Il paziente con obesità e sindrome metabolica: quali obiettivi terapeutici?

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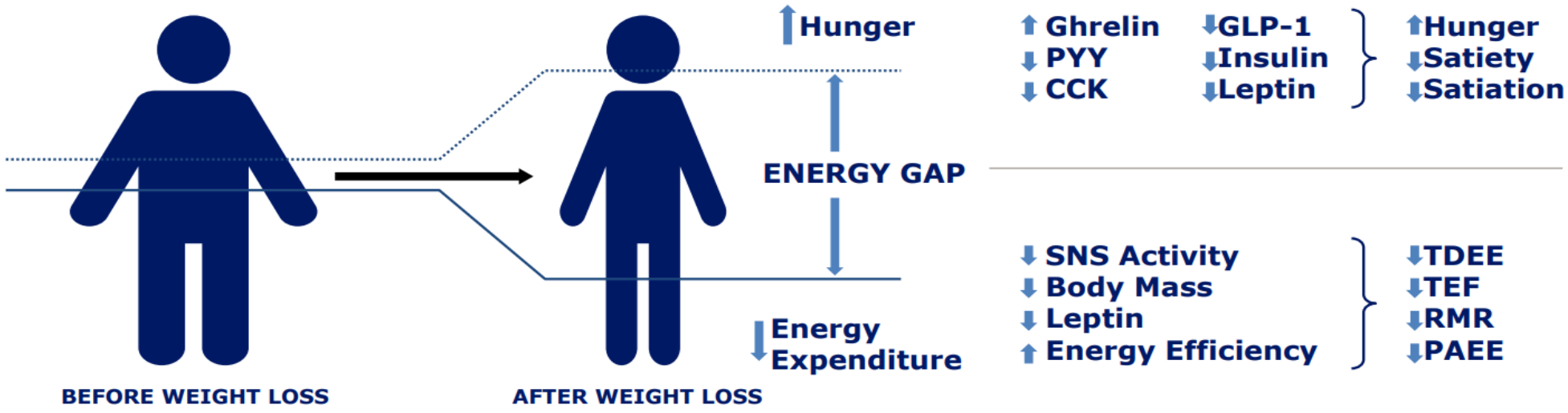
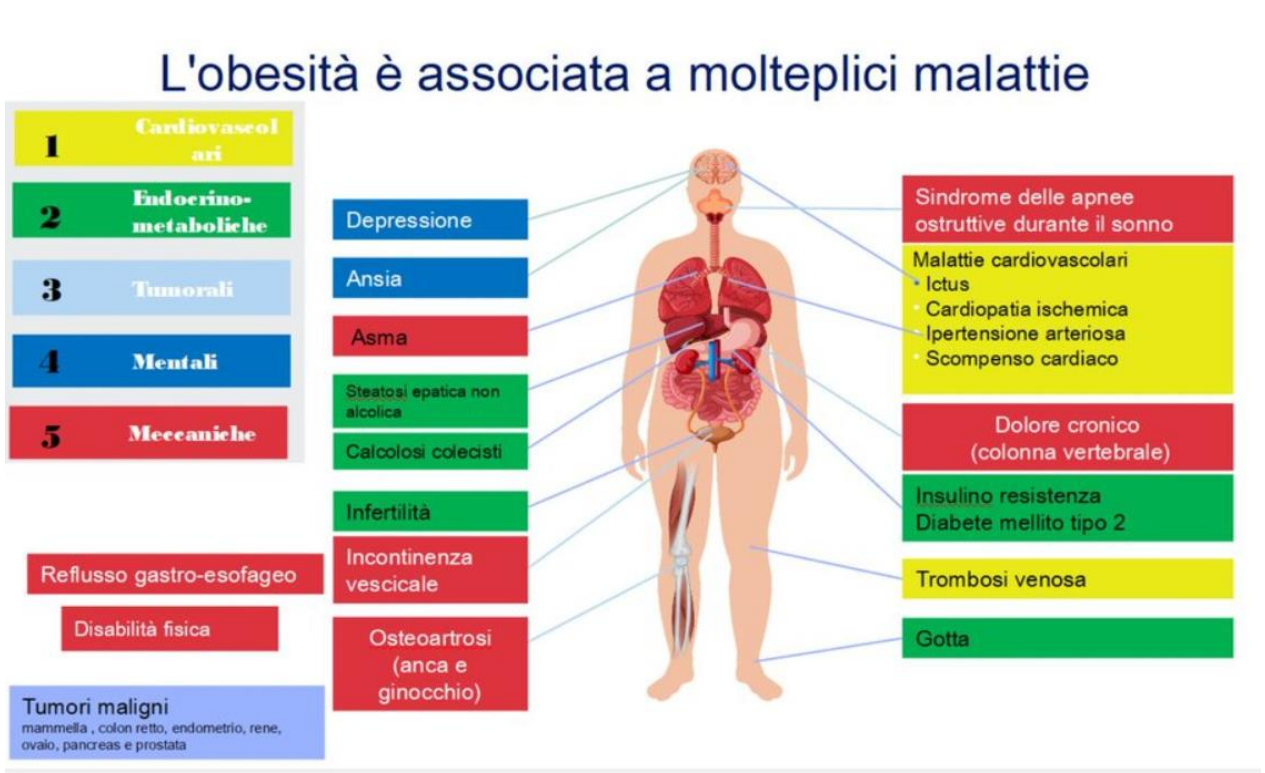
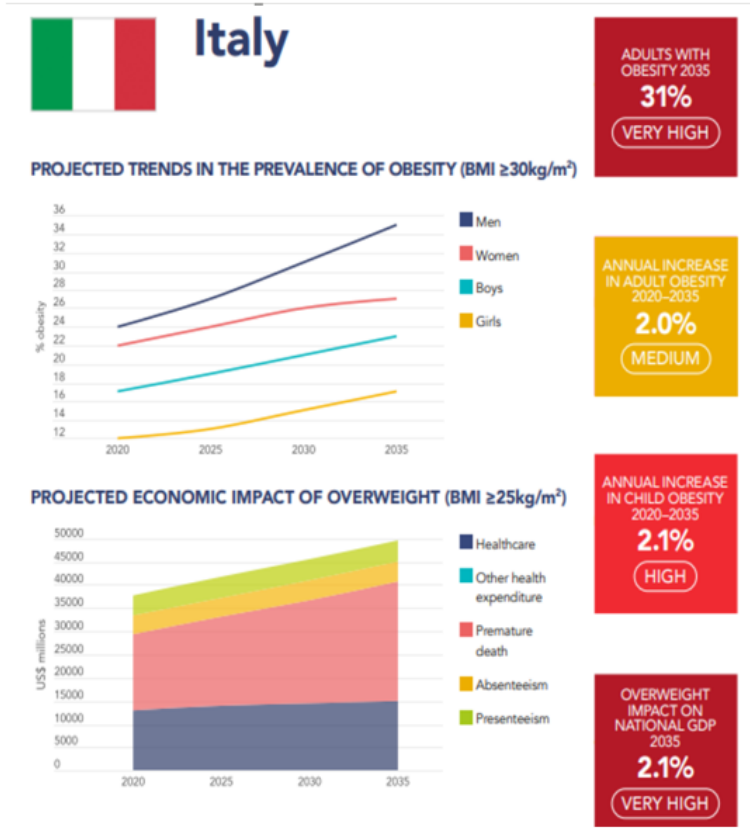
Obesità e SM: cosa è cambiato?

