugs is associated with biliary disease, sarcopenia, and alopecia. Rapid weight loss can also lead to what is known as an "Ozempic face", where the cheeks become hollowed out, and wrinkles, as well as eye bags, become more pronounced.

- 비동맥염성 전방 허혈성 시신경병증(non-arteritic anterior ischemic optic neuropathy (NAION)): m/c 제2형 당뇨병 환자

Table 1. Common adverse effects of GLP-1 agonists and approaches to minimizing these consequences.

Adverse Effect	Mitigating Strategies	References
Nausea, vomiting	Gradual increase in dose, small meals, anti-emetics	[156]
Diarrhea	Hydration, low fiber foods, reduce consumption of dairy, coffee, alcohol	[156]
Constipation	Encourage physical activity, hydration, ample fiber in diet	[156]
Pancreatitis	Discontinue drug, standard treatment for pancreatitis	[156]
Alopecia	Change to a different GLP-1 medication, topical hair loss treatments	[174]
"Ozempic face"	Cosmetic procedures such as facelift, dermatologic fillers, autologous fat transfer	[177,178]
Sarcopenia	Exercise (emphasize resistance-training), increase protein intake	[171,180]
Gastroparesis with anesthesia	Discontinue at least one week prior to procedure	[158,217]

scientific reports

OPEN

The risk of depression, anxiety, and suicidal behavior in patients with obesity on glucagon like peptide-1 receptor agonist therapy

Edy Kornelius[1,2,5], Jing-Yang Huang[3], Shih-Chang Lo[2], Chien-Ning Huang[1,2,4] & Yi-Sun Yang[1,2,5]✉

This large community-based cohort study investigates the impact of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), specifically Liraglutide and Semaglutide, on the risk of developing psychiatric conditions such as depression, anxiety, and suicidal behaviors in patients with obesity. Utilizing post-marketing data, this research compares patients prescribed GLP-1 RAs (cases) with those not taking these medications (controls). The analysis spanned data from January 1, 2015, to December 31, 2023. To minimize selection bias, we employed 1:1 propensity score matching to account for demographic factors such as age, sex, race, and comorbidities. After matching, the study included 162,253 case and control patients. This study showed a significant association between GLP-1 RA treatment and an 98% increased risk of any psychiatric disorders. Notably, patients on GLP-1 RAs exhibited a 195% higher risk of major depression, a 108% increased risk for anxiety, and a 106% elevated risk for suicidal behavior. These findings underscore the critical need for physicians to thoroughly assess patient history before prescribing GLP-1 RAs and highlight the urgent requirement for further prospective clinical trials to fully understand the implications of GLP-1 RA use on mental health in the obese patient population.

Subgroup	Any psychiatric disease	Major depressive disorder	Anxiety	Suicide ideations or attempts
Sex				
Female	2.05(2.01–2.09)	3.16(2.98–3.34)	2.19(2.14–2.24)	2.53(2.32–2.76)
Male	1.77(1.72–1.83)	2.89(2.63–3.19)	1.89(1.82–1.96)	1.70(1.50–1.92)
Age				
18–49	2.01(1.96–2.07)	2.34(2.15–2.55)	2.16(2.09–2.24)	3.01(2.70–3.37)
50–69	1.78(1.73–1.83)	2.44(2.25–2.64)	1.89(1.83–1.95)	2.40(2.13–2.71)
≥70	1.71(1.61–1.82)	2.49(2.07–2.99)	1.81(1.67–1.95)	1.65(1.21–2.27)
Race				
White	1.92(1.89–1.96)	3.03(2.87–3.21)	2.03(1.99–2.08)	2.18(2.01–2.36)
Black	2.18(2.08–2.28)	2.76(2.41–3.16)	2.37(2.25–2.50)	3.45(2.86–4.17)
Asian	1.78(1.57–2.02)	1.89(1.28–2.79)	1.98(1.71–2.29)	0.87(0.49–1.54)

Table 3. Risk of psychiatric outcomes stratified by age, sex, and race.

