24 mayo 2024

# I REUNIÓN DE RIESGO CARDIOVASCULAR

de la Sociedad Castellano-Manchega
de Cardiología

Hotel Intelier Airén
**Alcázar de San Juan**

SOCIEDAD
CASTELLANO-MANCHEGA
DE CARDIOLOGÍA

# Nuevas terapias para la obesidad

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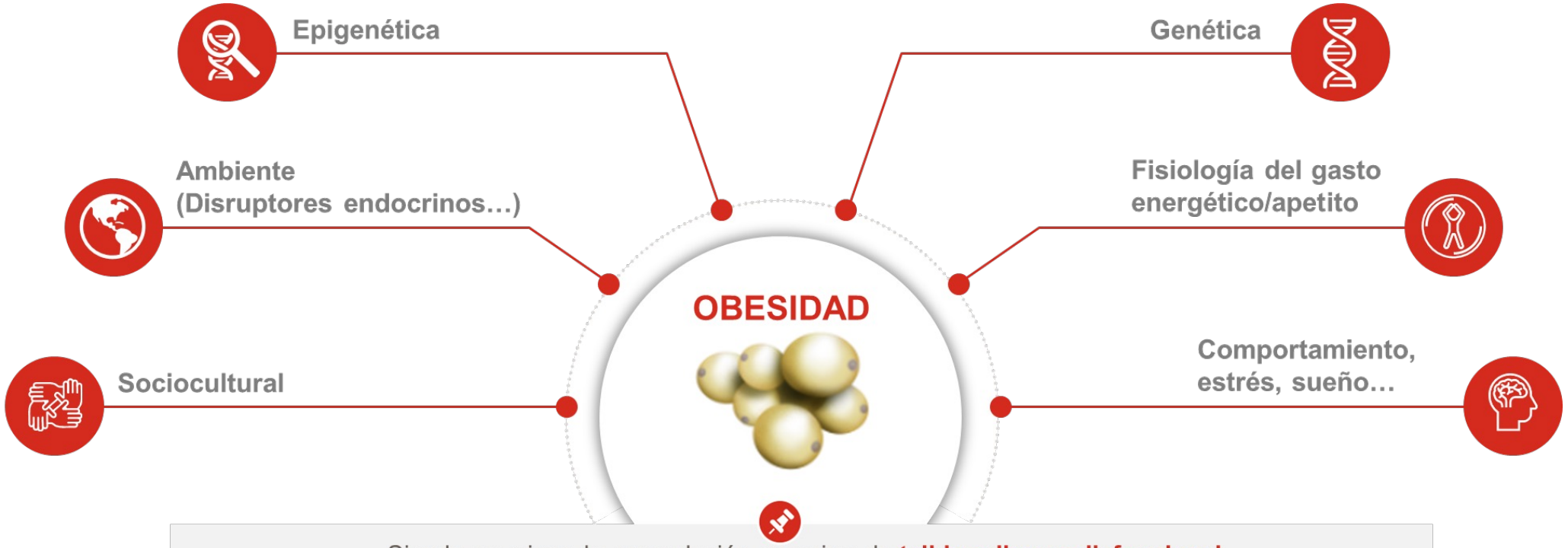
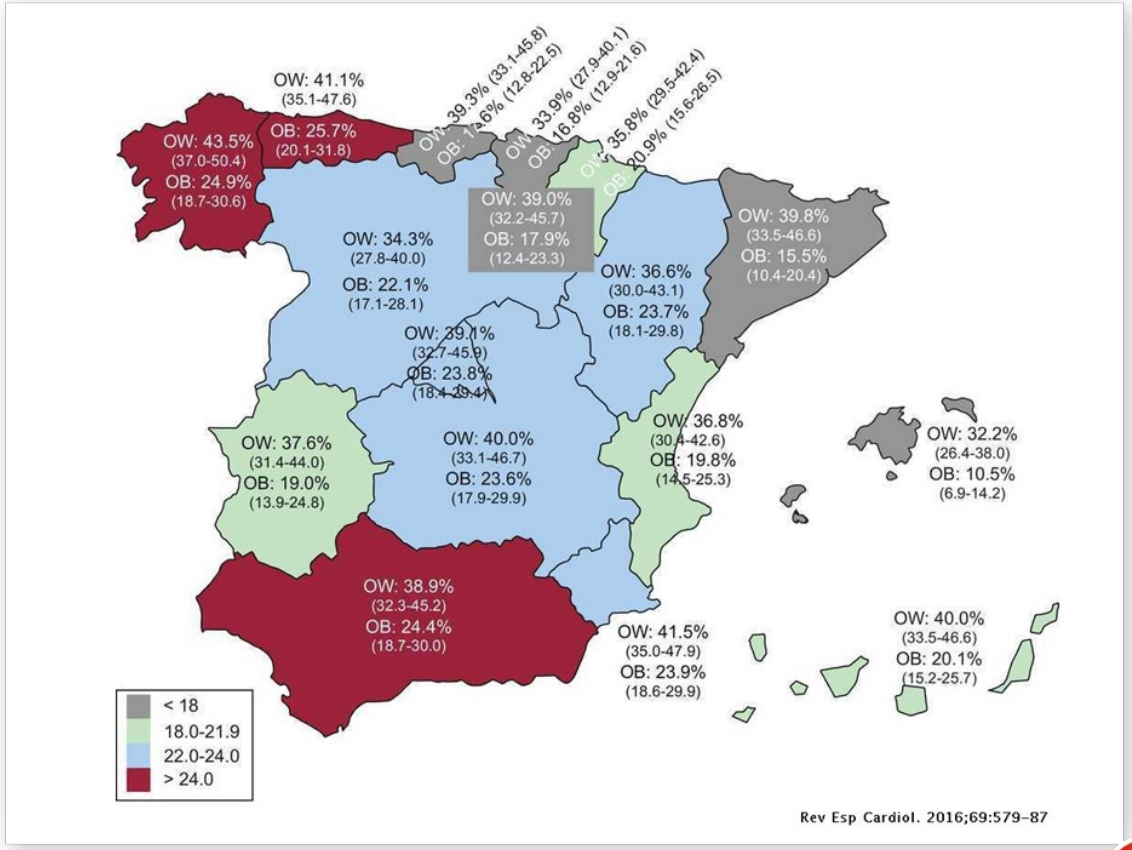
# La obesidad es una compleja **enfermedad crónica** que se define por una acumulación excesiva de grasa que puede ser perjudicial para la salud (OMS).

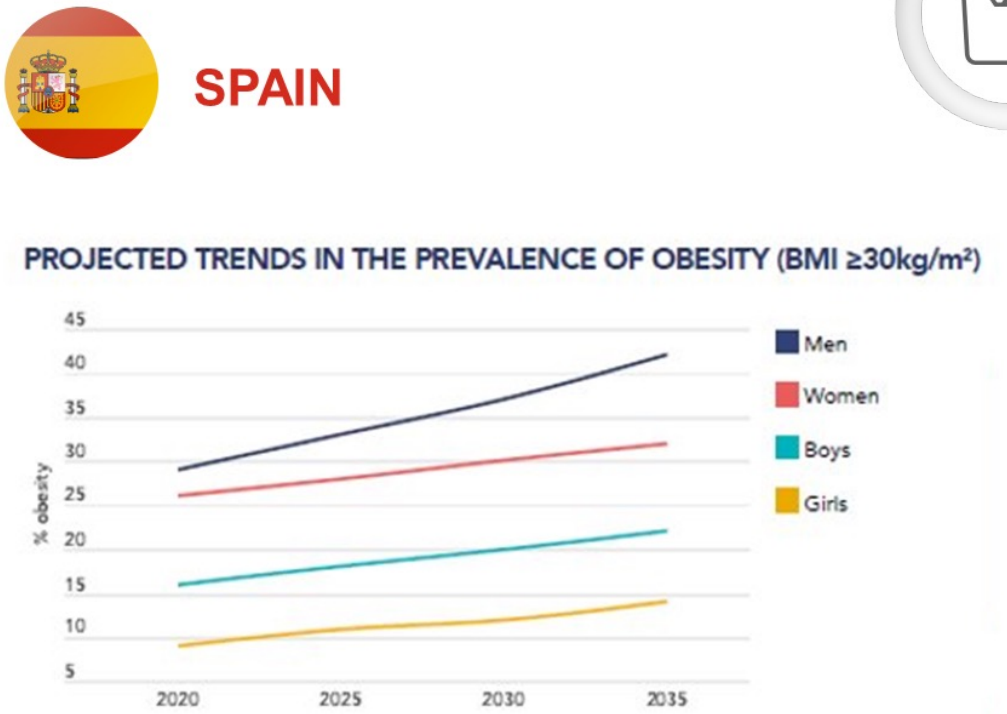



Siendo su origen la acumulación excesiva de **tejido adiposo disfuncional**
**(Enfermedad Crónica Basada en la Adiposidad, ABCD)**

Bray GA, *et al*. Lancet. 2016;387(10031):1947-1956. Chait A and den Hartigh LJ. Front Cardiovasc Med. 2020;7: 22. de Luca C and Olefsky JM. FEBS Lett. 2008;582(1): 97—105. Xu H, *et al*. J Clin Invest. 2003;112(12): 1821—1830. Garvey WT, Obesity 2020;28: 482-492. Hammarstedt A, Gogg S, Hedjazifar S, Nerstedt A, Smith U. Impaired adipogenesis and dysfunctional adipose tissue in human hypertrophic obesity. Physiol Rev. 2018;98(4):1911-1941.




## SPAIN




La **obesidad y el sobrepeso** tienen elevada prevalencia en España (obesidad **22.0%** y sobrepeso **36.1%**), con cifras que van en aumento (**37%** adultos con obesidad en **2035**)

**1.** DOI: 10.1016/j.rec.2020.12.020 ; **2.** DOI: 10.1016/j.rec.2016.02.009 https://data.worldobesity.org/publications/?cat=19

**Metabólico**

**Mecánico**

**SNC**

ERGE

Cánceres

Funcionamiento físico

Depresión

Ansiedad

Asma

MAFLD

Cálculos biliares

Infertilidad

Incontinencia

Osteoartritis de rodilla

**La obesidad reduce la esperanza de vida**

Apnea del sueño

Enfermedades cardiovaculares
- Ictus
- Dislipemia
- Hipertensión arterial
- Enfermedad coronaria
- Embolismo pulmonar
- HFpEF

Insuficiencia cardiaca

Dolor de espalda crónico

Diabetes tipo 2
Prediabetes

Trombosis

Gota

*Incluidos mama, colorrectal, endometrio, esófago, riñón, ovario, páncreas y próstata; **ERGE:** Enfermedad por Reflujo Gastroesofágico; **HGNA:** Enfermedad del Hígado Graso No Alcohólico; **IC-FEM:** Insuficiencia Cardiaca con Fracción de Eyección en Rango Medio; **SNC:** Sistema Nervioso Central.

Adaptado de Sharma. Obes Rev 2010;11:808–9; Guh *et al*. BMC Public Health 2009;9:88; Luppino *et al*. Arch Gen Psychiatry 2010;67:220–9; Simon *et al*. Arch Gen Psychiatry 2006;63:824–30; Church *et al*. Gastroenterology 2006;130:2023–30; Li *et al*. Prev Med 2010;51:18–23; Hosler. Prev Chronic Dis 2009;6:A48; Stefan, Birkenfeld and Schulze. Nat Rev Endocrinol 2021;17:135–49.

## Hacia una mayor pérdida de peso y una mejora general de la salud[1–5]

- Hipertensión[1]
- Hiperglucemia[1]
- Incontinencia urinaria de esfuerzo[1]
- Prevención de la DM2[1]
- SOP[1]
- Dislipidemia[1]
- Asma/enfermedades respiratorias[1]
- MAFLD[1]
- MASH[1]
- OSA[1]
- ERGE[1]
- OA de rodilla[1]
- Enfermedad cardiovascular[1]
- MASH[1]
- Remisión de la DM2[1,3,5]
- Mortalidad CV[1,4]
- HFpEF[1,4,5]

0–5% | 5–10% | 10–15% | ≥15%

**Magnitud de Pérdida de peso (%)**

**CV:** Cardiovascular; **DM2:** Diabetes Mellitus Tipo 2; **ERGE:** Enfermedad por Reflujo Gastroesofágico; **HFpEF:** Insuficiencia Cardiaca con Fracción de Eyección Preservada; **NAFLD:** Enfermedad del Hígado Graso No Alcohólico; **NASH:** Esteatohepatitis No Alcohólica; **OA:** Osteoartritis; **SAOS**: Síndrome de Apnea Obstructiva del Sueño; **SOP:** Síndrome de Ovario Poliquístico.

**1.** Garvey *et al*. Endocr Pract 2016;22(Suppl.3):1–203; **2.** Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21; **3.** Lean *et al*. Lancet 2018;391:541–51; **4.** Benraoune and Litwin. Curr Opin Cardiol 2011;26:555–61; **5.** Sundström *et al*. Circulation 2017;135:1577–85.

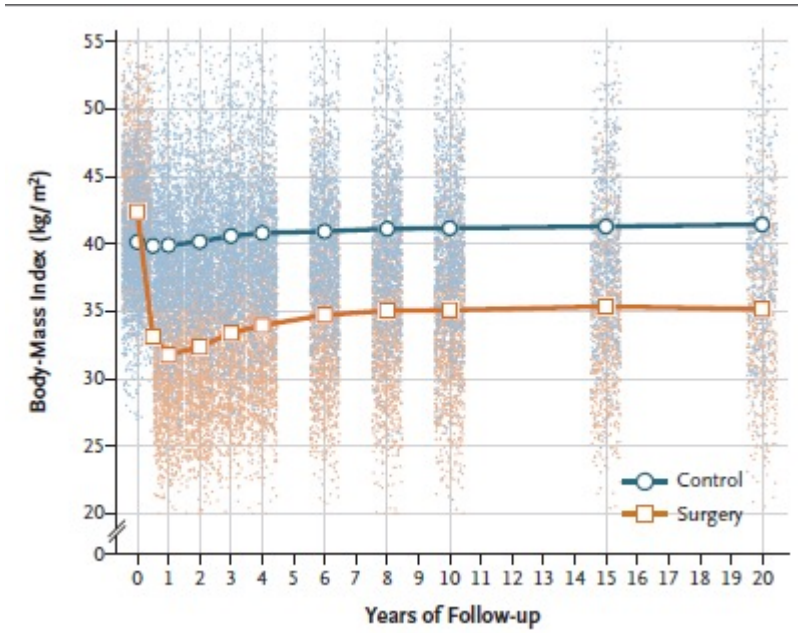
The NEW ENGLAND JOURNAL of MEDICINE

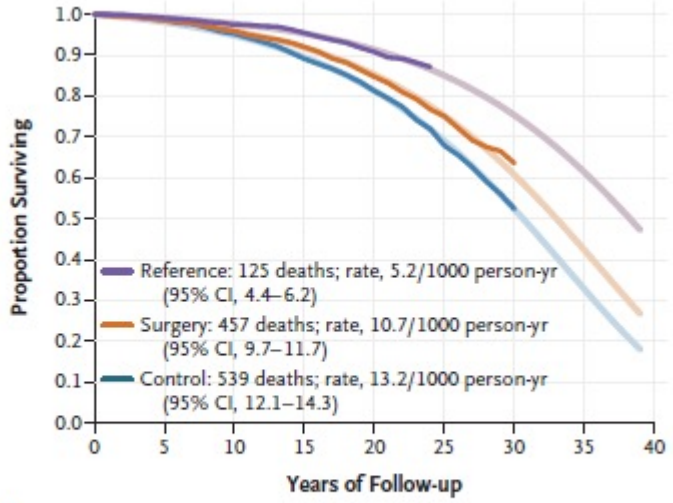
ORIGINAL ARTICLE

# Life Expectancy after Bariatric Surgery in the Swedish Obese Subjects Study

Lena M.S. Carlsson, M.D., Ph.D., Kajsa Sjöholm, Ph.D., Peter Jacobson, M.D., Ph.D., Johanna C. Andersson-Assarsson, Ph.D., Per-Arne Svensson, Ph.D., Magdalena Taube, Ph.D., Björn Carlsson, M.D., Ph.D., and Markku Peltonen, Ph.D.

