Sesión bibliográfica

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14 NOVIEMBRE 2025

LA OBESIDAD ES UNA ENFERMEDAD CRÓNICA QUE REPRESENTA AMENAZAS Y OPORTUNIDADES

World Obesity: "Obesity is a chronic, relapsing, progressive disease process …need for immediate action for prevention and control of this global epidemic"[1]

AMA: "AMA recognizes obesity as a disease state with pathophysiological aspects requiring… interventions to advance obesity treatment and prevention."[2]

Canadian Medical Association: "The Canadian Medical Association (CMA) recognizes obesity as a chronic medical disease."[3]

EASO: "A progressive disease, impacting severely on individuals and society alike…"[4]

FDA: "Obesity is a chronic relapsing health risk defined by excess body fat"[5]

Royal College of Physicians: "The RCP is calling for obesity to urgently be recognised as a disease by government and the broader health sector…"[6]

Israel Medical Association: "Obesity is a recurring chronic disease due to dysfunction of physiological-genetic mechanisms and is not due to behavioral weakness"[7]

Government of Germany: "We need care for people with obesity by family doctors and specialists that is worthy of its name, first and foremost, decent outpatient treatment…"[8]

Government of Italy: "Camera dei Deputati of the Italian Parliament voted unanimously to approve a motion that recognises obesity as a chronic disease…"[9]

European Medicines Agency: "Obesity is recognised as a chronic clinical condition and is considered to be the result of interactions of genetic, metabolic, environmental and behavioral factors…"[10]

2021
EU CLASSIFIES OBESITY AS A CHRONIC DISEASE

EASO

OBESITY: THE HARD FACTS

Obesity is a chronic, relapsing, and life-long disease which needs to be approached in the same way as other chronic diseases[1]. It is therefore imperative that policies which consider not only primary prevention, but also treatment and management along the life-course are targeted as an area for immediate action and priority for research and innovation at European level.

OBESITY IS ONE OF THE LEADING CAUSES OF DEATH AND DISABILITY WORLDWIDE[2]

23% of adults were estimated to have **obesity** and **36% pre-obesity** in the European Union in 2016[3]

Obesity is the **4th** highest independent **cause of premature mortality**[3]

10-13% **of deaths** in different parts of Europe are linked to **obesity**[3]

~7% of the **national budgets across the EU** is spent on non-communicable diseases associated with **obesity** every year[4]

8.4% of OECD countries **health budget is expected to be spent on obesity and related diseases** from 2020-2050 if obesity prevalence continues at the current rate[3]

Pre-obesity (overweight) and obesity are medical conditions marked by an abnormal and/or excessive accumulation of body fat that presents a risk to health. Obesity is a chronic relapsing disease, which in turn acts as a gateway to a range of other non-communicable diseases[1], such as:

Diabetes · **Cardiovascular diseases** · **Cancer**

By approaching obesity in the same way as other non-communicable diseases, we could prevent over 230 complications of obesity and specifically other major NCDs[3], including up to:

80% of type 2 diabetes

35% of ischaemic heart disease

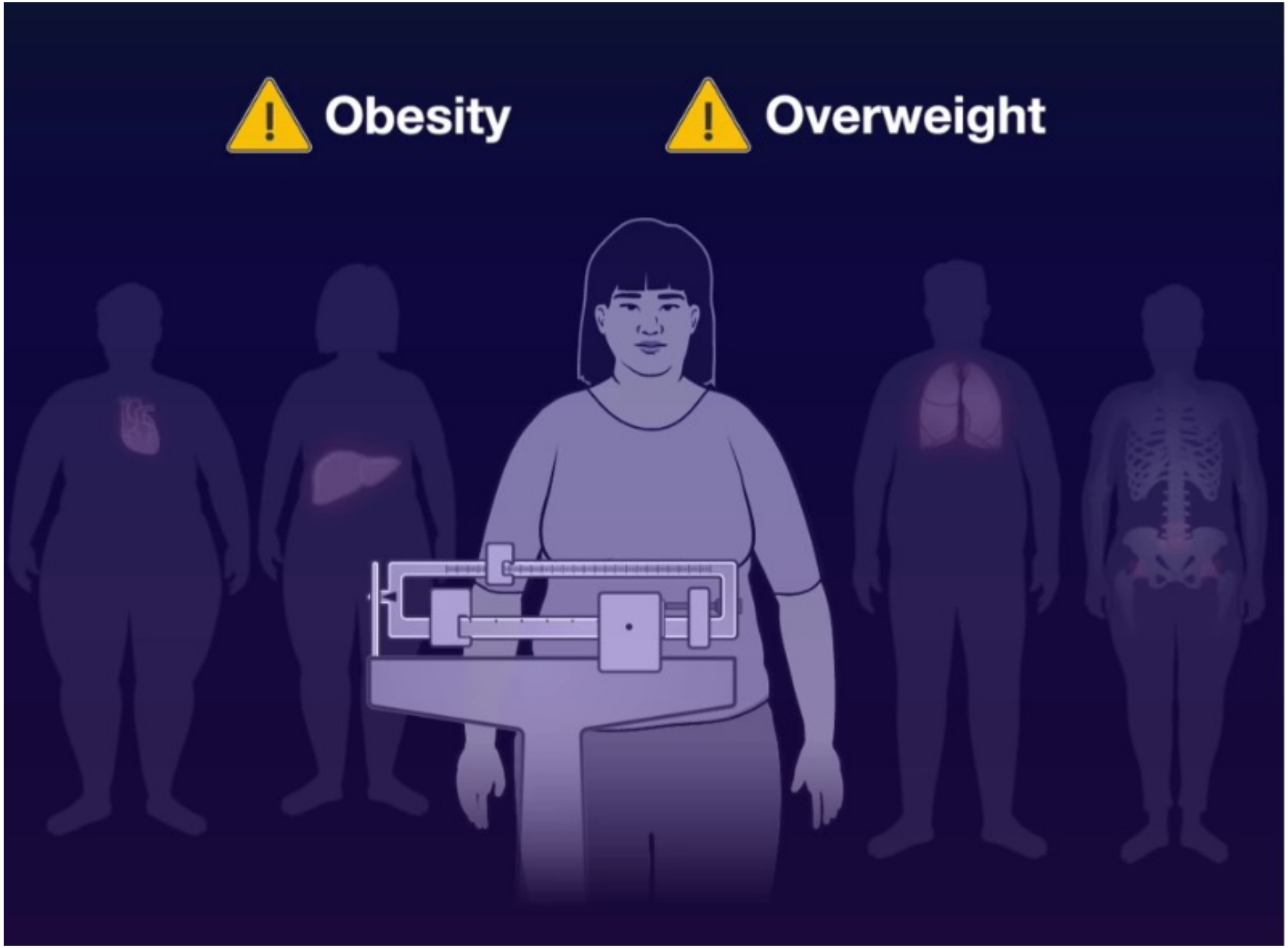
55% of hypertensive disease among adults

20% of adult cancers - including cancers of the colon, rectum, breast, endometrium, liver, kidney

In order to achieve the best possible outcomes for people living with pre-obesity and obesity we must work together to look past primary prevention, and instead consider the knock-on effects that good management and treatment could have for those currently living with obesity and prevention of complications.

Contact: Jacqueline Bowman-Busato, EASO Policy Lead, jbowman@easo.org | easo.org | @EASOobesity

EASO
European Association for the Study of Obesity


Obesity
Overweight

Crisis de salud pública a nivel mundial

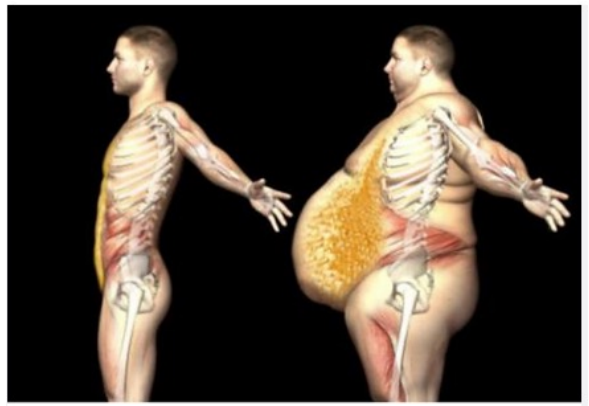
Magnitud del Problema

650 M.

Adultos con obesidad

340M.

Niños y adolescentes con sobrepeso u obesidad

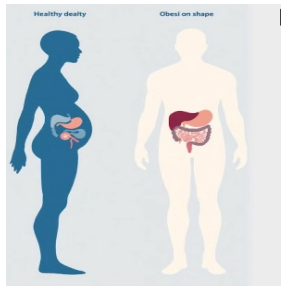


Sobrepeso y obesidad

- Más de **4 mil millones** de personas afectadas en 2035.
- Un incremento del **38%** al **50%** de la población mundial.

Obesidad

- Prevalencia aumentará del **14%** al **24%** en 2035.
- Impacto en casi **2 mil millones** de personas.



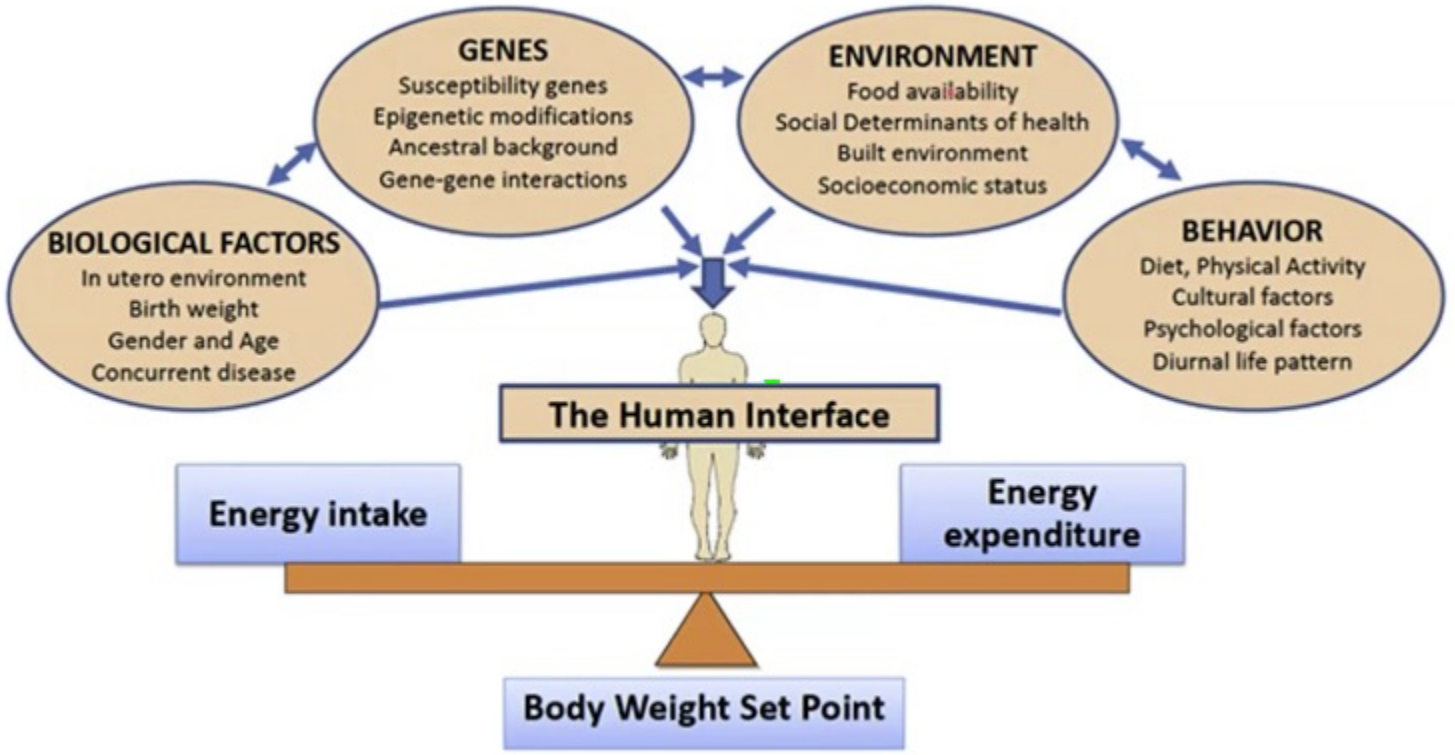
Estimación de costes

2,9 billones de euros anuales para 2030

Impacto a largo plazo

Más de 18 billones para 2060

ETIOPATOGENIA MULTIFACTORIAL DE LA OBESIDAD



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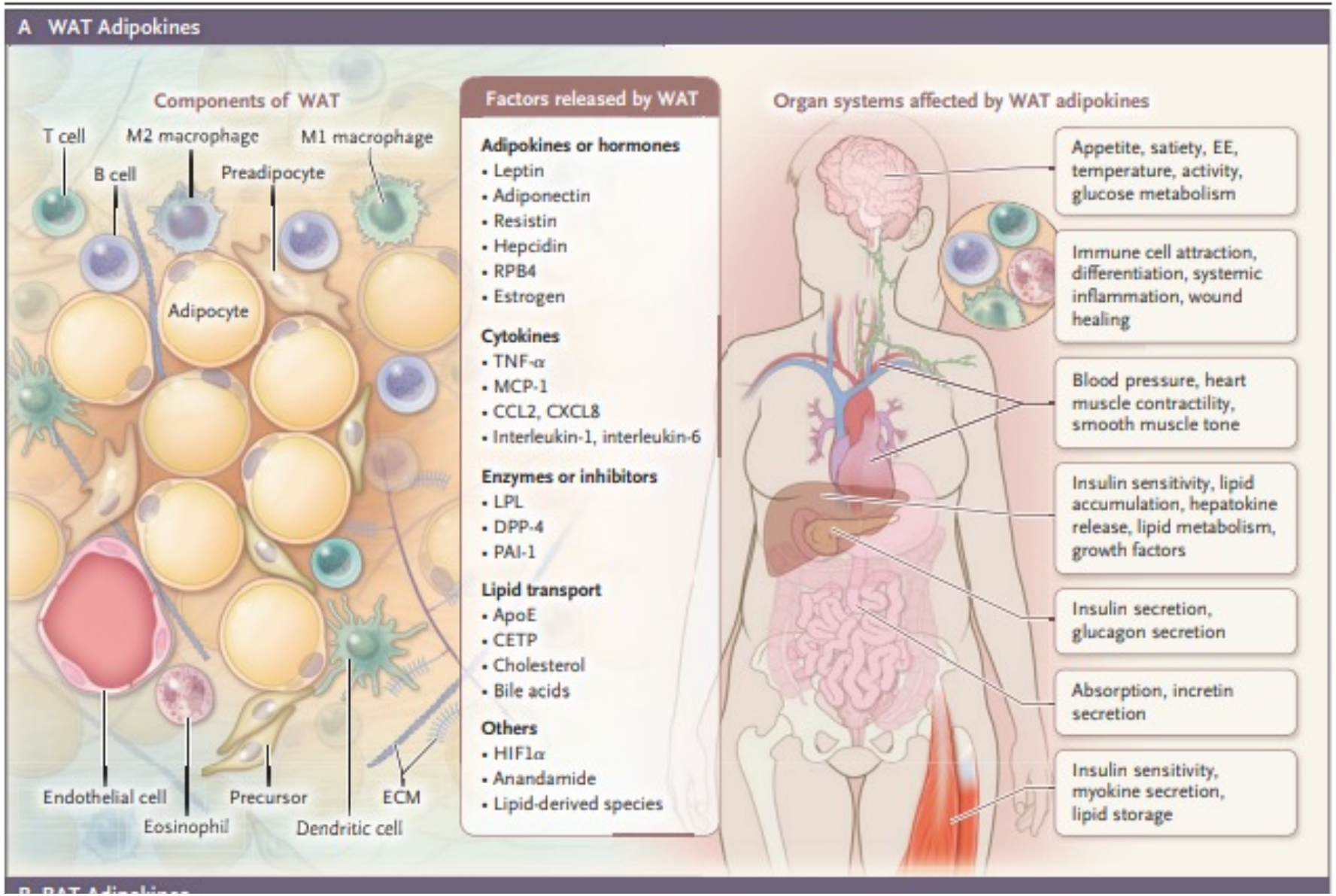
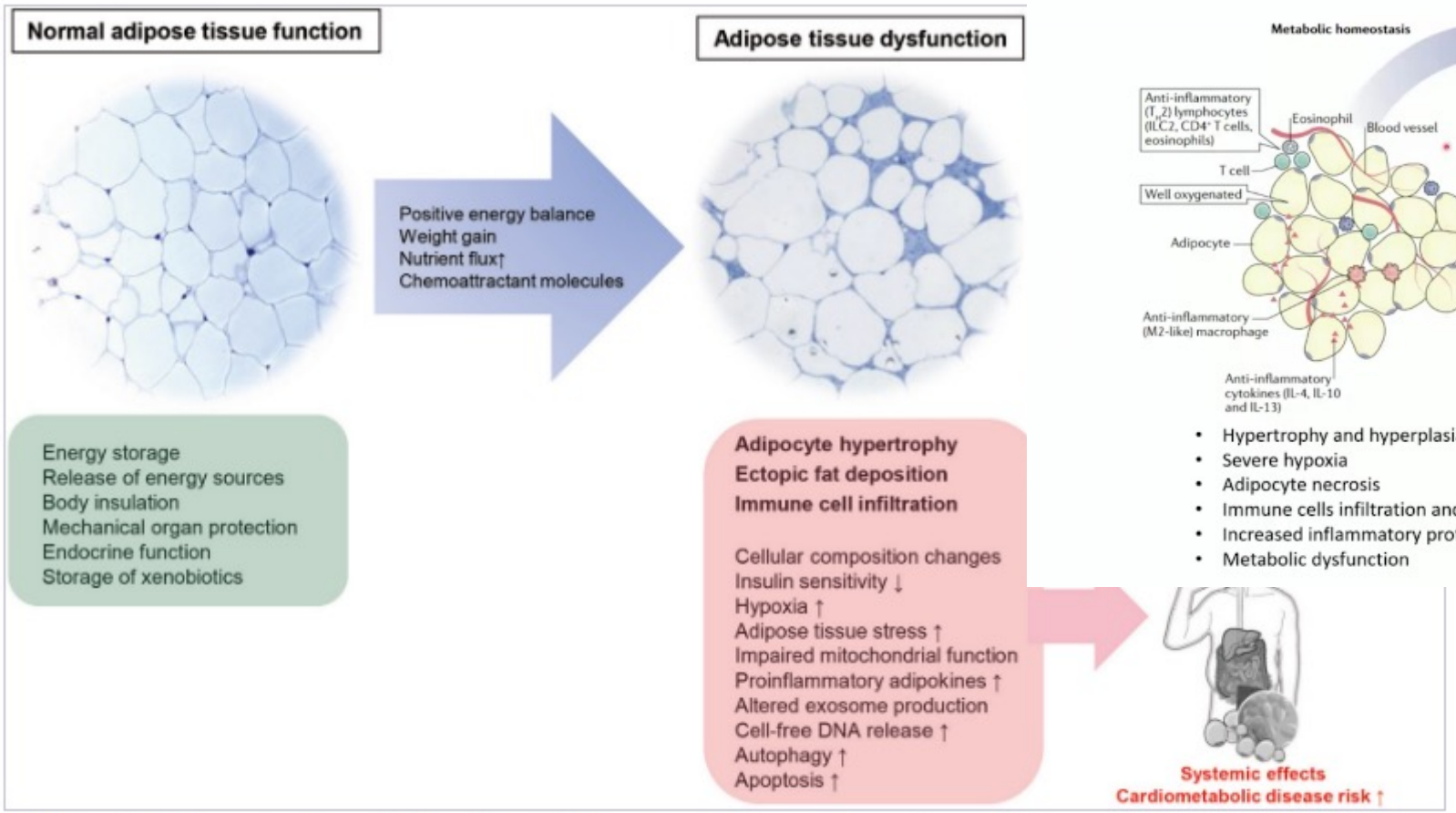


EL TEJIDO ADIPOSO ES UN ORGANO ENDOCRINO

N Engl J Med 2022;386:768-79.

DISFUNCIÓN DEL TEJIDO ADIPOSO



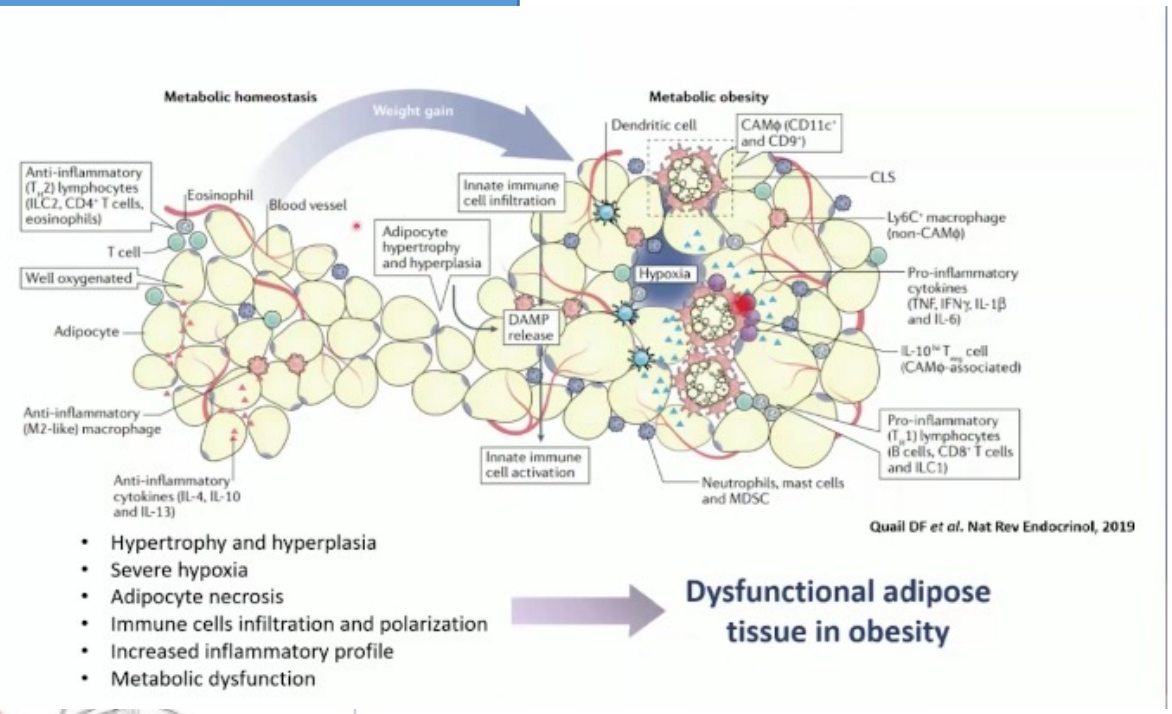
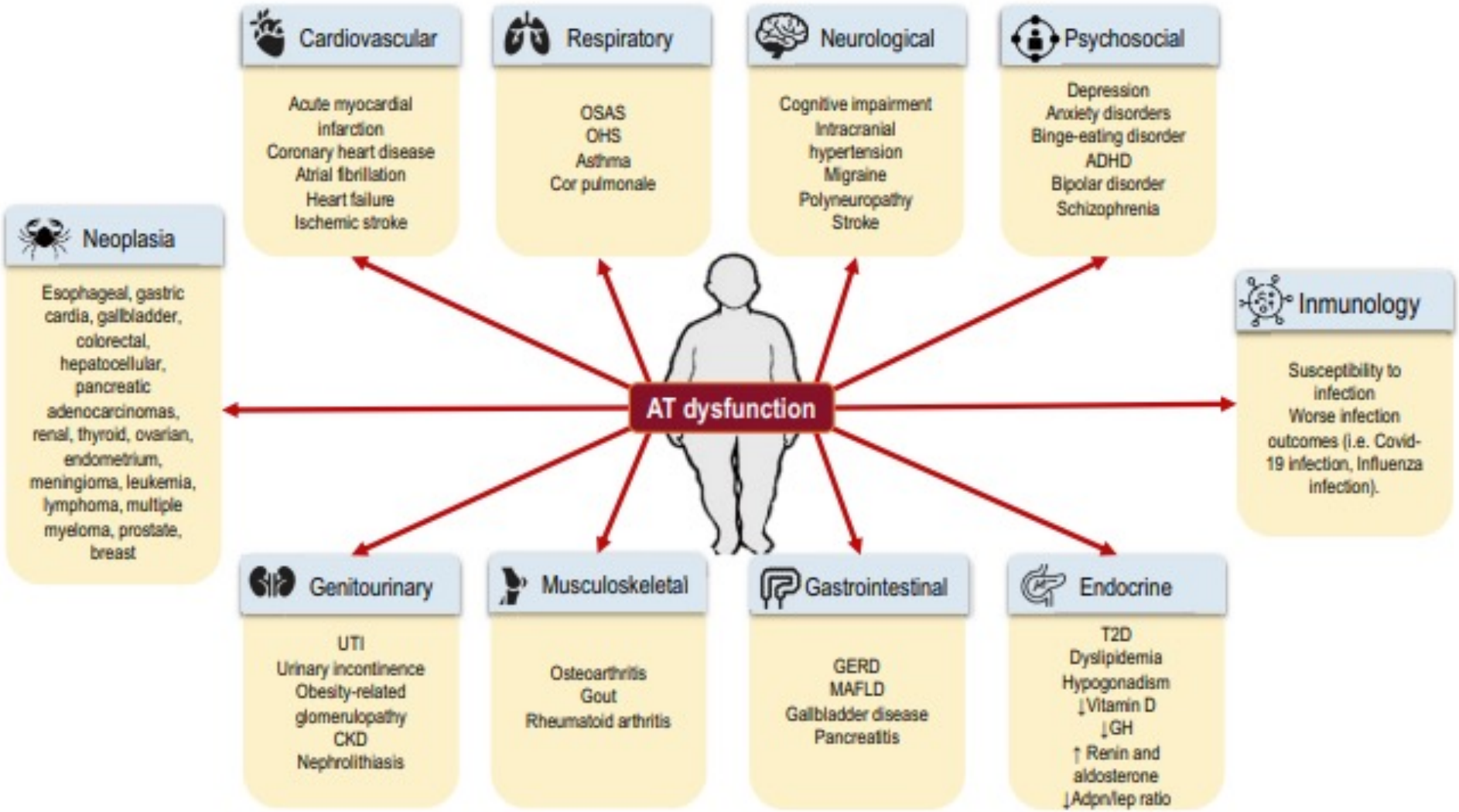