Legge Pella

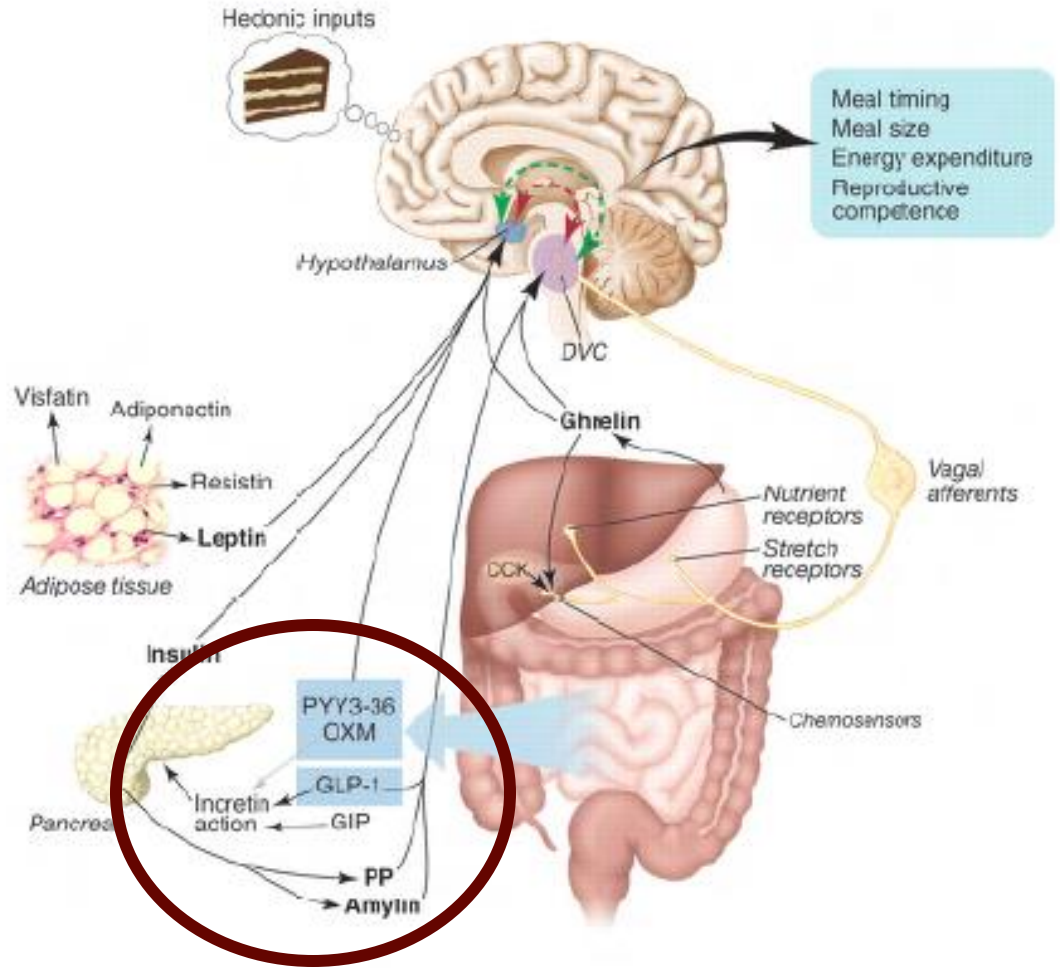
L'obesità è una malattia cronica recidivante causata da fattori genetici e ambientali

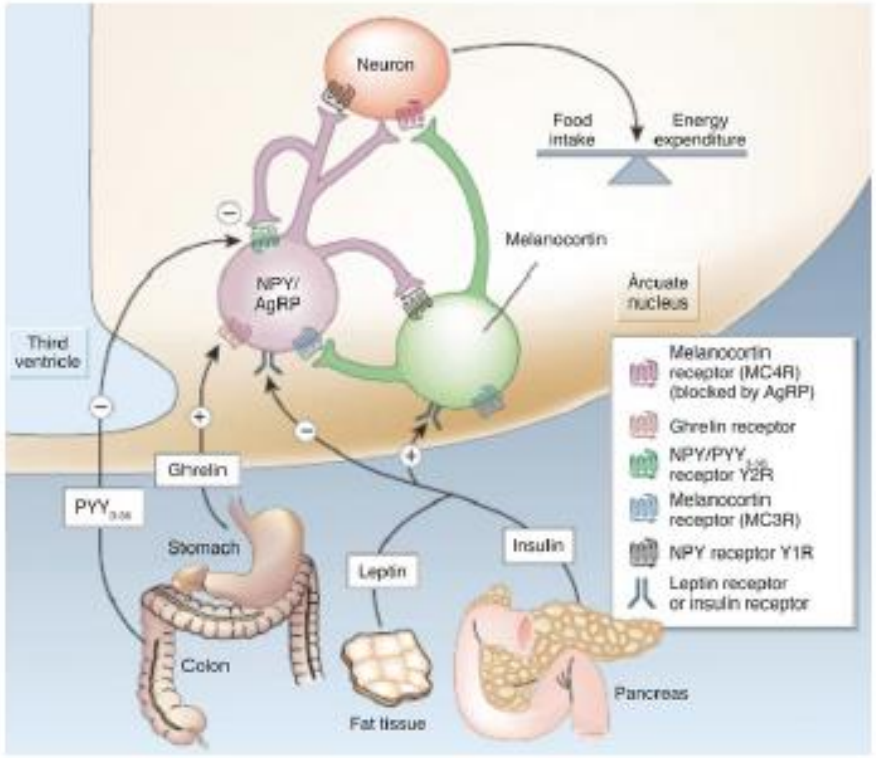






Patologia con complicanze metaboliche e non In continuo aumento





Badman & Flier. Science 2005

EASO
European Association for the Study of Obesity

GLP-1

Glucagon-like peptide-1

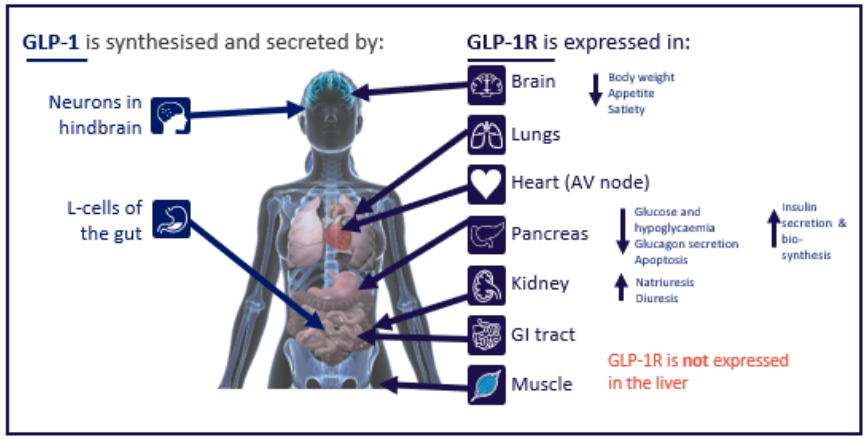
- Peptide comprised of 31 amino acids
- Member of the incretin family

Secreted predominantly from **L-cells in the gut**, but also the brain (nucleus tractus solitarius)

Human endogenous GLP-1

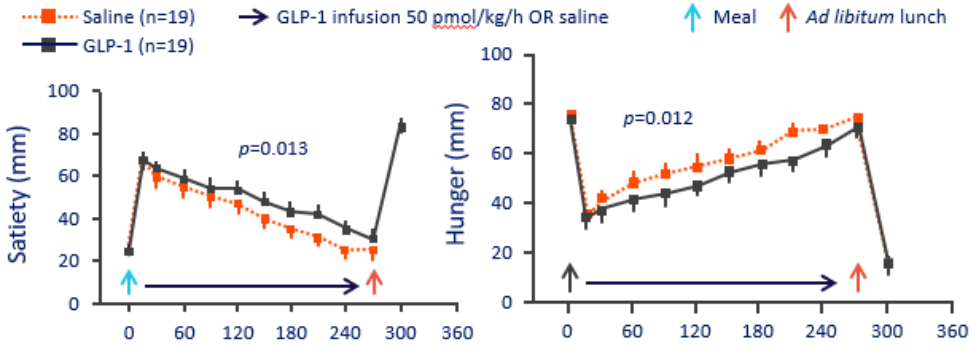
GLP-1 is **released** in response to **food intake**