La pérdida sostenida de peso con cirugía bariátrica se asoció con una reducción del 30% en la mortalidad CV y del 23 % por cáncer
La esperanza de vida fue 3 años mayor con cirugía (pero 5,5 años más corta que en la población general)




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Reference | 1135 | 1125 | 1106 | 1083 | 905 | 0 | 0 |
| Surgery | 2007 | 1915 | 1837 | 1744 | 1390 | 580 | 34 |
| Control | 2040 | 1961 | 1815 | 1589 | 1238 | 488 | 26 |

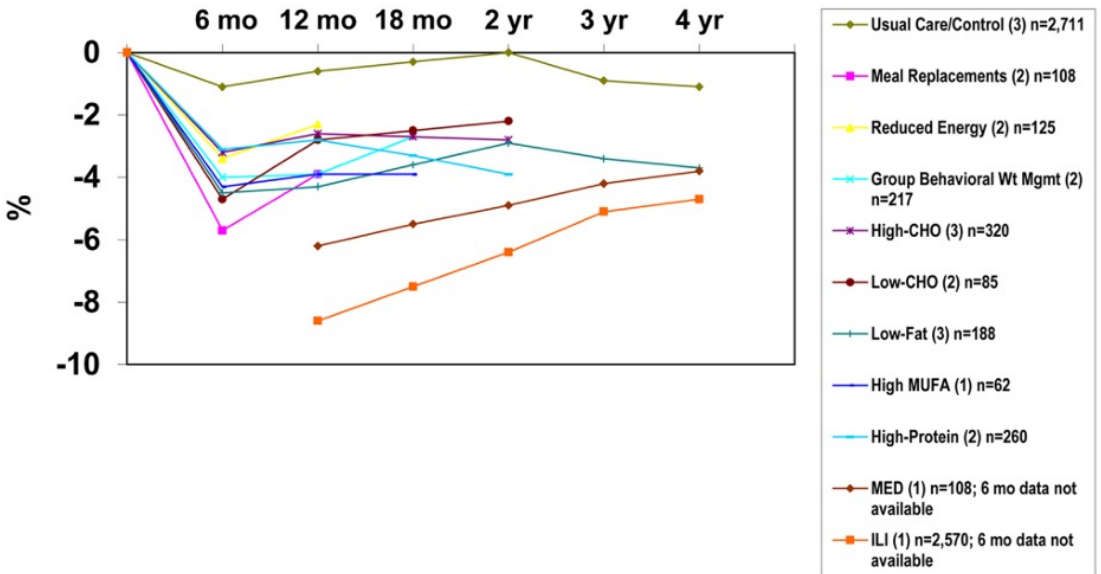
# Las medidas de intervención en el estilo de vida (dieta, ejercicio, terapia conductual) son fundamentales, pero no suficientes

eat right.

RESEARCH
Review

## Lifestyle Weight-Loss Intervention Outcomes in Overweight and Obese Adults with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Marion J. Franz, MS, RDN, LDN; Jackie L. Boucher, MS, RDN, LDN; Stephanie Rutten-Ramos, DVM, PhD; Jeffrey J. VanWormer, PhD




differing amounts of macronutrients and reported nonsignificant differences in weight loss, HbA1c, lipids, and blood pressure. The majority of lifestyle weight-loss interventions in overweight or obese adults with type 2 diabetes resulted in weight loss <5% and did not result in beneficial metabolic outcomes. A weight loss of >5% appears necessary for beneficial effects on HbA1c, lipids, and blood pressure. Achieving this level of weight loss requires intense interventions, including energy restriction, regular physical activity, and frequent contact with health professionals. Weight loss for many overweight or obese individuals with type 2 diabetes might not be a realistic primary treatment strategy for improved glycemic control. Nutrition therapy for individuals with type 2 diabetes should encourage a healthful eating pattern, a reduced energy intake, regular physical activity, education, and support as primary treatment strategies.

J Acad Nutr Diet. 2015;115:1447-1463.

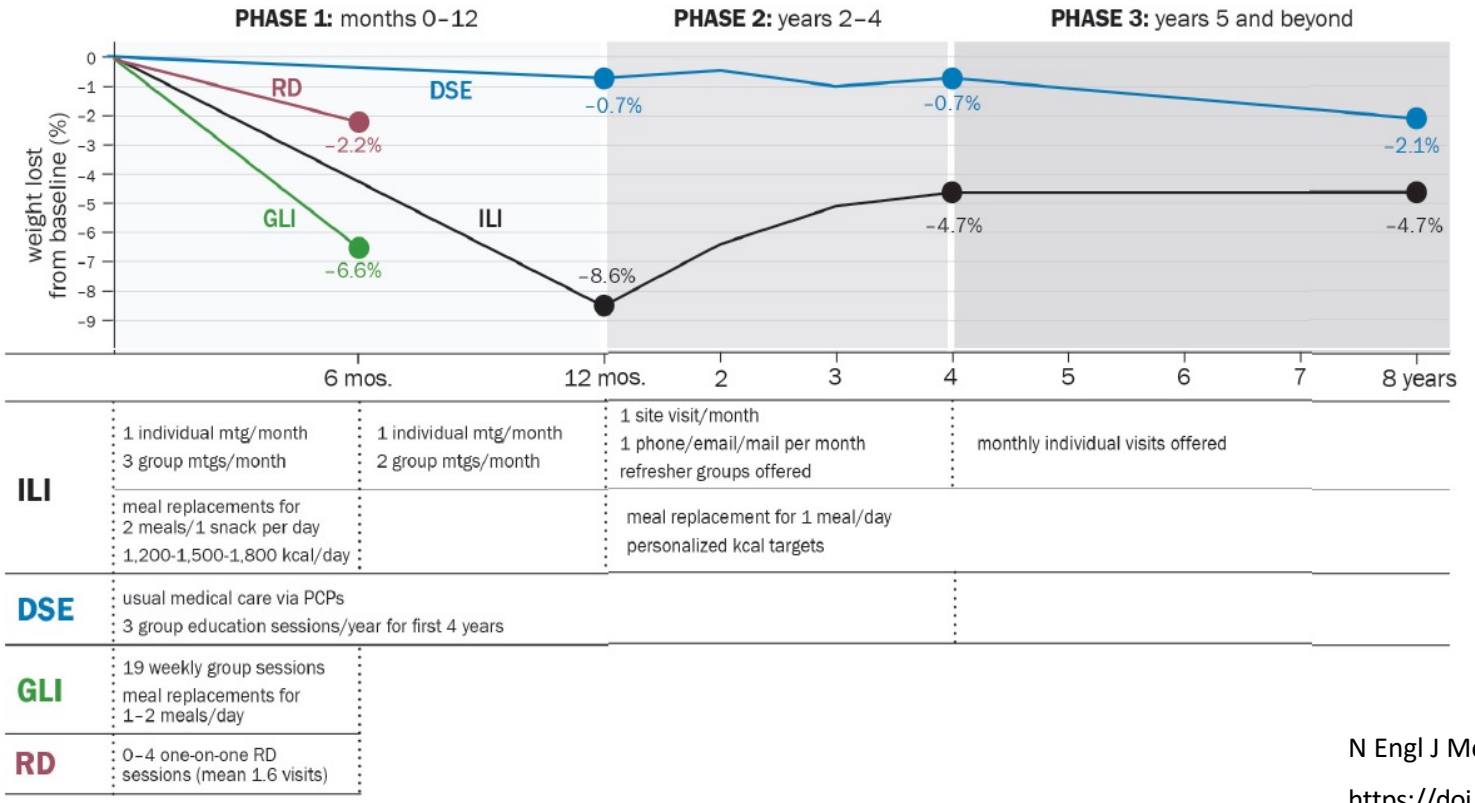
"La mayoría de las intervenciones en el estilo de vida para la pérdida de peso en adultos con sobrepeso u obesidad y DM tipo 2 dieron como resultado una pérdida de peso <5% y no produjeron resultados metabólicos beneficiosos".
La re-ganancia es la regla

Look AHEAD
Action for Health in Diabetes

5145 pac con sobrepeso u obesidad y diabetes tipo 2
Intervención intensiva en el estilo de vida Vs manejo hab + apoyo y educación sobre la diabetes
EP 1º: muerte CV, IAM no fatal, ACV no fatal u hospitalización por angina.
Detenido por futilidad a los 9,6 años

**Intervención intensiva en el estilo de vida (ILI)**

Objetivo:↓ ≥7% del peso inicial y ↑ actividad física moderada a ≥175 min/semana




N Engl J Med 2013;369:145-154
https://doi.org/10.2337/ds17-0016

# Improved CV Outcomes Among Weight Loss Responders
## *Post Hoc Analysis of the Look AHEAD Trial Data*

**Adults living with overweight or obesity and T2D were assigned to an intensive lifestyle intervention or to diabetes support and education**

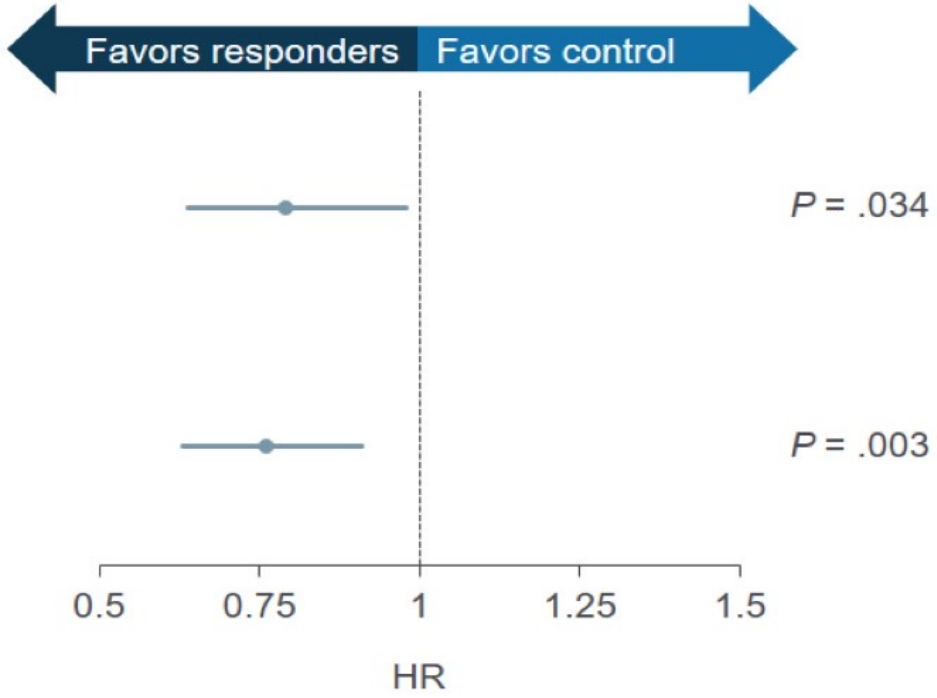
Responders lost ≥ 10% of their body weight in the first year of the study

Primary outcome – **21% lower**

**CV death, nonfatal acute MI, nonfatal stroke, or admission to hospital for angina**

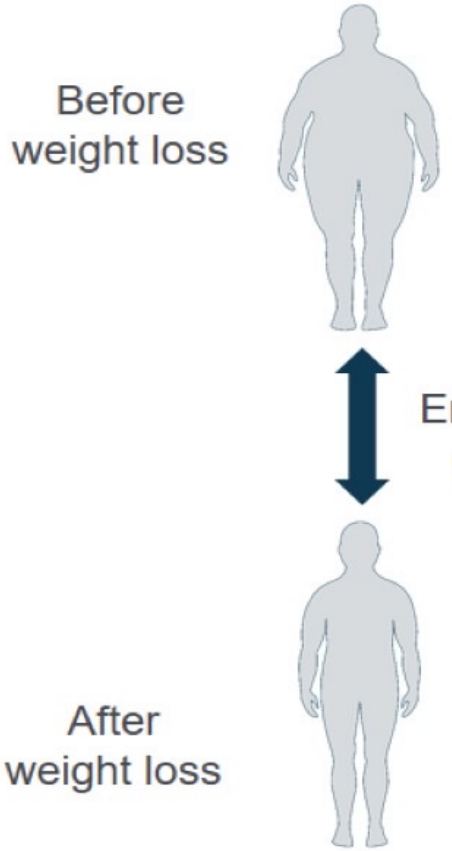
Secondary outcome – **24% lower**

**As above plus CABG, carotid endarterectomy, PCI, HHF, peripheral vascular disease, or total mortality**




CABG, coronary artery bypass grafting; HHF, hospitalization for heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.
Look AHEAD Research Group. Lancet Diabetes Endocrinol. 2016;4:913-921.

# ¿Por qué es tan difícil perder peso de forma sostenida?




- ↑ **Hunger**[1]
  - Preference for calorie-dense foods
- ↓ **Energy expenditure**[1]
  - **Metabolism**:
    - ↓ Fat oxidation[2]
    - ↑ Cortisol[2]

**Hormone levels**[1,3,4]
- ↓ **Satiety hormones** (leptin, PYY, GLP-1, CCK)
- ↑ **Hunger hormones** (ghrelin, GIP, NPY, AgRP)

- ↓ **Nervous system activity**[1]
- ↓ **Body mass**[1]
- ↓ **Leptin**[1]
- ↑ **Energy efficiency**[1]

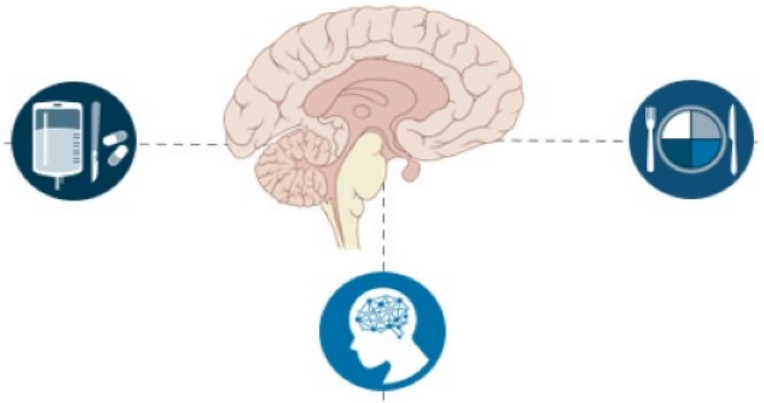
AgRP, agouti-related peptide; CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; NPY, neuropeptide Y; PYY, peptide YY.

1. Melby CL, et al. Nutrients. 2017;9:468; 2. Sumithran P, et al. Clin Sci (Lond). 2013;124:231-241; 3. Huang Y. Front Cell Dev Biol. 2021;9:695623; 4. Sumithran P, et al. N Engl J Med. 2011;365:1597-1604.

# ¿Por qué es tan difícil perder peso de forma sostenida?

## Homeostatic system[1,2]

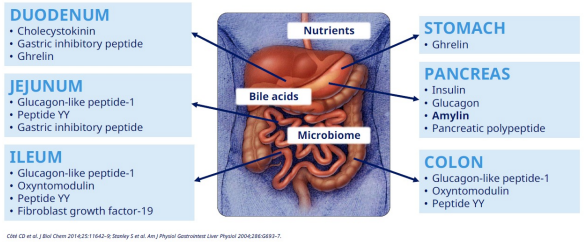
- **CCK, GLP-1, OXM, and other hormones** increase satiety
- **Ghrelin** increases hunger



## Executive function[4]

- **Behavioral interventions** to empower sustainable control of eating

Signals from the gastrointestinal tract regulate energy intake and glucose homeostasis




Cani CD et al. J Biol Chem 2014;25:11642–9; Stanley S et al. Am J Physiol Gastrointest Liver Physiol 2004;286:G693–7.