Fig 2. Transition from normal to impaired adipose tissue (AT) function and adverse systemic outcomes. AT serves important functions including

J Obes Metab Syndr 2024; 33(4): 275-288

Disfunción del tejido adiposo y complicaciones ABCD (Adiposity-Based Chronic Disease)



ABCD en la base del síndrome CKM

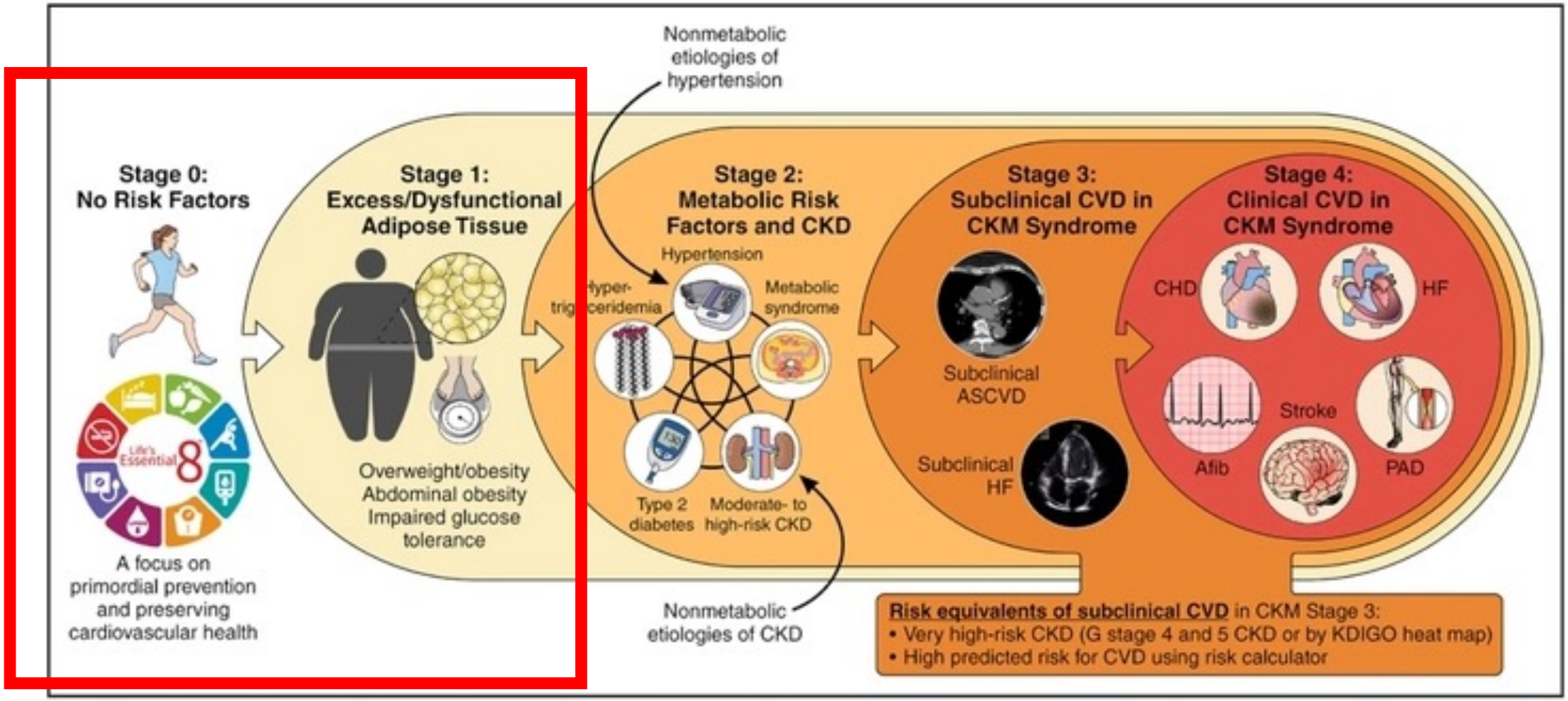


Figura 1 : *Estadios del síndrome cardio-renal-metabólico CRM (AHA)[1].*

Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association

Stages 1–3: Patient With CKM Syndrome at Risk for CVD

Promotion of cardiovascular health with an emphasis on Life's Essential 8 framework: eat better, be more active, quit tobacco, get healthy sleep, manage weight, control cholesterol, manage blood sugar, manage blood pressure

Systematic screening for SDOH using validated tools; incorporation of community health workers and care navigators into the care team; leveraging existing community resources and community programs

Interdisciplinary care – Use of CKM coordinator and interdisciplinary team; targeted referrals of high-risk CKM patients to subspecialists

Stage 1: Excess or Dysfunctional Adiposity

Discuss weight loss using STOP obesity alliance toolkit

Can consider **weight loss support via integrated team** to facilitate lifestyle change/ navigate weight loss options (obesity medicine, metabolic surgery, dietician, pharmacy, mental health, CHW/care manager):

- Intensive lifestyle intervention
- Pharmacotherapies (BMI ≥30 kg/m² without comorbidities)
- Bariatric surgery (BMI ≥40 kg/m² without comorbidities)

If persistent/progressive IGT despite intensive lifestyle modification → **consider metformin**

Stage 2: Established CKM Risk Factors

Presence of metabolic syndrome triggers intensive lifestyle intervention targeting multifactorial risk control

Pharmacotherapy for comprehensive control of residually uncontrolled MetS components

Hypertriglyceridemia
- Lifestyle modification
- Maximize statin therapy in intermediate or higher ASCVD risk
- TG ≥500 mg/dL → fibrates
- TG: 135-499 mg/dL + diabetes + additional risk factors → consider eicosapentaenoic acid (EPA)

Hypertension
- Lifestyle modification
- Follow established hypertension guidelines to achieve BP <130/80 mmHg
- In those with diabetes and albuminuria → prioritize ACEi/ARB
- In those with CKD → prioritize ACEi/ARB

Moderate- to High-Risk Chronic Kidney Disease*
- With albuminuria (UACR >30 mg/g) → ACEi/ARB
- CKD (with or without diabetes) → SGLT2i†
- DKD with residual albuminuria (>30 mg/g) on ACEi/ARB → finerenone‡ (can be used on background SGLT2i)

Diabetes
- Lifestyle modification
- Moderate-to-high intensity statin
- Ezetimibe for high risk

Comorbidity-based approach to antihyperglycemic pharmacotherapy:
- BMI ≥35 kg/m² → GLP-1RA
- HbA1c ≥9% or high insulin dose → GLP-1RA
- CKD → SGLT2i†

Considerations for Metformin Co-Utilization

HbA1c ≥7.5% or on insulin → Co-utilization of metformin§ and cardioprotective antihyperglycemics

HbA1c <7.5% → Cardioprotective antihyperglycemics without metformin initiation (continue metformin§ if already using)

Stage 3: Subclinical CVD in CKM Syndrome

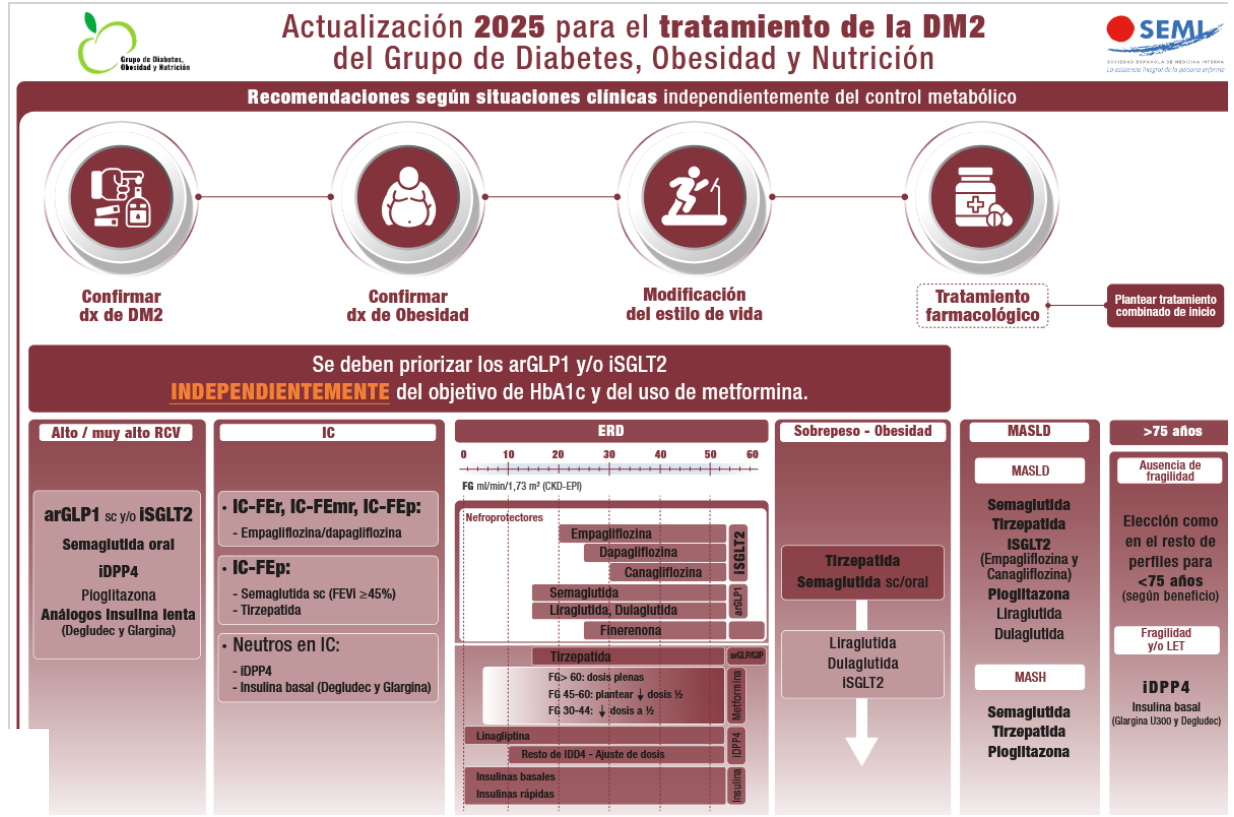
Subclinical Atherosclerosis

CAC >0
- Favors statin use in intermediate risk

CAC >100
- Favors aspirin use if low bleeding risk
- Favors considering other agents for ASCVD risk reduction (eg, PCSK9i, GLP-1RA, icosapent ethyl) based on CKM profile

Subclinical Heart Failure
- EF <40% → ACEi/ARB, ß-blocker
- In diabetes → SGLT2i†

CVD Risk Equivalents for Stage 3 CKM:
- Very high-risk CKD*
- High predicted CVD risk per risk calculator



Guía Española GIRO

Guía española del manejo Integral y multidisciplinaR de la Obesidad en personas adultas

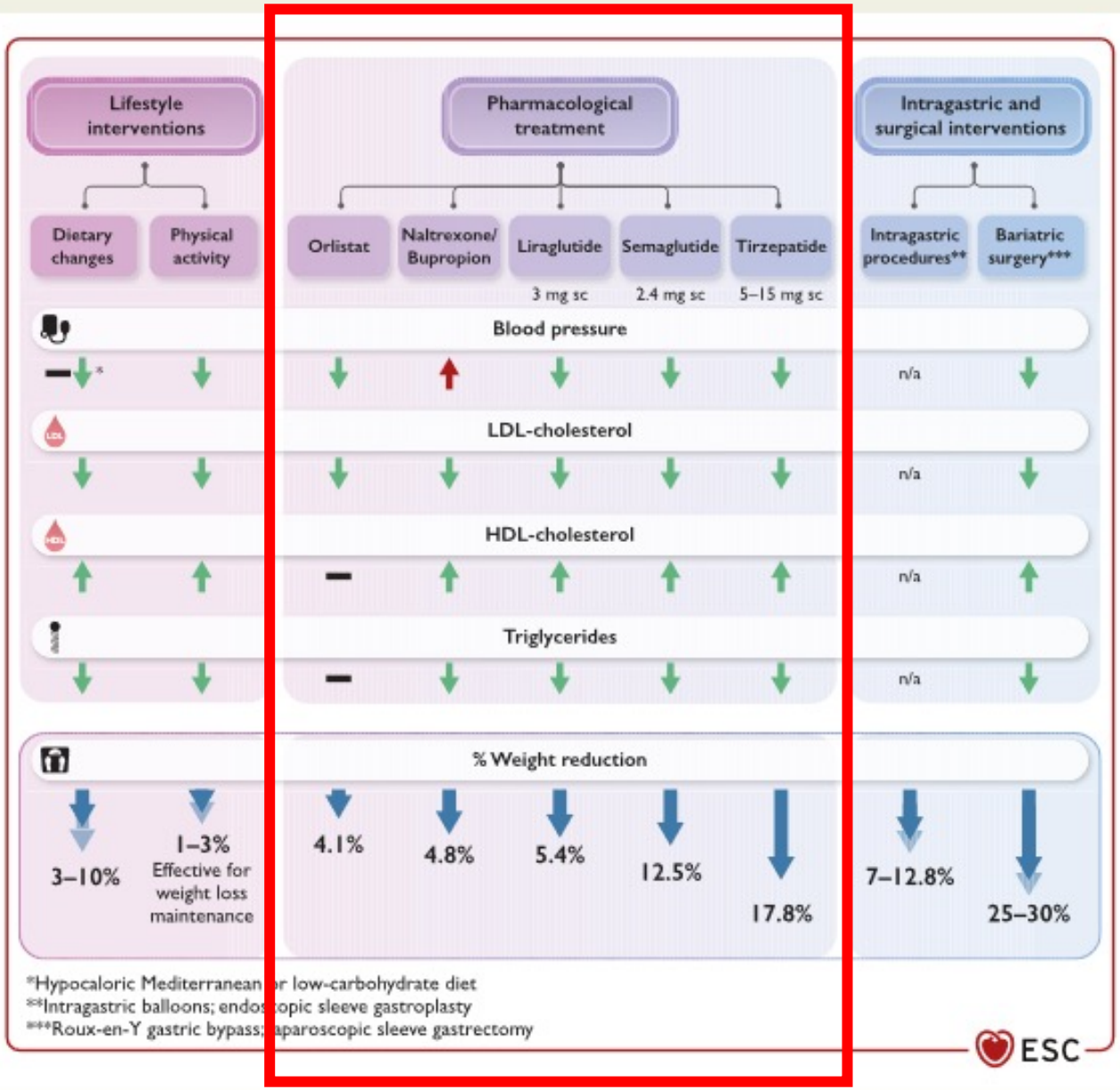


Figure 5 Expected effects of weight loss interventions on cardiovascular risk factors and body weight. HDL, high-density lipoprotein; LDL, low-density lipoprotein; n/a, not available

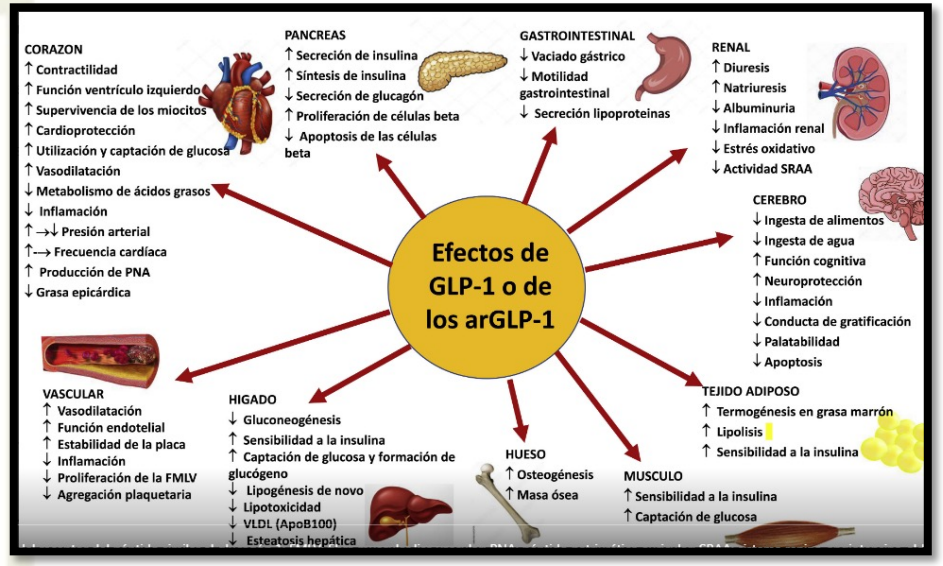


Table 2 Main adverse effects and contraindications for approved anti-obesity medications

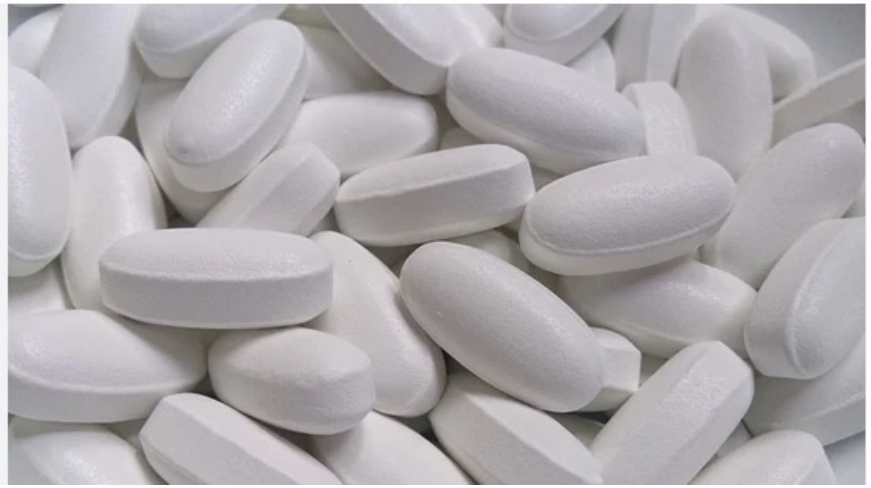
Medication	Adverse effects	Contraindications
Orlistat	• Gastrointestinal symptoms: oily rectal leakage, abdominal pain, flatulence with discharge, faecal urgency, steatorrhoea, faecal incontinence, increased defaecation	Chronic malabsorption syndrome; cholestasis; pregnancy
Naltrexone/ bupropion	• Gastrointestinal symptoms: nausea, constipation, vomiting, diarrhoea, dry mouth • Symptoms of the central nervous system: headaches, insomnia, sleep disorders	Chronic opioid use; acute opioid withdrawal; uncontrolled hypertension; seizure disorder; bulimia or anorexia nervosa; abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiseizure drugs; concomitant use of monoamine oxidase inhibitors; pregnancy
Liraglutide	• Gastrointestinal symptoms: nausea, vomiting, diarrhoea, constipation • Symptoms of the central nervous system: headache	Personal or family history of medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, pregnancy
Semaglutide	• Gastrointestinal symptoms: nausea, diarrhoea, vomiting, constipation, dyspepsia • Symptoms of the central nervous system: headache	Personal or family history of medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, pregnancy
Tirzepatide	• Gastrointestinal symptoms: Nausea, diarrhoea, decreased appetite, vomiting, constipation, dyspepsia, abdominal pain	Personal or family history of medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, pregnancy, known serious hypersensitivity to tirzepatide or any of the excipients
Setmelanotide	• Hypersensitivity reaction at injection site, hyperpigmentation, sexual dysfunction	Pregnancy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Semaglutide at a Dose of 25 mg in Adults with Overweight or Obesity

Sean Wharton, M.D.,[1-4] Ildiko Lingvay, M.D.,[5,6] Pawel Bogdanski, M.D.,[7] Ruben Duque do Vale, M.D.,[8] Stephan Jacob, M.D.,[9] Tobias Karlsson, M.D.,[8] Chaithra Shaji, M.Sc.,[10] Domenica Rubino, M.D.,[11] and W. Timothy Garvey, M.D.,[12] for the OASIS 4 Study Group*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes

J. Rosenstock,[1] S. Hsia,[2] L. Nevarez Ruiz,[3] S. Eyde,[4] D. Cox,[4] W.-S. Wu,[4] R. Liu,[4] J. Li,[4] L. Fernández Landó,[4] M. Denning,[4] L. Ludwig,[4] and Y. Chen,[4] for the ACHIEVE-1 Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment

Sean Wharton, M.D.,[1-3] Louis J. Aronne, M.D.,[4] Adam Stefanski, M.D., Ph.D.,[5] Nasreen F. Alfaris, M.D., M.P.H.,[6] Andreea Ciudin, M.D., Ph.D.,[7-11] Koutaro Yokote, M.D., Ph.D.,[12] Bruno Halpern, M.D., Ph.D.,[13] Alpana P. Shukla, M.D.,[4] Chunmei Zhou, M.S.,[5] Lisa Macpherson, M.S.P.H.,[5] Sheryl E. Allen, M.D.,[5] Nadia N. Ahmad, M.D., M.P.H.,[5] and Suzanne R. Klise, B.S.,[5] for the ATTAIN-1 Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Semaglutide at a Dose of 25 mg in Adults with Overweight or Obesity

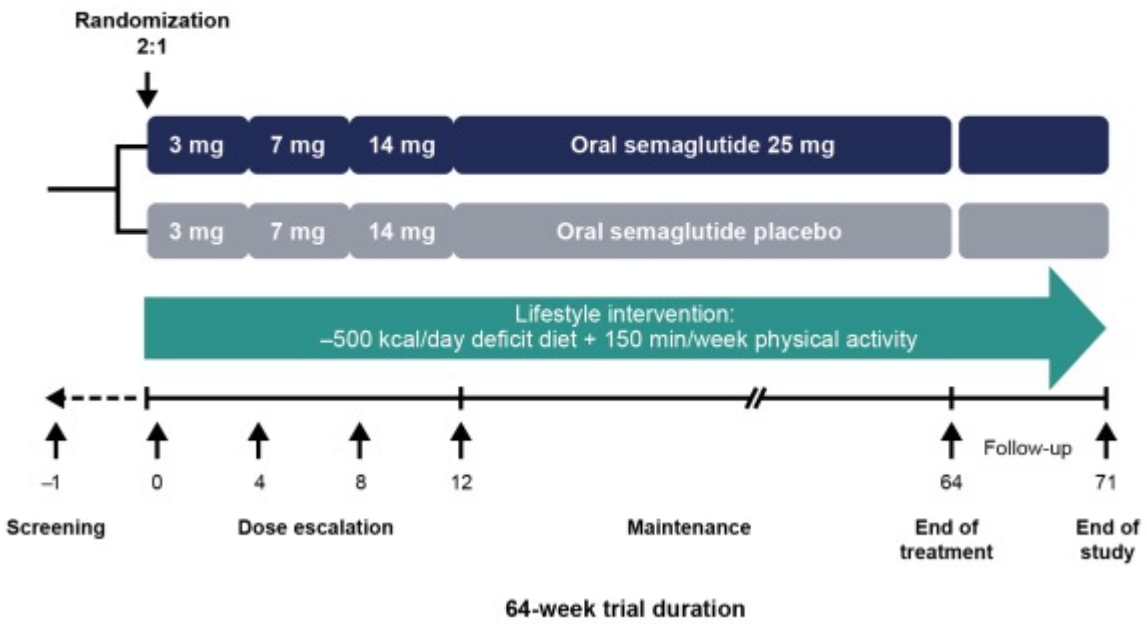
Sean Wharton, M.D.,[1-4] Ildiko Lingvay, M.D.,[5,6] Pawel Bogdanski, M.D.,[7] Ruben Duque do Vale, M.D.,[8] Stephan Jacob, M.D.,[9] Tobias Karlsson, M.D.,[8] Chaithra Shaji, M.Sc.,[10] Domenica Rubino, M.D.,[11] and W. Timothy Garvey, M.D.,[12] for the OASIS 4 Study Group*

N Engl J Med 2025;393:1077-87.