GLP-1 **reduces energy intake**

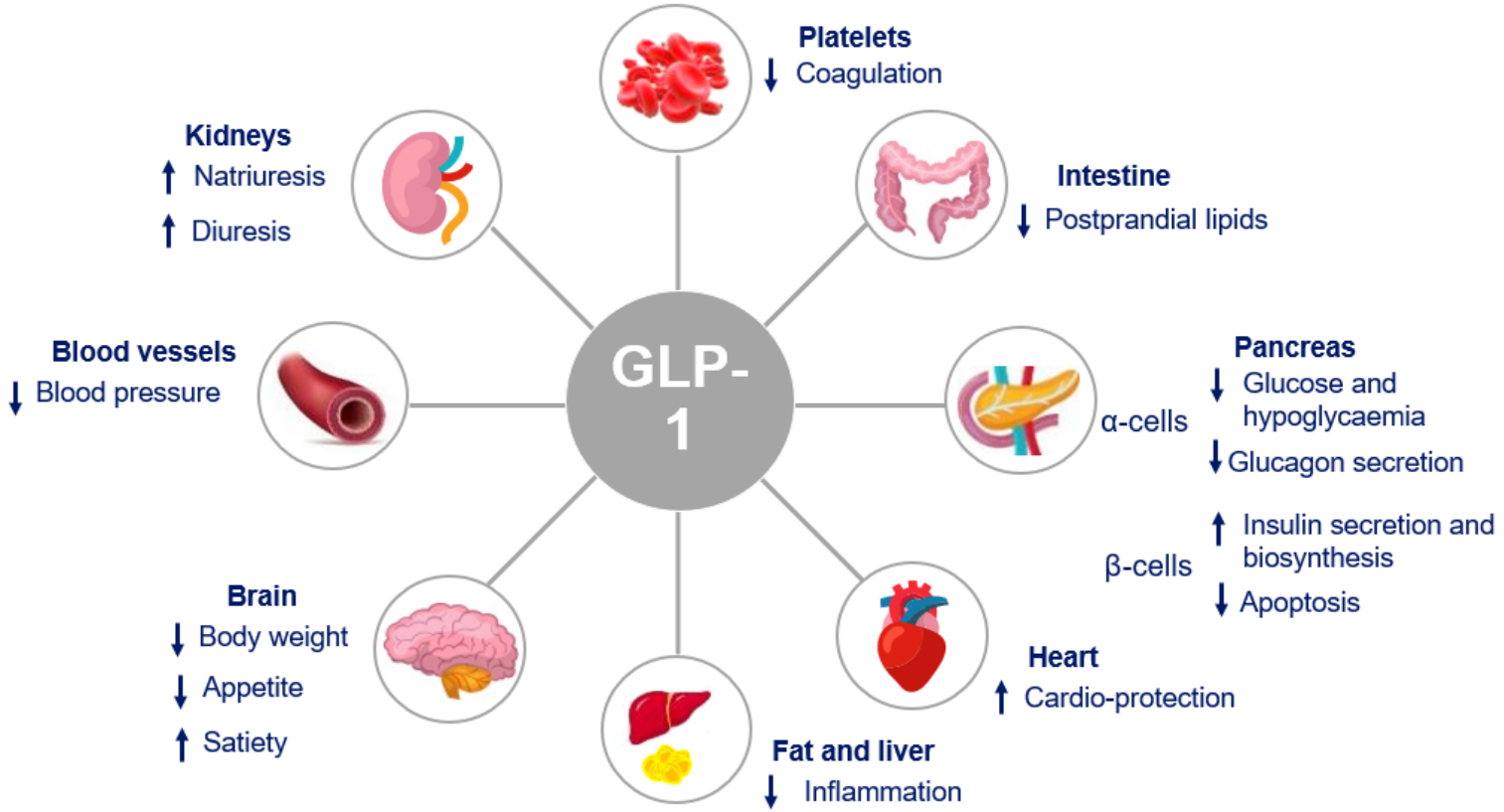


GLP-1, glucagon-like peptide-1.

GLP-1 **increases satiety and reduces hunger** in normal weight subjects



Main effects of GLP-1



GLP-1, glucagon-like peptide

1. Wang XC et al. World J Gastroenterol 2014;20:14821–14830; 2. Lee J et al. Diabetes Metab J 2012;36:262–267; 3. Sharma S et al. PLoS One 2011;6:e25269

Terapia farmacologica dell'obesità

1998
Orlistat

2015
Naltrexone/bupropione

2015
Liraglutide

Febbraio 2024
Setmelanotide

Luglio 2024
Semaglutide

Ottobre 2024
Tirzepatide

2017
approvazione negli USA come farmaco antidiabetico

2019
approvazione in Europa come farmaco antidiabetico

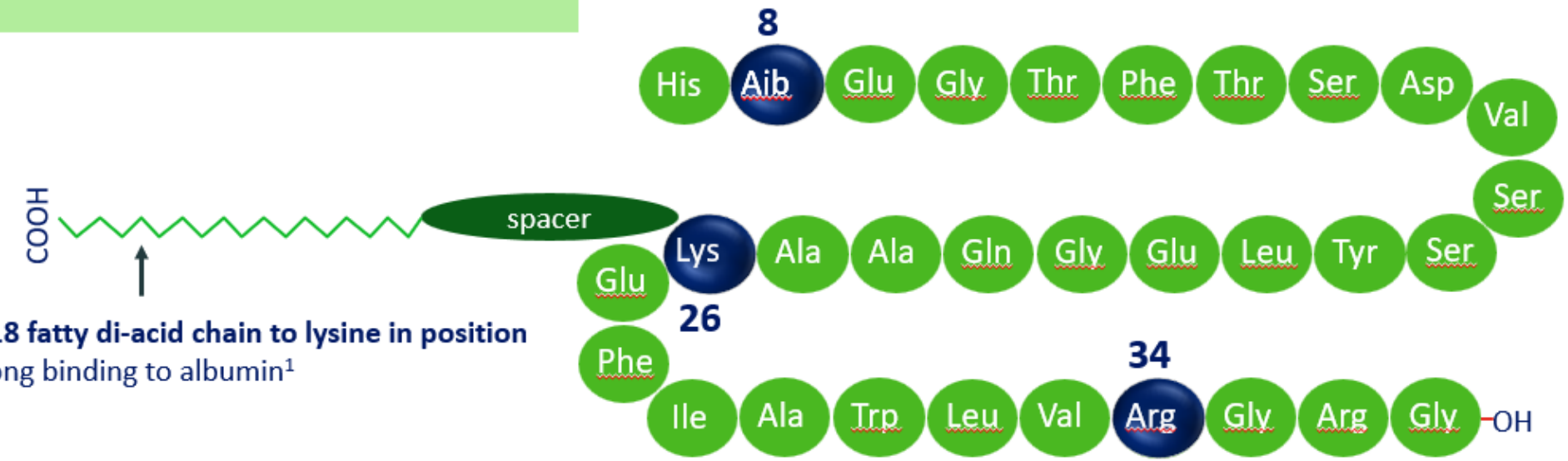
2021
Approvazione commercializzazione in USA come trattamento per l'obesità

2022
Approvazione in Europa (EMA e AIFA) come trattamento per l'obesità

Semaglutide è un analogo del GLP-1

- **94%** homology to human GLP-1[1]
- $t_{½}$ of approximately **1 week**[2,3]