## Hedonic system[3]

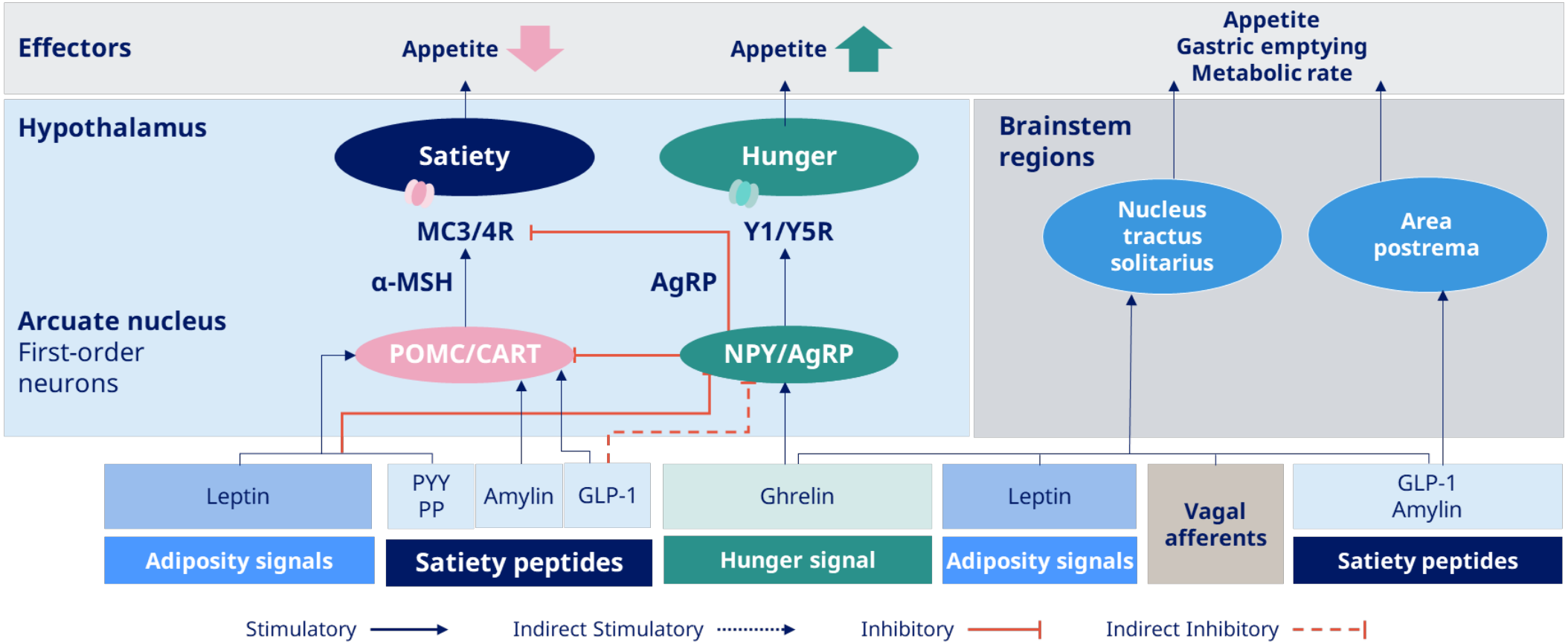
- **Dopamine** controls wanting, motivation/ drive to eat
- **Opioid and cannabinoid receptors** control liking, or the pleasure associated with food



OXM, oxyntomodulin.

1. Badman MK, et al. Science. 2005;307:1909-1914; 2. van Bloemendaal L, et al. Diabetes. 2014;63:4186-4196; 3. Berridge KC, et al. Brain Res. 2010;1350:43-64; 4. Vallis M. Clin Obes. 2019;9:e12299.

# Homeostatic regulation of appetite




*α-MSH, α-melanocyte stimulating hormone; AgRP, Agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; GLP-1, glucagon-like peptide-1; MC3/4R, melanocortin 3/4 receptor; NPY, neuropeptide Y; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY; Y1/Y5R, Y1/Y5 receptor.*
*Adapted from: Badman et al. Science 2005;307:1909–14; Seo et al. Endocr J 2008;55:867–74; Secher et al. J Clin Invest 2014;124:4473–88; Picó et al. Reviews in Endocrine and Metabolic Disorders 2022; 23(1): 13-30*

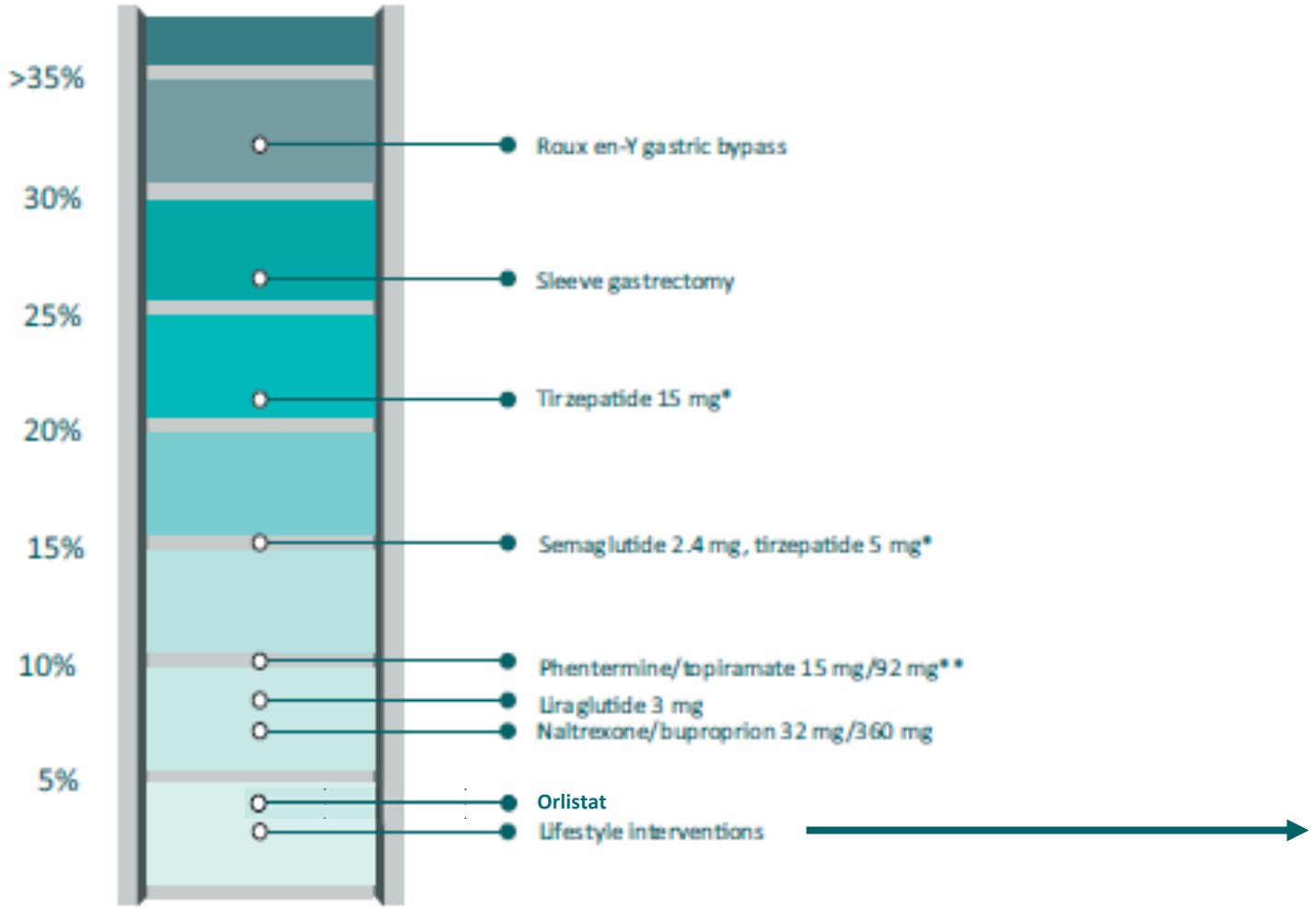
# Fármacos aprobados en Europa

Orlistat (Xenical®)
Liraglutide 3 mg (Saxenda®)
Semaglutide 2,4 mg (Wegovy®)

Tirzepatide (Mounjaro®)

Naltrexona/Bupropión (Mysimba®)

Metreleptin (Myalepta®): solo en lipodistrofias por déficit de leptina
Setmelanotide (Imcivree®): solo en obesidad monogénica por deficiencia de proopiomelanocortina, deficiencia receptor leptina y Sd Bardet Bield)




Media reducción peso a un año con dieta para déficit calórico de 500 Kcal/d y consejo de ejercicio moderado 150 mn/s

Modificado de Clinical Medicine 2023 Vol 23, No 4: 337–46

# SEMAGLUTIDE 2,4


*Friedrichsen et al. Diabetes Obes Metab 2021;23:754–62.*

# The cardiometabolic effects of GLP-1RAs

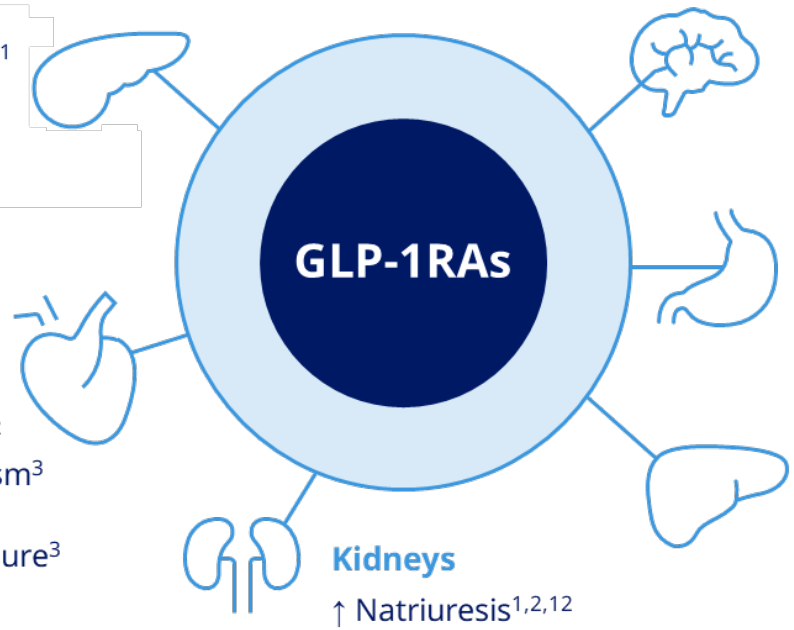
## GLP-1RAs have a multitude of pharmacological effects and CV benefits

### Pancreas

↑ Beta-cell function[1]
↑ Insulin biosynthesis[1]
↑ Glucose-dependent insulin secretion[1]
↓ Glucose-dependent glucagon secretion[1]

### Heart

↓ Cardiovascular risk[2]
↓ Fatty acid metabolism[3]
↑ Cardiac function[3]
↓ Systolic blood pressure[3]
↓ Inflammation[4]




### Brain

↓ Body weight[5]
↓ Food intake[6]
↑ Satiety[7,8]

### Stomach

↓ Gastric emptying[9]

### Liver

↓ Endogenous glucose production[10]
↑ Hepatic insulin sensitivity[10]
↓ *De novo* lipogenesis[10]
↓ Lipotoxicity[10]
↓ Steatosis[11]

### Kidneys

↑ Natriuresis[1,2,12]
↓ Risk of worsening kidney function[13]

**Meta-analyses of trials of GLP-1RAs (inc. semaglutide) in T2D indicate:[13]**

- ↓ Risk of **MACE**
- ↓ Risk of **myocardial infarction**
- ↓ Risk of **stroke**
- ↓ Risk of **death from CV causes**
- ↓ Risk of **hospitalisation due to heart failure**
- ↓ Risk of **adverse kidney outcomes***

**Reduction in the risk of a composite kidney outcome of development of macroalbuminuria, worsening kidney function, kidney replacement therapy and death due to kidney disease.*
*CV, cardiovascular; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events.*
*Adapted from Campbell, Drucker. Cell Metab 2013;17:819–37 and Pratley, Gilbert. Rev Diabet Stud 2008;5:73–94.*

*1. Campbell JE, DJ Drucker. Cell Metab 2013;17:819–37; 2. Marso SP et al. N Engl J Med 2016;375:311–22; 3. Ryan D, Acosta A. Obesity 2015;23:1119–29; 4. Hogan AE et al. Diabetologia 2014;57:781–4; 5. Baggio LL, Drucker DJ. J Clin Invest 2014;124:4223–6; 6. Bagger JI et al. Clin Endocrinol Metab 2015;100:4541–52; 7. Flint A et al. J Clin Invest 1998;101:515–20; 8. Blundell J et al. Diabetes Obes Metab. 2017;19(9):1242–51; 9. Tong J, D'Alessio D. Diabetes 2014;63:407–9;*
*10. Armstrong MJ et al. J Hepatol 2016;64:399–408; 11. Armstrong MJ et al. Lancet 2016;387:679–90; 12. Muskiet MHA, et al. Nat Rev Nephrol. 2017;13:605–628; 13. Sattar N, et al. Lancet Diabetes Endocrinol. 2021;9:653–662.*

# STEP programme at a glance

## Completed

| STEP 1 | STEP 2 | STEP 3 | STEP 4 | STEP 5 |
|---|---|---|---|---|
| Weight management | WM in T2D | WM with IBT | Sustained WM | Long-term WM |

| STEP 6 | STEP 7 | STEP 8 | STEP 10 | STEP TEENs |
|---|---|---|---|---|
| East Asian trial | China, Brazil, Korea, Hong Kong MRCT | H2H vs liraglutide | Reversal of pre-diabetes | WM in adolescents |

| SELECT | STEP HFpEF | STEP HFpEF DM | STEP 9 | STEP 11 |
|---|---|---|---|---|
| CVOT | Obesity and HFpEF | Obesity and HFpEF with T2D | Semaglutide in knee OA | Obesity in Korea/ Thailand |

## Ongoing

| STEP Young | STEP UP | STEP UP T2D |
|---|---|---|
| WM in children and adolescents | WM with 7.2 mg | WM with 7.2 mg in T2D |

| STEP 12 | POSEY |
|---|---|
| Obesity in Mainland China/Taiwan | US employer trial |

*STEP 7: China, Brazil, Korea, Hong Kong (left to right) multi-regional clinical trial.*
*CVOT, cardiovascular outcomes trial; HFpEF, heart failure with preserved ejection fraction; H2H, head-to-head; IBT, intensive behavioural therapy; MRCT, multi-regional clinical trial (including China and ≥1 additional East Asian country); OA, osteoarthritis; WM, weight management. Novo Nordisk A/S. Data on file; Clinicaltrials.gov. ClinicalTrials.gov (Accessed 20 Jan 2023)*

# Phase 3 programme

The primary endpoint for all STEP trials is **weight loss**

STEP is the phase 3a/3b clinical development programme for subcutaneous semaglutide 2.4 mg weekly for weight management