Evaluar la eficacia de la formulación oral de semaglutida en dosis de 25 mg diarios, con el objetivo de determinar si esta presentación puede ofrecer beneficios comparables a la semaglutida inyectable

SUPPLEMENTARY FIGURES

Figure S1. Study Design.



Aleatorizados a recibir semaglutida oral 25 mg diarios o placebo

Período de 64 semanas de seguimiento

Diseño del estudio Fase 3, aleatorizado, doble ciego, controlado con placebo.

N Engl J Med 2025;393:1077-87.

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

Characteristic	Oral Semaglutide (N=205)	Placebo (N=102)
Age — yr	48±13	47±13
Female sex — no. (%)	155 (75.6)	87 (85.3)
Body weight — kg	106.4±23.5	104.8±19.7
Race or ethnic group — no. (%)†		
White	190 (92.7)	91 (89.2)
Black or African American	13 (6.3)	9 (8.8)
Asian	1 (0.5)	1 (1.0)
Other	1 (0.5)	1 (1.0)
Hispanic or Latino ethnic group — no. (%)†		
No	188 (91.7)	95 (93.1)
Yes	17 (8.3)	7 (6.9)
BMI‡	37.5±6.7	37.8±6.1
BMI category — no. (%)		
<30	13 (6.3)	5 (4.9)
30 to <35	73 (35.6)	39 (38.2)
35 to <40	64 (31.2)	22 (21.6)
≥40	55 (26.8)	36 (35.3)
Waist circumference — cm	114.0±15.8	113.6±14.7
Glycated hemoglobin — %	5.7±0.4	5.7±0.3
Blood pressure — mm Hg		
Systolic	131.3±16	131.0±18
Diastolic	83.0±10	83.2±10
Glycemic status — no. (%)§		
Normoglycemia	105 (51.2)	53 (52.0)
Prediabetes	97 (47.3)	47 (46.1)
Diabetes	3 (1.5)	2 (2.0)

307 adultos (OCTUBRE 2022-MAYO 2024)

Participantes: (79 % mujeres, edad media 48 años, obesidad grado 1).

Criterios de inclusión:
IMC ≥ 30, o ≥ 27 con al menos una comorbilidad relacionada con obesidad.

N Engl J Med 2025;393:1077-87.

Exclusion criteria

Obesity-related:

1. A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening, irrespective of medical records

2. Treatment with any medication indicated for weight management within 90 days prior to screening

3. Previous or planned (during the study period) obesity treatment with surgery or a weight-l device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if perforn >1 year prior to screening, (2) lap banding, if the band has been removed >1 year prior to screening, (3) intragastric balloon, if the balloon has been removed >1 year prior to screenir or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year prior to screening

4. Uncontrolled thyroid disease per investigator's discretion

Glycemia-related:

5. Glycated hemoglobin (HbA_{1c}) ≥6.5% (48 mmol/mol) as measured by the central laboratory at screening

Table S2. Additional Baseline Characteristics and Comorbidities at Screening.

	Oral semaglutide (N=205)	Placebo (N=102)
Country, no. (%)		
United States	78 (38.0)	36 (35.3)
Germany	57 (27.8)	24 (23.5)
Poland	51 (24.9)	29 (28.4)
Canada	19 (9.3)	13 (12.7)

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Table 2. Primary, Confirmatory Secondary, and Selected Exploratory End Points.*

End Point	Oral Semaglutide (N=205)	Placebo (N=102)	Difference (95% CI)†
Primary end points			
Percent change in body weight from baseline to week 64	−13.6	−2.2	−11.4 (−13.9 to −9.0)
Body-weight reduction of ≥5% at week 64 — no./total no. (%)‡	152/192 (79.2)	28/90 (31.1)	7.3 (4.2 to 12.8)
Confirmatory secondary end points			
Body-weight reduction of each target — no./total no. (%)‡			
≥10% at week 64	121/192 (63.0)	13/90 (14.4)	9.1 (4.7 to 17.3)
≥15% at week 64	96/192 (50.0)	5/90 (5.6)	15.7 (6.2 to 40.2)
≥20% at week 64	57/192 (29.7)	3/90 (3.3)	12.2 (3.7 to 40.3)
Change in IWQOL-Lite-CT Physical Function score from baseline to week 64 — points§	16.2	8.4	7.7 (3.3 to 12.2)
Supportive secondary end points¶			
Change in IWQOL-Lite-CT Physical Function score ≥14.6 at week 64 — no./total no. (%)‡	104/188 (55.3)	31/89 (34.8)	2.4 (1.4 to 4.1)
Change in cardiometabolic risk factors from baseline to week 64			
Body weight — kg	−14.2	−2.16	−12.0 (−14.6 to −9.5)
BMI	−5.1	−0.8	−4.3 (−5.2 to −3.4)
Waist circumference — cm	−12.2	−2.8	−9.5 (−12.4 to −6.6)
Systolic blood pressure — mm Hg	−6.8	−5.4	−1.4 (−4.6 to 1.8)
Diastolic blood pressure — mm Hg	−2.7	−2.1	−0.7 (−2.8 to 1.5)
Glycated hemoglobin — percentage points	−0.3	−0.1	−0.2 (−0.3 to −0.2)
Fasting plasma glucose — mg/dl	−6.6	0.4	−7.0 (−11.2 to −2.8)
Change in laboratory test results — ratio to baseline at week 64‖			
Total cholesterol	0.96	0.99	0.97 (0.93 to 1.02)
Triglycerides	0.82	0.92	0.88 (0.80 to 0.97)
Free fatty acids	0.86	0.93	0.93 (0.80 to 1.07)
HDL cholesterol	1.03	1.00	1.04 (0.99 to 1.08)
LDL cholesterol	0.96	1.00	0.95 (0.89 to 1.02)
VLDL cholesterol	0.82	0.92	0.89 (0.81 to 0.99)
Fasting serum insulin	0.76	0.99	0.77 (0.63 to 0.94)
C-reactive protein	0.54	0.96	0.56 (0.42 to 0.74)
Post hoc exploratory analyses			
Participants with prediabetes at baseline and normoglycemia at week 64 — no./total no. (%)‡	64/90 (71.1)	13/39 (33.3)	—
Participants with BMI ≥30 at baseline and <30 at week 64 — no./total no. (%)‡	77/179 (43.0)	9/86 (10.5)	11.6 (4.9 to 27.7)

End point 1º

-Reducción media del peso corporal:
Semaglutida**: −13.6 %**
Placebo: −2.2 %

Diferencia estimada: −11.4 puntos porcentuales **(p < 0.001)**

-Reducción de peso ≥ 5% en la semana 64

End point 2 º

-Reducción de peso ≥ 10% , 15% y 20% en la semana 64

-Cambios en IWQOL función física
-**Perfil lipídico**, con descensos en colesterol LDL y triglicéridos.
-Marcadores de RCV con reducciones en presión arterial y circunferencia de cintura.

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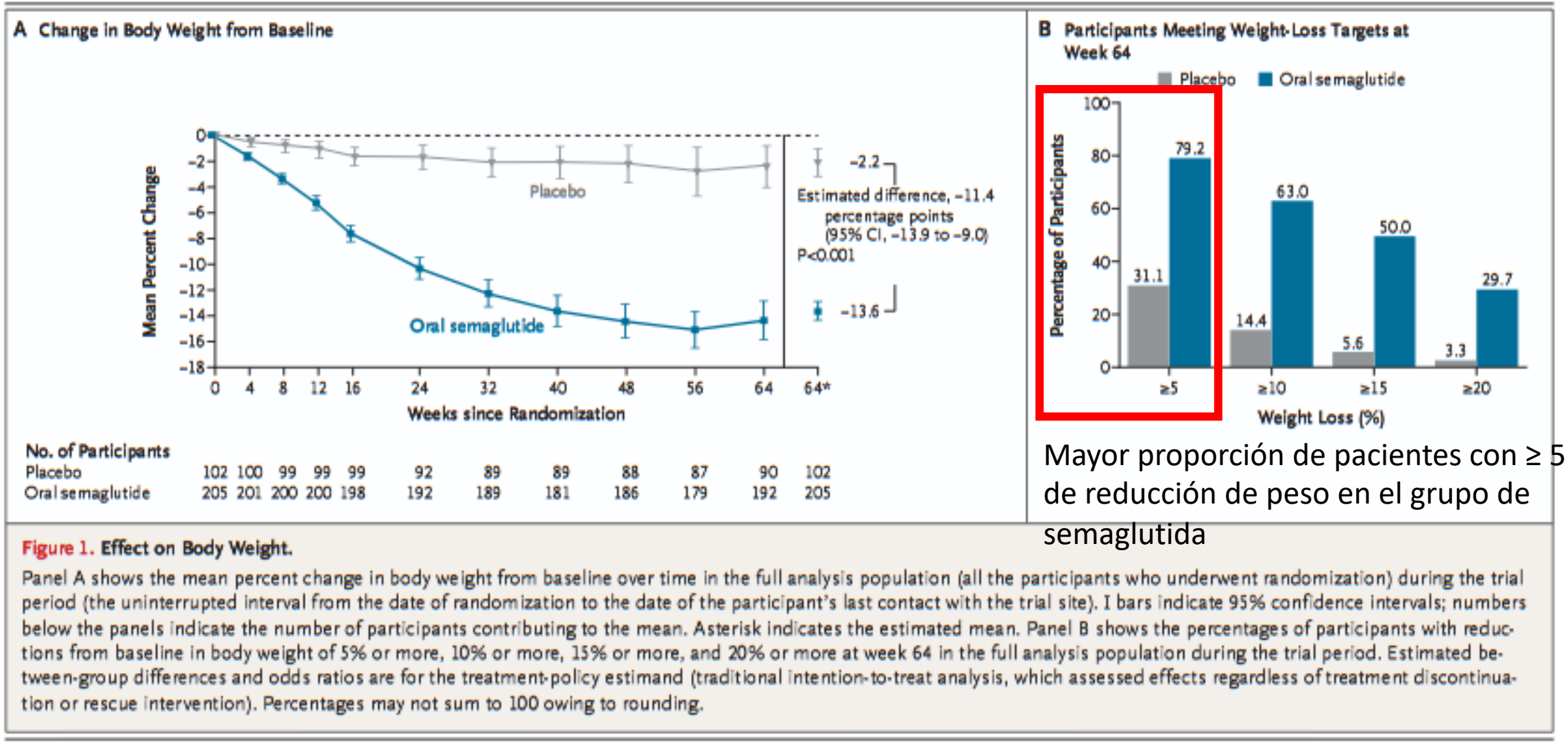

Mayor proporción de pacientes con ≥ 5 % de reducción de peso en el grupo de semaglutida

Figure 1. Effect on Body Weight.

Panel A shows the mean percent change in body weight from baseline over time in the full analysis population (all the participants who underwent randomization) during the trial period (the uninterrupted interval from the date of randomization to the date of the participant's last contact with the trial site). I bars indicate 95% confidence intervals; numbers below the panels indicate the number of participants contributing to the mean. Asterisk indicates the estimated mean. Panel B shows the percentages of participants with reductions from baseline in body weight of 5% or more, 10% or more, 15% or more, and 20% or more at week 64 in the full analysis population during the trial period. Estimated between-group differences and odds ratios are for the treatment-policy estimand (traditional intention-to-treat analysis, which assessed effects regardless of treatment discontinuation or rescue intervention). Percentages may not sum to 100 owing to rounding.

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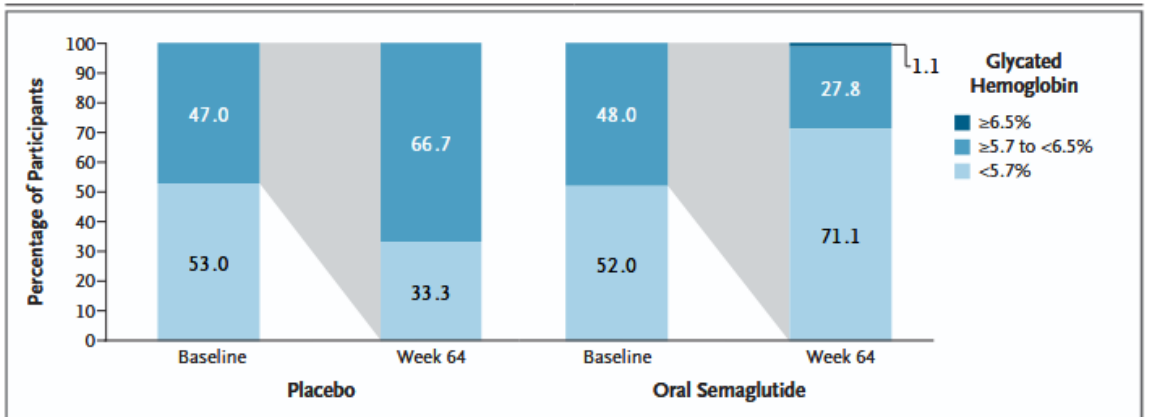

Figure 2. Change in Glycemic Status.

Shown is the change in glycemic status at week 64 according to glycemic status at baseline among participants in the full analysis population. Baseline glycemic status included all participants with normoglycemia (glycated hemoglobin <5.7%) or prediabetes (glycated hemoglobin ≥5.7 to <6.5%). The shading shows that the denominator for the percentages at week 64 are the participants who had prediabetes at baseline. The presence of type 2 diabetes at screening was an exclusion criterion. However, between screening and baseline, glycated hemoglobin levels in the range for diabetes diagnosis (≥6.5%) developed in five participants (three in the oral semaglutide group and two in the placebo group); data from these participants are not included here.

Figure S10. Change from Baseline in Glycated Hemoglobin Level by Week.

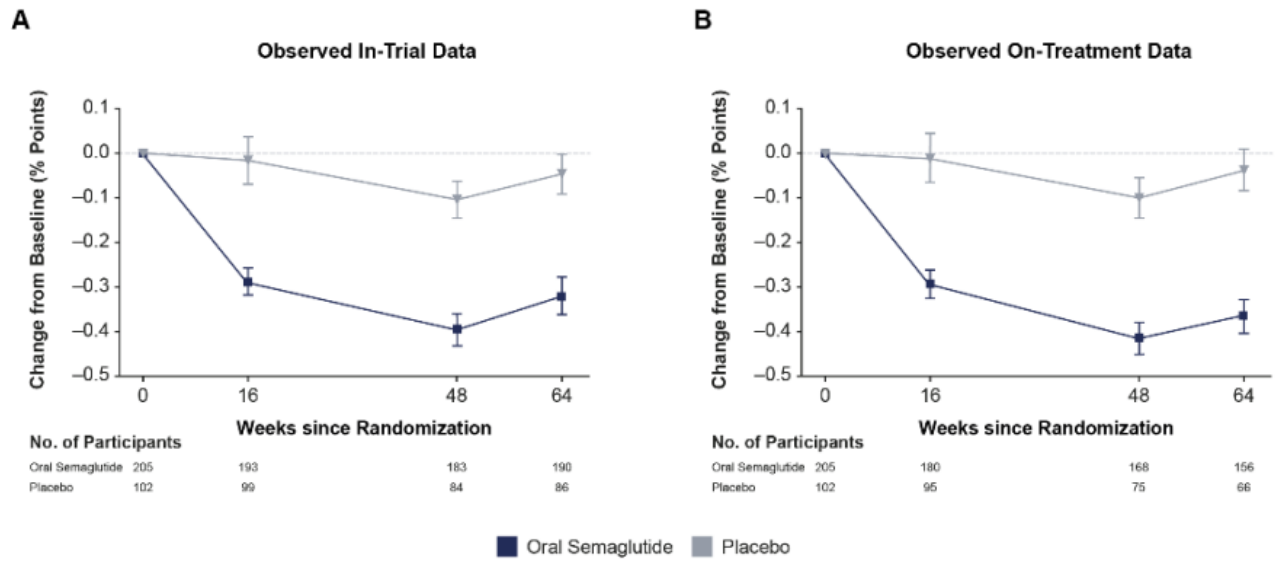

Figure S11. Change from Baseline in Fasting Plasma Glucose Level by Week.

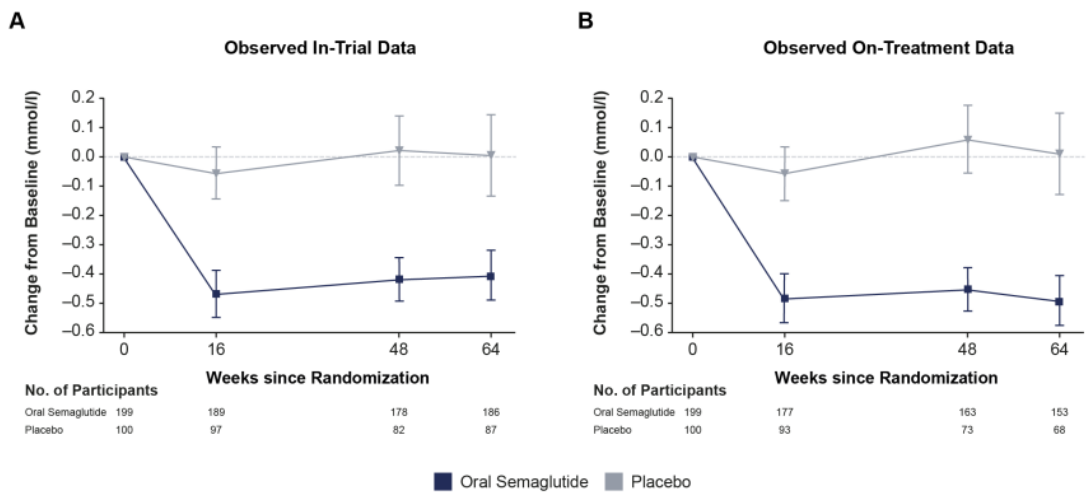

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Figure S9. Change from Baseline in Waist Circumference by Week.

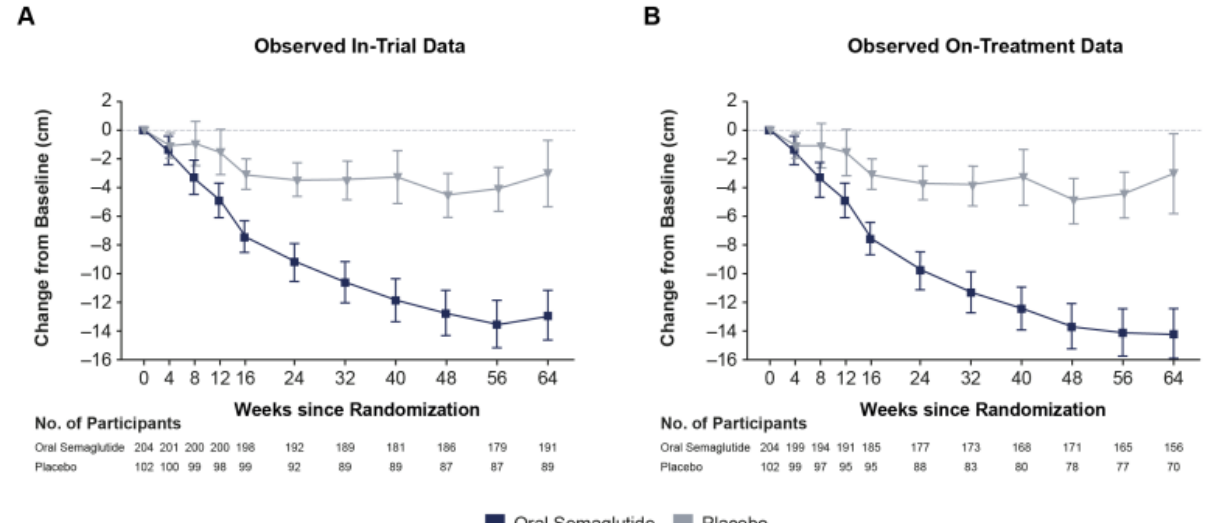
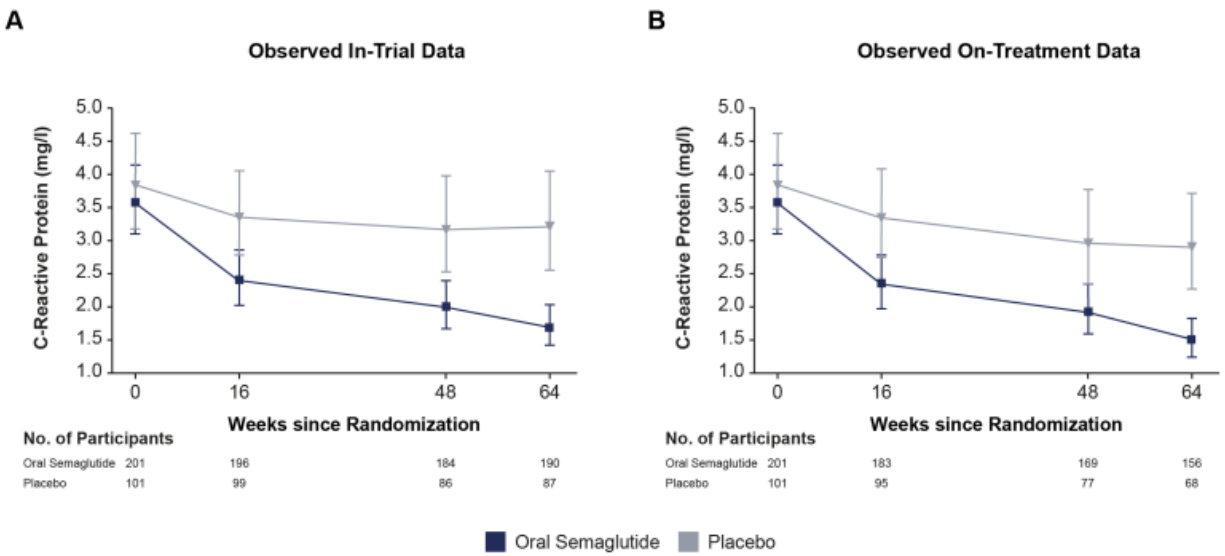


Figure S14. C-Reactive Protein Levels by Week.



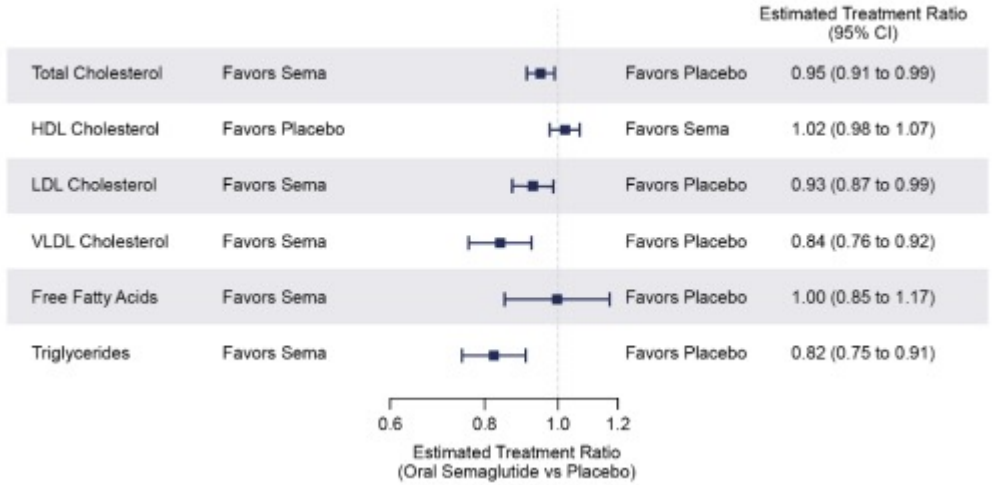


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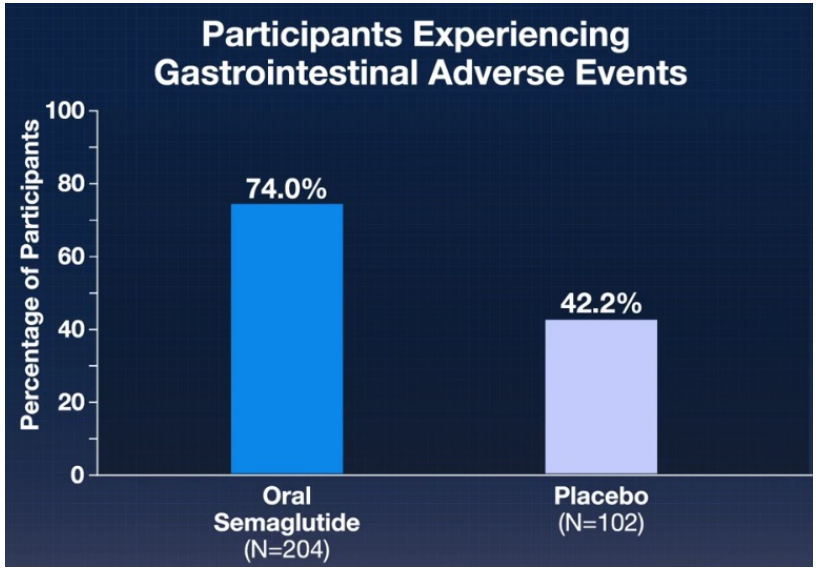
Table 3. Adverse Events.*

Event	Oral Semaglutide (N=204)			Placebo (N=102)		
	no. of participants (%)	*no. of events*	*events per 100 participant-yr of exposure*	*no. of participants (%)*	*no. of events*	*events per 100 participant-yr of exposure*
Any adverse event	190 (93.1)	1239	493.5	87 (85.3)	432	355.9
Serious adverse events	8 (3.9)	17	6.8	9 (8.8)	13	10.7
Adverse events leading to discontinuation of semaglutide or placebo	14 (6.9)	14	5.6	6 (5.9)	6	4.9
Gastrointestinal disorders	7 (3.4)	7	2.8	2 (2.0)	2	1.6
Fatal events	0	0	0	0	0	0
Adverse events reported in ≥10% of participants						
Nausea	95 (46.6)	157	62.5	19 (18.6)	27	22.2
Vomiting	63 (30.9)	105	41.8	6 (5.9)	6	4.9
Nasopharyngitis	43 (21.1)	59	23.5	27 (26.5)	40	33.0
Coronavirus disease 2019	42 (20.6)	[illegible]	18.3	18 (17.6)	19	15.7
Constipation	41 (20.1)	59	23.5	10 (9.8)	11	9.1
Dyspepsia	37 (18.1)	50	19.9	9 (8.8)	11	9.1
Diarrhea	36 (17.6)	61	24.3	9 (8.8)	10	8.2
Headache	24 (11.8)	35	13.9	9 (8.8)	10	8.2
Eructation	21 (10.3)	23	9.2	2 (2.0)	2	1.6

Eventos adversos gastrointestinales más frecuentes con semaglutida



El perfil de seguridad fue consistente con el ya conocido para los agonistas de GLP-1: efectos gastrointestinales leves a moderados como **náuseas, vómitos y diarrea**, que tendieron a disminuir con el tiempo.