	Adjusted HR (95% CI) GLP-1 RA compared with non-GLP1 RA			
Type of GLP-1	Any psychiatric disease	Major depressive Disorder	Anxiety	Suicide ideation or attempts
Victoza (n = 28,375)	1.65(1.59–1.72)	1.98(1.75–2.24)	1.66(1.58–1.74)	1.32(1.11–1.57)
Saxenda (n = 17,160)	1.73(1.64–1.83)	2.16(1.85–2.53)	1.66(1.55–1.78)	1.67(1.31–2.13)
Ozempic (n = 76,801)	1.72(1.67–1.76)	2.19(2.03–2.37)	1.85(1.79–1.91)	1.66(1.49–1.86)
Wegovy (n = 30,962)*	2.14(2.05–2.24)	2.22(1.94–2.54)	2.36(2.23–2.49)	2.42(1.90–3.08)

Table 4. Psychiatric outcomes in different GLP-1 RA groups. *The outcome of Wegovy was evaluated within 3 years.

JAMA Internal Medicine | Original Investigation

Psychiatric Safety of Semaglutide for Weight Management in People Without Known Major Psychopathology

Post Hoc Analysis of the STEP 1, 2, 3, and 5 Trials

Thomas A. Wadden, PhD; Gregory K. Brown, PhD; Christina Egebjerg, PhD; Ofir Frenkel, MD; Bryan Goldman, MS; Robert F. Kushner, MD; Barbara McGowan, PhD; Maria Overvad, MD; Anders Fink-Jensen, MD

IMPORTANCE Obesity is associated with numerous psychosocial complications, making psychiatric safety a consideration for treating people with obesity. Few studies have investigated the psychiatric safety of newly available antiobesity medications.

OBJECTIVE To evaluate the psychiatric safety of subcutaneous semaglutide, 2.4 mg, once weekly in people without known major psychopathology.

DESIGN, SETTING, AND PARTICIPANTS This post hoc analysis of pooled data from the randomized, double-blind, placebo-controlled, multicenter phase 3a STEP 1, 2, and 3 trials (68 weeks; 2018-2020) and phase 3b STEP 5 trial (104 weeks; 2018-2021) included adults with overweight or obesity; STEP 2 participants also had type 2 diabetes. Trial designs have been published previously.

INTERVENTIONS Semaglutide, 2.4 mg, vs placebo.

MAIN OUTCOMES AND MEASURES Depressive symptoms and suicidal ideation/behavior were assessed using the Patient Health Questionnaire (PHQ-9) and Columbia-Suicide Severity Rating Scale, respectively. Psychiatric and nervous system disorder adverse events were investigated.

RESULTS This analysis included 3377 participants in the STEP 1, 2, and 3 trials (2360 women [69.6%]; mean [SD] age, 49 [13] years) and 304 participants in STEP 5 (236 women [77.6%]; mean [SD] age, 47 [11] years). In the STEP 1, 2, and 3 trials, mean (SD) baseline PHQ-9 scores for the semaglutide, 2.4 mg, and placebo groups were 2.0 (2.3) and 1.8 (2.3), respectively, indicating no/minimal symptoms of depression. PHQ-9 scores at week 68 were 2.0 (2.9) and 2.4 (3.3), respectively; the estimated treatment difference (95% CI) between groups was −0.56 (−0.81 to −0.32) ($P < .001$). Participants treated with semaglutide vs placebo were less likely to shift (from baseline to week 68) to a more severe category of PHQ-9 depression (odds ratio, 0.63; 95% CI, 0.50-0.79; $P < .001$). Based on the Columbia-Suicide Severity Rating Scale, 1% or fewer of participants reported suicidal ideation/behavior during treatment, with no differences between semaglutide, 2.4 mg, and placebo. Psychiatric disorder adverse events were generally balanced between groups. Similar results were observed in STEP 5.