**STEP 1–4**
Phase 3a
**Semaglutide 2.4 mg**
68 weeks + 7 week follow-up

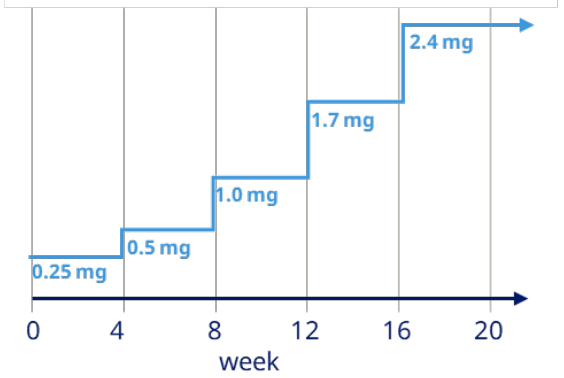
The treatment period in all STEP trials is followed by a 7-week period off treatment to account for the long half-life of semaglutide

**STEP 5**
Phase 3b
**Semaglutide 2.4 mg**
104 weeks + 7 week follow-up

**STEP 6**
East Asian
Phase 3a
**Semaglutide 2.4 mg**
68 weeks + 7 week follow-up

## Dose escalation

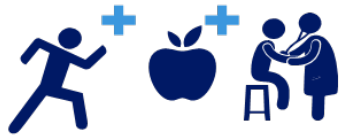
Semaglutide 2.4 mg OW treatment is initiated at 0.25 mg, followed by increments every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg OW




## Across the STEP programme

Treatment with semaglutide 2.4 mg OW will be compared to placebo, as an adjunct to lifestyle intervention

## STEP 3



In STEP 3 only, lifestyle intervention comprises IBT, an initial 8-week low-energy diet and higher target for physical activity

**STEP 7 (China MRCT)** Weight management in predominantly Asian population (44 weeks)

**STEP 8** Head-to-head vs liraglutide

**STEP 9** in participants with obesity and knee osteoarthritis

**STEP 10** reversal of pre-diabetes in participants with obesity and pre-diabetes

**HFpEF** in participants with obesity and heart failure with preserved ejection fraction

**HFpEF DM** in participants with type 2 diabetes

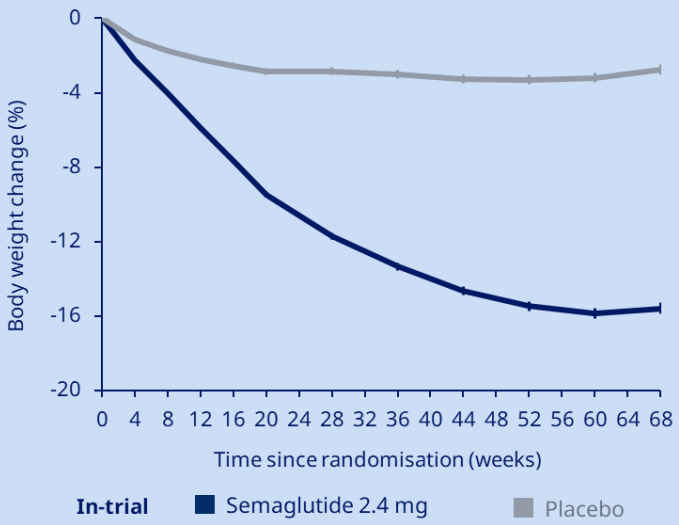
**SELECT** CV outcomes trial

# STEP 1

## How effective is semaglutide 2.4 mg at achieving weight loss?

### STEP 1 Observed body weight change over time

Mean body weight at baseline: 105.3 kg




Both placebo and semaglutide arms received regular diet and exercise counseling

**Mean percent change in body weight at Week 68**

| | Intention-to-treat‡ | Adherent to treatment‡ |
|---|---|---|
| Placebo | -2.4% | -2.4% |
| Semaglutide 2.4 mg | -14.9% | -16.9% |

**1 in 3**
Patients achieved
**≥20%**
**weight loss**
with Semaglutide 2.4 mg*

- *Supportive secondary endpoint; † treatment policy estimand; ‡ trial product estimand

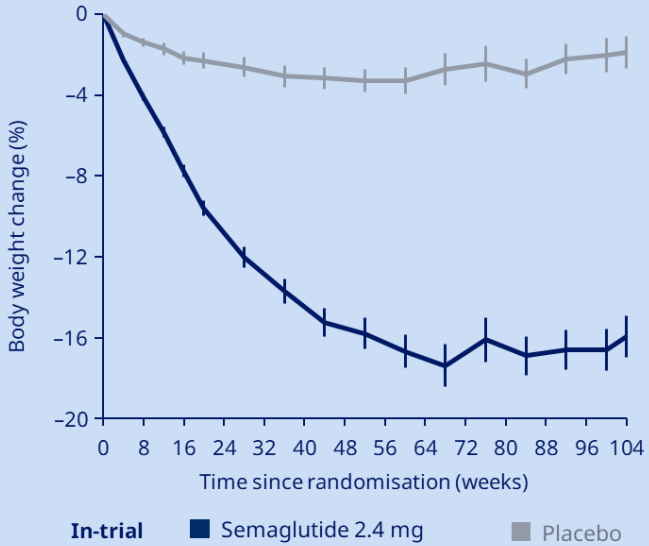
1. Wilding et al. N Engl J Med 2021;384:989-1002; 2. Wadden et al. JAMA 2021;325:1403-13; 3. Rubino et al. JAMA. 2021;325:1414-25; 4. Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021; 5. Wadden et al. N Engl J Med 2005;353:2111–20; 6. Torgerson J. S., et al. Diabetes care 2004;27:155-61; 7. Apovian C., et al. Obesity 2013;21:935-43; 8. Pi-Sunyer, X., et al. N Engl J Med 2015;373:11-22; 9. Allison D. B., et al. Obesity 2012;20:330-42

# STEP 5

## Is weight loss with semaglutide 2.4 mg sustainable long-term?

### STEP 5 Observed body weight change over time

Mean body weight at baseline: 106.0 kg




| | STEP 1 | STEP 5 |
|---|---|---|
| **Co-primary endpoint*** | | |
| | **-14.9%** body weight change in Semaglutide 2.4 mg arm | **-15.2%** body weight change in Semaglutide 2.4 mg arm |
| **Confirmatory Secondary endpoint*** | | |
| | **50.5%** achieved ≥15% weight loss in Semaglutide 2.4 mg arm | **52.1%** achieved ≥15% weight loss in Semaglutide 2.4 mg arm |
| | over **68 weeks** | over **104 weeks** |

- *Treatment policy estimand

1. *Wilding et al. N Engl J Med 2021;384:989-1002; 2.* Garvey WT et al. Nat med 2022;28:2083-91; 3. Fothergill E et al. Obesity (Silver Spring) 2016;24:1612–19.

# STEP 3

Physical activity ↑ | Caloric intake ↓

**Behavioural counselling: 30 sessions**

**100** minutes per week (prescribed at randomisation)

Moderate intensity

Increase by **25 minutes** every 4 weeks

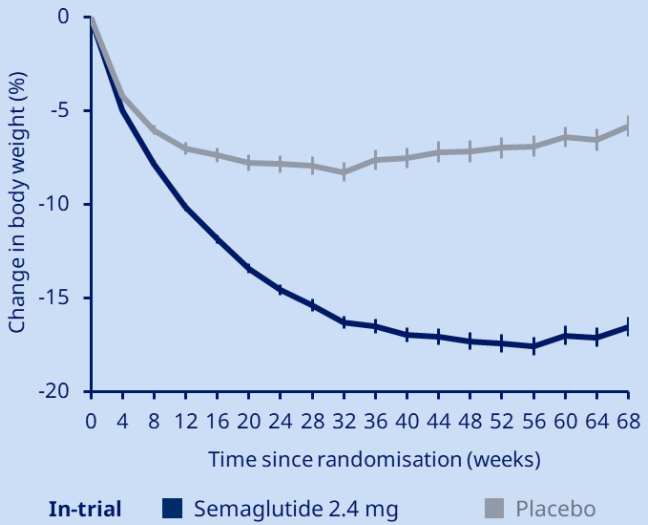
**200** minutes per week (target duration)

| Hypo-caloric diet (conventional food) | |
|---|---|
| **Weight at randomisation** | **Daily caloric intake** |
| <200 lb | 1,200 kcal |
| 200–300 lb | Body weight (lb) x 6 (kcal/lb) |
| >300 lb | 1,800 kcal |

## Must semaglutide 2.4 mg be combined with intensive behavioural therapy to be effective?

**STEP 3 Observed body weight change over time**

Mean at baseline: 105.8 kg




| STEP 1 | STEP 3 |
|---|---|
| Co-primary endpoint | |
| **-14.9%** body weight change in Semaglutide 2.4 mg arm | **-16.0%** body weight change in Semaglutide 2.4 mg + IBT arm |
| **Lifestyle recommendations in STEP 1** | **Lifestyle recommendations and IBT in STEP 3** |
| • Individual counseling sessions every 4 weeks<br>• Reduced calorie diet<br>• 150 min/week of physical activity | • 30 individual sessions with registered dietician<br>• Low / hypocaloric diet<br>• Intensified physical activity up to 200 min/week |

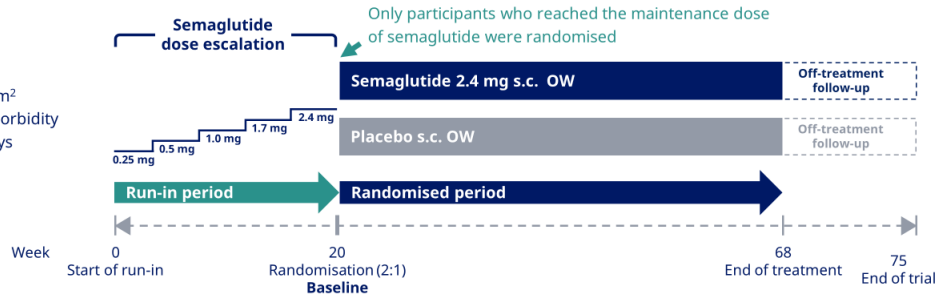
- *IBT, intensive behavioural therapy.*

*1. Wilding et al. N Engl J Med 2021;384:989-1002; 2. Wadden et al. JAMA 2021;325:1403-13.*

# STEP 4

**902 participants with overweight or obesity**

- Male or female ≥18 years
- BMI: ≥30 kg/m² or ≥27 kg/m² and ≥1 weight-related comorbidity
- Stable body weight ≥90 days
- $HbA_{1c}$ ≤6.5%




**Trial objectives**

*Week 20 to week 68*

- To compare the effect of continued semaglutide treatment versus a switch to placebo# on body weight, cardiovascular risk factors, COAs, glucose metabolism, and other factors related to body weight
- To compare the safety and tolerability of continued semaglutide treatment versus a switch to placebo#

*Week 0 to week 68*

- To evaluate the efficacy and safety of semaglutide during the entire 68 weeks of treatment

**Primary endpoint** *(Week 20 to week 68)*

- % weight loss

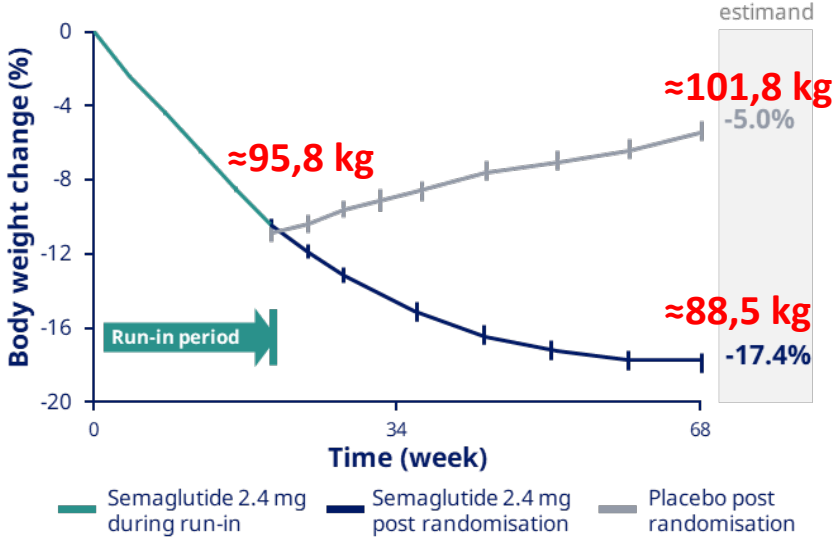
**Confirmatory secondary endpoints** *(Week 20 to week 68)*

- Waist circumference
- Systolic blood pressure
- SF-36 (Physical Functioning)

*# As an adjunct to lifestyle intervention (-500 kcal/day diet + 150 min/week physical activity).*
*BMI, body mass index; COAs, clinical outcome assessments; FU, follow-up; $HbA_{1c}$, glycated haemoglobin; IWQOL-Lite-CT, Impact of Weight on Quality of Life-lite; OW, once-weekly; s.c., subcutaneous; SF-36, Short Form 36-item Health Survey.*
*Rubino et al. JAMA. 2021;325:1414-25.*

## Observed body weight change over time*

Media peso basal: **107,2 Kg**




**Subjects who persisted with semaglutide 2.4 mg continued to lose weight, while placebo-treated participants regained approx. half of their weight loss**

**Weight loss during run-in period (all subjects)**
**(Week 0-20)**
**−10.6%**

**Weight loss post-randomization**
**(Week 20-68)**

| Continued semaglutide 2.4 mg | Switched to placebo |
|---|---|
| -7.9% | +6.9% |

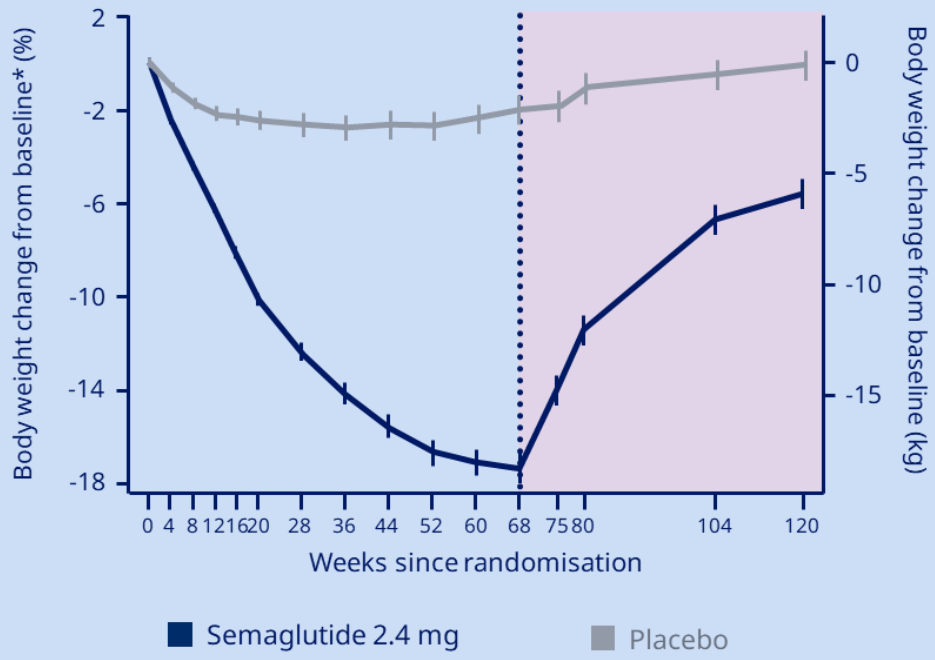
- #Treatment policy estimand (regardless of treatment adherence). §Trial product estimand.
  Error bars are +/- standard error of the mean.
  CI, confidence interval; ETD, estimated treatment difference; IT, in-trial; OT, on-treatment.
  Rubino et al. JAMA. 2021;325:1414-25.