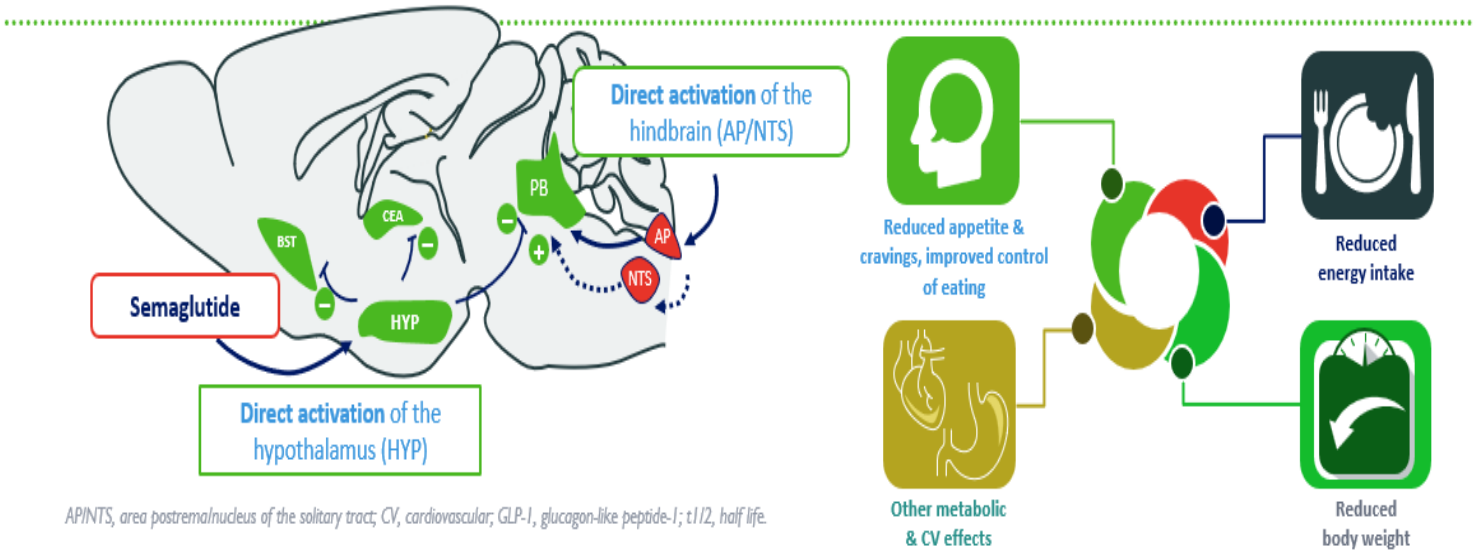
Amino acid substitution at position 8
(alanine to alpha-aminoisobutyric acid)
protects against DPP-4 degradation[1]



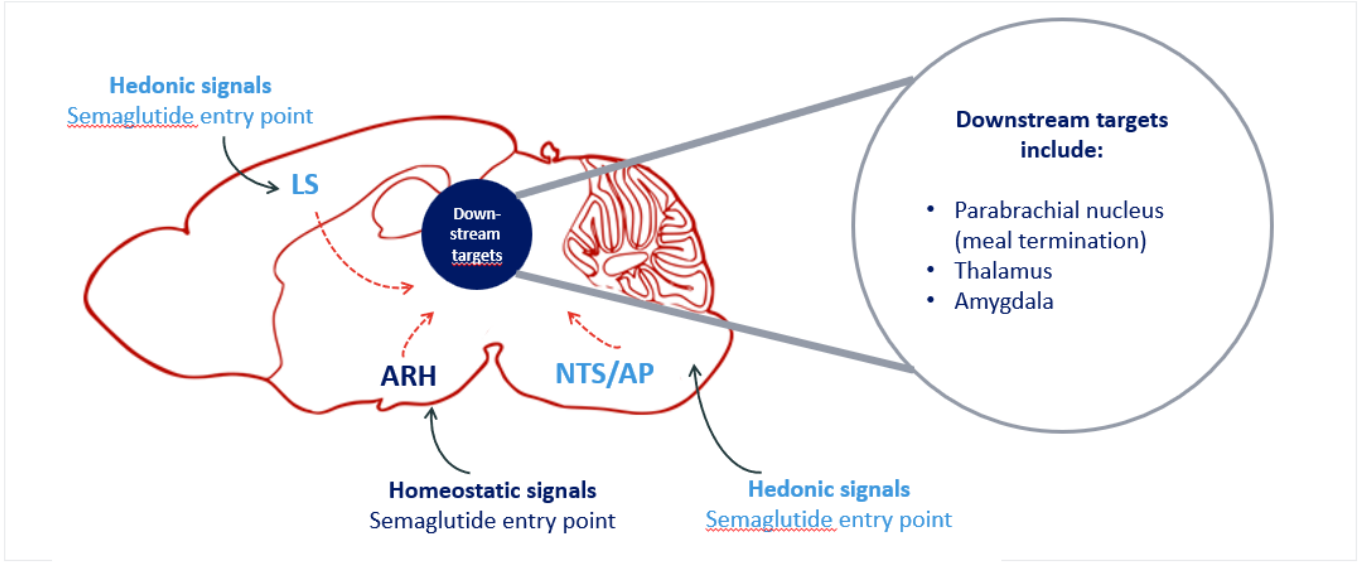
Spacer and C-18 fatty di-acid chain to lysine in position 26 provide strong binding to albumin[1]

Amino acid substitution at position 34
(lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site[1]

Meccanismo d'azione



AP/NTS, area postrema/nucleus of the solitary tract; CV, cardiovascular; GLP-1, glucagon-like peptide-1; t1/2, half life.

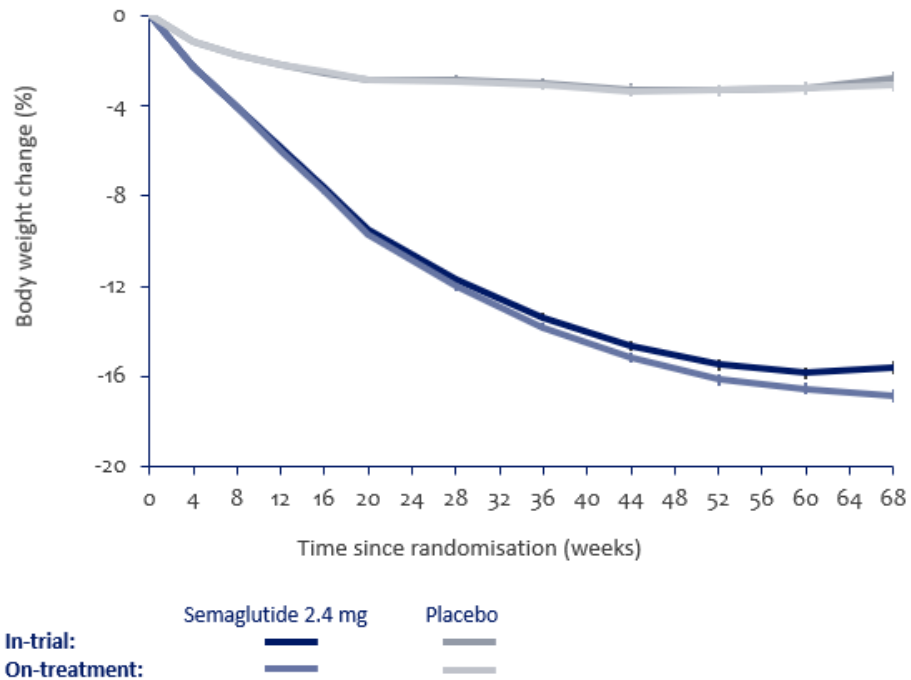


AP, area postrema; ARH, arcuate nucleus; LS, lateral septal nucleus; NTS, nucleus of the solitary tract; Modified from Campos et al. Cell metabolism 2016;23(5):811-820