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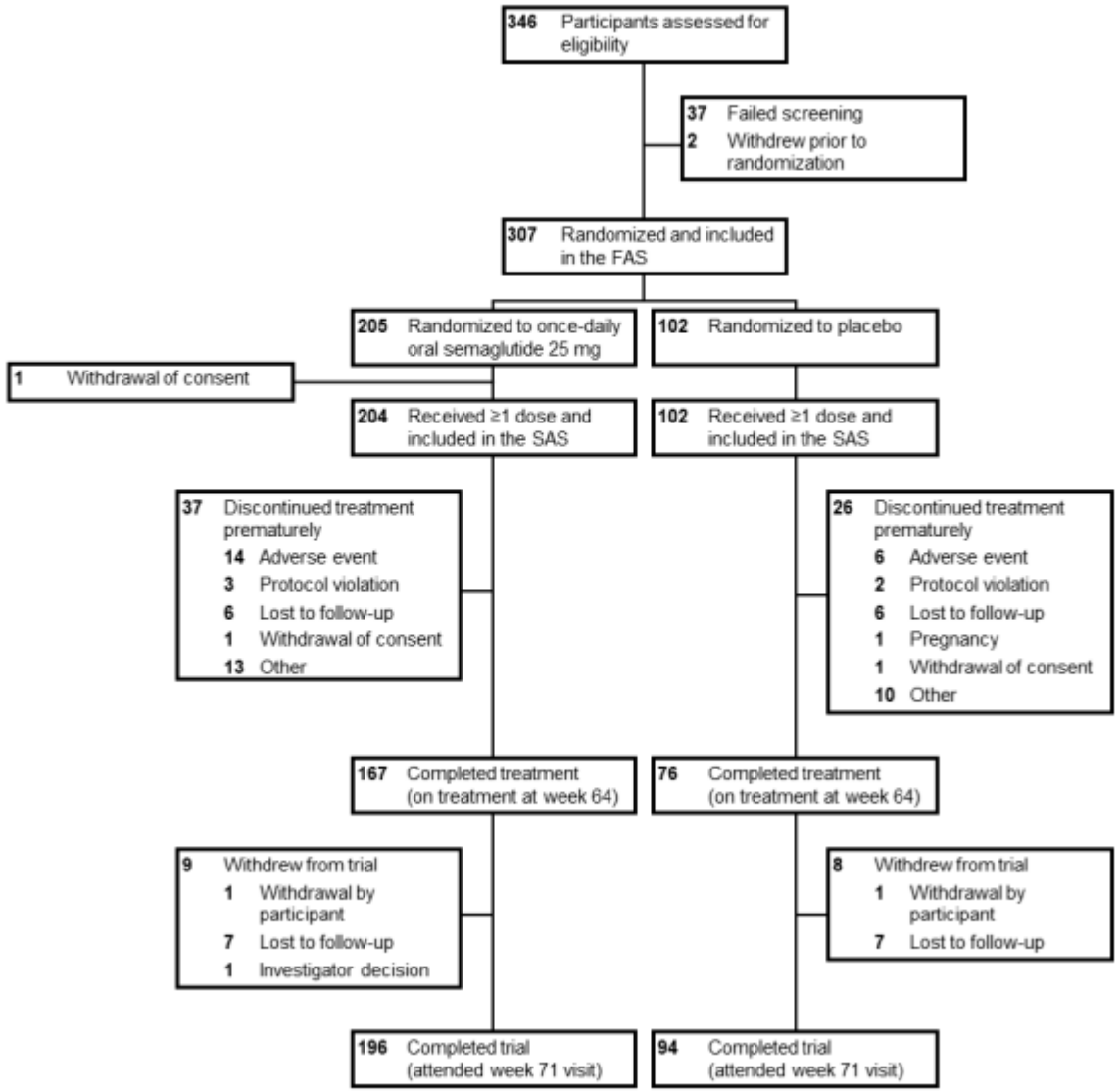
Figure S2. Participant Disposition.



Limitaciones

-20 % de los participantes no completaron el estudio

-Predominio de mujeres → posible limitación para generalizar resultados.

-No se comparó con semaglutida inyectable ni con dosis mayores orales

OASIS 1 : SEMAGLUTIDE 50 MG (12.7%)

STEP 1:SEMAGLUTIDE 2.4 SC (12.4%)

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Conclusiones

- En adultos con sobrepeso y obesidad, la **semaglutida oral 25 mg** una vez al día produjo una pérdida de peso significativamente mayor que el placebo a las 64 semanas, con beneficios adicionales sobre parámetros metabólicos y un perfil de seguridad predecible

- **Alternativa oral** con eficacia comparable a la vía inyectable, lo que podría mejorar la adherencia.

  A diferencia de las formulaciones de menor dosis (7 y 14 mg), que mostraban eficacia limitada para el control de peso, la dosis de 25 mg diarios logra por primera vez un impacto clínico equiparable al de la versión inyectable.

- **Estudios de mayor duración** para confirmar la **sostenibilidad de la pérdida de peso a largo plazo**, así como para evaluar su impacto en eventos cardiovasculares y complicaciones metabólicas mayores, áreas en las que la semaglutida inyectable ya cuenta con más evidencia.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes

J. Rosenstock,[1] S. Hsia,[2] L. Nevarez Ruiz,[3] S. Eyde,[4] D. Cox,[4] W.-S. Wu,[4] R. Liu,[4] J. Li,[4] L. Fernández Landó,[4] M. Denning,[4] L. Ludwig,[4] and Y. Chen,[4] for the ACHIEVE-1 Trial Investigators*

- **Agonista no peptídico del receptor GLP-1**, con afinidad selectiva hacia la activación de proteínas G, lo que evita el reclutamiento de β-arrestinas y podría estar asociado a una menor desensibilización del receptor.

-**Biodisponibilidad de hasta el 40%** sin requerimientos prandiales.

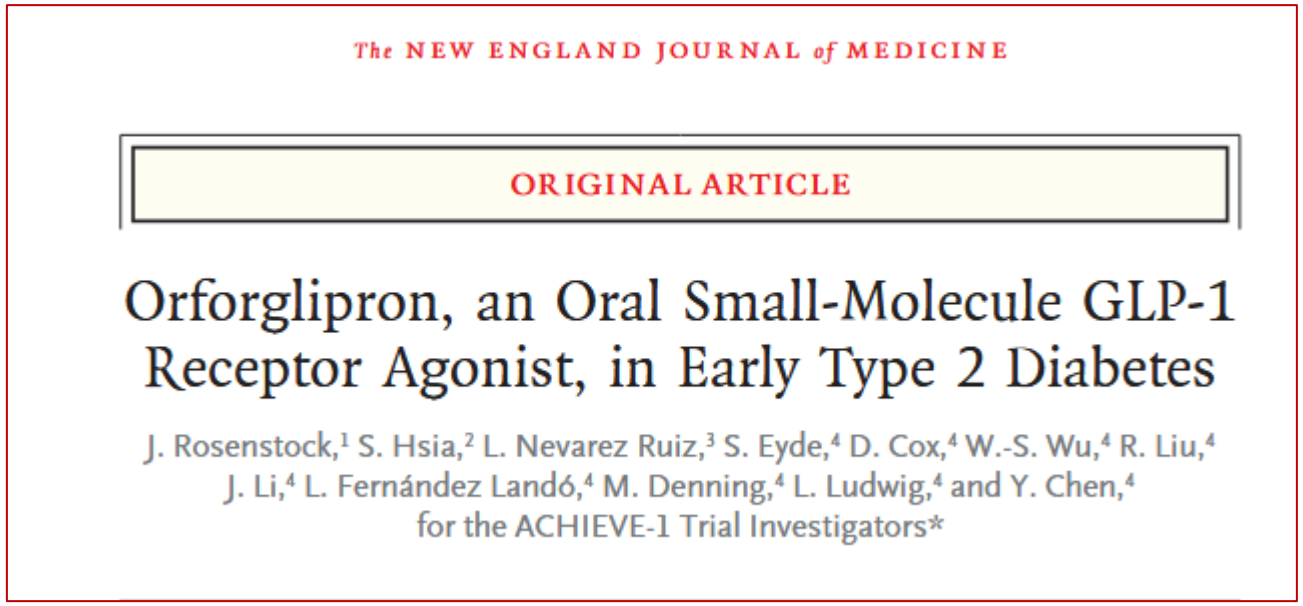
-Su vida media entre **25 y 68 horas** permite una administración diaria simple

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment

Sean Wharton, M.D.,[1-3] Louis J. Aronne, M.D.,[4] Adam Stefanski, M.D., Ph.D.,[5] Nasreen F. Alfaris, M.D., M.P.H.,[6] Andreea Ciudin, M.D., Ph.D.,[7-11] Koutaro Yokote, M.D., Ph.D.,[12] Bruno Halpern, M.D., Ph.D.,[13] Alpana P. Shukla, M.D.,[4] Chunmei Zhou, M.S.,[5] Lisa Macpherson, M.S.P.H.,[5] Sheryl E. Allen, M.D.,[5] Nadia N. Ahmad, M.D., M.P.H.,[5] and Suzanne R. Klise, B.S.,[5] for the ATTAIN-1 Trial Investigators*

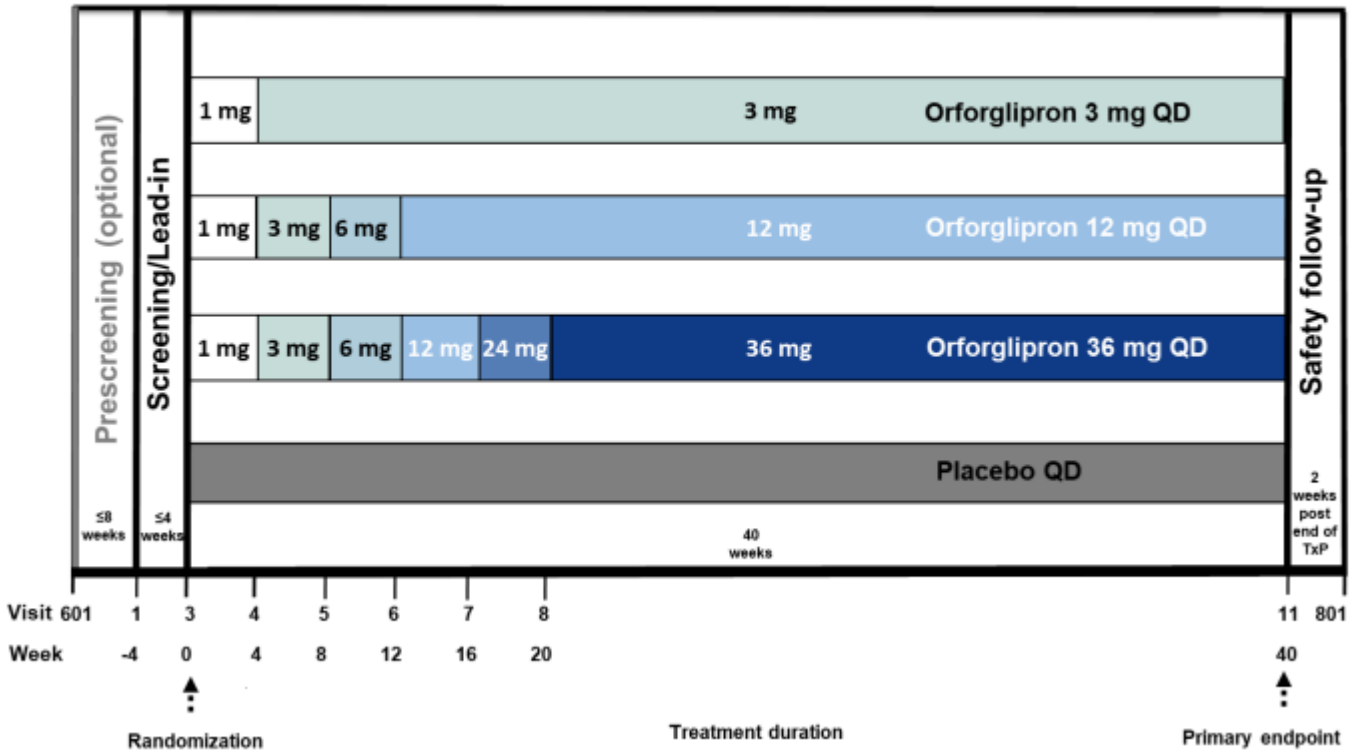


N Engl J Med 2025;393:1065-76.

La familia de los agonistas del receptor del péptido similar al glucagón tipo 1 (GLP-1) ha revolucionado la forma en que tratamos la diabetes tipo 2 (DM2) y la obesidad.

Sin embargo, la vía de administración ha sido tradicionalmente una barrera: la mayoría de estos fármacos son inyectables y los pacientes suelen manifestar preferencia por terapias orales

Figure S1. ACHIEVE-1 Study Design



Se compararon tres dosis de orforglipron (3, 12 y 36 mg) versus placebo durante **40 semanas.**

Ensayo clínico fase 3, doble ciego y controlado con placebo

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

Characteristic	Orforglipron, 3 mg (N=143)	Orforglipron, 12 mg (N=137)	Orforglipron, 36 mg (N=141)	Placebo (N=138)	Overall (N=559)
Age — yr	53.3±11.3	54.1±11.8	52.8±11.8	53.3±12.5	53.4±11.8
Female sex — no. (%)	63 (44.1)	71 (51.8)	72 (51.1)	63 (45.7)	269 (48.1)
Race or ethnic group — no. (%)†					
Asian	63 (44.1)	59 (43.1)	62 (44.0)	61 (44.2)	245 (43.8)
White	37 (25.9)	30 (21.9)	40 (28.4)	38 (27.5)	145 (25.9)
American Indian	35 (24.5)	38 (27.7)	35 (24.8)	35 (25.4)	143 (25.6)
Black	8 (5.6)	9 (6.6)	4 (2.8)	3 (2.2)	24 (4.3)
Hispanic or Latino	57 (39.9)	55 (40.1)	55 (39.0)	56 (40.6)	223 (39.9)
Country — no. (%)					
United States	42 (29.4)	40 (29.2)	42 (29.8)	41 (29.7)	165 (29.5)
Mexico	40 (28.0)	41 (29.9)	40 (28.4)	38 (27.5)	159 (28.4)
Japan	26 (18.2)	25 (18.2)	25 (17.7)	25 (18.1)	101 (18.1)
India	21 (14.7)	19 (13.9)	22 (15.6)	21 (15.2)	83 (14.8)
China	14 (9.8)	12 (8.8)	12 (8.5)	13 (9.4)	51 (9.1)
Glycated hemoglobin level — %‡	7.93±0.86	7.98±0.91	8.07±0.90	7.96±0.89	7.99±0.89
Glycated hemoglobin category — no. (%)					
≤8.0%	81 (56.6)	83 (60.6)	78 (55.3)	81 (58.7)	323 (57.8)
>8.0%	62 (43.4)	54 (39.4)	63 (44.7)	57 (41.3)	236 (42.2)
Fasting glucose level — mg/dl	142.9±38.7	155.3±55.1	148.8±40.0	143.3±42.2	147.5±44.5
Duration of diabetes — yr	4.0±4.8	5.1±6.0	4.2±5.1	4.4±5.6	4.4±5.4
Body weight — kg	90.3±25.7	90.6±23.1	90.1±22.9	90.0±20.7	90.2±23.1
BMI§	32.9±8.0	33.3±7.8	33.1±7.3	32.9±6.8	33.0±7.5
Waist circumference — cm	107.0±16.5	107.7±16.9	107.6±17.0	106.9±14.1	107.3±16.1
Triglycerides — mg/dl	170.4±104.0	168.9±103.2	192.9±187.1	170.7±155.1	175.8±142.2
Non-HDL cholesterol — mg/dl	140.3±40.6	141.6±40.3	140.6±41.3	141.2±42.1	140.9±41.0
Blood pressure — mm Hg					
Systolic	126.5±14.1	127.5±14.5	128.3±14.3	128.4±14.1	127.7±14.2
Diastolic	79.9±9.5	80.5±9.3	80.8±9.1	80.1±8.6	80.3±9.1
Pulse rate — beats/min	74.3±10.3	75.9±9.3	76.6±9.6	74.1±10.9	75.2±10.1
Previous use of any glucose-lowering medication — no. (%)	55 (38.5)	53 (38.7)	52 (36.9)	54 (39.1)	214 (38.3)

559 adultos con DM2 temprana, tratados sólo con dieta y ejercicio.

Los criterios de inclusión incluyeron
-HbA1c entre 7,0 y 9,5%,
-IMC ≥23 kg/m² y ausencia de tratamiento farmacológico reciente.

Edad media 53 años
♀ 48.1%,
predomimio asiático
Duracion media de la DM2 4.4 años

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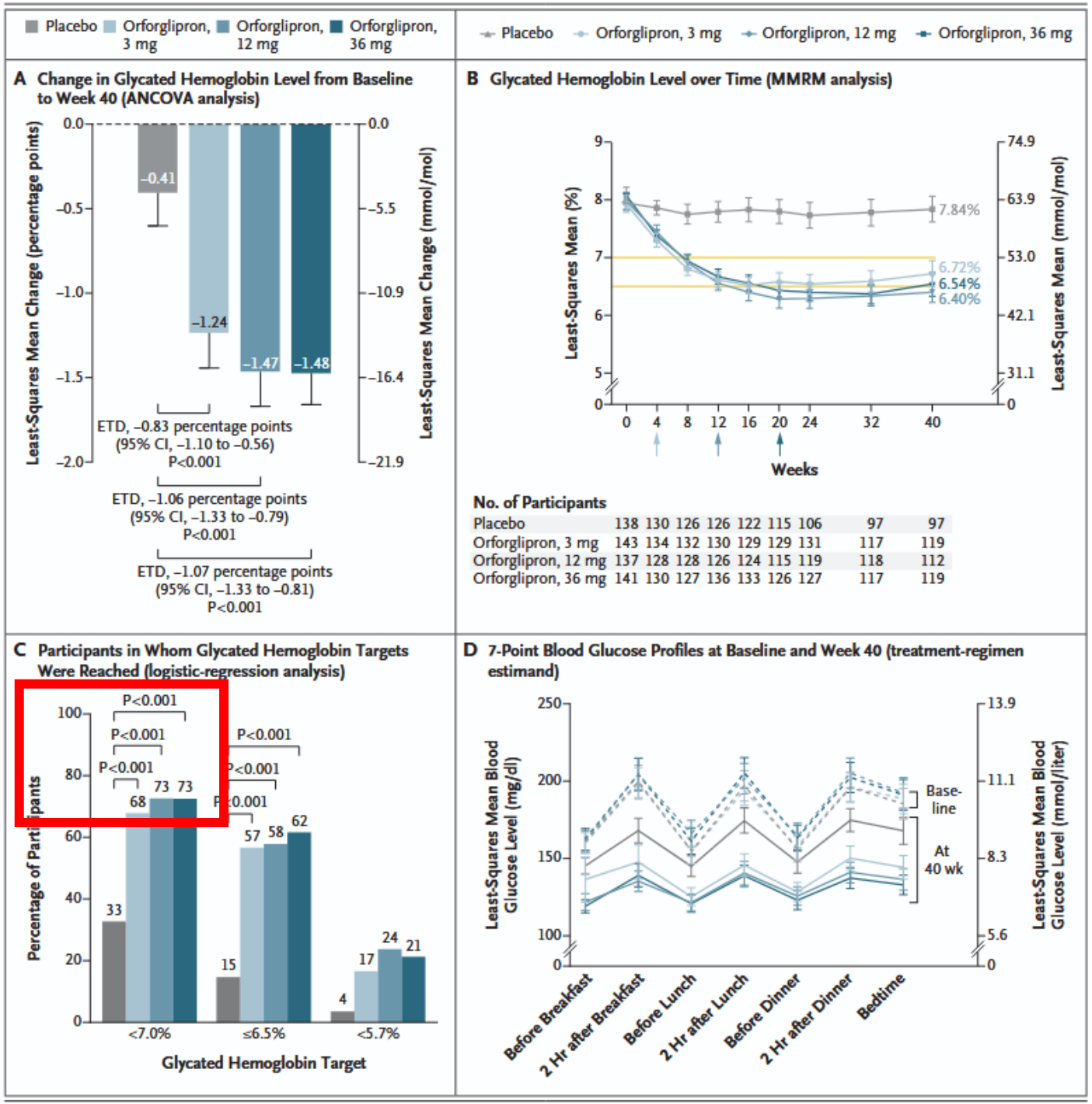


Objetivos principales y secundarios

Primario: Cambio en HbA1c desde el inicio hasta la semana 40.

Todos los grupos tratados con orforglipron lograron una reducción significativa de HbA1c frente a placebo:

- 3 mg: −1,24%
- 12 mg: −1,47%
- 36 mg: −1,48%
- Placebo: −0,41%

Secundarios : Porcentaje de cambio en el peso corporal, logro de metas de HbA1c (<7%, ≤6,5% y <5,7%), glucosa en ayunas, perfil lipídico y parámetros antropométricos.

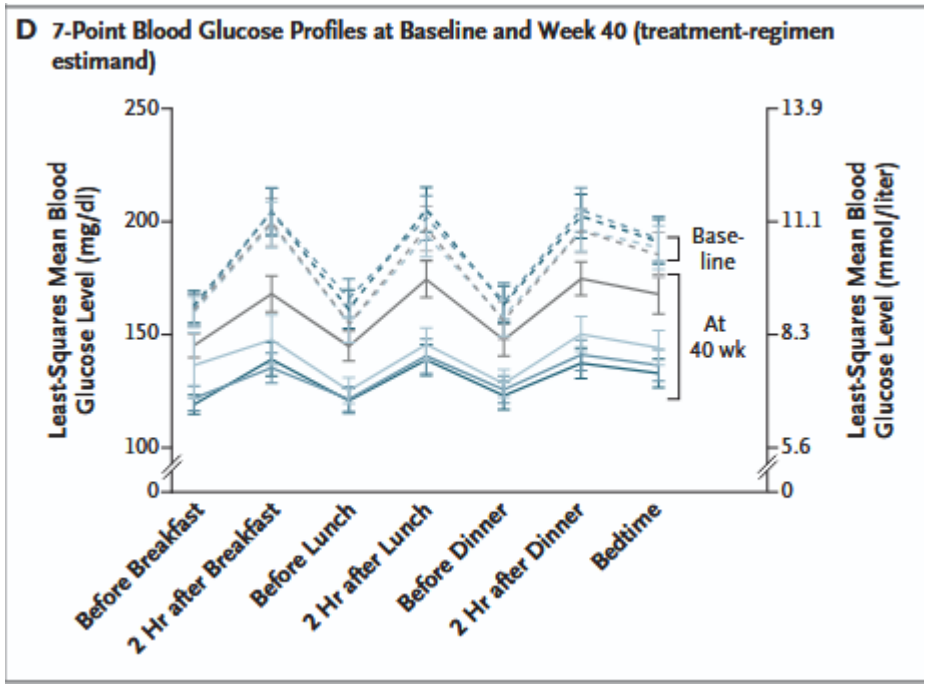
El 73% de los pacientes con orforglipron alcanzaron una HbA1c <7%, y hasta un 24% logró <5,7%, acercándose a valores normoglucémicos. **N Engl J Med 2025;393:1065-76.**

Efectos sobre glucosa en ayunas y perfil glucémico

-La glucosa en ayunas disminuyó entre **31 y 37 mg/dl con orforglipron**, comparado con solo 11 mg/dl con placebo.