# STEP 1

## Following weight loss, how would you approach the treatment of a chronic disease such as obesity?

### STEP 1 extension Change in body weight

Extension analysis set mean at baseline: 105.5 kg




### One year after withdrawal

After withdrawal of once-weekly semaglutide 2.4 mg and lifestyle intervention,

Participants regained approx **2/3rd** of their prior weight loss

Weight remained **5.6% below baseline** in the semaglutide arm

- *Treatment policy estimand

1. Wilding JPH et al. Diabetes Obes Metab. 2022. doi: 10.1111/dom.14725; 2. Rubino D et al. JAMA. 2021; 325:1414–25.

# Más allá del IMC y peso corporal, ¿qué otros beneficios?

## Persistent improvements in cardiometabolic parameters were demonstrated in the semaglutide treatment arm*

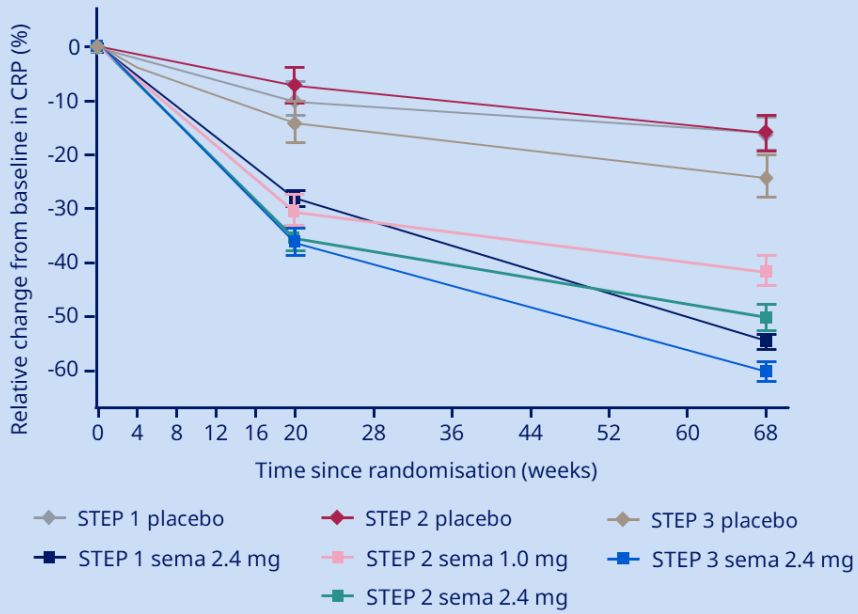
| 68 weeks | Waist circumference | Systolic BP | Diastolic BP | LDL cholesterol | Triglycerides |
|---|---|---|---|---|---|
| **STEP 1** | **-13.5 cm** | **-6.2 mmHg** | **-2.8 mmHg** | **-3%** | **-22%** |
| Placebo | -4.1 cm | -1.1 mmHg | -0.4 mmHg | +1% | -7% |

**Exploratory analysis**

**STEP 1**

**Proportion of participants achieving prediabetes reversion†**


## STEP 1, 2 and 3 relative change from baseline in CRP




Reductions in CRP were **significantly greater** with semaglutide 2.4 mg versus placebo*

| | ETD [95%] |
|---|---|
| STEP 1 | -44% [-49 to -39] |
| STEP 2 | -39% [-46 to -30] |
| STEP 3 | -48% [-55 to -39] |

- *Treatment policy estimand; †Exploratory endpoint, proportion of patients who reverted to normoglycaemia (according to American Diabetes Glycaemic category) by end of trial.
BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; sema, semaglutide.
1. Wilding et al. N Engl J Med 2021;384:989-1002; 2. Davies et al. Lancet 2021;397:971-84; 3. Yuen et al. Obesity Week 2016. Oct 31–Nov 4 2016. New Orleans: T-P-3166.

- *Treatment policy estimand
CRD, c-reactive protein; ETD, estimated treatment difference; sema, semaglutide.
1. Verma S et al. EClinicalMedicine 2023;55:101737; 2. Yuen et al. Obesity Week 2016. Oct 31–Nov 4 2016. New Orleans: T-P-3166

# SELECT TRIAL

## Semaglutida y resultados cardiovasculares en la obesidad sin diabetes

- 17604 pacientes
- ≥ 45 años
- ECV establecida (infarto, ictus o E
  sin DM (HBA1c ≥ 6,5% excluidos)
- Sema 2,4 semanal Vs placebo
- EP 1º: MACE-3 (tiempo hasta pri
- EP 2º (jerárquico): muerte CV, co
  hopitalización o visita urgente) ,

Reclutamiento entre octubre de
N= 1760

**Semaglutide**
N= 8803 (100%)

**Completan el ensayo**
N= 8544 (97,1%)

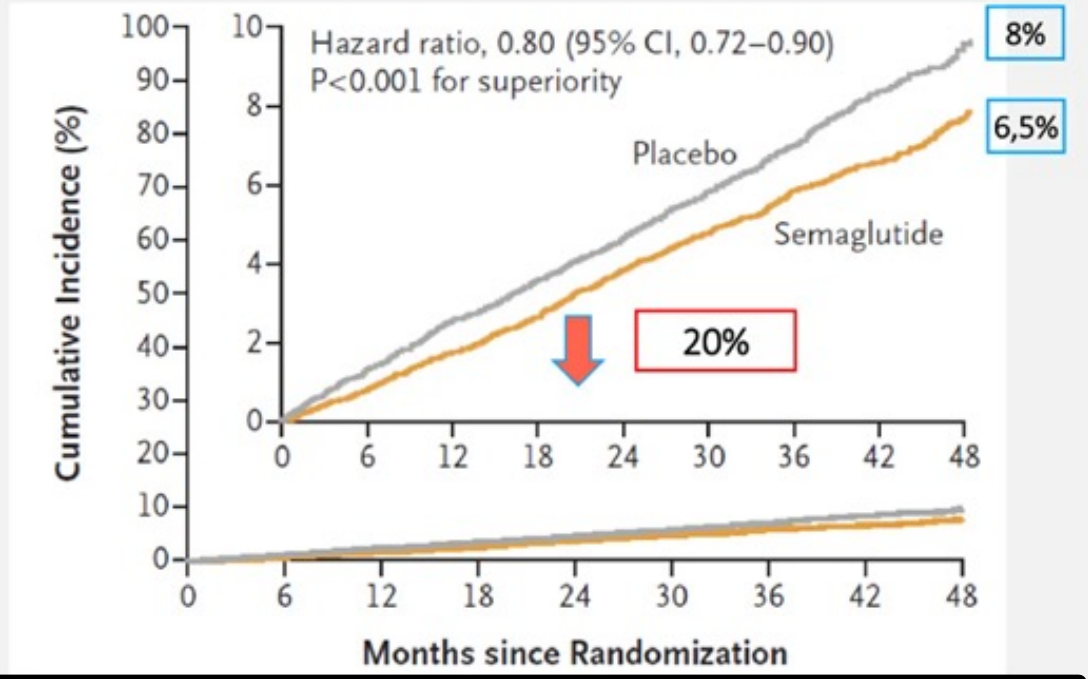
**Discontinúan el tratamiento**
N= 2351 (26,7%)
- Efectos adversos N=1417 (16,1%)
- Ausencia de efecto N=62 (0,7%)
- Otros N=972 (9,9%)

**Exposición media** 33,3 ±14,4 meses

**Follow up** 39,8 ±9,

El 77% de los pacientes alcan
2,4 mg en la semana 104

## RESULTADOS: objetivo primario compuesto de muerte CV, IAM no fatal o ictus no fatal



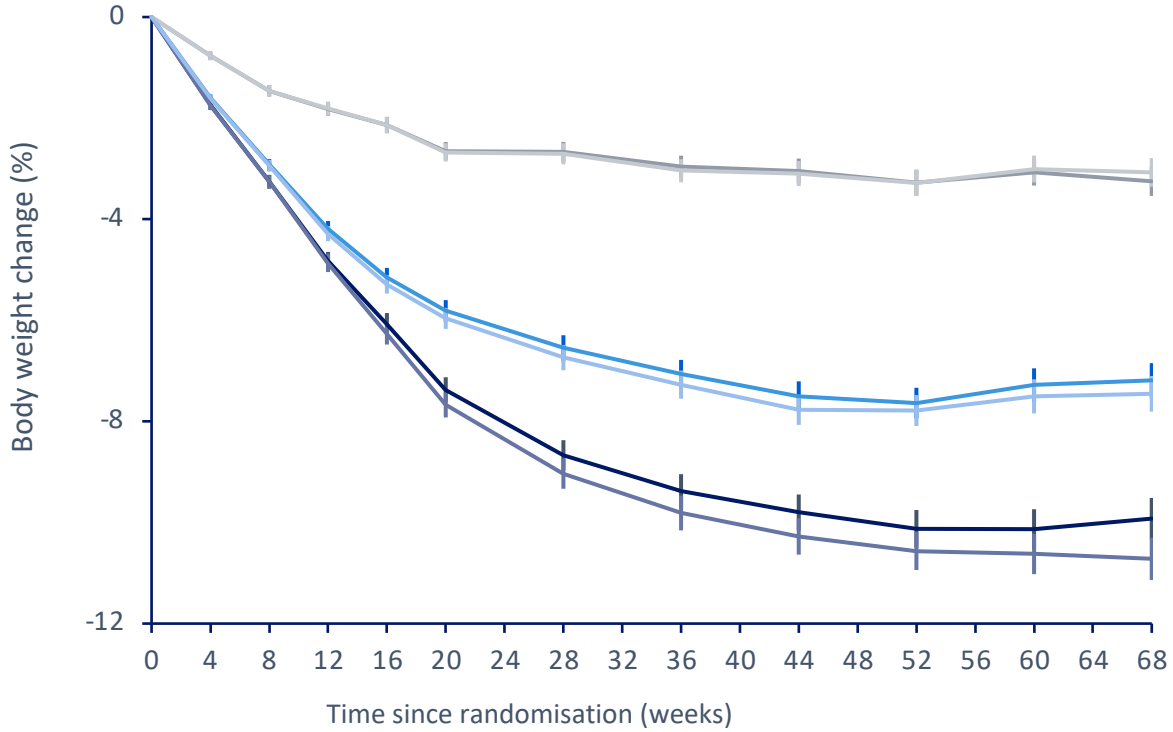

REDUCCIÓN NETA DEL PESO CORPORAL: – 8,51%

N Engl J Med 2023;389:2221-32.

# STEP 2 (diabetes)

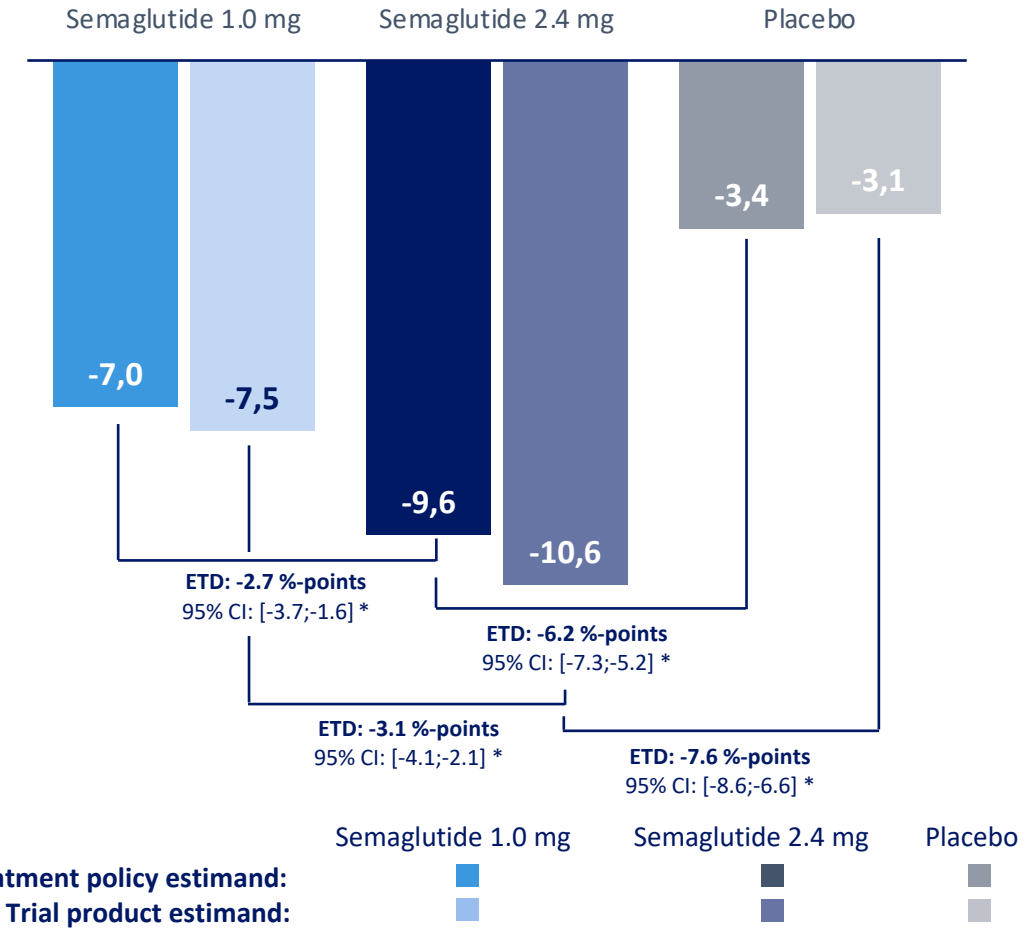
## Observed body weight change over time

(Mean at baseline: 99.8 kg)



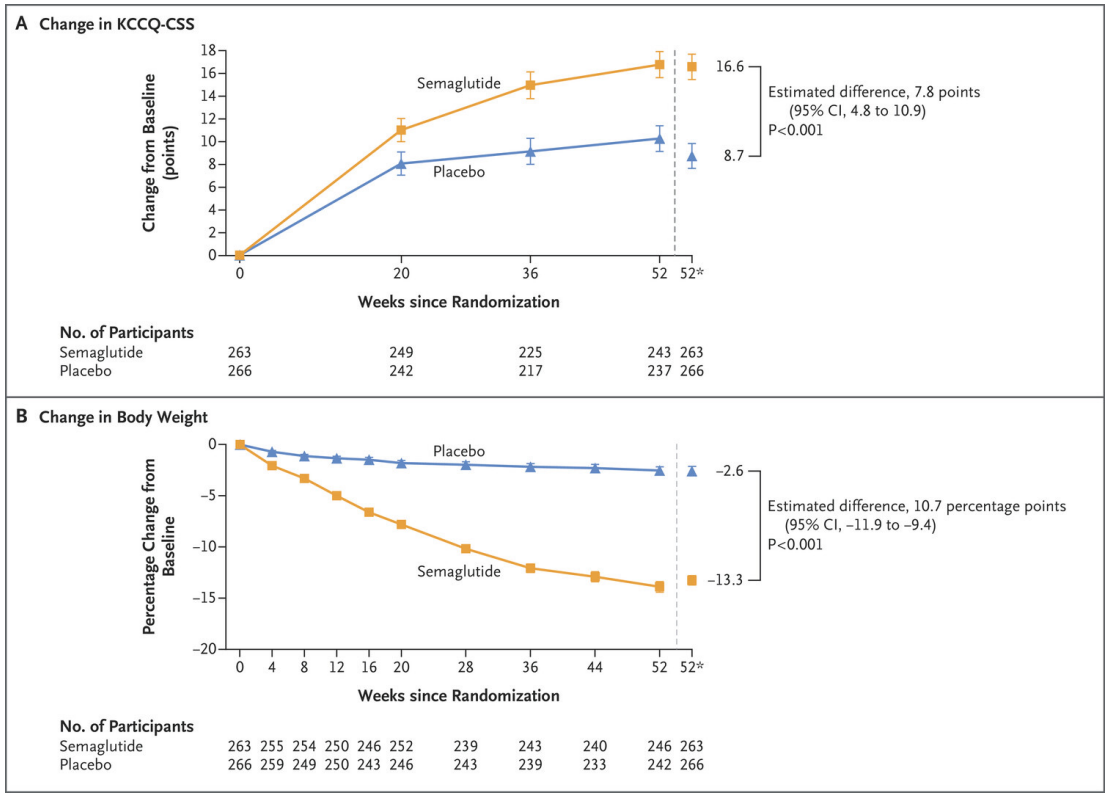

*Error bars are +/- standard error of the mean.*
*CI, confidence interval ETD; estimated treatment difference. *p<0.0001.*
*Davies et al. Lancet 2021;397:971-84.*