STEP 1: Body weight change

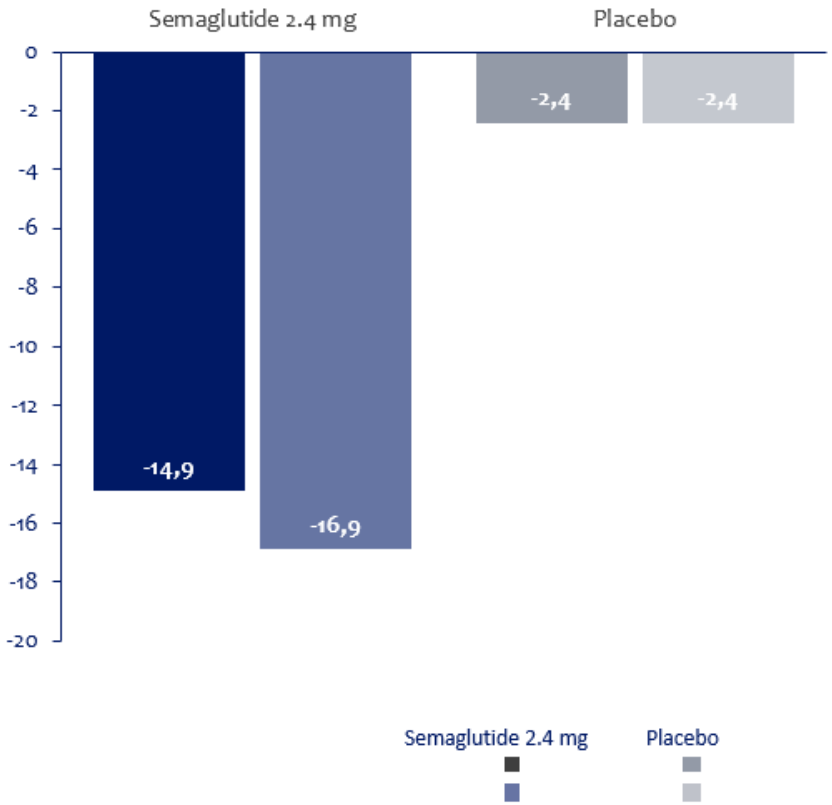
Observed body weight change over time

(Mean at baseline: 105.8 kg)

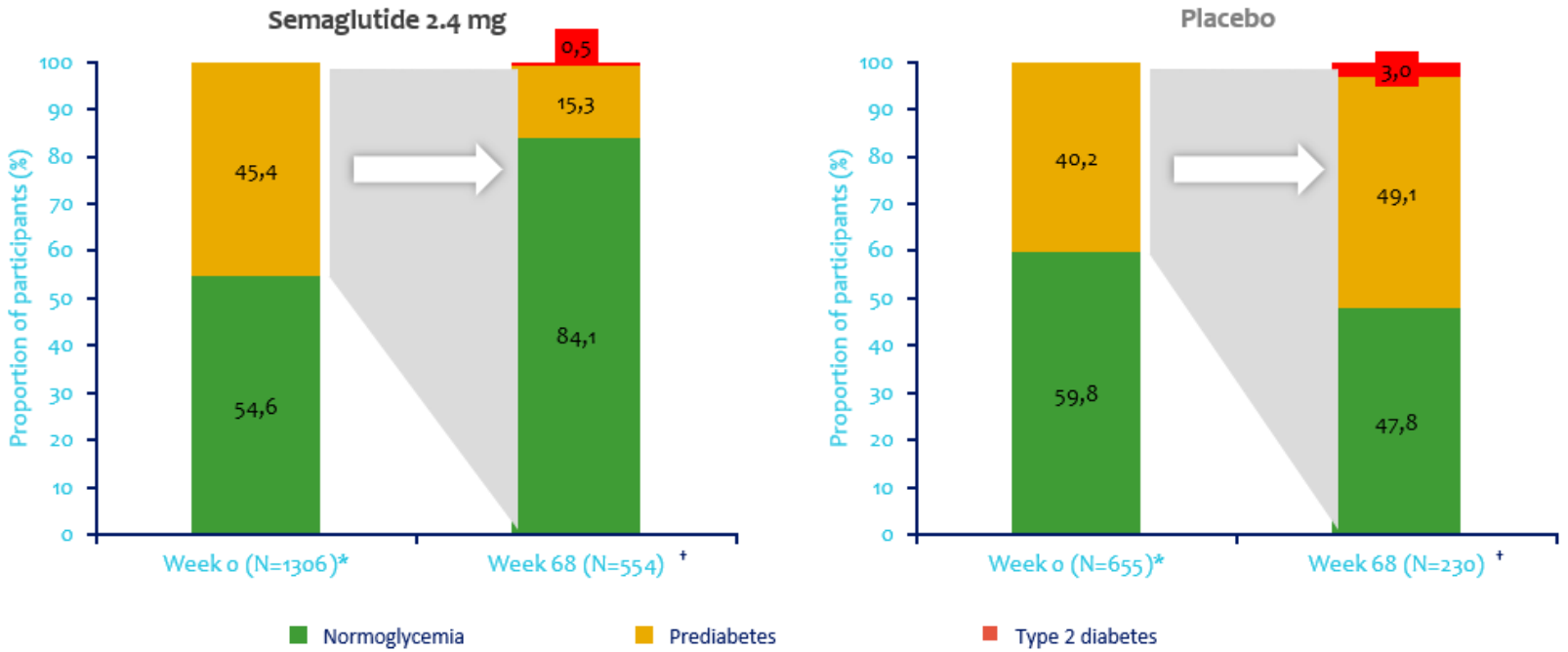


Error bars are +/- standard error of the mean.
CI, confidence interval; ETD, estimated treatment difference.
Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183.

Estimated change from baseline to week 68



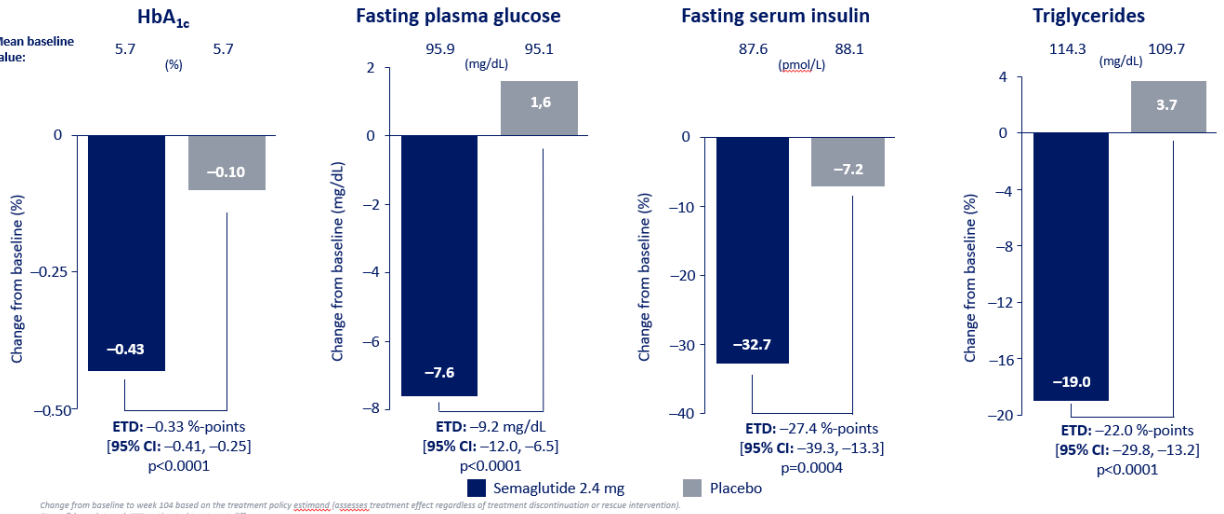
Valutazione pazienti con prediabete



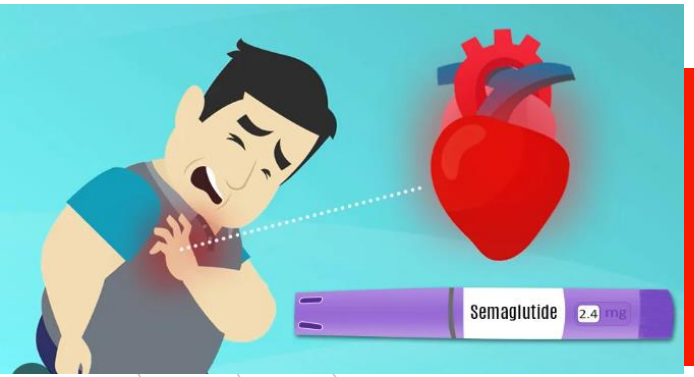
Data are observed data during the in-trial period (regardless of treatment discontinuation or rescue intervention).
glycaemic category was evaluated by the investigator based on all available relevant information (e.g. concomitant medication, medical records and blood glucose parameters) in accordance with American Diabetes Association definitions.
Perreault et al. Presented at the American Diabetes Association (ADA) virtual meeting. June 25–29, 2021.