CONCLUSIONS AND RELEVANCE The results of this post hoc analysis suggest that treatment with semaglutide, 2.4 mg, did not increase the risk of developing symptoms of depression or suicidal ideation/behavior vs placebo and was associated with a small but statistically significant reduction in depressive symptoms (not considered clinically meaningful). People with obesity should be monitored for mental health concerns so they can receive appropriate support and care.

TRIAL REGISTRATION ClinicalTrials.gov Identifiers: STEP 1 (NCT03548935), 2 (NCT03552757), 3 (NCT03611582), and 5 (NCT03693430)

Editor's Note page 1312
Related article page 1301
Supplemental content

Figure. Patient Health Questionnaire 9 (PHQ-9) Scores Over Time During the STEP 1, 2, 3, and 5 Trials

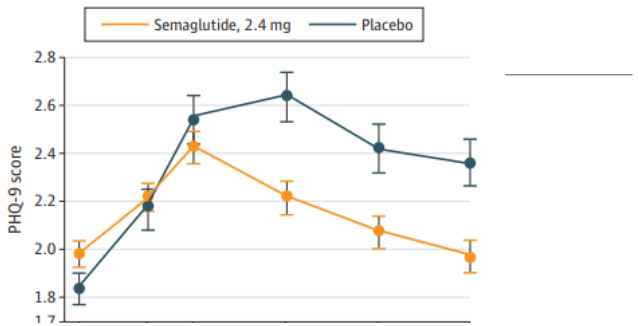


Table 2. Categorical Shift in Patient Health Questionnaire 9 (PHQ-9) Score From Baseline to End of Treatment in the STEP 1, 2, 3, and 5 Trials[a,b]

STEP 1, 2, and 3: baseline PHQ-9 category by score[c]	No. (%)	End of treatment PHQ-9 category at week 68 for semaglutide (n = 1947) or placebo (n = 1125), No. (%)				
		None (0-4)	Mild (5-9)	Moderate (10-14)	Moderately severe (15-19)	Severe (20-27)
None (0-4)						
Semaglutide	1697 (87.2)	1520 (89.6)[d]	147 (8.7)[e]	22 (1.3)[e]	5 (0.3)[e]	3 (0.2)[e]
Placebo	999 (88.8)	848 (84.9)[d]	123 (12.3)[e]	15 (1.5)[e]	11 (1.1)[e]	2 (0.2)[e]
Mild (5-9)						
Semaglutide	215 (11.0)	139 (64.7)[f]	60 (27.9)[d]	14 (6.5)[e]	1 (0.5)[e]	1 (0.5)[e]
Placebo	109 (9.7)	61 (56.0)[f]	38 (34.9)[d]	6 (5.5)[e]	3 (2.8)[e]	1 (0.9)[e]
Moderate (10-14)						
Semaglutide	26 (1.3)	11 (42.3)[f]	9 (34.6)[f]	5 (19.2)[d]	1 (3.8)[e]	0
Placebo	12 (1.1)	8 (66.7)[f]	0	4 (33.3)[d]	0	0
STEP 5: baseline PHQ-9 category by score[g]	No. (%)	End of treatment PHQ-9 category at week 104 for semaglutide (n = 141) or placebo (n = 126), No. (%)				
		None (0-4)	Mild (5-9)	Moderate (10-14)	Moderately severe (15-19)	Severe (20-27)
None (0-4)						
Semaglutide	119 (84.4)	110 (92.4)[d]	8 (6.7)[e]	1 (0.8)[e]	0	0
Placebo	113 (89.7)	97 (85.8)[d]	12 (10.6)[e]	4 (3.5)[e]	0	0
Mild (5-9)						
Semaglutide	21 (14.9)	15 (71.4)[f]	4 (19.0)[d]	1 (4.8)[e]	0	1 (4.8)[e]
Placebo	12 (9.5)	9 (75.0)[f]	2 (16.7)[d]	1 (8.3)[e]	0	0
Moderate (10-14)						
Semaglutide	1 (0.7)	1 (100)[f]	0	0	0	0
Placebo	1 (0.8)	1 (100)[f]	0	0	0	0