## Estimated change from baseline to week 68



ORIGINAL ARTICLE

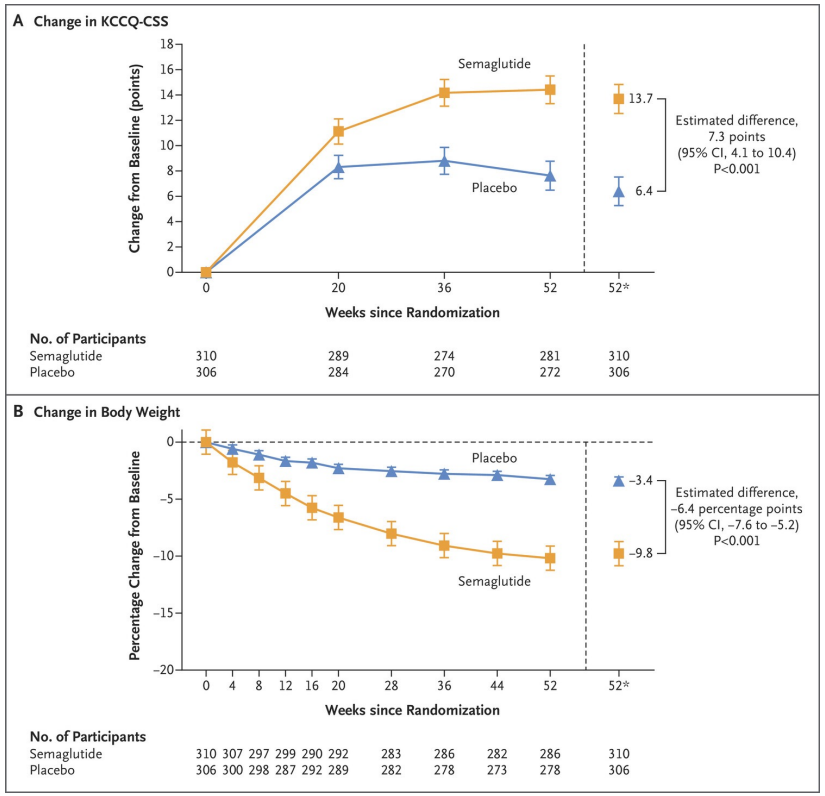
# Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity



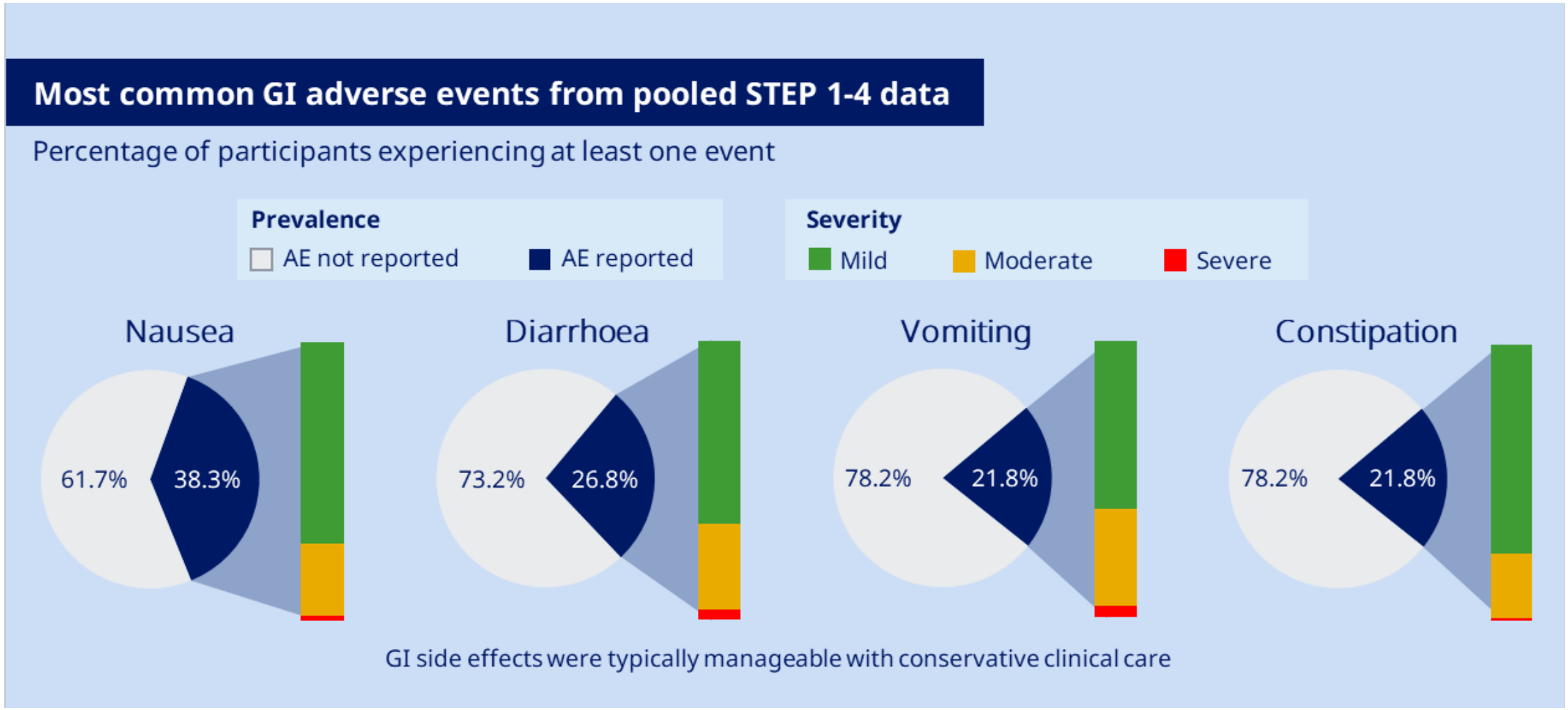

N Engl J Med 2023;389:1069-1084

ORIGINAL ARTICLE

# Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

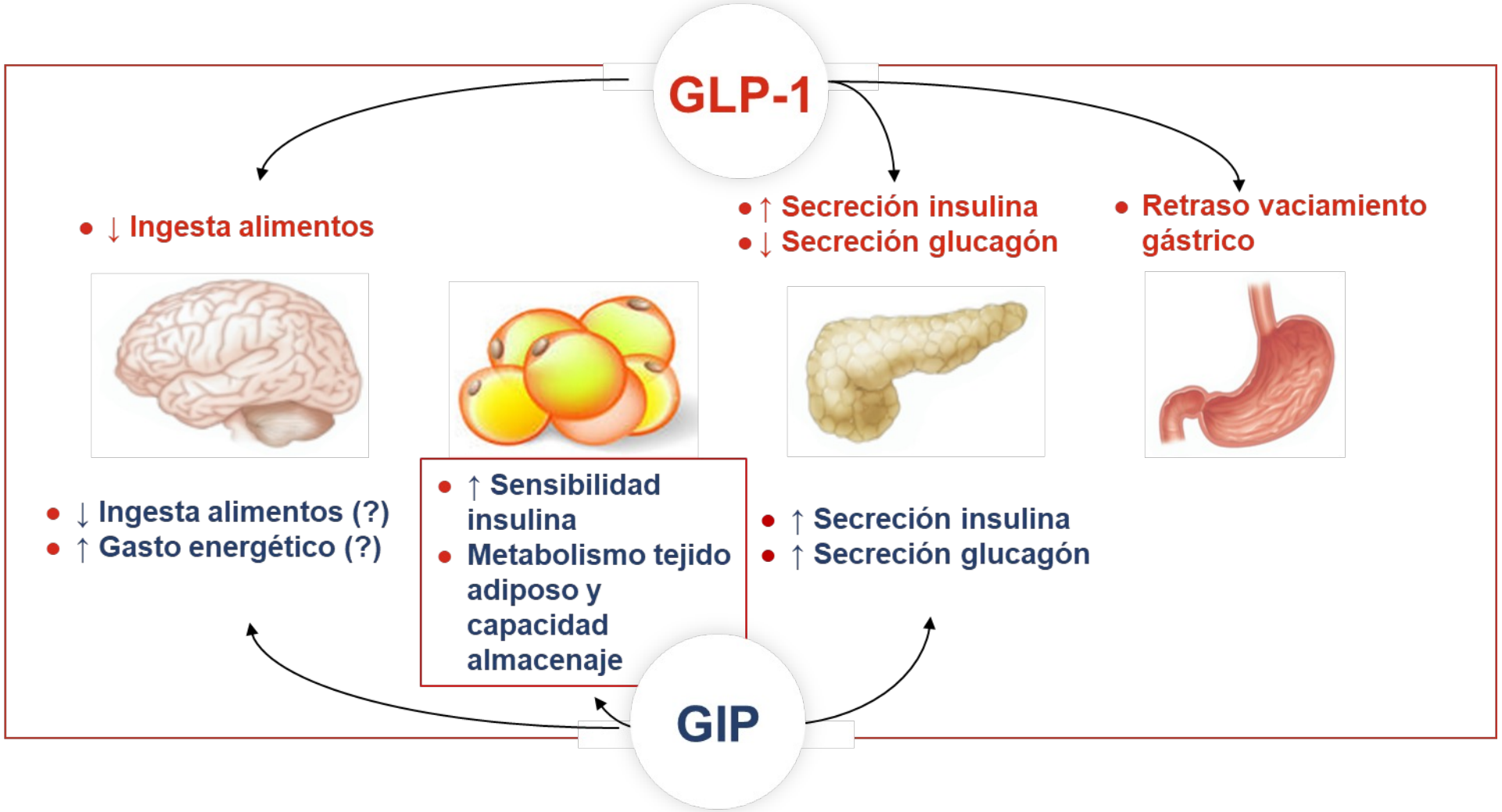



N Engl J Med 2024;390:1394-407.



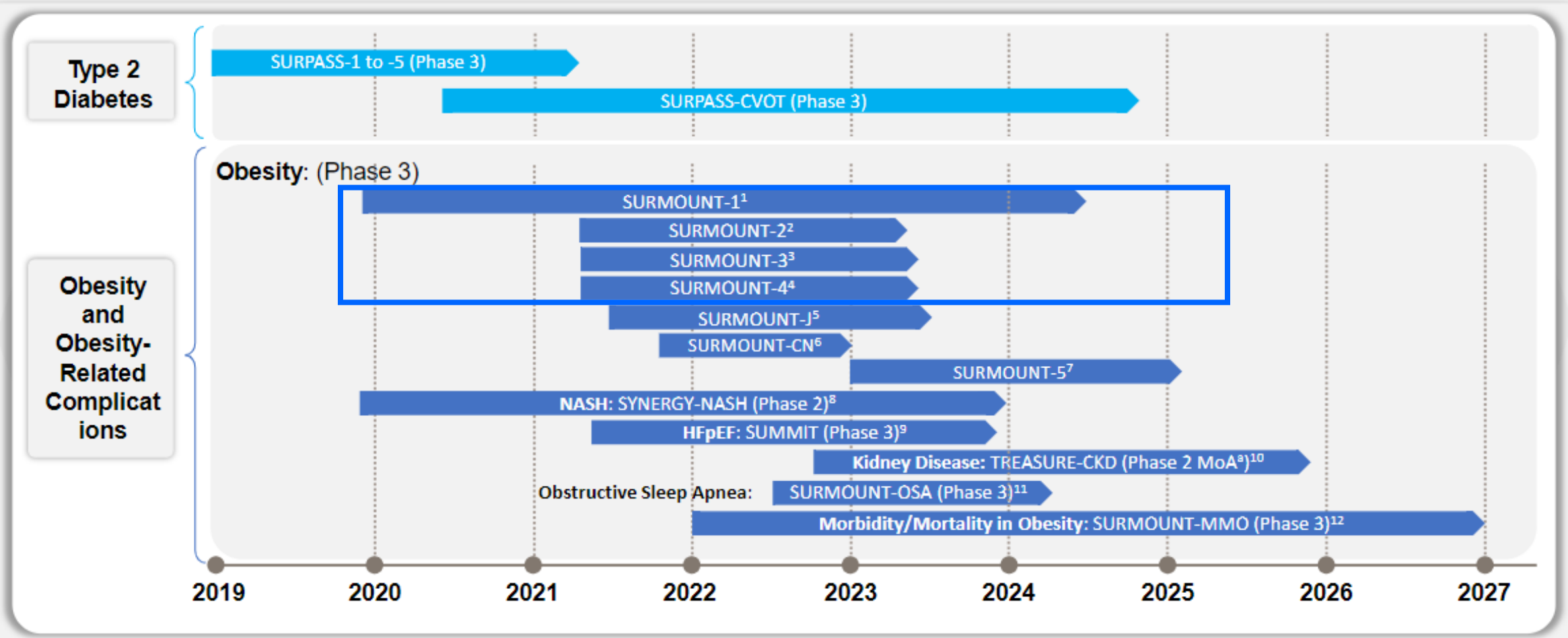

- AE, adverse events; GI, gastrointestinal.
  1. Novo Nordisk, data on file; 2. Wharton et al. Postgraduate Med 2022;134:14-9.

# TIRZEPATIDE



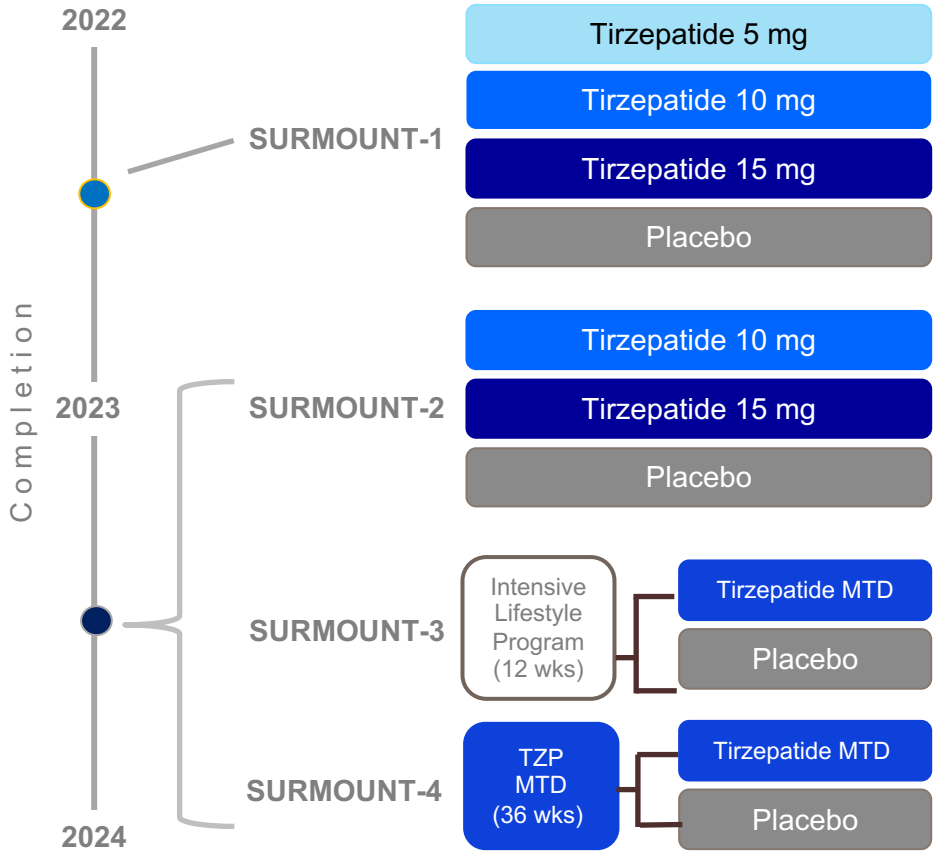

**CNS:** central nervous system; **GIP:** glucose-dependent insulinotropic polypeptide; **GLP-1:** glucagon-like peptide-1.