-Asimismo, los perfiles de glucosa monitoreados por los participantes evidenciaron mejoras consistentes en glucemias preprandiales y postprandiales con las tres dosis activas.

-



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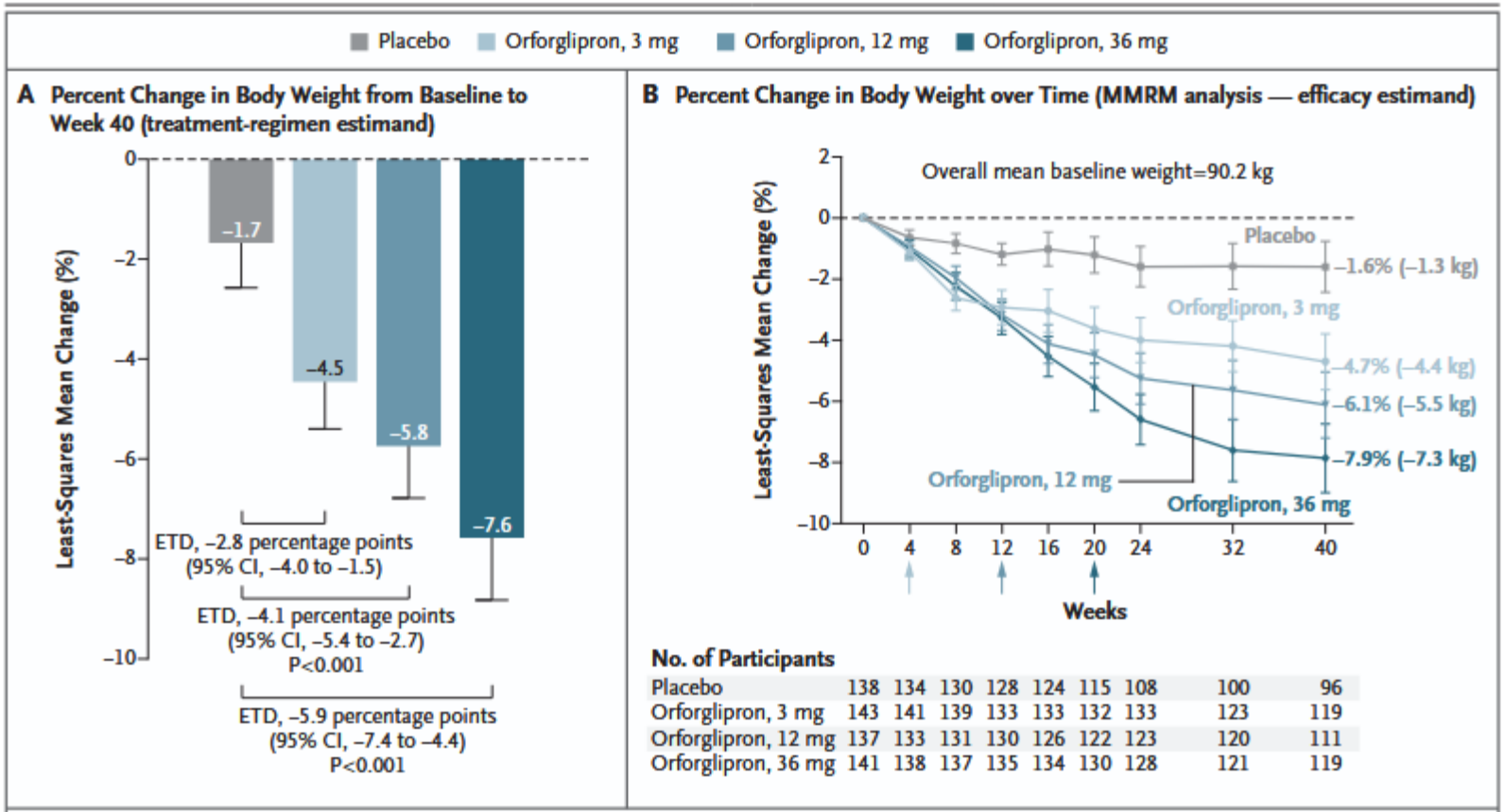

Pérdida de peso corporal

La reducción porcentual del peso corporal también fue significativa y dependiente de la dosis:

- 3 mg: −4,5%
- 12 mg: −5,8%
- **36 mg: −7,6%**
- Placebo: −1,7%

Estos resultados confirman el efecto dual sobre glucemia y peso corporal, característico de los agonistas GLP-1

Casi 1/3 de los participantes con orforglipron 36 mg alcanzaron una pérdida ≥10% del peso corporal, y hasta un 10% lograron perder ≥15%

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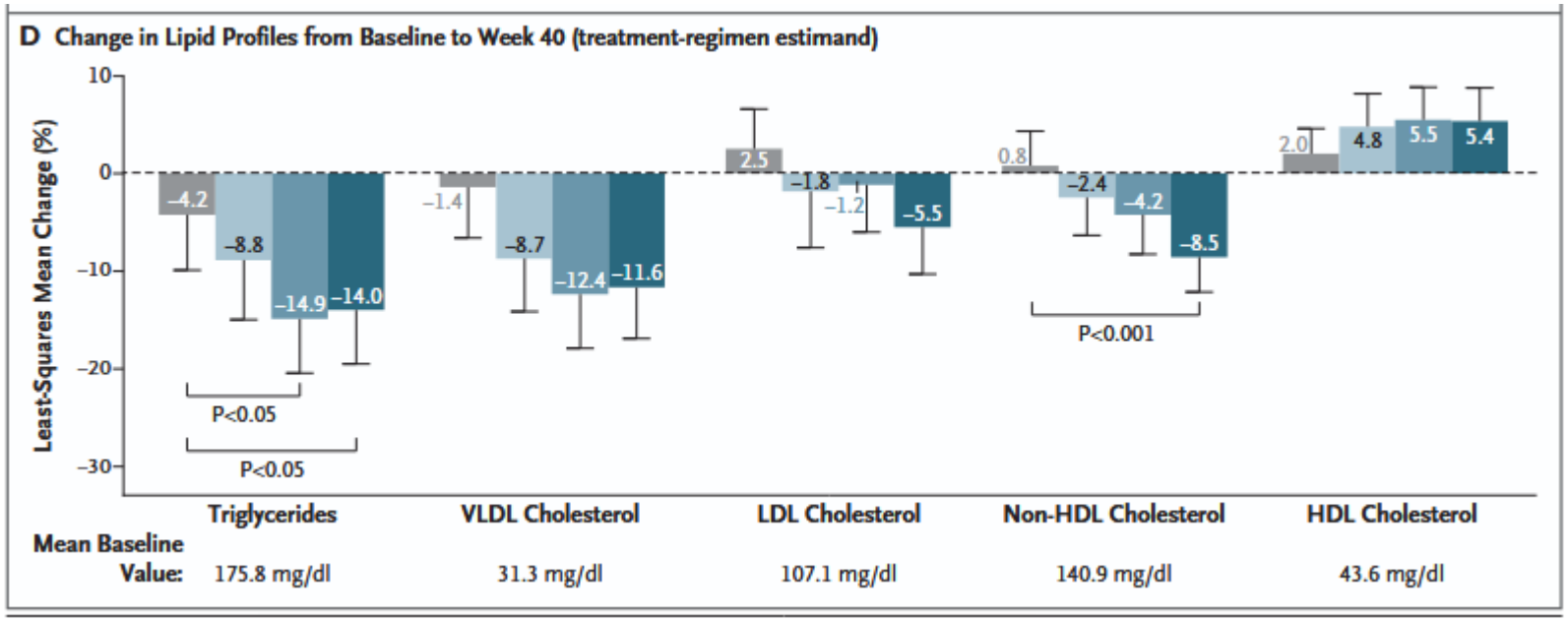

Beneficios cardiometabólicos

Además de la reducción de peso y glucosa, se observaron efectos beneficiosos sobre marcadores de riesgo cardiovascular, incluyendo:

- Disminución de triglicéridos y colesterol no-HDL (especialmente con 12 y 36 mg).
- Reducción de presión arterial sistólica (−3,3 a −5,7 mmHg).

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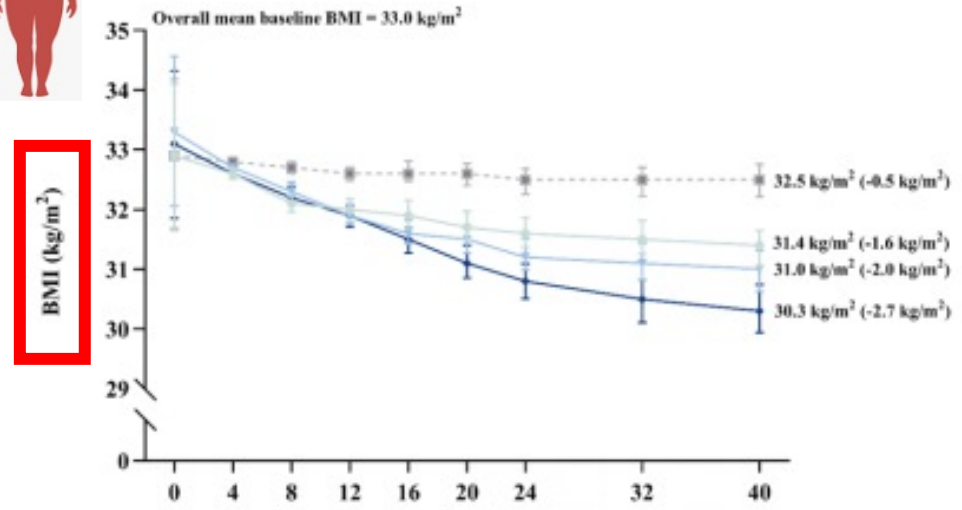
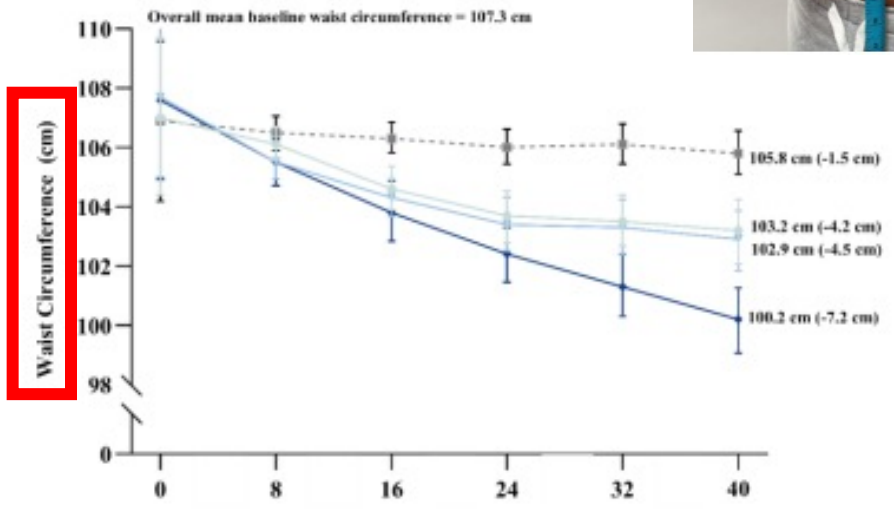
Figure S5. Mean BMI and Waist Circumference Over Time



No. of participants								
PBO	138	134	130	128	124	115	108	100	96
OFG 3 mg	143	141	139	133	133	132	133	123	119
OFG 12 mg	137	133	131	130	126	122	123	120	111
OFG 36 mg	141	138	137	135	134	130	128	121	119

B



No. of participants						
PBO	138	130	124	108	100	96
OFG 3 mg	143	139	133	133	123	119
OFG 12 mg	137	131	126	123	120	111
OFG 36 mg	141	137	134	128	121	119

Orforglipron 3 mg
Orforglipron 12 mg
Orforglipron 36 mg
Placebo

Reducción de circunferencia de cintura y del IMC

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Table 2. Adverse Events.*

Event	Orforglipron, 3 mg (N=143)	Orforglipron, 12 mg (N=137)	Orforglipron, 36 mg (N=141)	Placebo (N=138)	Overall (N=559)
	number of participants (percent)				
Any adverse event emerging during treatment	102 (71.3)	111 (81.0)	119 (84.4)	102 (73.9)	434 (77.6)
Any serious adverse event	8 (5.6)	7 (5.1)	4 (2.8)	5 (3.6)	24 (4.3)
Death†	2 (1.4)	1 (0.7)	0	1 (0.7)	4 (0.7)
Adverse event leading to discontinuation of orforglipron or placebo	8 (5.6)	6 (4.4)	11 (7.8)	2 (1.4)	27 (4.8)
Gastrointestinal adverse event leading to discontinuation of orforglipron or placebo	4 (2.8)	3 (2.2)	8 (5.7)	0	15 (2.7)
Adverse events that emerged during treatment and occurred in ≥5% of participants in any trial group					
Diarrhea	27 (18.9)	29 (21.2)	36 (25.5)	12 (8.7)	104 (18.6)
Dyspepsia	15 (10.5)	28 (20.4)	21 (14.9)	9 (6.5)	73 (13.1)
Nausea	18 (12.6)	25 (18.2)	23 (16.3)	3 (2.2)	69 (12.3)
Hyperglycemia	10 (7.0)	6 (4.4)	9 (6.4)	37 (26.8)	62 (11.1)
Constipation	12 (8.4)	23 (16.8)	19 (13.5)	5 (3.6)	59 (10.6)
Abdominal distention	6 (4.2)	7 (5.1)	16 (11.3)	11 (8.0)	40 (7.2)
Decreased appetite	5 (3.5)	14 (10.2)	16 (11.3)	3 (2.2)	38 (6.8)
Vomiting	7 (4.9)	9 (6.6)	20 (14.2)	2 (1.4)	38 (6.8)
Headache	8 (5.6)	5 (3.6)	10 (7.1)	6 (4.3)	29 (5.2)
Diabetic retinopathy	5 (3.5)	2 (1.5)	13 (9.2)	6 (4.3)	26 (4.7)
Eructation	5 (3.5)	6 (4.4)	10 (7.1)	0	21 (3.8)
Nasopharyngitis	2 (1.4)	9 (6.6)	3 (2.1)	6 (4.3)	20 (3.6)
Gastroesophageal reflux	3 (2.1)	7 (5.1)	5 (3.5)	2 (1.4)	17 (3.0)
Abdominal pain	1 (0.7)	4 (2.9)	7 (5.0)	2 (1.4)	14 (2.5)
Upper abdominal pain	0	8 (5.8)	4 (2.8)	1 (0.7)	13 (2.3)
Lipase increase	2 (1.4)	7 (5.1)	2 (1.4)	2 (1.4)	13 (2.3)
Other adverse events emerging during treatment					
Hypoglycemia‡	2 (1.4)	0	1 (0.7)	1 (0.7)	4 (0.7)
Severe hypoglycemia§	0	0	0	0	0
Initiation of rescue therapy for severe persistent hyperglycemia	9 (6.3)	6 (4.4)	8 (5.7)	32 (23.2)	55 (9.8)
Thyroid cancer	0	0	0	0	0
Pancreatitis as confirmed by adjudication	0	0	0	0	0
Cholelithiasis	0	2 (1.5)	0	0	2 (0.4)

Orforglipron presentó un **perfil de seguridad aceptable**, con predominio de eventos gastrointestinales leves a moderados (**náuseas, diarrea, dispepsia**) durante el período de escalamiento.

Las **tasas de discontinuación fueron bajas** (2,2–5,7%), sin diferencias sustanciales en eventos adversos serios versus placebo.

No episodios de hipoglucemia severa alteraciones hepáticas destacables

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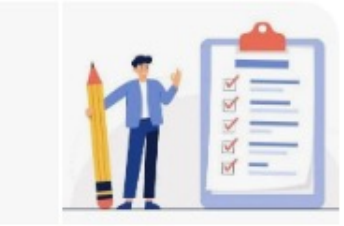
CONCLUSIÓN



- Orforglipron representa una **innovación terapéutica** significativa en el tratamiento de la diabetes tipo 2 , en etapas tempranas. (particularmente para pacientes reticentes a las inyecciones o con necesidades de simplificación terapéutica)

- Prometedora opción oral, **no peptídica,** sin restricciones alimentarias

  Reducción sostenida de HbA1c
  Pérdida significativa de peso corporal
  Efectos cardiometabólicos adicionales
  Perfil de seguridad favorable

- Potencia clínica comparable a agentes inyectables

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Relevancia global y poblacional

El estudio incluyó una población diversa en términos de etnicidad y regiones geográficas (EE.UU., México, Japón, India y China), lo que refuerza **la generalizabilidad** de los resultados.

La media de duración de la diabetes fue de **4,4 años**, lo que representa una ventana terapéutica temprana ideal para implementar estrategias farmacológicas eficaces y con bajo riesgo.

Comparación con semaglutida oral

La eficacia de orforglipron es comparable con la de semaglutida oral (PIONEER 1) e incluso superior en algunos aspectos como la pérdida de peso.

N Engl J Med 2025;393:1065-76.

Limitaciones del estudio

•Población tratada **exclusivamente con dieta y ejercicio**, sin coadministración con metformina u otros hipoglucemiantes.

•Duración limitada **a 40 semanas**. Serán necesarios datos a largo plazo para evaluar sostenibilidad del efecto glucémico, impacto CV y función β-pancreática.

•**No se incluyó población con enfermedad cardiovascular** establecida ni con insuficiencia renal avanzada. Estudios en curso como ACHIEVE-3 y ACHIEVE-4 proporcionarán información adicional sobre comparaciones con semaglutida e insulina glargina a mayor plazo.

N Engl J Med 2025;393:1065-76.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment

Sean Wharton, M.D.,[1-3] Louis J. Aronne, M.D.,[4] Adam Stefanski, M.D., Ph.D.,[5] Nasreen F. Alfaris, M.D., M.P.H.,[6] Andreea Ciudin, M.D., Ph.D.,[7-11] Koutaro Yokote, M.D., Ph.D.,[12] Bruno Halpern, M.D., Ph.D.,[13] Alpana P. Shukla, M.D.,[4] Chunmei Zhou, M.S.,[5] Lisa Macpherson, M.S.P.H.,[5] Sheryl E. Allen, M.D.,[5] Nadia N. Ahmad, M.D., M.P.H.,[5] and Suzanne R. Klise, B.S.,[5] for the ATTAIN-1 Trial Investigators*

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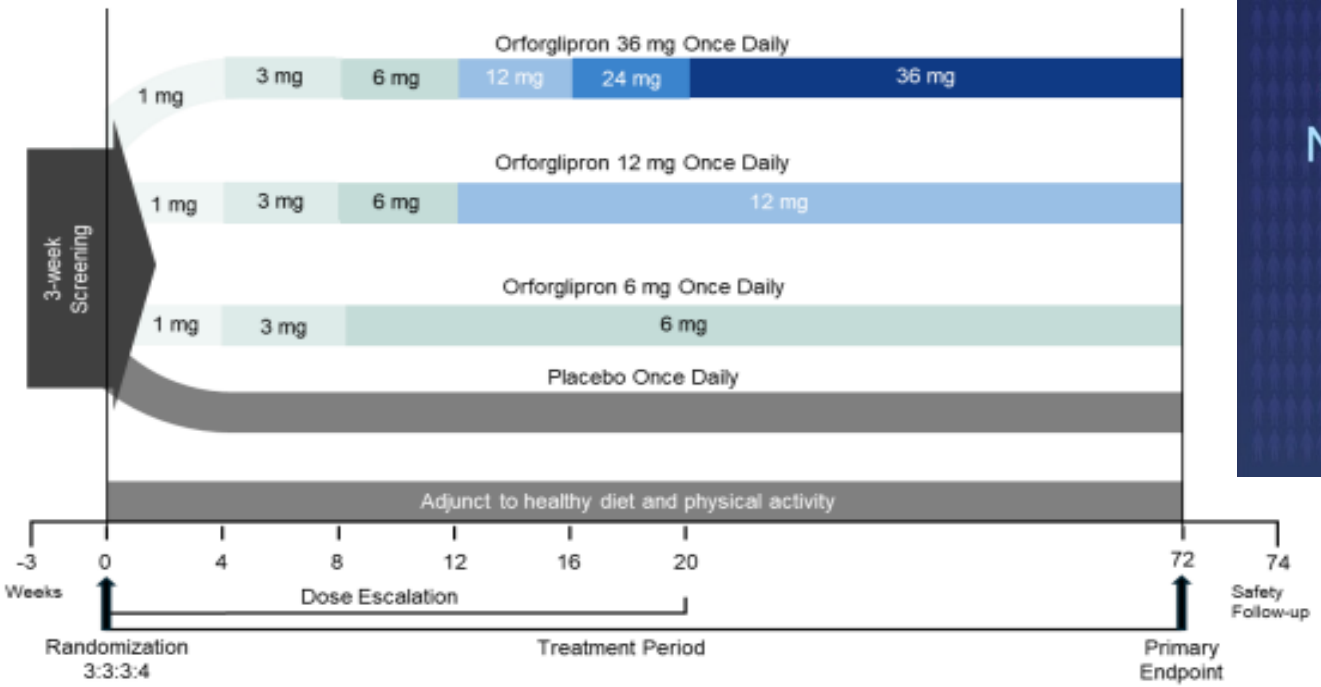
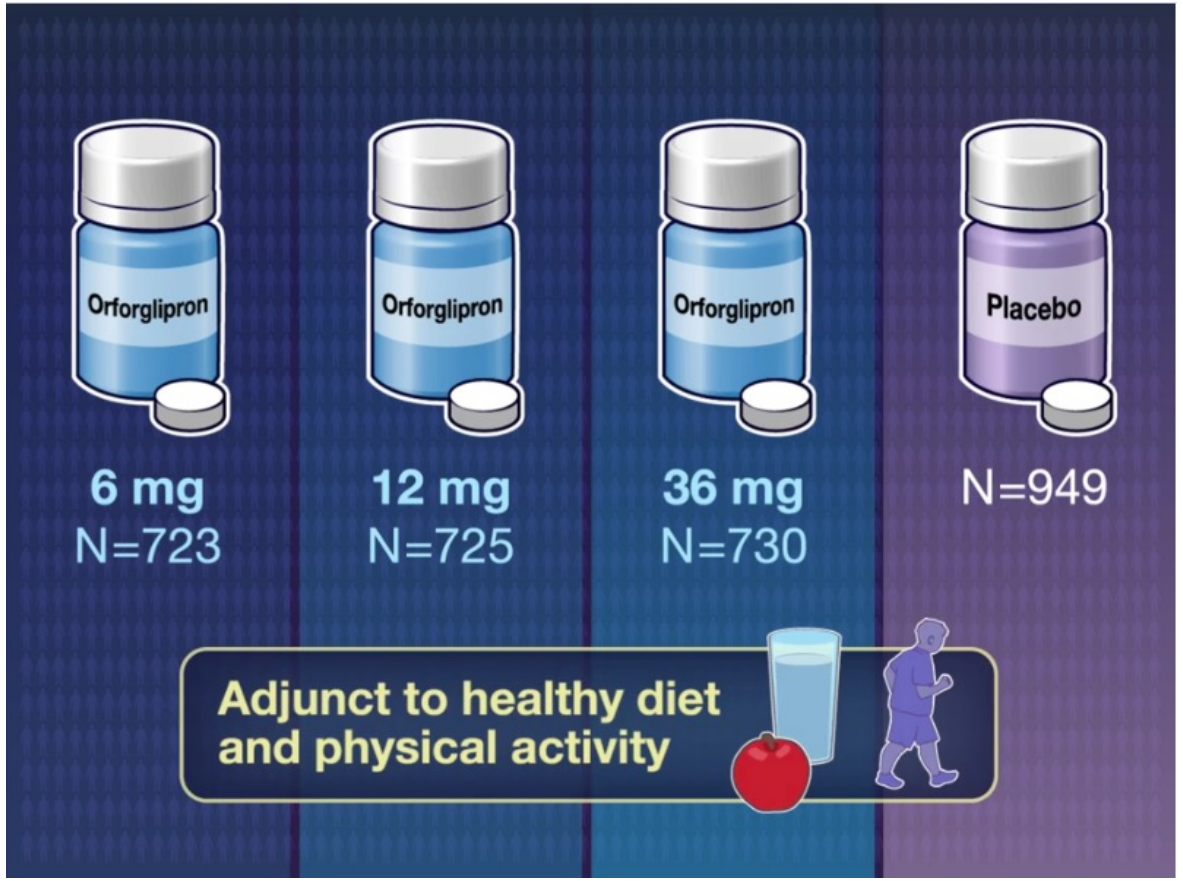
N Engl J Med 2025;393:1796-806

3127 PACIENTES

ATTAIN-1 Trial

- Phase 3
- Randomized
- Placebo-controlled





JUNIO 2023-JULIO 2025

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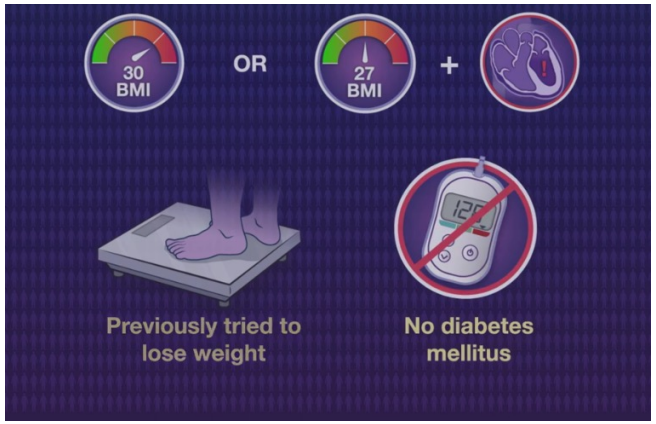
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