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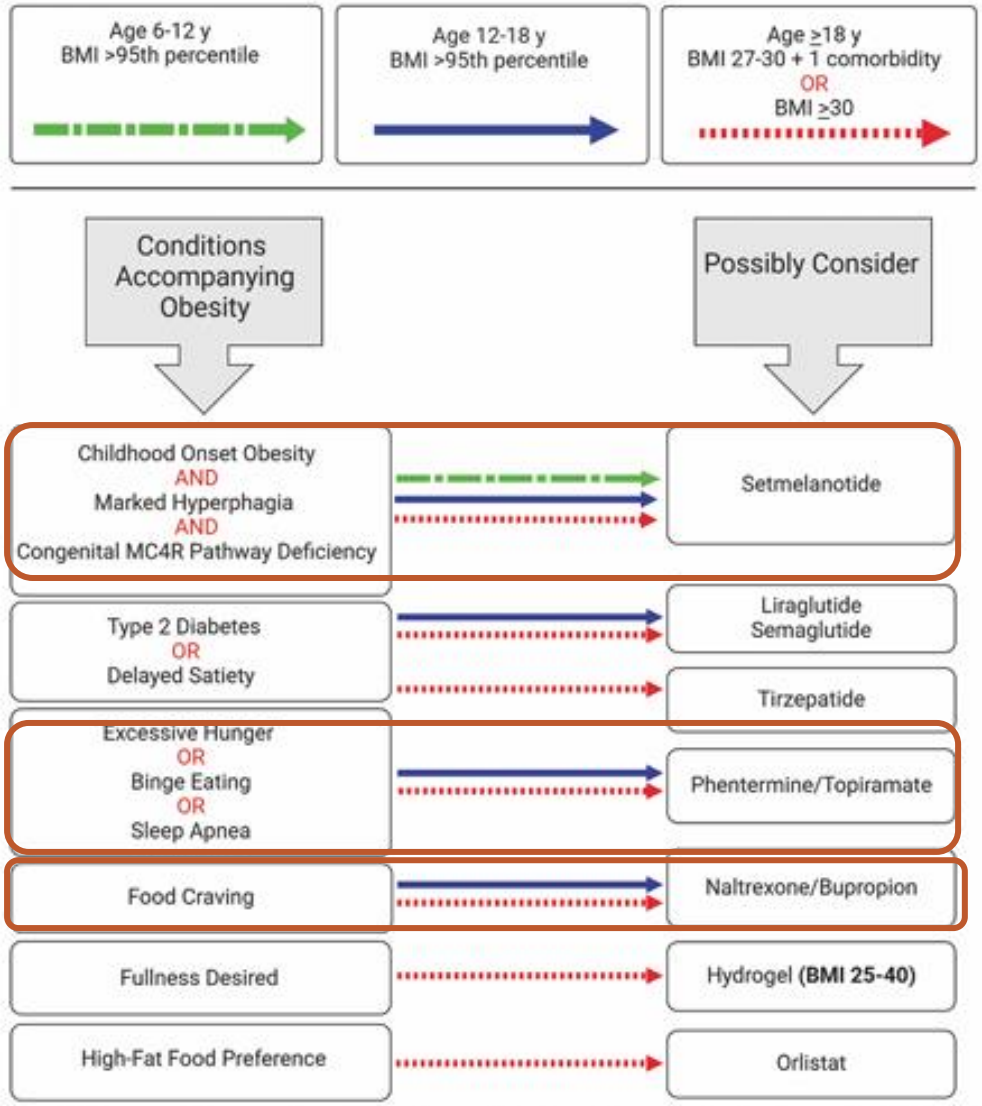


Fig. 1 Considerations for condition-specific use of anti-obesity medications. Arrow styles indicate the BMI and age groups approved for receiving obesity medications listed below.