TREY research

STEP 5

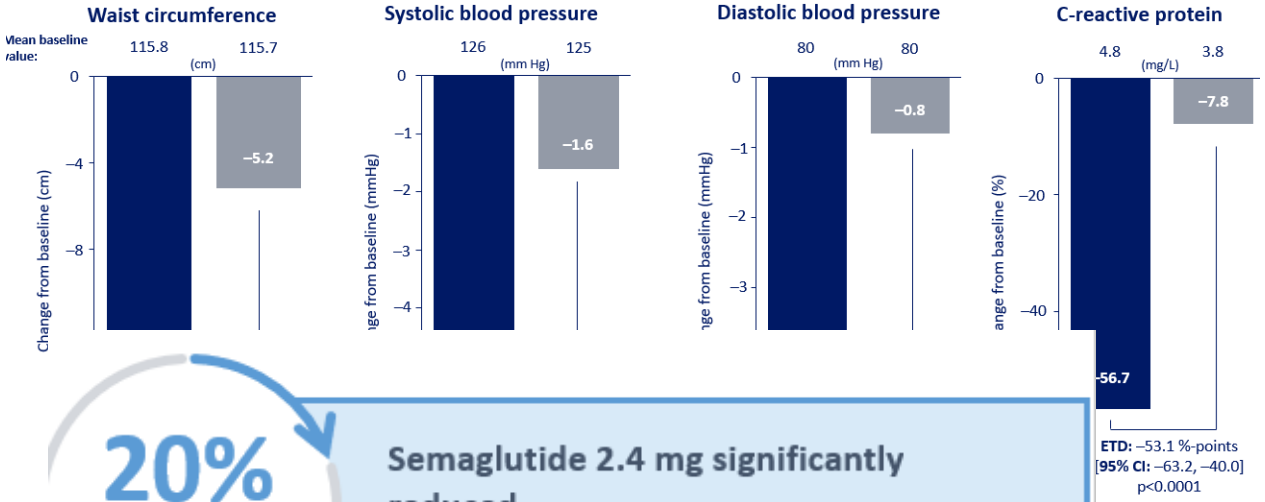


Change from baseline to week 104 based on the treatment policy estimand (assesses treatment effect regardless of treatment discontinuation or rescue intervention).
CI, confidence interval; ETD, estimated treatment difference.
Garvey et al. Nat Med 28, 2083–2091 (2022).



Riduzione de
(anche in p

STEP 5



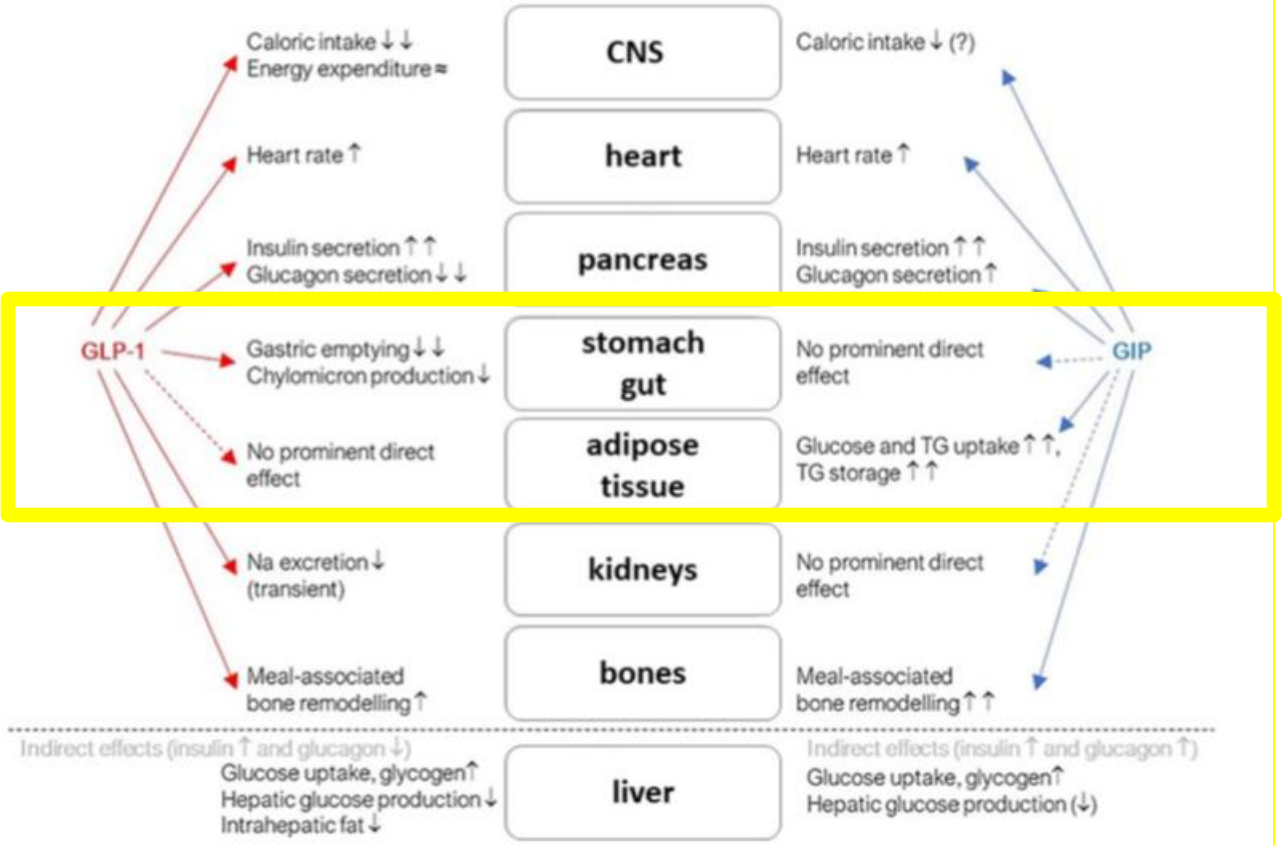
20%
reduction in risk of MACE*

Semaglutide 2.4 mg significantly reduced the risk of MACE by 20% compared with placebo in people with obesity and established CVD, without T2D[1,2]

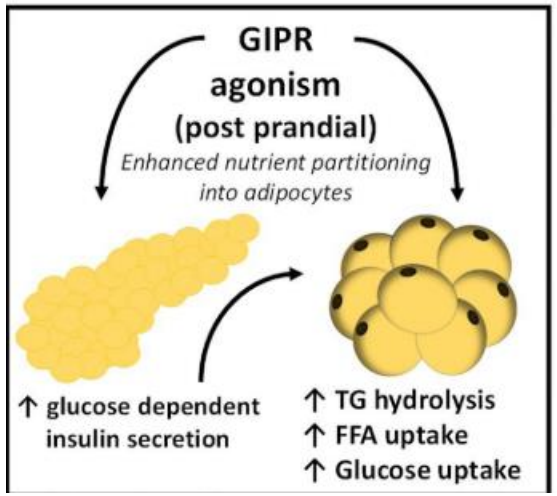
All three components (death from CV causes, non-fatal MI and non-fatal stroke) contributed to MACE risk reduction