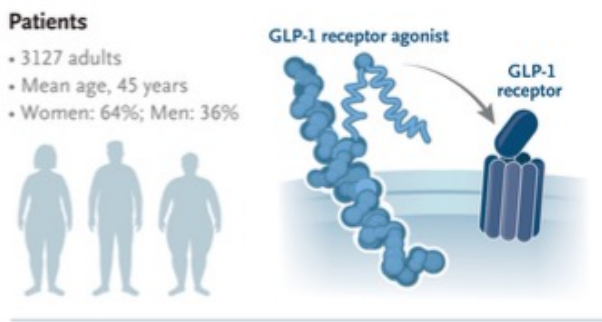
Characteristic	Orforglipron, 6 mg (N=723)	Orforglipron, 12 mg (N=725)	Orforglipron, 36 mg (N=730)	Placebo (N=949)	Total (N=3127)
Age — yr	44.9±12.1	45.4±12.6	44.9±11.9	45.1±11.9	45.1±12.1
Female sex — no. (%)	469 (64.9)	467 (64.4)	465 (63.7)	608 (64.1)	2009 (64.2)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	2 (0.3)	3 (0.4)	2 (0.3)	4 (0.4)	11 (0.4)
Asian	202 (28.3)	201 (28.1)	214 (29.6)	267 (28.5)	884 (28.6)
Black	68 (9.5)	60 (8.4)	67 (9.3)	72 (7.7)	267 (8.6)
White	408 (57.1)	405 (56.6)	394 (54.4)	539 (57.5)	1746 (56.5)
Native Hawaiian or other Pacific Islander	0	1 (0.1)	0	2 (0.2)	3 (0.1)
Multiple	35 (4.9)	45 (6.3)	47 (6.5)	54 (5.8)	181 (5.9)
Hispanic or Latino	273 (37.8)	275 (37.9)	258 (35.3)	369 (38.9)	1175 (37.6)
Body weight — kg	103.2±21.7	102.2±21.6	103.1±23.2	103.9±22.0	103.2±22.1
Body-mass index‡					
Mean	37.0±6.5	36.7±6.5	36.9±6.7	37.1±6.3	37.0±6.5
Distribution — no. (%)					
<30	62 (8.6)	72 (9.9)	68 (9.3)	86 (9.1)	288 (9.2)
30 to <35	263 (36.4)	272 (37.5)	285 (39.0)	331 (34.9)	1151 (36.8)
35 to <40	202 (27.9)	198 (27.3)	183 (25.1)	266 (28.0)	849 (27.2)
≥40	196 (27.1)	183 (25.2)	194 (26.6)	266 (28.0)	839 (26
Waist circumference — cm	112.2±14.1	112.0±14.2	112.4±15.3	112.8±14.5	112.4±1
Blood pressure — mm Hg					
Systolic	125.4±14.1	125.1±13.7	125.8±15.9	125.8±14.5	125.5±1
Diastolic	81.0±9.3	81.2±9.4	80.9±10.1	81.8±9.9	81.3±9
Lipid measure — mg/dl					
Total cholesterol	196.2±37.6	195.0±39.0	196.3±39.5	196.5±39.5	196.0±3
HDL cholesterol	49.6±12.5	50.1±12.4	48.5±12.6	49.3±12.4	49.4±12
LDL cholesterol	119.6±32.2	118.3±34.1	119.4±33.6	119.0±33.6	119.1±3
Non-HDL cholesterol	146.4±36.1	144.6±38.0	147.5±38.7	147.0±38.1	146.4±37.7
VLDL cholesterol	26.1±11.8	25.9±11.7	27.3±13.2	27.3±12.9	26.7±12.5
Triglycerides	135.4±72.5	133.5±75.8	142.8±89.1	142.4±91.9	138.8±83.5



9 paises

Type of participant and disease characteristics

2. Have a BMI
   - ≥30.0 kg/m², or
   - ≥27.0 kg/m² and presence of at least 1 of the following weight-related comorbidities (treated or untreated) at Visit 1:
     - Hypertension
     - Dyslipidemia
     - Obstructive sleep apnea
     - Cardiovascular disease (for example, ischemic cardiovascular disease, New York Heart Association Functional Class I-III heart failure).
3. Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight.



56.5% Raza blanca
28.6% asiaticos
8.6% r.negra
IMC 37
103.2kg
112 cm PA ,
36% prediabetes

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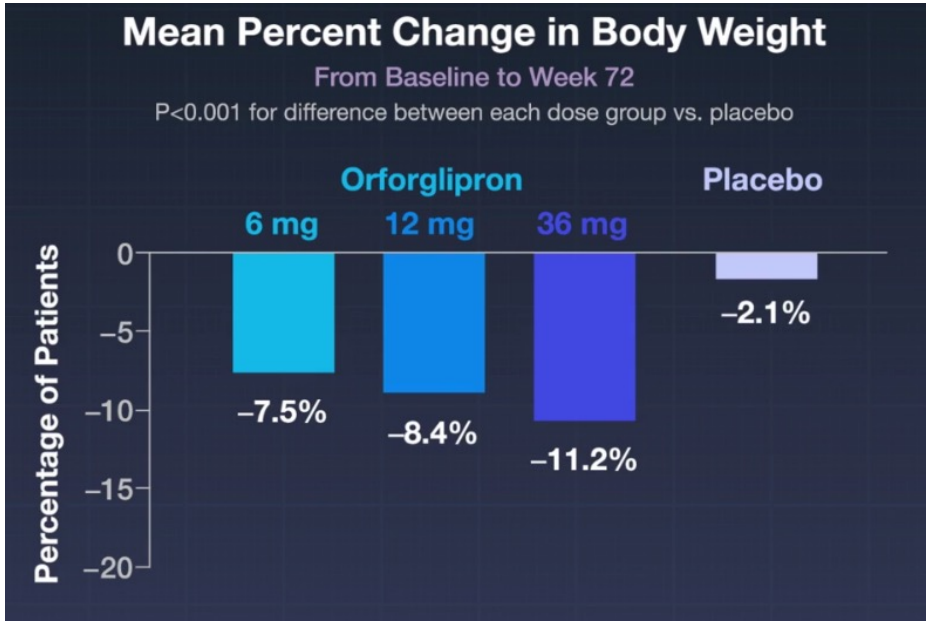
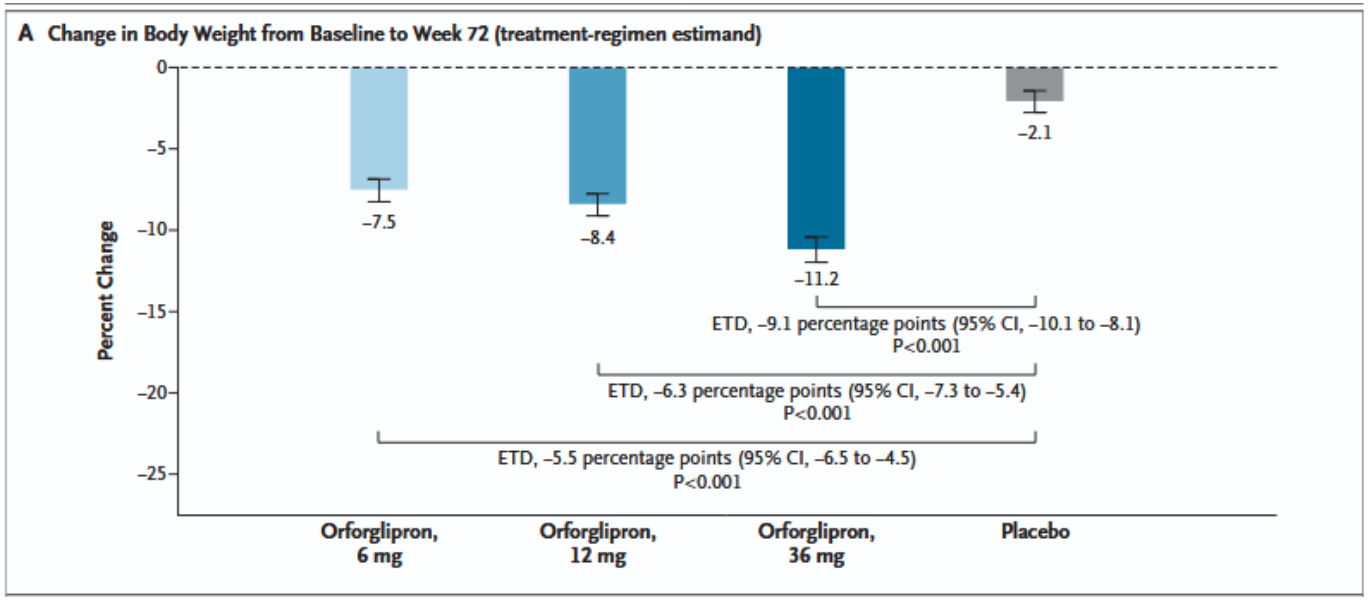
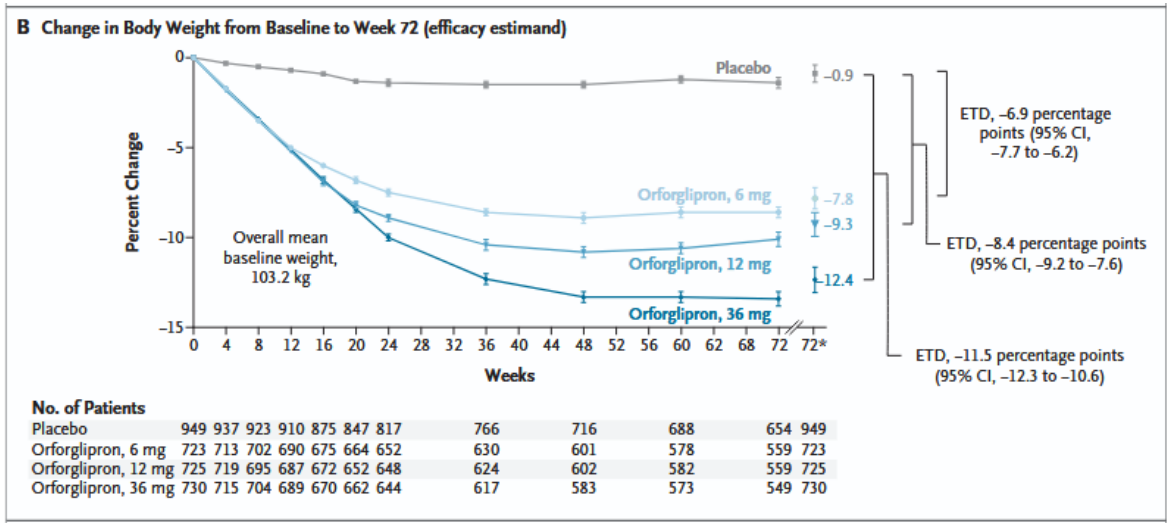
Table 2. Primary and Key Secondary End Points.*

End Point	Orforglipron, 6 mg (N=723)	Orforglipron, 12 mg (N=725)	Orforglipron, 36 mg (N=730)	Placebo (N=949)
Primary end point				
Percent change in body weight (95% CI)†	−7.5 (−8.2 to −6.8)	−8.4 (−9.1 to −7.7)	−11.2 (−12.0 to −10.4)	−2.1 (−2.8 to −1.4)
Difference vs. placebo (95% CI) — percentage points	−5.5 (−6.5 to −4.5)	−6.3 (−7.3 to −5.4)	−9.1 (−10.1 to −8.1)	—
Key secondary end points				
Category of weight reduction — % of patients (95% CI)‡				
≥5%	60.6 (56.5 to 64.6)	63.5 (59.8 to 67.2)	71.8 (68.1 to 75.4)	26.8 (23.3 to 30.2)
≥10%	33.3 (29.7 to 36.9)	40.0 (36.4 to 43.7)	54.6 (50.7 to 58.4)	12.9 (10.3 to 15.6)
≥15%	15.1 (12.4 to 17.8)	20.3 (17.3 to 23.3)	36.0 (32.4 to 39.5)	5.9 (4.0 to 7.8)
≥20%	6.4 (4.6 to 8.3)§	9.0 (6.9 to 11.1)	18.4 (15.5 to 21.3)	2.8 (1.6 to 4.0)
Change in waist circumference (95% CI) — cm†	−7.1 (−7.7 to −6.5)	−8.2 (−8.9 to −7.5)	−10.0 (−10.7 to −9.3)	−3.1 (−3.7 to −2.4)







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Outcome secundarios

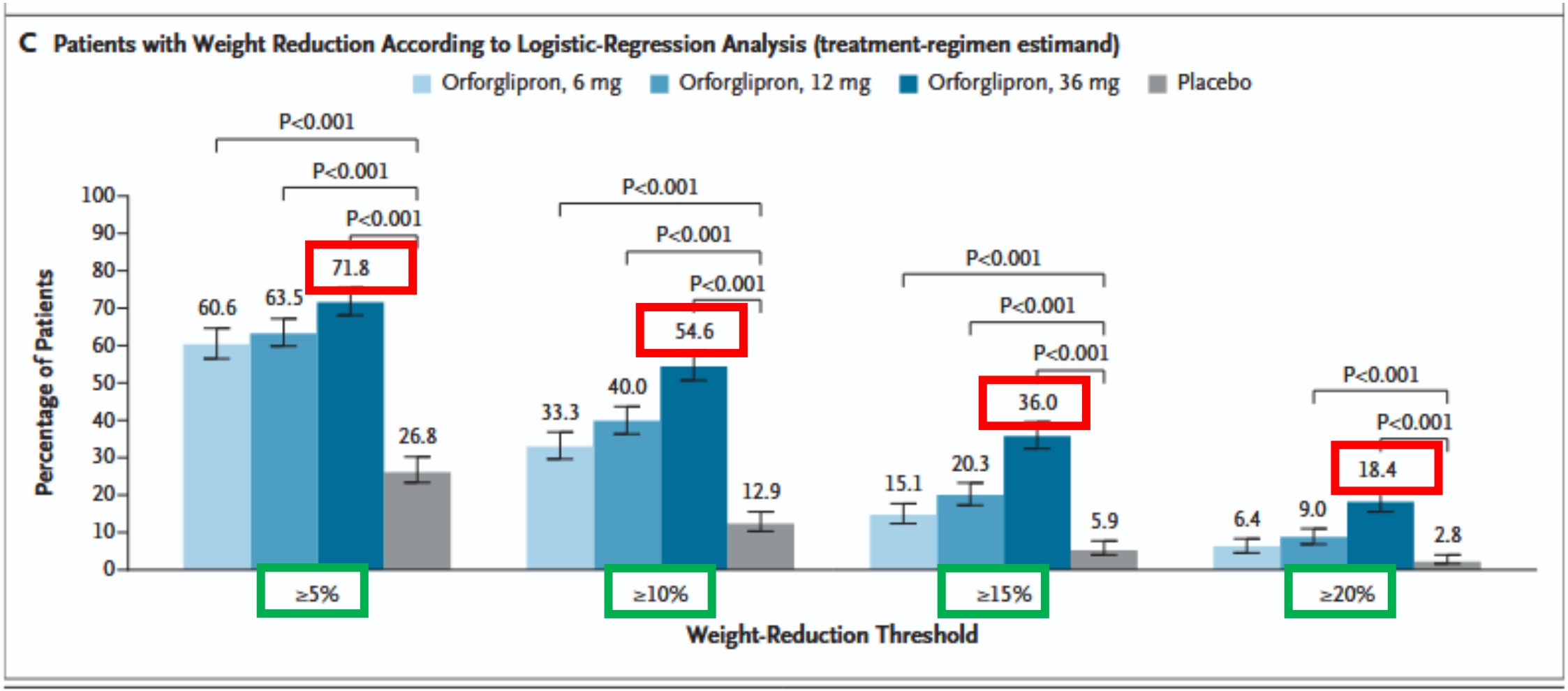

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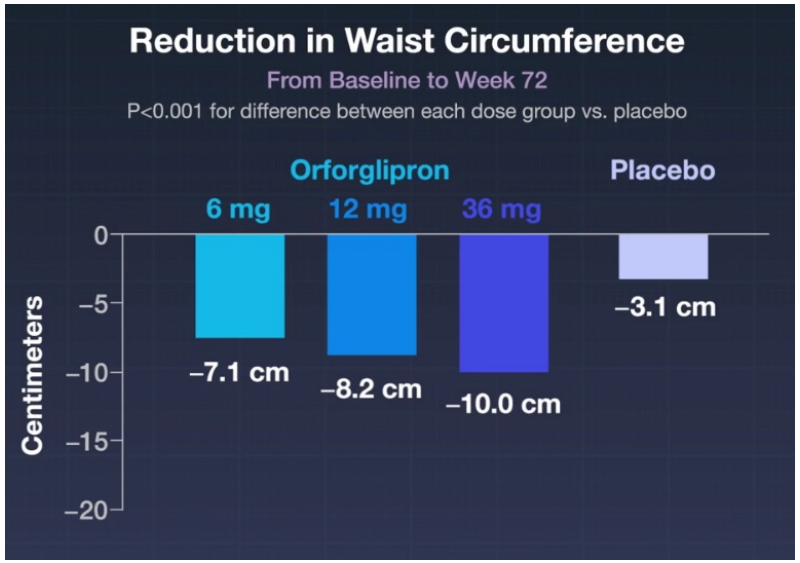
Table 3. Key Secondary and Additional Secondary End Points.*

End Point	Pooled Orforglipron† (N=2178)	Placebo (N=949)	Estimated Treatment Difference vs. Placebo (95% CI)
Key secondary end points‡			
Change in systolic brood pressure (95% CI) — mm Hg	−5.7 (−6.3 to −5.0)	−1.4 (−2.4 to −0.5)	−4.2 (−5.3 to −3.2)
Percent change (95% CI)§			
Triglycerides	−14.8 (−16.3 to −13.3)	−3.8 (−6.8 to −0.7)	−11.5 (−14.5 to −8.3)
Non-HDL cholesterol	−6.7 (−7.6 to −5.8)	−1.9 (−3.6 to −0.2)	−4.9 (−6.7 to −3.1)
Additional secondary end points			
Change in diastolic blood pressure (95% CI) — mm Hg	−2.4 (−2.9 to −2.0)	−1.4 (−2.1 to −0.7)	−1.0 (−1.8 to −0.2)
Percent change (95% CI)§			
Total cholesterol	−4.1 (−4.8 to −3.4)	−2.0 (−3.3 to −0.6)	−2.1 (−3.7 to −0.6)
LDL cholesterol	−4.8 (−5.8 to −3.7)	−1.3 (−3.0 to 0.4)	−3.5 (−5.5 to −1.5)
VLDL cholesterol	−14.6 (−16.1 to −13.1)	−3.5 (−6.3 to −0.6)	−11.5 (−14.5 to −8.5)

Outcome secundarios



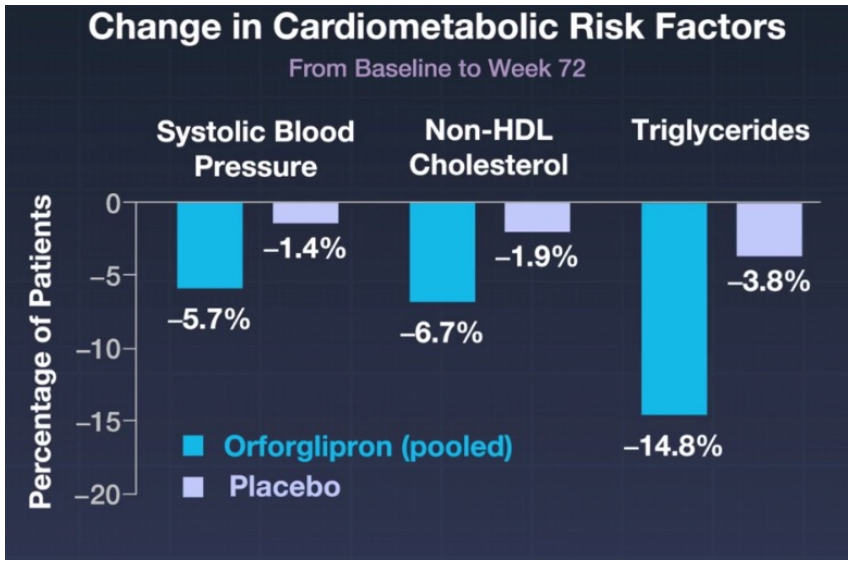


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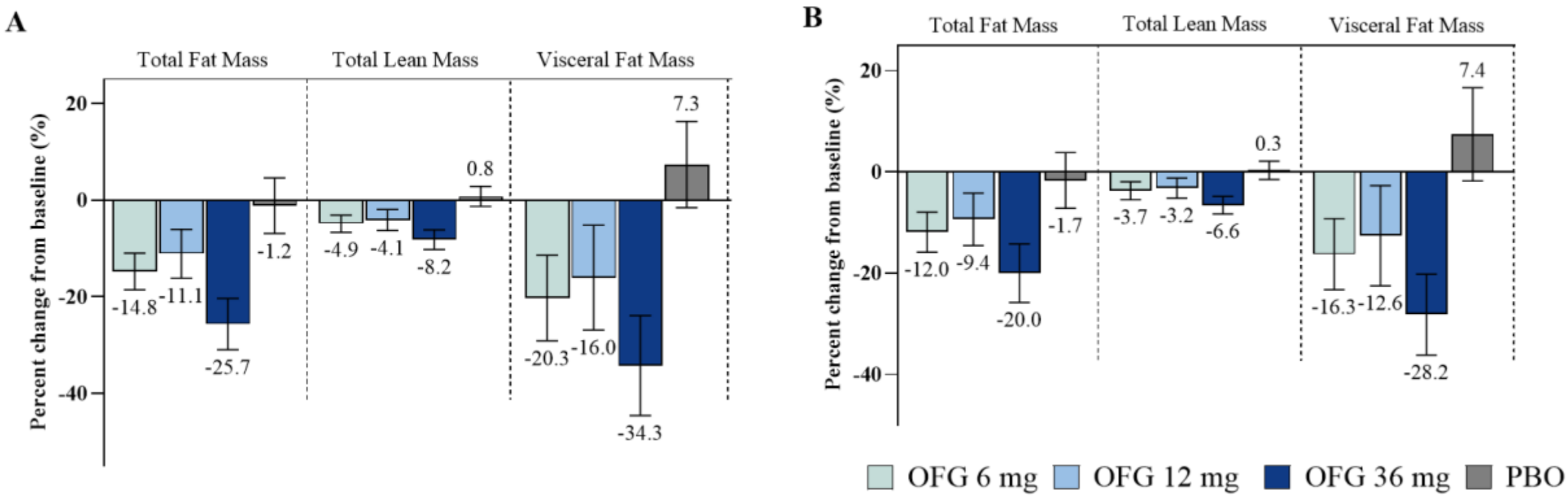
Figure S8. Change in body composition



La mayor parte de la pérdida de peso lograda es masa grasa (75% del peso total perdido fue grasa corporal)

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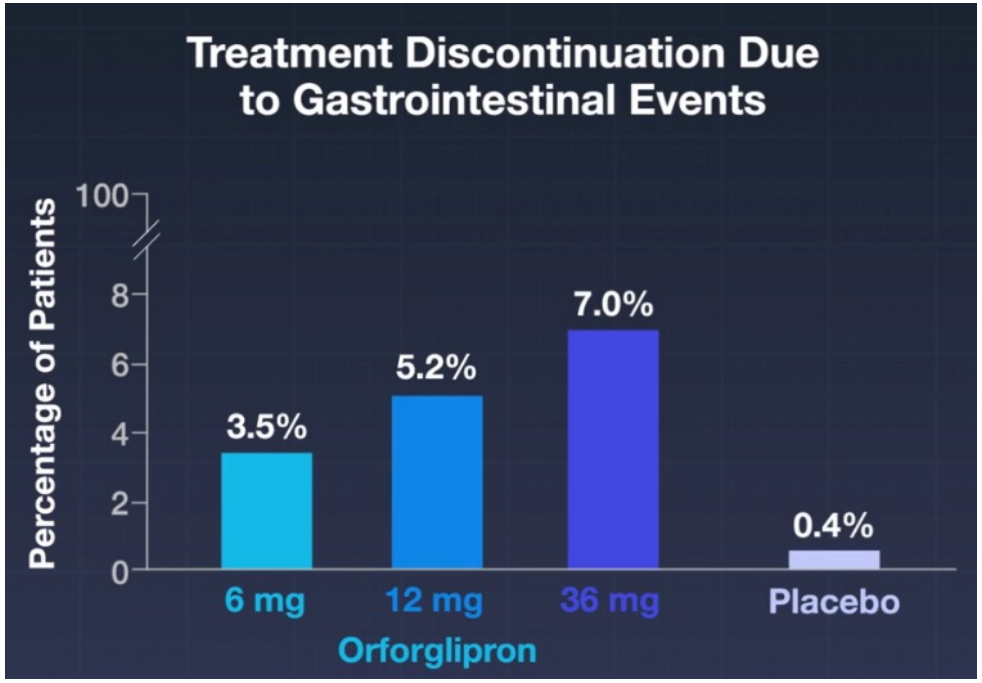
Table 4. Adverse Events.*