비만 약물 처방의 우선순위

청소년
삭센다,
큐시미아,
세마글루타이드

나이

10% 미만

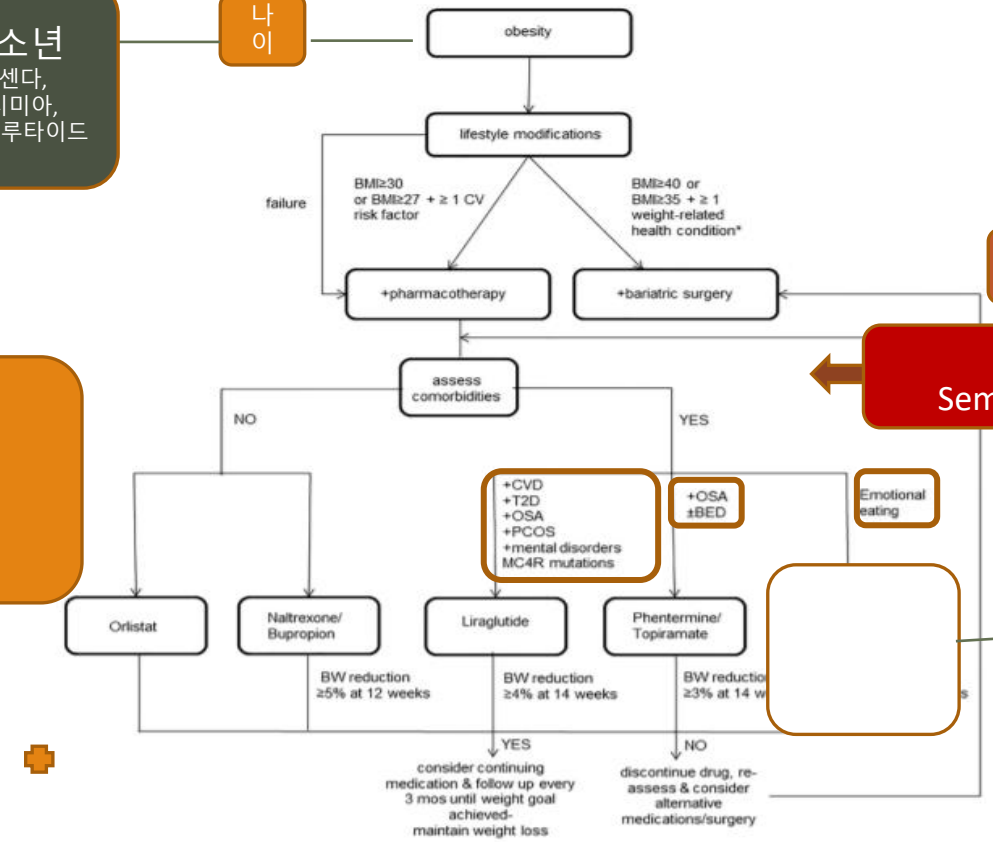
2nd line
Phentermine/Topiramate
Liraglutide
Naltrexone/Bupropion
Orlistat