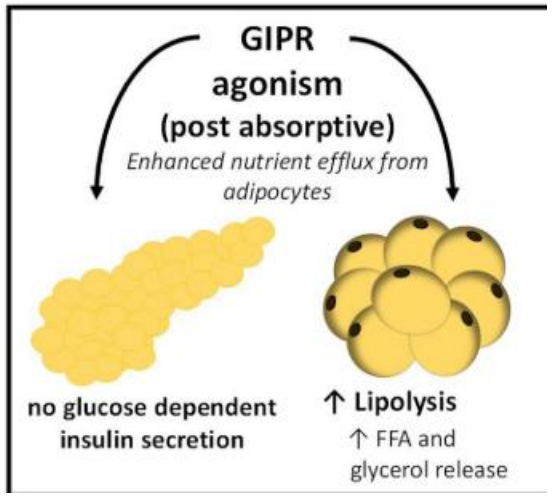
Mean follow-up time was 39.8 months

DUAL GIP/GLP1 AGONIST



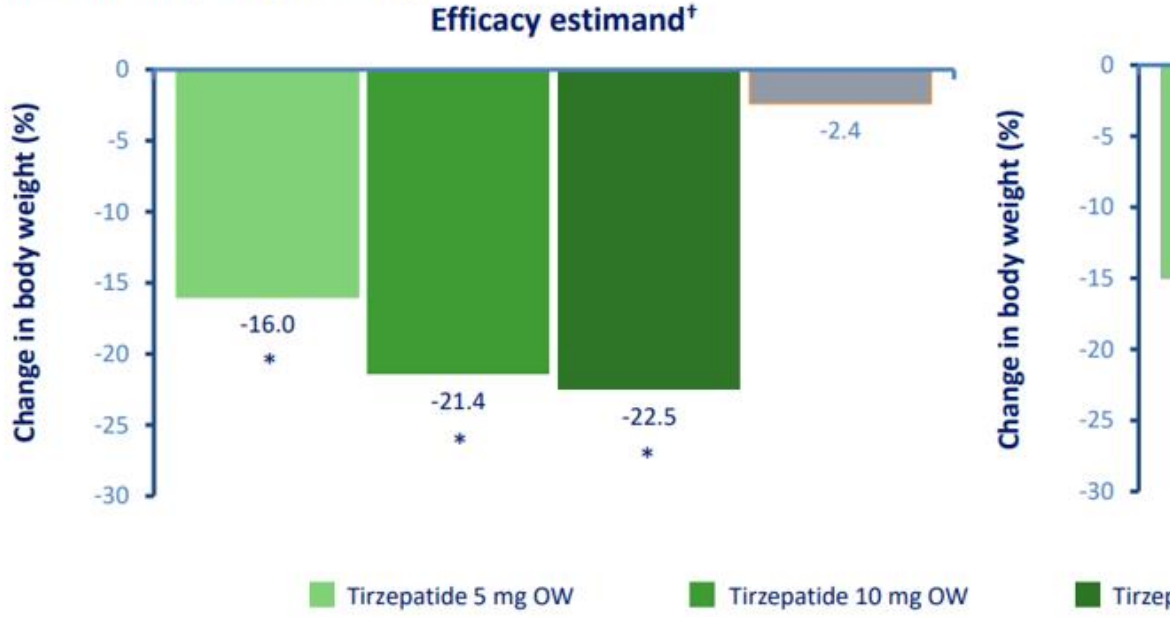
Tirzepatide

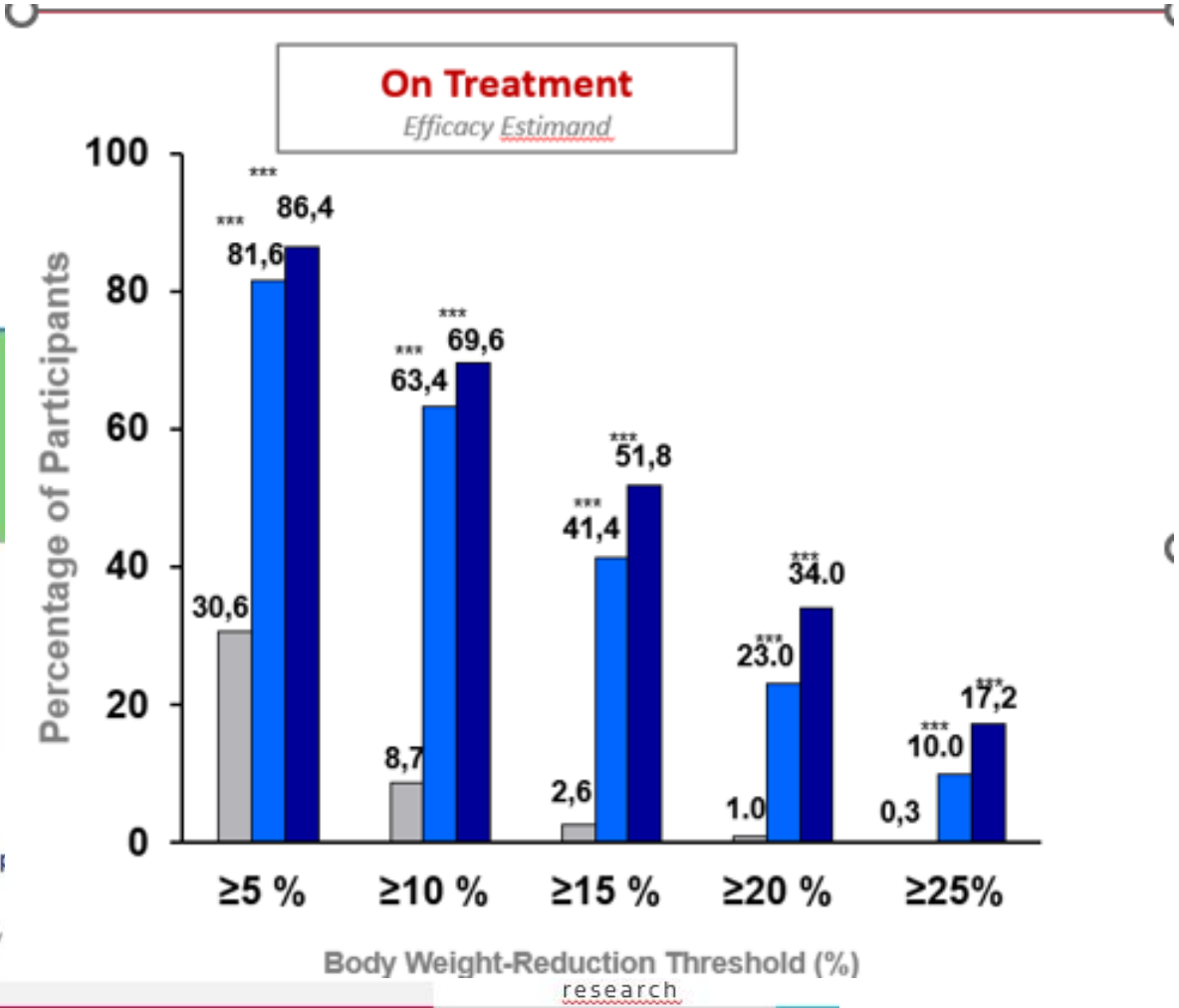




SURMOUNT 1 (vs placebo)

Baseline body weight: 105 kg





†Trial product estimand. ‡Treatment policy estimand. *Statistically
OW, once weekly.

research

New Horizons. A New Paradigm for Treating to Target with Second-Generation Obesity Medications