**1.** Müller TD, *et al. Mol Metab*. 2019;30:72-130. **2.** Seino Y, *et al. J Diabetes Investig*. 2010;1(1-2):8-23. **3.** Fukuda M. *Diabetes*. 2021;70(8):dbi210001. **4.** Nauck MA, *et al. Diabetes Obes Metab*. 2021 (Ahead of Print);doi:10.1111/dom.14496. **5.** Samms RJ, *et al. Trends Endocrinol. Metab*. 2020;31(6):410-421. **6.** Bastin M, *et al. Diabetes Metab Syndr Obes*. 2019;12:1973-1985.




[a]Not an outcomes study.
CKD=Chronic Kidney Disease; CVOT = Cardiovascular Outcomes; 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 October 10, 2022); Jastreboff et al. N Engl J Med. 2022;387(3):205-216. 2. https://clinicaltrials.gov/ct2/show/NCT04657003 (Accessed October 10, 2022). 3. https://clinicaltrials.gov/ct2/show/NCT04657016 (Accessed October 10, 2022). 4. https://clinicaltrials.gov/ct2/show/NCT04660643 (Accessed October 10, 2022). 5. https://www.clinicaltrials.gov/ct2/show/NCT04844918 (Accessed October 10, 2022). 6. https://www.clinicaltrials.gov/ct2/show/NCT05024032 (Accessed October 10, 2022). 7. https://clinicaltrials.gov/ct2/show/NCT05822830 (Accessed April 24, 2023). 8. https://clinicaltrials.gov/ct2/show/NCT04166773 (Accessed October 10, 2022). 9. https://clinicaltrials.gov/ct2/show/NCT04847557 (Accessed October 10, 2022). 10. https://clinicaltrials.gov/ct2/show/NCT05536804 (Accessed October 10, 2022). 11. https://clinicaltrials.gov/ct2/show/NCT05412004 (Accessed October 10, 2022). 12. https://clinicaltrials.gov/ct2/show/NCT05556512 (Accessed October 10, 2022).

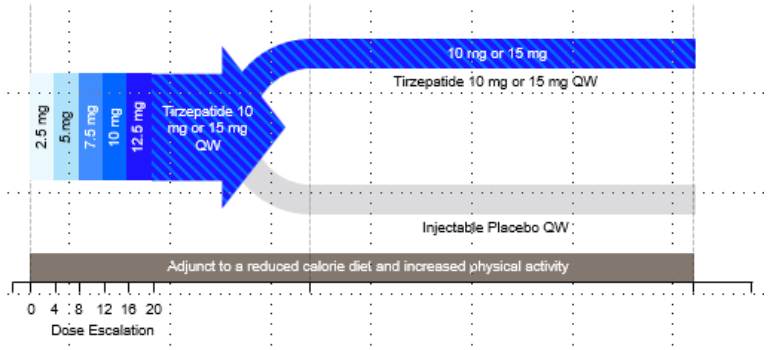



**Manejo del peso en personas con sobrepeso/obesidad sin DT2**
N=2539
Duration: 72 weeks
**Pre-DM estudio adicional con seguimiento durante 2 años**

**Manejo del peso en personas con DT2**
N=938
Duration: 72 weeks

**Manejo del peso tras programa intensivo sobre estilo de vida**
Enrolled: N=807, Randomized: N~600
Duration: 84 weeks

**Mantenimiento del peso**
Enrolled: N=783, Randomized: N~600
Duration: 88 weeks




## PHASE 3b TRIAL:
### SURMOUNT-5

Tirzepatide 10/15 mg

Semaglutide 2.4 mg

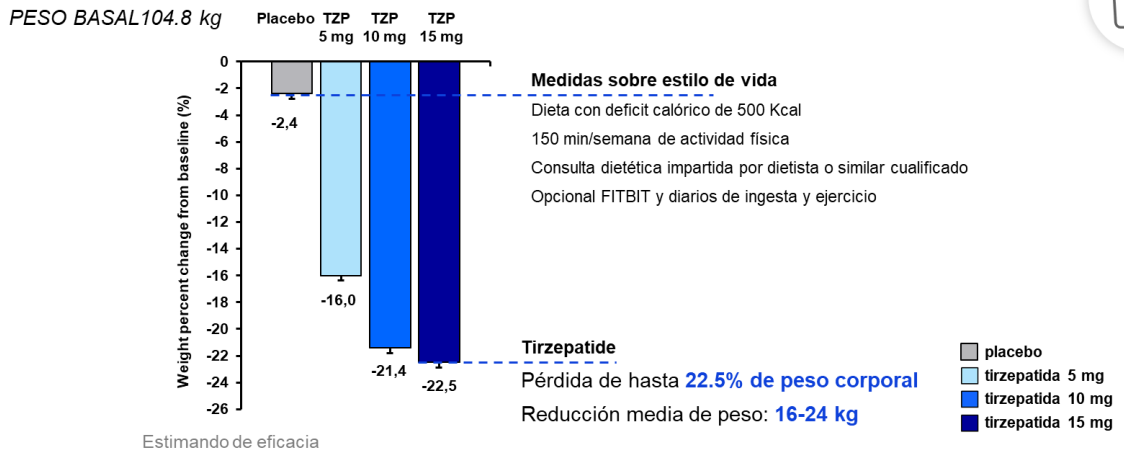
**Weight management**
**N= 700**
**Duration: 72weeks**

**DM:** Diabetes Mellitus; **T2D:** Type 2 Diabetes; **TZP:** Tirzepatide; **MTD:** Maximal Tolerated Dose/Dosis Máxima Tolerada

**1.** Le Roux CW, Zhang S, Aronne LJ, *et al.* Obesity (Silver Spring). 2022. **2.** A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight With Weight Related Comorbidities. **3.** SURMOUNT-MMO https://clinicaltrials.gov/ct2/show/NCT05556512

# SURMOUNT-1

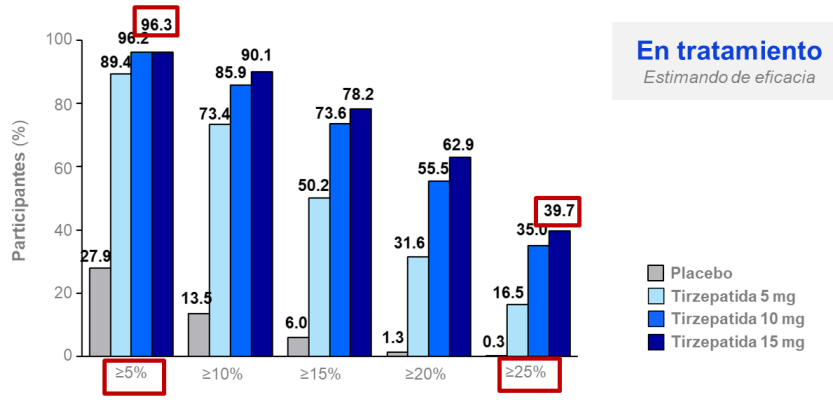
## % de reducción de peso a la semana 72




Estimando de eficacia

**Superioridad frente a placebo en todas las dosis de Tirzepatida**
**Reducción de hasta 22,5% de peso (hasta ~24 kg) en comparación con placebo.**

## ¿Qué % de pacientes logran reducción de peso?




**Todas las dosis** logran **superioridad** en la reducción de peso (≥5%, ≥10%, ≥15%, ≥20% y ≥25% ) frente a placebo.
Un **39,7%** de los pacientes alcanzaron el criterio de valoración exploratorio preespecificado **de ≥25% de reducción del peso corporal** con tirzepatida 15 mg.

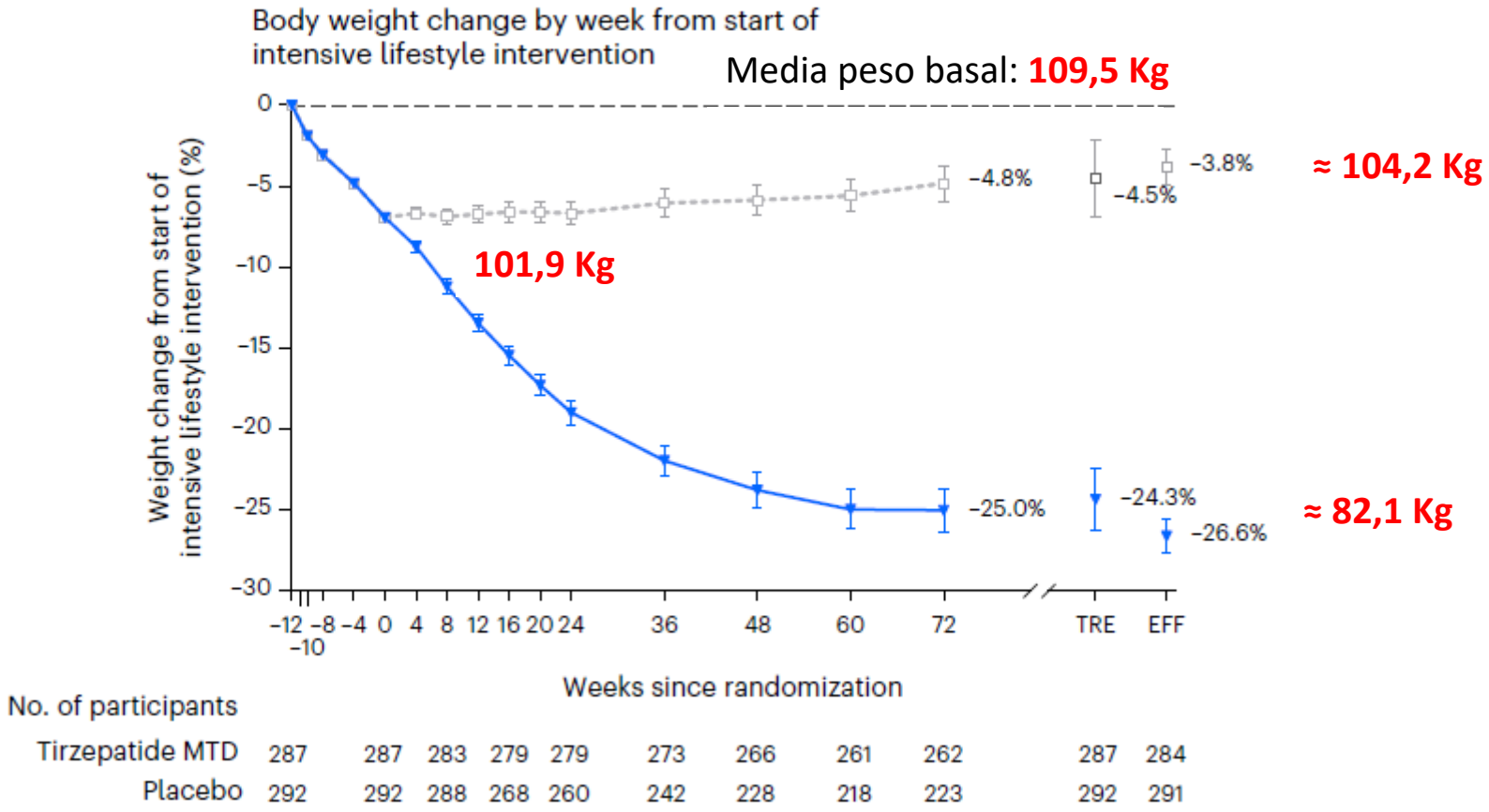
- ↓ TAs 8,1 mmHg
- ↓ TAd 5,3 mmHg
- ↓ TG 27,6%
- ↓ Col no HDL -11,3%
- ↓ LDL 6,9%
- ↓ P abd 14-19,9 cm

**De los participantes con prediabetes* >95% revirtió a normoglucemia en las ramas con tirzepatida**

*40,6% de la población de estudio
Normoglucemia: HbA1c ≤ 5,7%

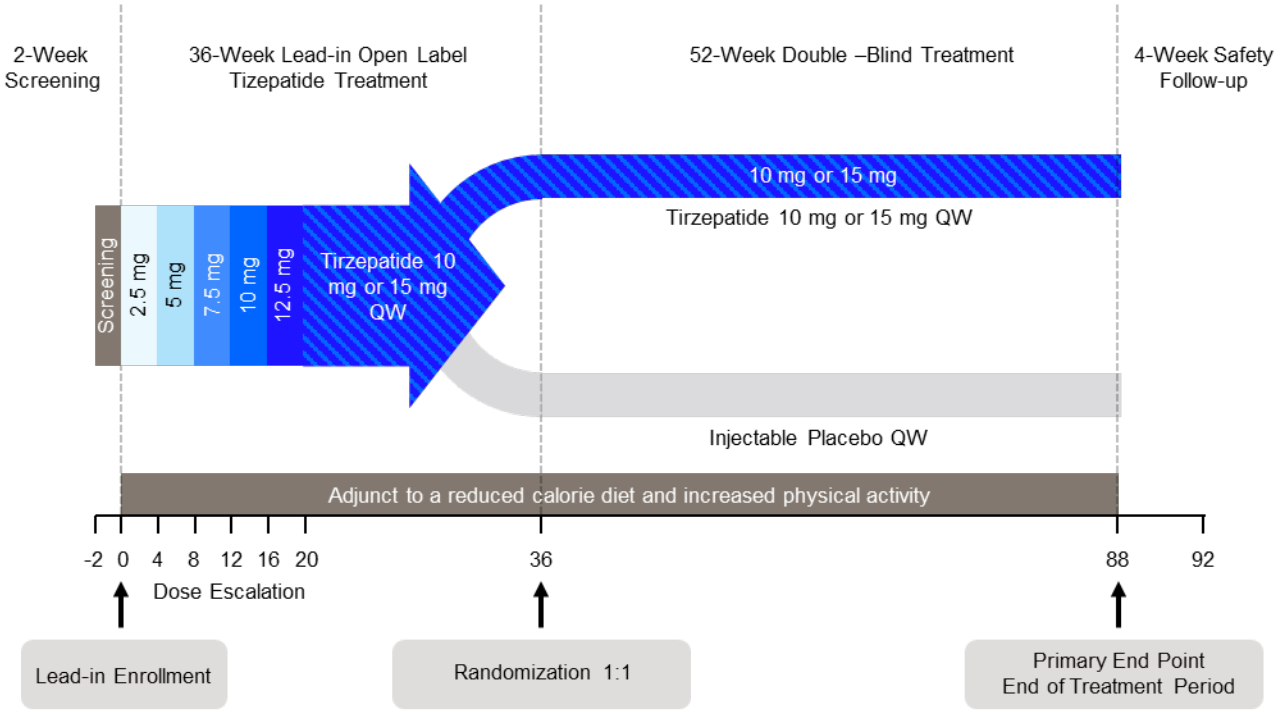
# SURMOUNT-3

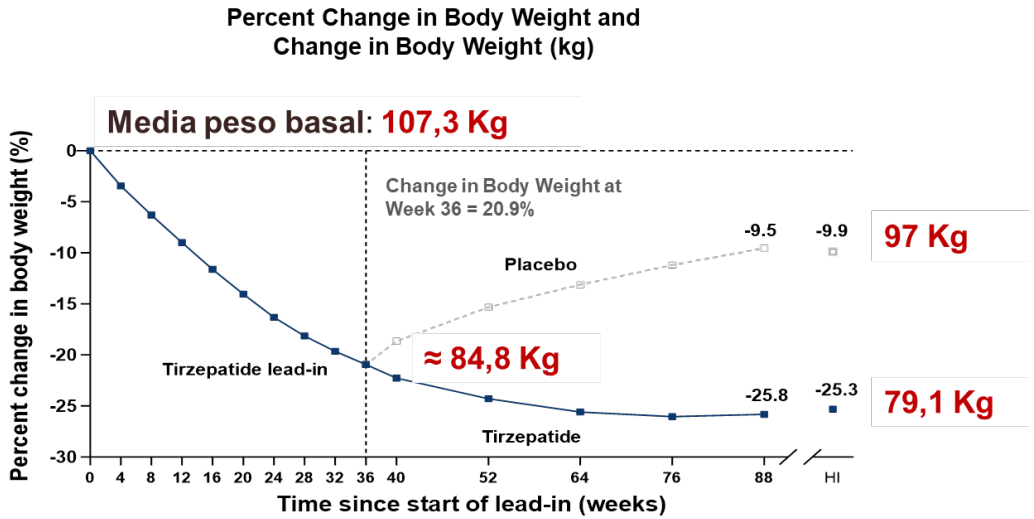
808 entran en programa de 12 semanas de intervención intensiva en el estilo de vida
579 (71,8%) consiguen perder ≥ 5% (media 6,9 %) del peso inicial y son aleatorizados a la dosis máxima tolerada de tirzepatide Vs placebo 72 semanas