10% 이상

1st line
Semaglutide or Tirzepatide

Imcivree

Orlistat



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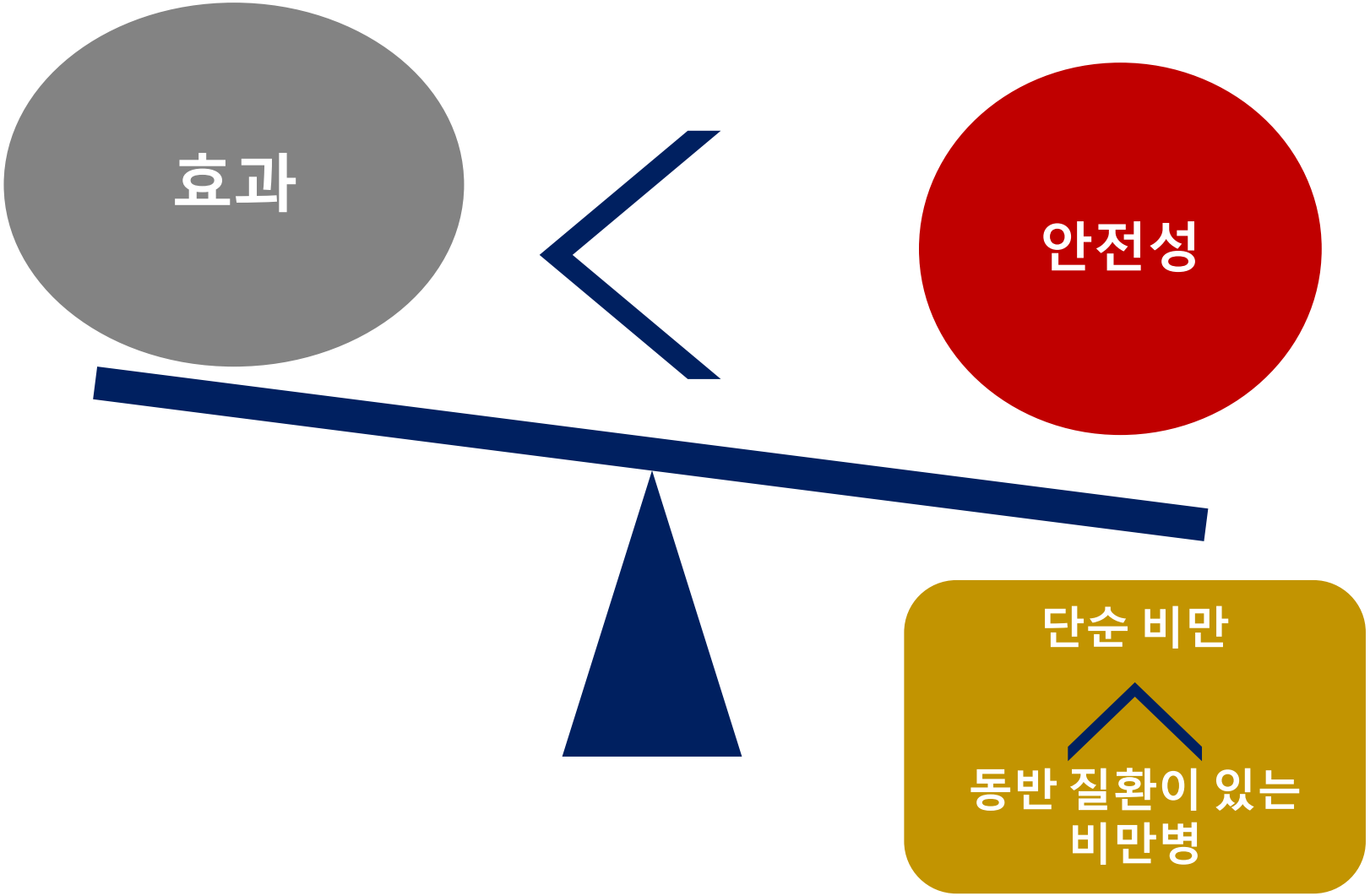

모든 비만 약물 치료는 식사와 운동을 병행해야 최고의 효과를 거둘 수 있음

맺음말

- 당분간 GLP-1 agonist를 기반으로 한 치료시장이 확대
- 더 많은 고도 비만 환자 (BMI≥ 35kg/m²) 에서 치료 효과 기대
- 단순한 체중감량 효과 보다 안전성도 주의 깊게 봐야 함
- 향후 비만 치료 약제의 방향성은 심혈관계 효과 및 장기적 사용여부, 체중 유지, 근 손실 억제가 중요한 이슈가 될 것임
- 체중을 뺀 이후 유지에 대한 치료 전략 필요
- 가격부담을 낮추고, 안전한 약물 사용을 위한 법 제정과 교육이 필요함 (보험 등 고려)

경청해 주셔서 감사합니다