W. Timothy Garvey[1]

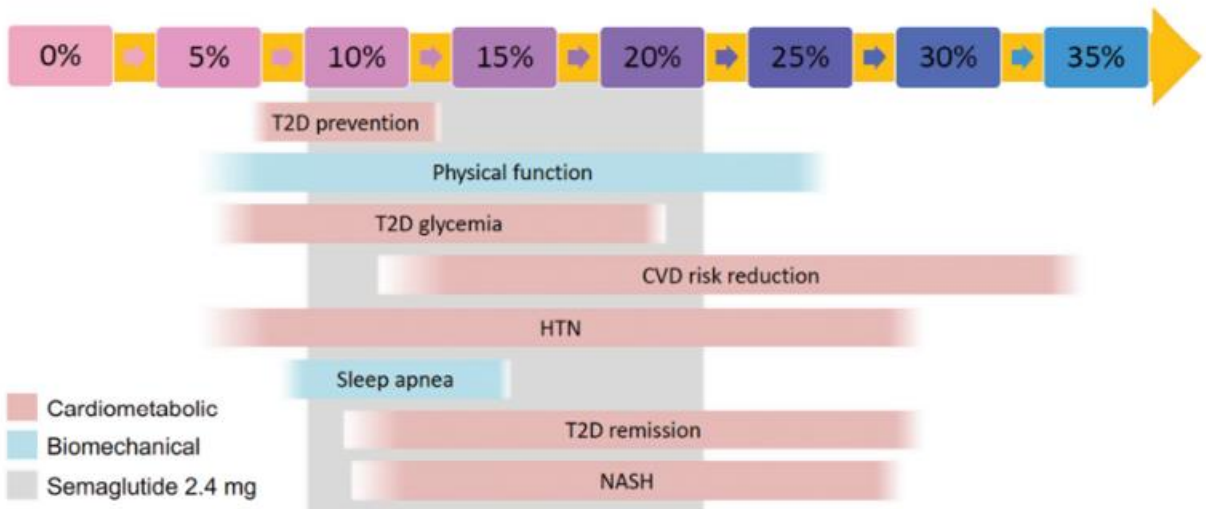
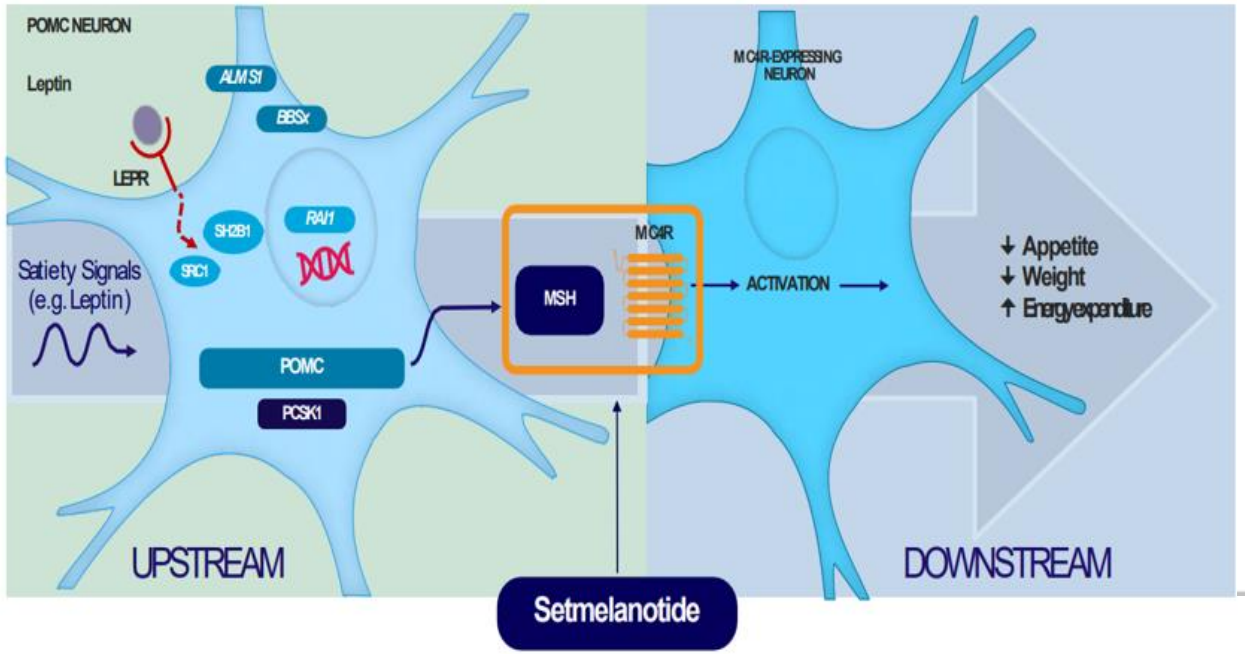


Figure 2. Treating ABCD/obesity to target for prevention and treatment of complications. Abbreviations: ABCD: adiposity-based chronic disease; CVD: cardiovascular disease; HTN: hypertension; NASH, nonalcoholic steatohepatitis; T2D, type 2 diabetes.

Timoty Garvey - The Journal of Clinical Endocrinology & Metabolism, 2021,

Target genetico

melanocortin 4 (MC4) receptor agonist



Severe Obesity due to MC4R Pathway Deficiencies

This ultra-rare disease is a genetic disorder, linked to the presence of variants in the POMC, LEPR or PCSK1 genes, leading to an alteration in the function of the MC4R pathway

BMI > 40 Kg/ M²

- Early-onset, severe obesity
- Hyperphagia: a pathological hunger associated with persistent and potentially extreme food- seeking behavior
- Resistant or refractory to therapies and interventions for general obese
- Multiple complications and co-morbidities associated with obesity

Shah BM et al. Keystone Symposia on Molecular and Cellular Biology: Functional Neurocircuitry of Feeding and Feeding Disorders; 2019; Alberta, Canada. I
Melanocortin -4 Receptor: POMC-proopiomelanocortin; LEPR-leptin receptor; PCSK1-proprotein convertase subtilisin /kexin type 1

Un cenno alle molecole più promettenti

Retatrutide:

questo farmaco viene anche definito come 'triplice agonista' in quanto agisce contemporaneamente sui recettori di GLP-1, GIP e Glucagone, ormone prodotto dal pancreas. Negli studi preliminari (Fase 2) si riscontra un calo ponderale molto importante, di circa il 24% in 48 settimane, con una perdita assoluta media di circa 26 Kg alle dosi più elevate testate. Oltre il 90% dei pazienti perde almeno il 10% di peso, due terzi il 20% e un quarto oltre il 30% del peso iniziale

Cagrilintide:

questo farmaco agisce come analogo dell'amilina, un altro ormone coinvolto nella regolazione del peso corporeo. È in corso di sperimentazione, sia da solo sia in associazione con semaglutide, e i risultati preliminari sono molto incoraggianti. Gli studi in corso termineranno nel 2024, 2025 e 2027 e indagheranno anche le ricadute sull'obesità e sull'apparato cardiovascolare;

Survodutide:

duplice analogo per glucagone e GLP-1 pare anch'esso in grado di ottenere cali ponderali significativi. È in corso lo studio di fase 3;

Orforglipron:

questa è una piccola molecola che agisce sempre sul recettore del GLP-1 e che viene assunta per via orale. I risultati preliminari evidenziano una riduzione ponderale di oltre il 14% (almeno la metà dei partecipanti allo studio hanno ottenuto cali superiori al 15%). È in corso lo studio di fase 3.

Conclusioni

- La terapia farmacologica ci permette di trattare l'obesità e la maggior parte della sue complicanze ottenendo un calo ponderale > 15-20%
- Sono farmaci sicuri, che devono essere usati non solo nella fase di calo ponderale, ma verosimilmente in modo cronico o a cicli.
- Il limite maggiore è l'elevato costo.
- Molte nuove molecole verranno prodotte e questo potrebbe ridurre i costi.