Adverse Event	Orforglipron, 6 mg (N=723)	Orforglipron, 12 mg (N=724)	Orforglipron, 36 mg (N=728)	Placebo (N=948)	Total (N=3123)
	number of patients (percent)				
Any adverse event emerging during treatment period	603 (83.4)	627 (86.6)	620 (85.2)	763 (80.5)	2613 (83.7)
Serious adverse event	40 (5.5)	39 (5.4)	28 (3.8)	46 (4.9)	153 (4.9)
Death†	1 (0.1)	1 (0.1)	0	1 (0.1)	3 (0.1)
Event leading to discontinuation of orforglipron or placebo					
Any adverse event	38 (5.3)	57 (7.9)	75 (10.3)	26 (2.7)	196 (6.3)
Gastrointestinal disorder	25 (3.5)	38 (5.2)	51 (7.0)	4 (0.4)	118 (3.8)
Adverse event of special interest and other safety topics					
Hepatic event‡	1 (0.1)	0	2 (0.3)	2 (0.2)	5 (0.2)
Cancer	6 (0.8)	8 (1.1)	6 (0.8)	10 (1.1)	30 (1.0)
Adjudication-confirmed pancreatitis§	1 (0.1)	2 (0.3)	2 (0.3)	0	5 (0.2)
Hypotension or syncope‡	0	0	1 (0.1)	1 (0.1)	2 (0.1)
Adjudication-confirmed MACE	7 (1.0)	0	4 (0.5)	4 (0.4)	15 (0.5)
Any cardiac disorder¶	1 (0.1)	1 (0.1)	0	2 (0.2)	4 (0.1)
Gastrointestinal event‡	10 (1.4)	19 (2.6)	25 (3.4)	6 (0.6)	60 (1.9)
Gallbladder disease‡	3 (0.4)	6 (0.8)	6 (0.8)	4 (0.4)	19 (0.6)
Acute renal event‡	0	0	0	1 (0.1)	1 (<0.1)
Major depressive disorder or suicidal ideation or behavior‡	1 (0.1)	1 (0.1)	2 (0.3)	1 (0.1)	5 (0.2)
Hypersensitivity‡	0	0	0	1 (0.1)	1 (<0.1)
Dysesthesia‖	1 (0.1)	1 (0.1)	9 (1.2)	6 (0.6)	17 (0.5)
Other adverse event emerging during treatment period					
Cholelithiasis	6 (0.8)	11 (1.5)	11 (1.5)	8 (0.8)	36 (1.2)
Acute cholecystitis	1 (0.1)	2 (0.3)	4 (0.5)	1 (0.1)	8 (0.3)
Chronic cholecystitis	2 (0.3)	3 (0.4)	1 (0.1)	1 (0.1)	7 (0.2)



GI , Dosis dependientes y transitorios

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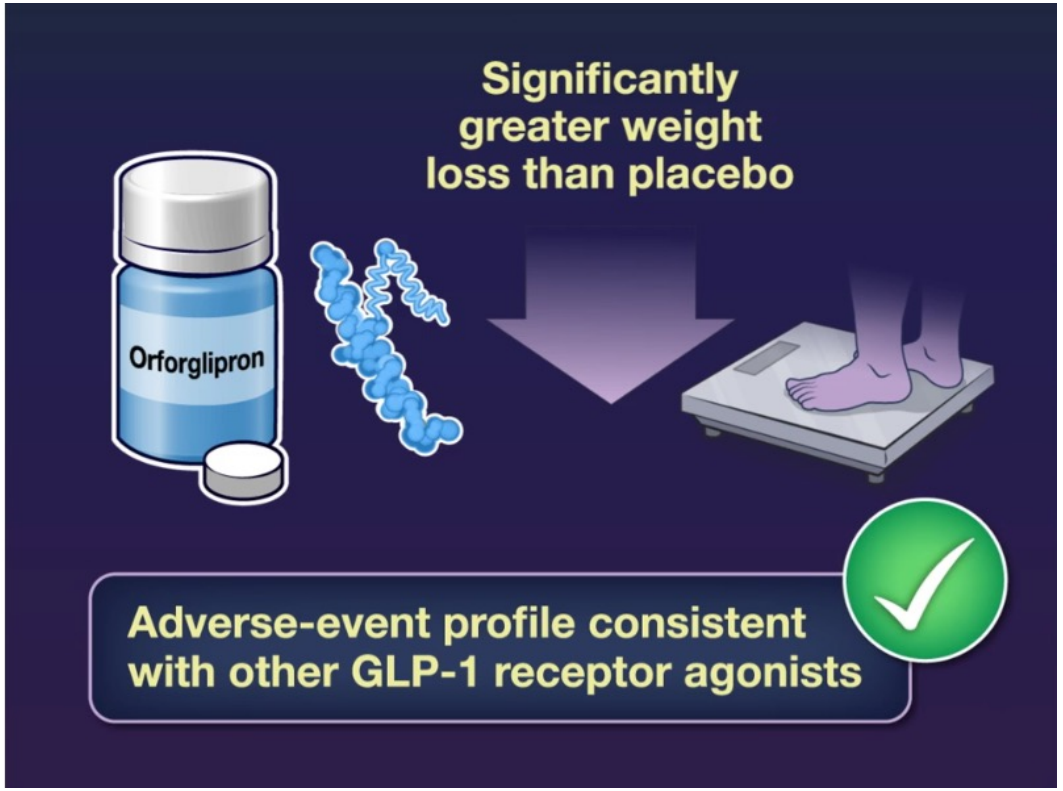
Conclusión

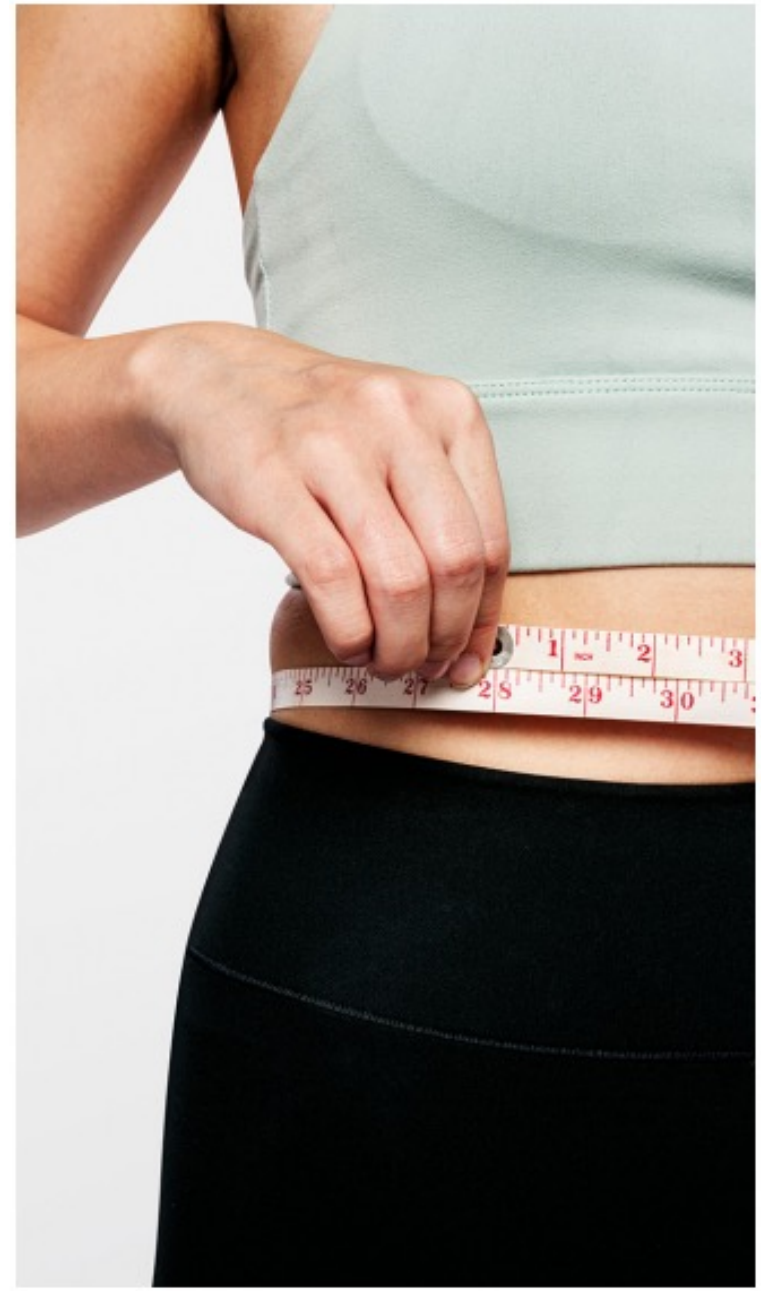
- Orforglipron es un análogo GLP1 no peptídico que demostró en adultos con obesidad **reducciones significativas de pérdida de peso**, especialmente de masa grasa durante 72 semanas de tratamiento.

- Reducción de PA , perfil lipídico, glucemia e inflamación

- Perfil de seguridad aceptable

- Potencial para ampliar el tratamiento de la obesidad



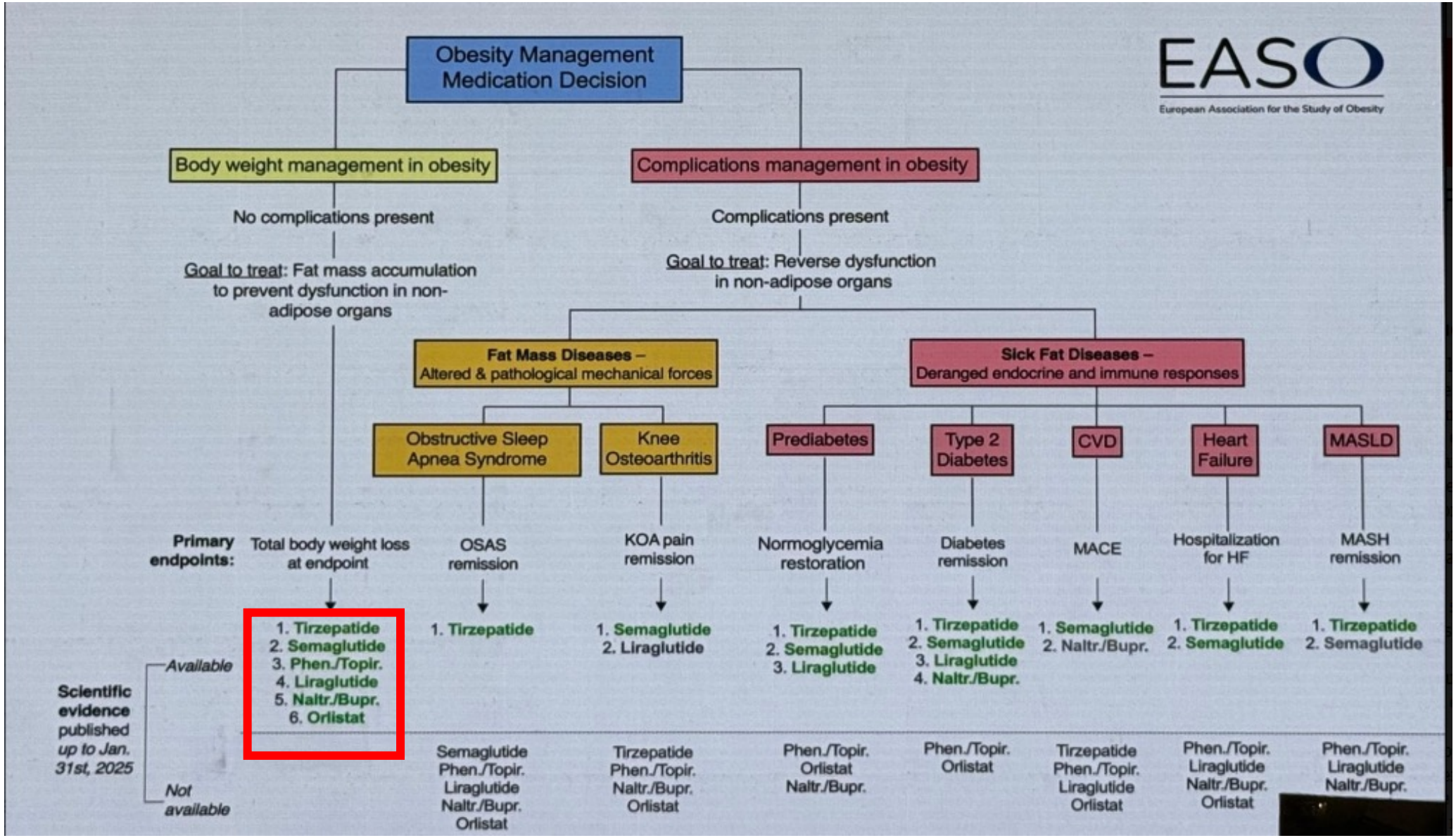


Trial	Oral Therapy	Max Dose Studied	Population	Duration	Mean Weight Loss	Key Points
OASIS-4	Semaglutide	25 mg/day	Obesity without diabetes	64 wks	−14%	Stronger efficacy than Rybelsus 14 mg; GI side effects common
ATTAIN-1	Orforglipron	36 mg/day	Obesity without diabetes	72 wks	−11%	Over half achieved ≥10% weight loss; improved metabolic markers
ACHIEVE-1	Orforglipron	36 mg/day	Early type 2 diabetes	40 wks	−8%	Also reduced HbA1c by −1.5%; good option in

Comparison With Rybelsus 14 mg

Rybelsus (oral semaglutide 14 mg) is already FDA-approved for type 2 diabetes and sometimes used off-label for weight management. However, weight loss averages **4–6%** at 14 mg, significantly lower than seen with newer trials.

- **Semaglutide 25 mg:** In OASIS-4, weight loss reached **−14%**, nearly triple the Rybelsus 14 mg effect.
- **Orforglipron 36 mg:** In ATTAIN-1, **−11%** weight loss was achieved, again well above Rybelsus outcomes.
- ***Clinical relevance:*** *These data suggest that both orforglipron and higher-dose oral semaglutide (25 mg) may soon offer oral alternatives that match injectable GLP-1s in efficacy. This could reshape prescribing patterns for obesity and diabetes, especially for patients reluctant to use injections.*

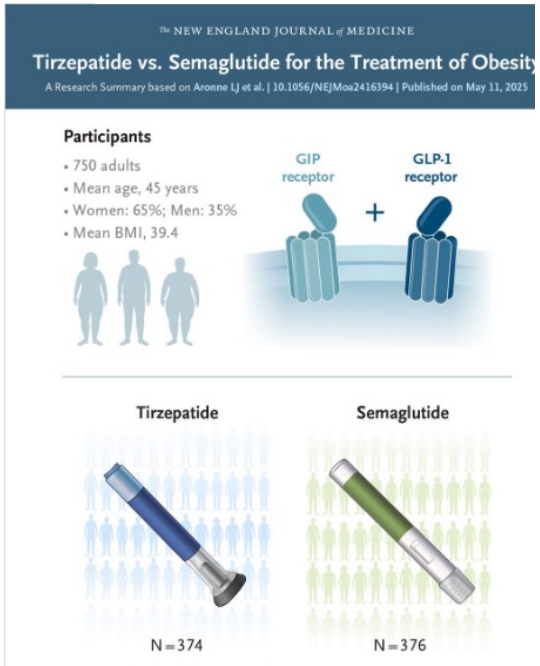

Obesity Management Medication Decision
EASO
European Association for the Study of Obesity
Body weight management in obesity
Complications management in obesity
No complications present
Complications present
Goal to treat: Fat mass accumulation to prevent dysfunction in non-adipose organs
Goal to treat: Reverse dysfunction in non-adipose organs
Fat Mass Diseases – Altered & pathological mechanical forces
Sick Fat Diseases – Deranged endocrine and immune responses
Obstructive Sleep Apnea Syndrome
Knee Osteoarthritis
Prediabetes
Type 2 Diabetes
CVD
Heart Failure
MASLD
Primary endpoints:
Total body weight loss at endpoint
OSAS remission
KOA pain remission
Normoglycemia restoration
Diabetes remission
MACE
Hospitalization for HF
MASH remission
1. Tirzepatide
2. Semaglutide
3. Phen./Topir.
4. Liraglutide
5. Naltr./Bupr.
6. Orlistat
1. Tirzepatide
1. Semaglutide
2. Liraglutide
1. Tirzepatide
2. Semaglutide
3. Liraglutide
1. Tirzepatide
2. Semaglutide
3. Liraglutide
4. Naltr./Bupr.
1. Semaglutide
2. Naltr./Bupr.
1. Tirzepatide
2. Semaglutide
1. Tirzepatide
2. Semaglutide
Scientific evidence published up to Jan. 31st, 2025
Available
Not available
Semaglutide
Phen./Topir.
Liraglutide
Naltr./Bupr.
Orlistat
Tirzepatide
Phen./Topir.
Naltr./Bupr.
Orlistat
Phen./Topir.
Orlistat
Naltr./Bupr.
Phen./Topir.
Orlistat
Tirzepatide
Phen./Topir.
Liraglutide
Orlistat
Phen./Topir.
Liraglutide
Naltr./Bupr.
Orlistat
Phen./Topir.
Liraglutide
Naltr./Bupr.

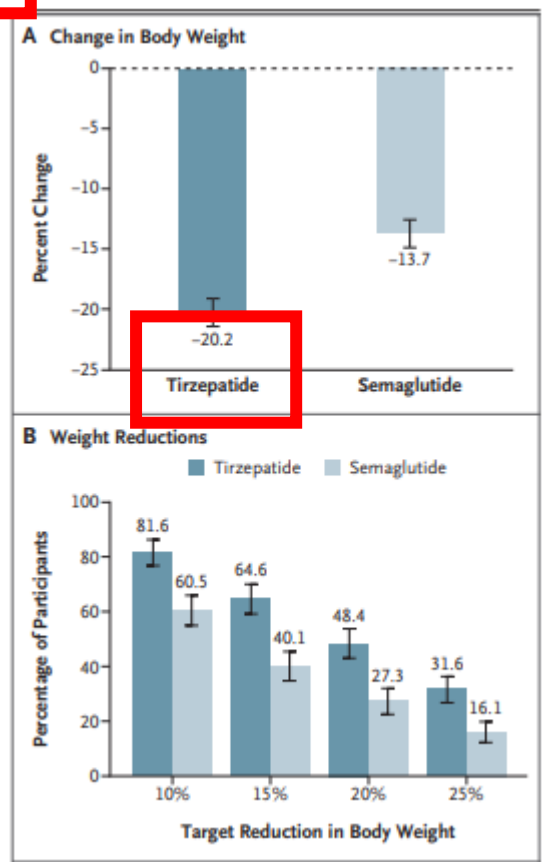
The NEW ENGLAND JOURNAL of MEDICINE

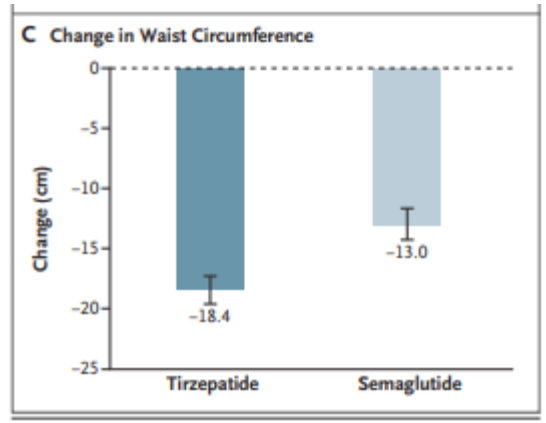
ORIGINAL ARTICLE

Tirzepatide as Compared with Semaglutide for the Treatment of Obesity

Louis J. Aronne, M.D.,[1] Deborah Bade Horn, D.O.,[2]
Carel W. le Roux, M.D., Ph.D.,[3,4] Wayne Ho, M.D.,[5,6] Beverly L. Falcon, Ph.D.,[7]
Elisa Gomez Valderas, M.Sc.,[7] Sagar Das, M.Sc.,[7] Clare J. Lee, M.D., M.H.S.,[7]
Leonard C. Glass, M.D.,[7] Cagri Senyucel, M.D., Ph.D.,[7] and Julia P. Dunn, M.D.,[7]
for the SURMOUNT-5 Trial Investigators*







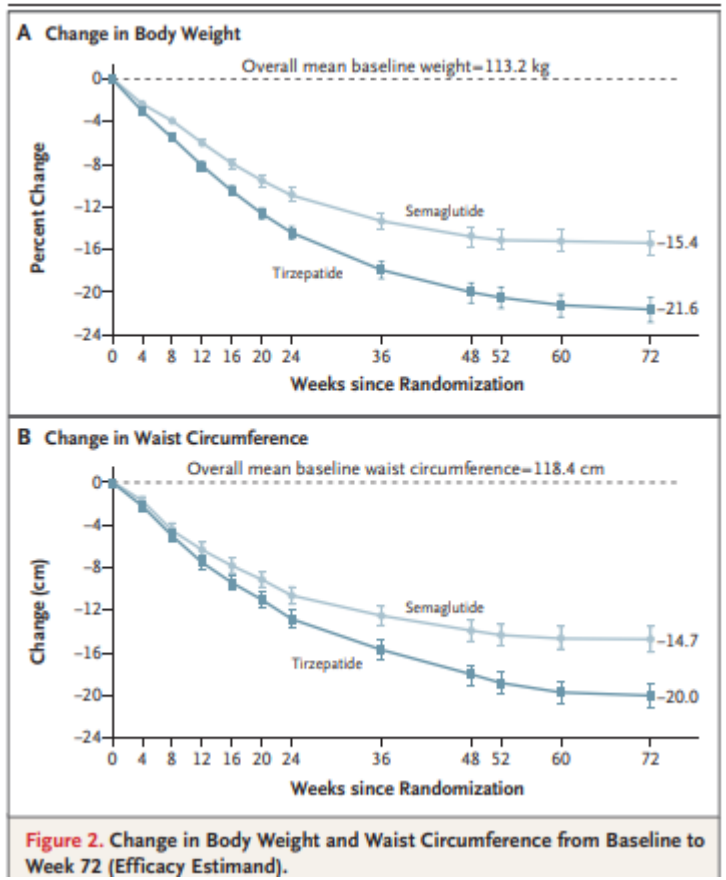


Figure 2. Change in Body Weight and Waist Circumference from Baseline to Week 72 (Efficacy Estimand).

N Engl J Med 2025;393:26-36.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cagrilintide–Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes

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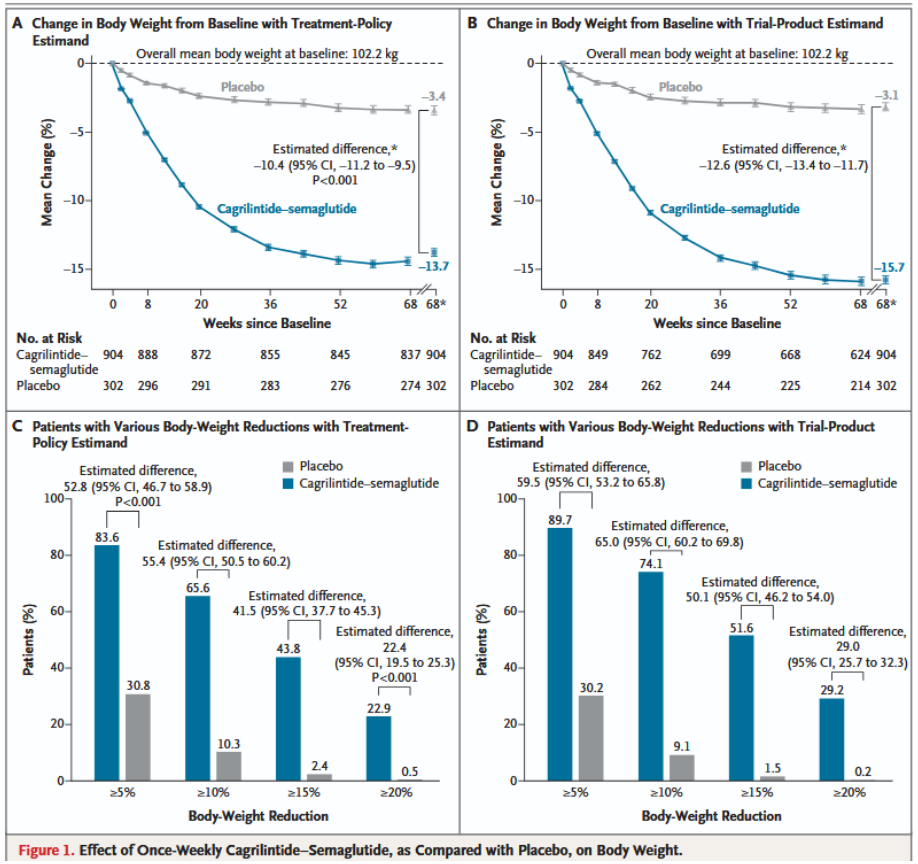
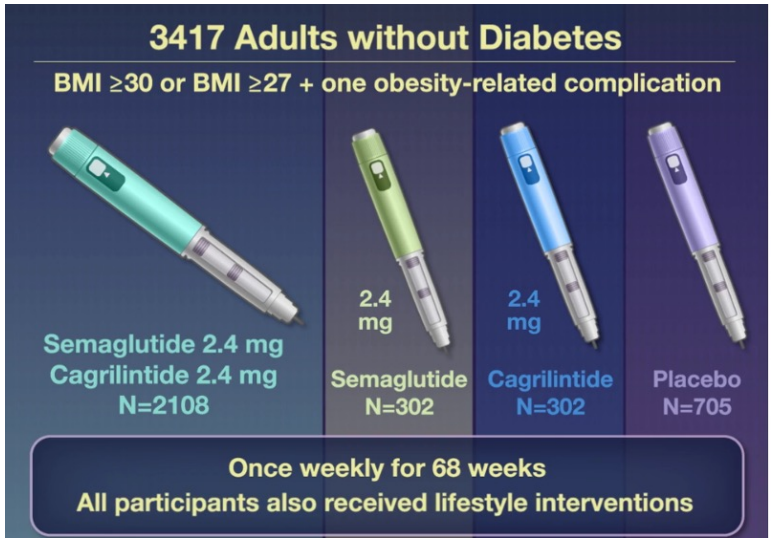


Figure 1. Effect of Once-Weekly Cagrilintide–Semaglutide, as Compared with Placebo, on Body Weight.