Nature Medicine | Volume 29 | November 2023 | 2909–2918

# SURMOUNT-4

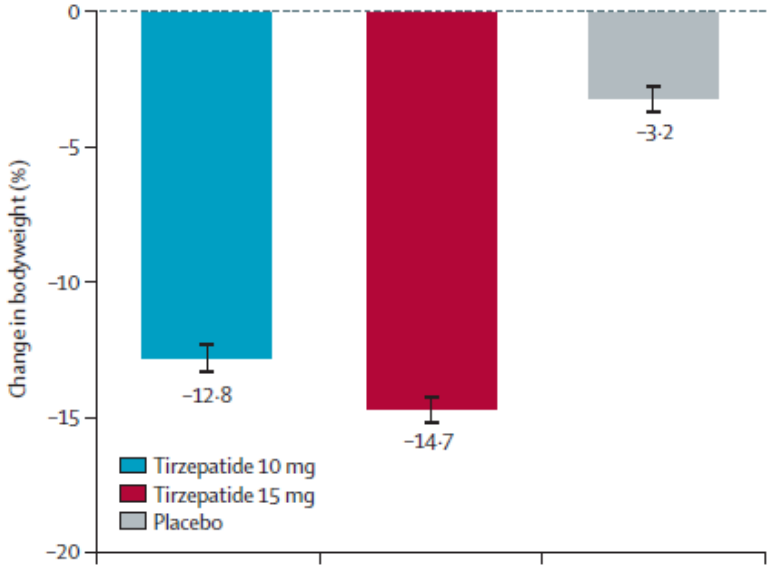


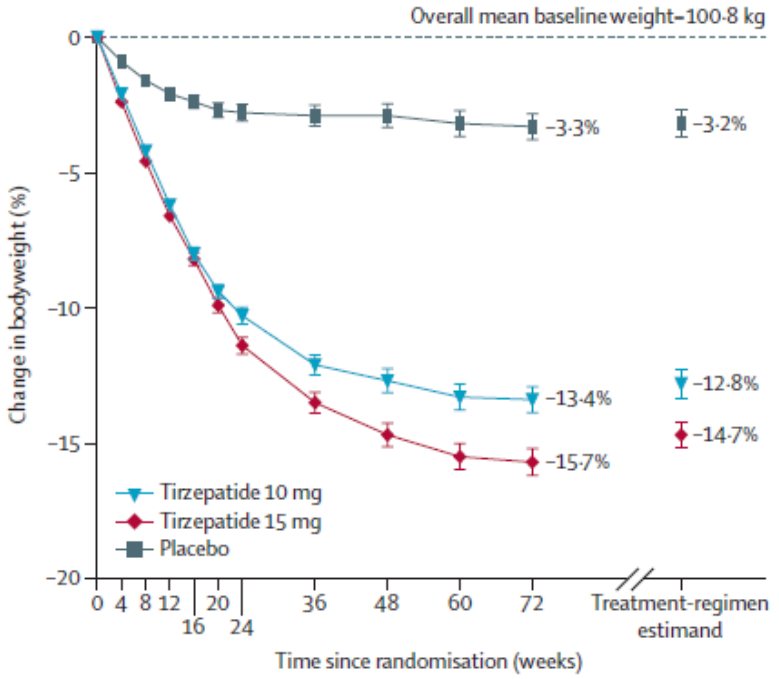



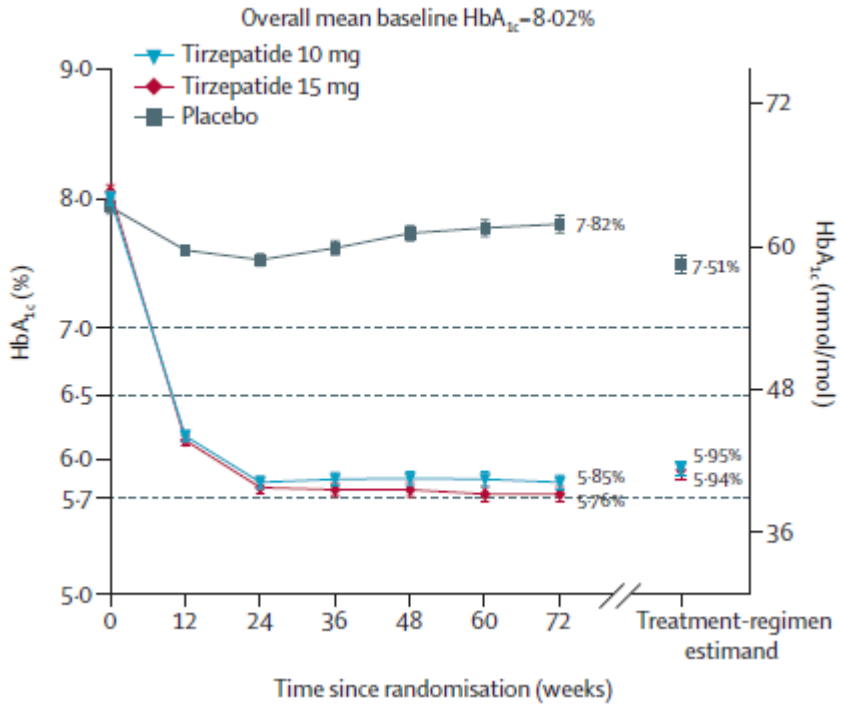

| Treatment group | Number of participants at each time point | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tirzepatide lead-in | 670 | 666 | 669 | 668 | 667 | 667 | 669 | 663 | 659 | 670 | |
| Tirzepatide | | | | | | | | 335 | 333 | 328 | 317 | 310 |
| Placebo | 310 | | 335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

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).

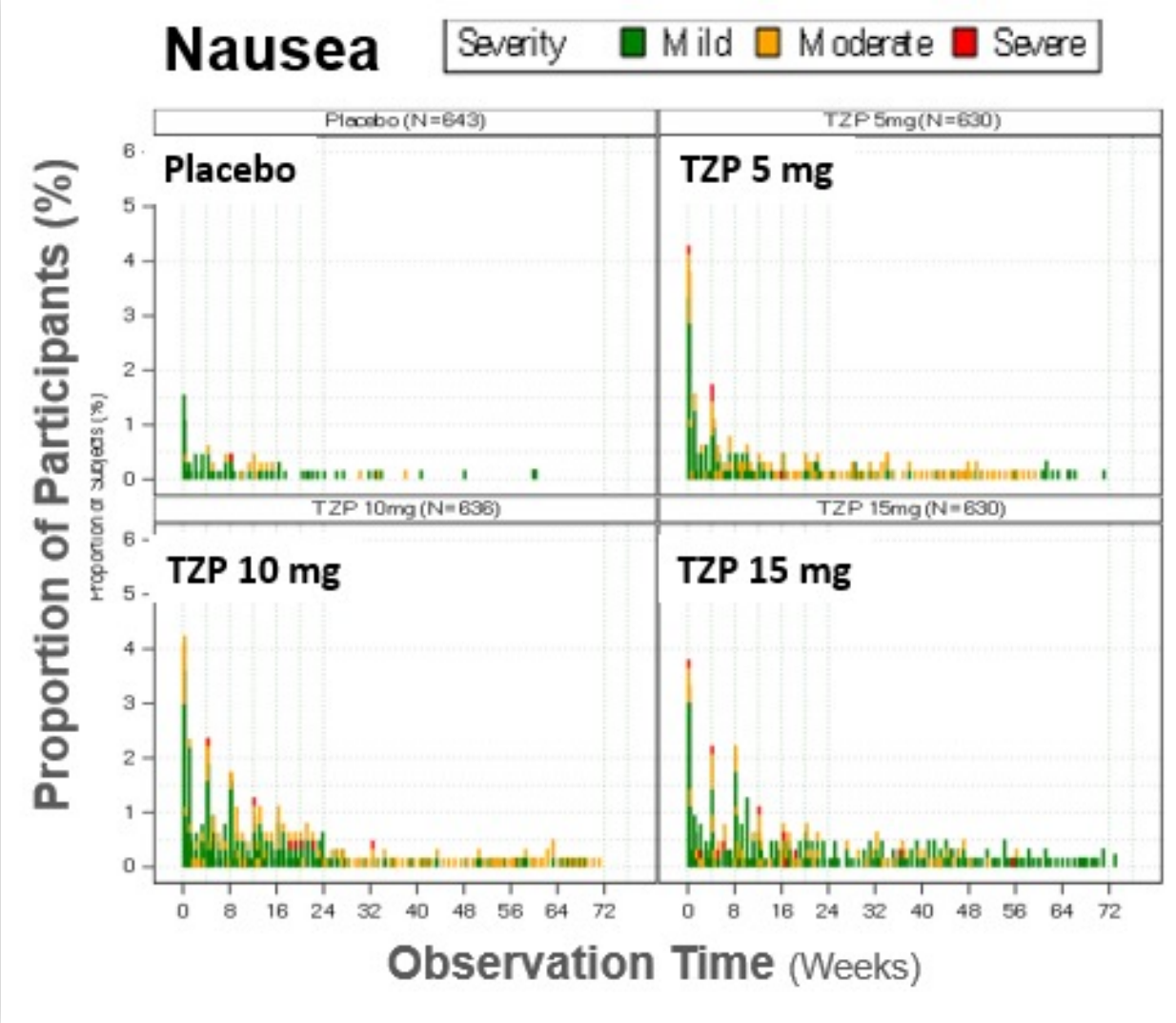
# SURMOUNT-2 (IMC ≥ 27 + HBA1c 7-10%)



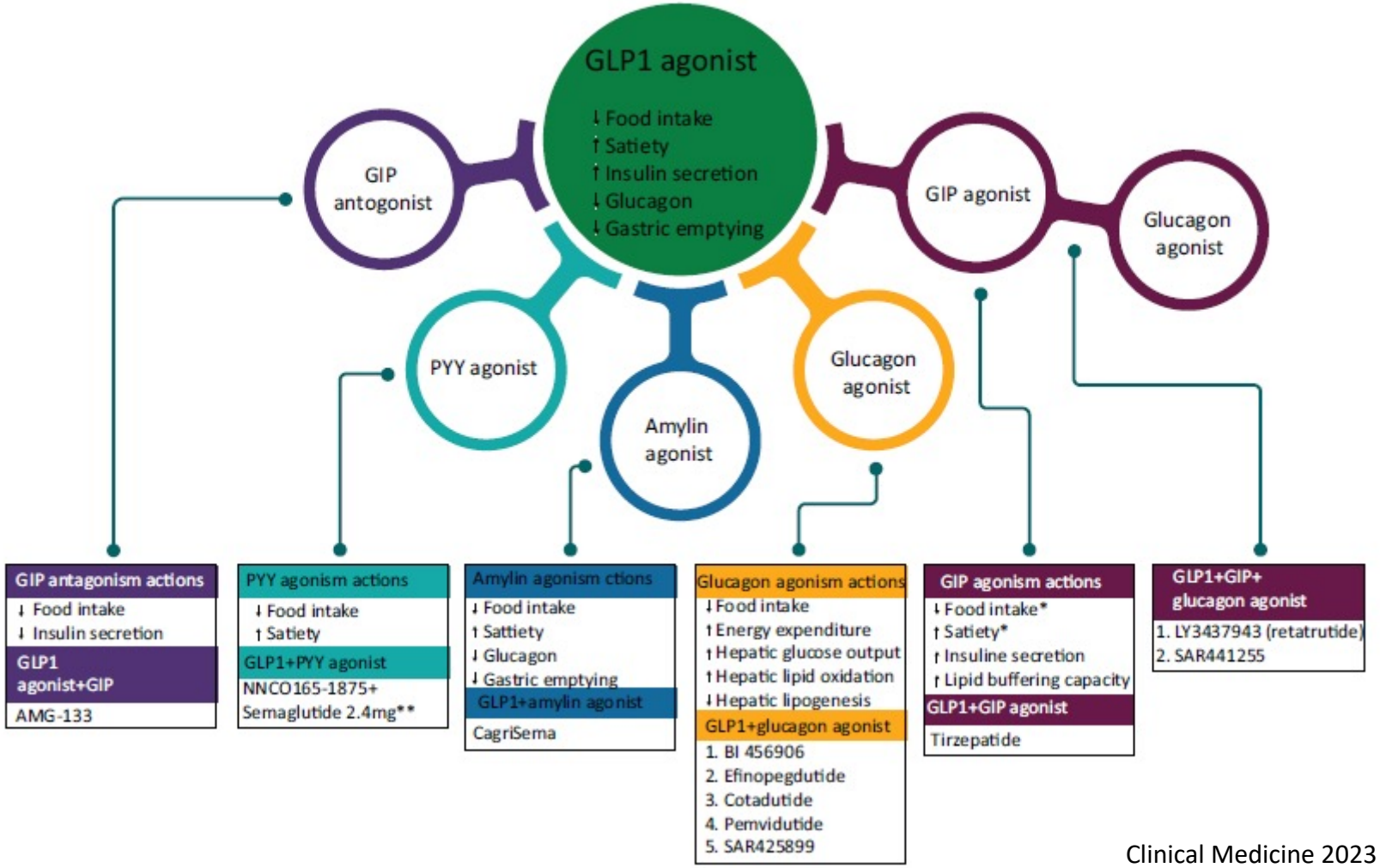

*Lancet* 2023; 402: 613–26




**EA GI ocurrieron principalmente durante periodo escalado de dosis** con reducción posterior.

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

# EL FUTURO INMEDIATO




Clinical Medicine 2023 Vol 23, No 4: 337–46

# CONCLUSIONES

- La obesidad en **una enfermedad crónica compleja** que se asocia a múltiples patologías que empeoran la calidad de vida y reducen la esperanza de vida
- Su origen es multifactorial y su abordaje, por tanto, debe ser holístico
- Las medidas de intervención en el estilo de vida son fundamentales, pero claramente insuficientes en la inmensa mayoría de los casos
- La llegada de los nuevos fármacos para el tratamiento de la obesidad supone una **REVOLUCIÓN** en la medicina preventiva, consiguiendo objetivos hasta ahora solo al alcance de la cirugía
- Son fármacos seguros que tiene efectos preventivos cardiovasculares que van más allá de la mera reducción de peso

# ¡GRACIAS!

# I REUNIÓN DE RIESGO CARDIOVASCULAR

de la Sociedad Castellano-Manchega
de Cardiología