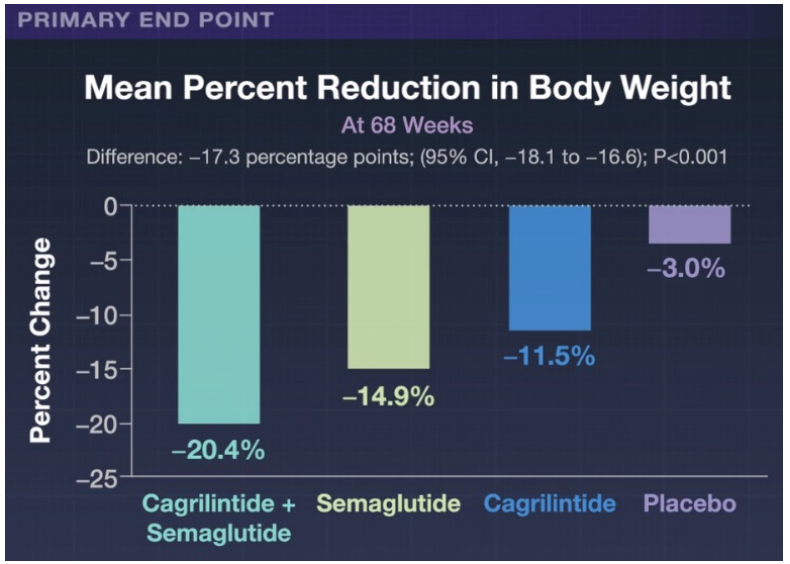


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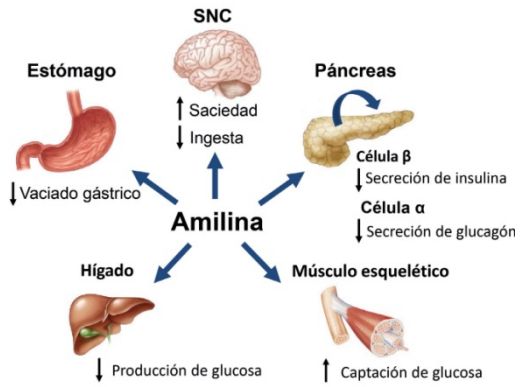
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Cagrilintide–Semaglutide (N=904)	Placebo (N=302)
Age — yr	55.9±11.8	56.5±10.7
Female sex — no. (%)	429 (47.5)	140 (46.4)
Race or ethnic group — no. (%)†		
White	597 (66.0)	204 (67.5)
Asian	262 (29.0)	84 (27.8)
Black	33 (3.7)	10 (3.3)
Other‡	12 (1.3)	4 (1.3)
Body weight — kg	101.9±22.6	103.3±23.5
Body-mass index	36.1±6.7	36.4±7.1
Waist circumference — cm	115.6±14.7	116.4±15.2
Glycated hemoglobin level — %	8.0±0.8	8.0±0.8
Fasting plasma glucose level — mmol/liter	9.3±2.4	9.5±2.8
Blood pressure — mm Hg		
Systolic	130.2±14.0	130.2±13.8
Diastolic	80.4±9.6	80.4±9.3
Estimated glomerular filtration rate — ml/min/per 1.73 m^2	94.2±19.3	93.4±17.2
Duration of diabetes — yr	8.5±6.3	8.7±5.9
Oral glucose-lowering medication — no. (%)		
Metformin	773 (85.5)	263 (87.1)
SGLT2 inhibitor	305 (33.7)	98 (32.5)
Sulfonylurea	238 (26.3)	87 (28.8)
Thiazolidinedione	41 (4.5)	15 (5.0)
None	64 (7.1)	18 (6.0)
Physical function		
IWQOL-Lite-CT score§	59.0±24.3	59.7±24.0
SF-36v2 score¶	44.8±9.8	44.6±9.6

péptido análogo de acción prolongada de los receptores de amilina y calcitonina.



The NEW ENGLAND JOURNAL of MEDICINE

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Once-Monthly Maridebart Cafraglutide for the Treatment of Obesity — A Phase 2 Trial

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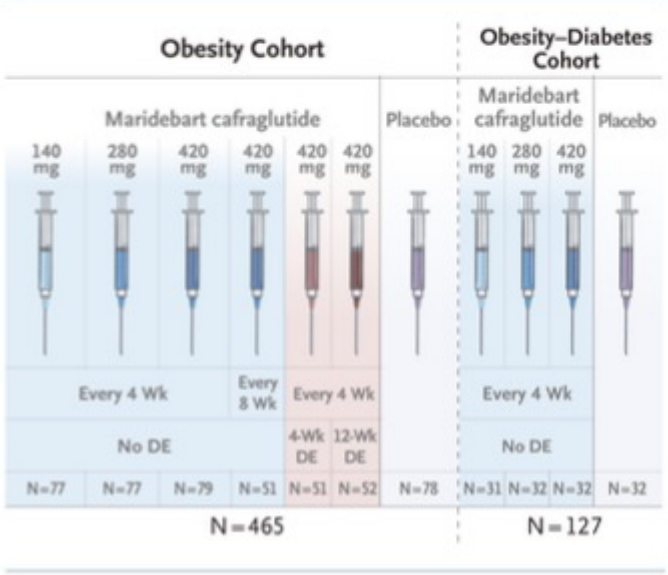
ABSTRACT

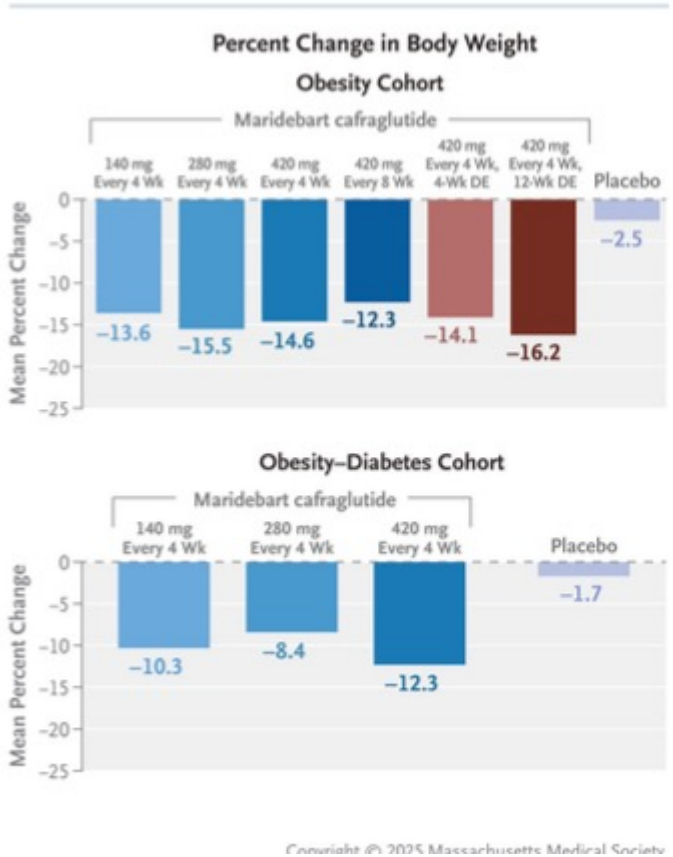
Es un conjugado de péptido y anticuerpo de acción prolongada que actúa como agonista del receptor GLP-1 y antagonista del receptor GIP
Inyección mensual.

Participants

Obesity Cohort
- 465 adults
- Women: 63%; Men: 37%
- Mean age, 48 years
- Mean BMI: 37.9

Obesity–Diabetes Cohort
- 127 adults
- Women: 42%; Men: 58%
- Mean age, 55 years
- Mean BMI: 36.5





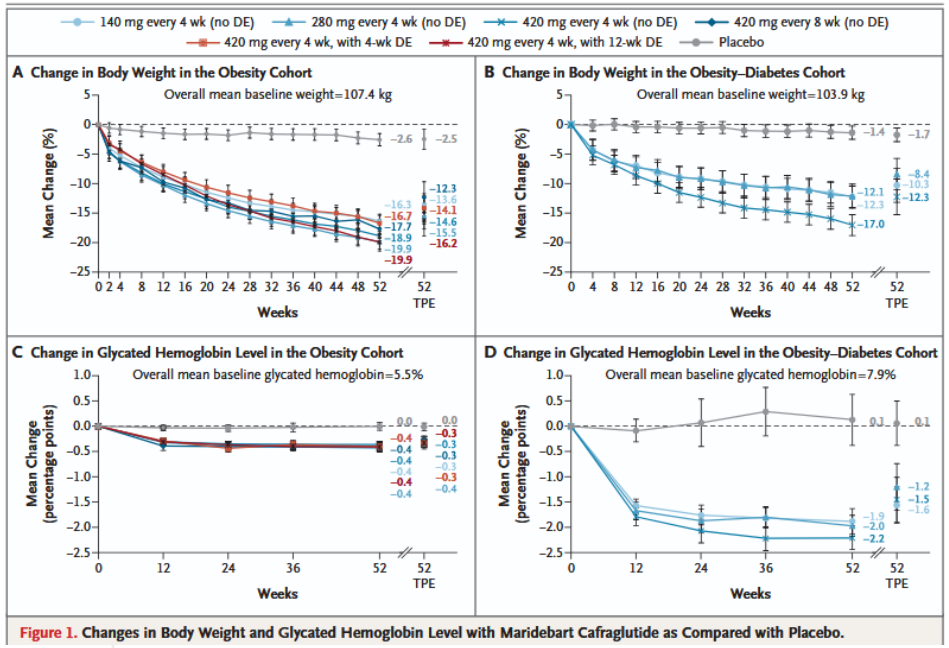


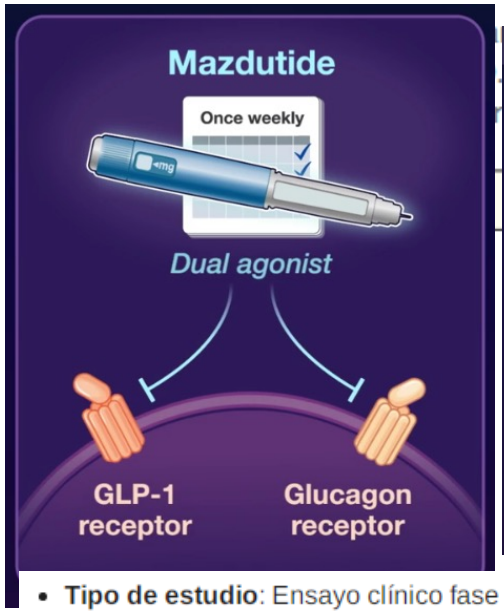
Figure 1. Changes in Body Weight and Glycated Hemoglobin Level with Maridebart Cafraglutide as Compared with Placebo.

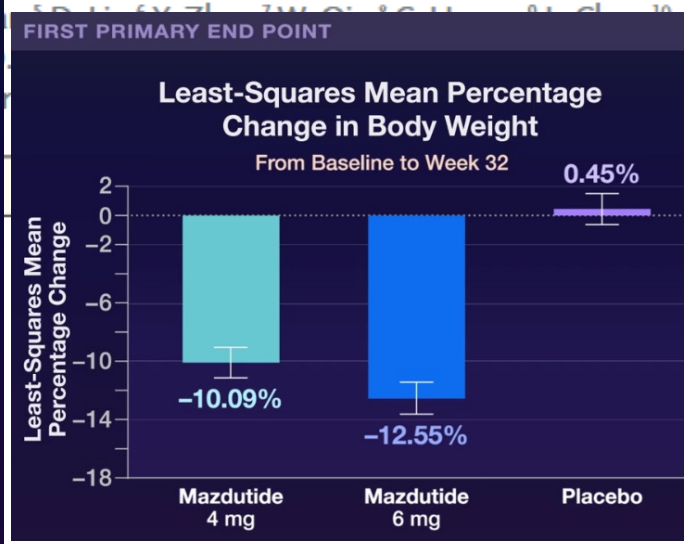
N Engl J Med 2025;393:843-57

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Once-Weekly Mazdutide in Chinese Adults with Obesity or Overweight





- **Tipo de estudio**: Ensayo clínico fase 3, aleatorizado, doble ciego, controlado con placebo.
- **Lugar**: 23 hospitales en China.
- **Duración**: 48 semanas de tratamiento + 12 semanas de seguimiento post-tratamiento.
- **Participantes**: 610 adultos (IMC ≥28 o IMC ≥24 con al menos una comorbilidad).
- **Intervención**:
  - Mazdutide 4 mg semanal.
  - Mazdutide 6 mg semanal.
  - Placebo.
  - Todos los grupos recibieron orientación en dieta y ejercicio.

Table 2. Primary and Key Secondary End Points (Treatment-Policy Estimand Analysis).*

Variable	Mazdutide, 4 mg (N=203)	Mazdutide, 6 mg (N=202)	Placebo (N=205)
No. of participants with body-weight and waist-circumference measures			
At wk 32	200	187	196
At wk 48	190	184	196
Primary end points			
Percentage change in body weight from baseline to wk 32 (95% CI)	−10.09 (−11.15 to −9.04)	−12.55 (−13.64 to −11.45)	0.45 (−0.61 to 1.52)
Difference vs. placebo (95% CI) — percentage points	−10.54 (−11.83 to −9.26)†	−13.00 (−14.31 to −11.70)†	—
Weight reduction of ≥5% at wk 32 (95% CI) — %‡	73.9 (67.8 to 79.9)	82.0 (76.7 to 87.4)	10.5 (6.2 to 14.7)
Relative rate vs. placebo (95% CI)	7.1 (4.6 to 11.0)†	7.9 (5.1 to 12.2)†	—
Key secondary end points			
Percentage change in body weight from baseline to wk 48 (95% CI) — %	−11.00 (−12.27 to −9.73)	−14.01 (−15.36 to −12.66)	0.30 (−0.98 to 1.58)
Difference vs. placebo (95% CI) — percentage points	−11.30 (−12.84 to −9.76)†	−14.31 (−15.88 to −12.74)†	—
Weight reduction of ≥10% at wk 32 (95% CI) — %	49.0 (42.1 to 55.9)	61.6 (54.8 to 68.5)	0.6 (−0.5 to 1.8)
Relative rate vs. placebo (95% CI)	81.7 (19.3 to 346.1)†	101.7 (24.1 to 429.2)†	—
Weight reduction of ≥15% at wk 32 (95% CI) — %‡	27.2 (21.0 to 33.3)	43.6 (36.6 to 50.6)	0.0 (0.0 to 1.8)
Relative rate vs. placebo (95% CI)	113.1 (88.7 to 144.1)†	178.5 (145.8 to 218.6)†	—
Weight reduction of ≥5% at wk 48 (95% CI) — %‡	71.6 (65.3 to 77.9)	81.6 (75.9 to 87.2)	10.8 (6.5 to 15.2)
Relative rate vs. placebo (95% CI)	6.7 (4.4 to 10.1)†	7.6 (5.1 to 11.3)†	—
Weight reduction of ≥10% at wk 48 (95% CI) — %‡	53.5 (46.6 to 60.4)	66.7 (60.0 to 73.4)	2.6 (0.4 to 4.8)
Relative rate vs. placebo (95% CI)	21.1 (7.6 to 58.2)†	26.1 (9.4 to 72.0)†	—
Weight reduction of ≥15% at wk 48 (95% CI) — %‡	35.7 (29.1 to 42.4)	49.5 (42.4 to 56.6)	2.0 (0.1 to 3.9)
Relative rate vs. placebo (95% CI)	18.5 (5.6 to 61.8)†	25.3 (7.6 to 84.0)†	—
Change in waist circumference from baseline to wk 32 (95% CI) — cm	−7.86 (−8.69 to −7.03)	−9.27 (−10.12 to −8.42)	−0.99 (−1.82 to −0.16)
Difference vs. placebo (95% CI)	−6.87 (−7.88 to −5.86)†	−8.28 (−9.30 to −7.25)†	—
Change in waist circumference from baseline to wk 48 (95% CI) — cm	−9.12 (−10.11 to −8.12)	−10.72 (−11.76 to −9.68)	−1.41 (−2.41 to −0.42)
Difference vs. placebo (95% CI)	−7.70 (−8.91 to −6.50)†	−9.31 (−10.54 to −8.08)†	—

N Engl J Med 2025;392:2215-25.

Desafíos …..

- ¿Cuál es el **perfil ideal** de paciente para tratamiento oral vs inyectable?

- ¿Cómo afectará la **disponibilidad de la vía oral** a la adherencia, los costes, al acceso e implementación en los sistemas de salud?

- ¿Cuál será la **magnitud de la pérdida de peso sostenida** con la formulación oral y cómo se compara con la inyectable en Términos de respuesta a largo plazo?

CLINICAL DECISIONS
INTERACTIVE AT NEJM.ORG

Managing Obesity

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options as assigned. Readers can participate in forming community opinion by choosing one of the options.

CASE VIGNETTE

A Man with Obesity

Christos P. Kotanidis, M.D., D.Phil.[1]

A 42-year-old man presents to your primary care practice with concerns about his weight. Eleven months earlier, he had an acute myocardial infarction, for which he was treated with angioplasty and stenting. His cardiologist initiated dual antiplatelet therapy, a statin, and an angiotensin-converting–enzyme inhibitor and, given the patient's body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 36.3 and active smoking status, urged him to stop smoking and to lose weight. His medical history is otherwise unremarkable, and he takes no other medications.

Over the past 7 months, he has been trying to follow a diet of 1500 kcal per day and has walked his dog daily for 30 minutes. However, he finds it difficult to adhere to the diet, primarily because of frequent cravings for sweet snacks; he has lost only 2 kg of weight. He has reduced his smoking to three cigarettes per day and consumes a glass of wine about once a week. He wonders whether pharmacologic or surgical interventions might be appropriate to help with weight loss.

On physical examination, his blood pressure is 128/75 mm Hg, and his heart rate is 103 beats per minute. He is 1.81 m (5 ft 11 in.) tall and weighs 117 kg (258 lb); his BMI is 35.7, and his waist circumference is 109 cm (43 in.). The rest of the examination is unremarkable. Laboratory results include a glycated hemoglobin value of 5.6% and a total cholesterol level of 190 mg per deciliter (4.9 mmol per liter) (both considered to be in the normal or desirable range), as well as normal liver and kidney function.

You must decide which strategy for losing weight would be most effective and safest for this patient. You consider whether to initiate therapy with semaglutide or to refer the patient for metabolic and bariatric surgery.

TREATMENT OPTIONS

Which one of the following approaches would you take if this were your patient? Base your choice on the literature, your own experience, published guidelines, and other information.

1. **Initiate therapy with semaglutide.**
2. **Recommend metabolic and bariatric surgery.**

To aid in your decision making, we asked experts in the field to summarize the evidence in favor of approaches assigned by the editors. Given your knowledge of the patient and the points made by the experts, which approach would you choose?

[1]Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom.

OPTION 1

Initiate Therapy with Semaglutide

A. Michael Lincoff, M.D.[1]

Obesity is an independent risk factor for the development and progression of coronary artery disease, even after accounting for the influence of associated intermediate risk factors such as hypertension, dyslipidemia, and diabetes.[1] For the patient described in the vignette who has obesity and has recently had a myocardial infarction, initiation of therapy with semaglutide would not only address his stated desire to lose weight, but would also reduce his residual risk for recurrent cardiovascular events.

Initially developed for management of glycemia, agonists of glucagon-like peptide-1 (GLP-1) can induce clinically meaningful levels of weight loss. In a trial involving patients with overweight or obesity who were treated for 104 weeks, the average reduction in body weight was 12.6 percentage points greater, and the reduction in waist circumference was 9.2 cm greater, with semaglutide, a long-acting analogue of GLP-1, than with placebo.[2] GLP-1 agonists also favorably affect a broad range of cardiometabolic pathways and have shown cardioprotective effects among patients with type 2 diabetes.[3]

The SELECT trial was conducted to determine whether the addition of semaglutide to evidence-based standard care would improve cardiovascular outcomes among patients, such as the one in this vignette, who had overweight or obesity but not diabetes. In that trial, 17,604 patients with preexisting cardiovascular disease (previous myocardial infarction, stroke, or symptomatic peripheral arterial disease) and a BMI of 27 or greater, but without diabetes, were randomly assigned to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo.[4] Over a mean duration of follow-up of 39.8 months, treatment with semaglutide resulted in a lower risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (the composite end point) than placebo (6.5% vs. 8.0% of patients; hazard ratio, 0.80 [95% confidence interval, 0.72 to 0.90]; P<0.001). Findings also suggested lower risks of death from any cause, nonfatal myocardial infarction, coronary revascularization, and a heart-failure composite of death from cardiovascular causes or hospitalization or urgent visit for heart failure. The mean reduction in body weight was 8.5 percentage points greater with semaglutide than with placebo, and the mean reduction in waist circumference was 6.5 cm greater with semaglutide. The incidence of serious adverse events was not greater with semaglutide than with placebo, although more patients discontinued semaglutide than placebo (16.6% vs. 8.2%) owing primarily to gastrointestinal symptoms, such as nausea, vomiting, or diarrhea.

The magnitude of weight reduction with semaglutide is on average less than that reported with bariatric surgery, although data directly comparing these therapeutic approaches are lacking. An important consideration, however, is the effect of obesity management strategies on secondary prevention of cardiovascular complications. Observational studies have suggested reductions in mortality and in the incidence of ischemic and heart-failure events[5] with bariatric surgery, but such studies are subject to potential confounding, and evidence from randomized trials that bariatric surgery improves cardiovascular outcomes is lacking. Thus, in this patient with coronary artery disease and obesity, semaglutide should be the first-line choice as the treatment that has been rigorously proven to lower cardiovascular risk while producing clinically meaningful reductions in adiposity.

Disclosure forms provided by the author are available at NEJM.org.

[1]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland.

OPTION 2

Recommend Metabolic and Bariatric Surgery

Scott A. Shikora, M.D.[1]

The case vignette involves a middle-aged man who has obesity (BMI of 35.7), coronary artery disease, and metabolic syndrome (hypertension and hyperlipidemia). After having a myocardial infarction, he was encouraged to lose weight and stop smoking. He succeeded in reducing his smoking but was unsuccessful in losing weight.

This patient must lose weight and therefore should be considered for metabolic and bariatric surgery. This surgery is the most effective long-term therapy for severe obesity and its associated conditions. Currently, the sleeve gastrectomy is the most common metabolic and bariatric surgical procedure performed worldwide. It is more popular than the gastric bypass because it is easier to perform, is associated with fewer complications, and does not bypass any of the intestine, thereby avoiding the risk of nutritional deficiencies. Metabolic and bariatric procedures were once considered to be high-risk surgeries. However, the use of laparoscopy, improvement in surgical instrumentation, and better surgical training have made these procedures less complex and safer. The 30-day mortality is below 1%.[6] Long-term complications include severe acid reflux and hiatal hernias after sleeve gastrectomy and internal hernias, ulcers, and vitamin deficiencies after gastric bypass. Approximately 25% of patients have inadequate weight loss or

El sorprendente alimento que debes tomar antes de beber alcohol si quieres evitar la resaca, según una doctora

El alimento milagroso que debes comer para evitar resacas

Diverso estudios apuntan a que es un remedio sencillo que ayuda a mitigar los efectos del alcohol tras grandes fiestas

Alimentación

El queso: uno de los mejores remedios para la resaca, según un estudio

Puede parecer extraño pero así lo confirma un estudio

Journal of Functional Foods 108 (2023) 105736

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Probiotic cheese improves alcohol metabolism and alleviates alcohol-induced liver injury via the SIRT1/AMPK signaling pathway

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