

S.I.C.O.B.
EVENTI

S.I.C.O.B.

SICOB CONVEGNO EMILIA-ROMAGNA
CESENA 19 - 20 Aprile 2024

PRESIDENTE: A.M. SCHETTINO

RESP. SCIENTIFICI: S. CARIANI, V. CORSO, A. LUCCHI

**Dall'Alimento alla Chirurgia:
il Trattamento Integrato
dell'Obesità**

POLICLINICO DI **SANT'ORSOLA**



SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di Ricovero e Cura a Carattere Scientifico



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

I nuovi farmaci nella terapia dell'obesità

Silvia Garelli

*Unità Operativa Complessa di Endocrinologia e
Prevenzione e Cura del Diabete
IRCCS Policlinico di Sant'Orsola*

silvia.garelli@aosp.bo.it

Dove eravamo rimasti...

ORLISTAT

- Inibitore lipasi gastrointestinali e pancreatiche
- Azione periferica

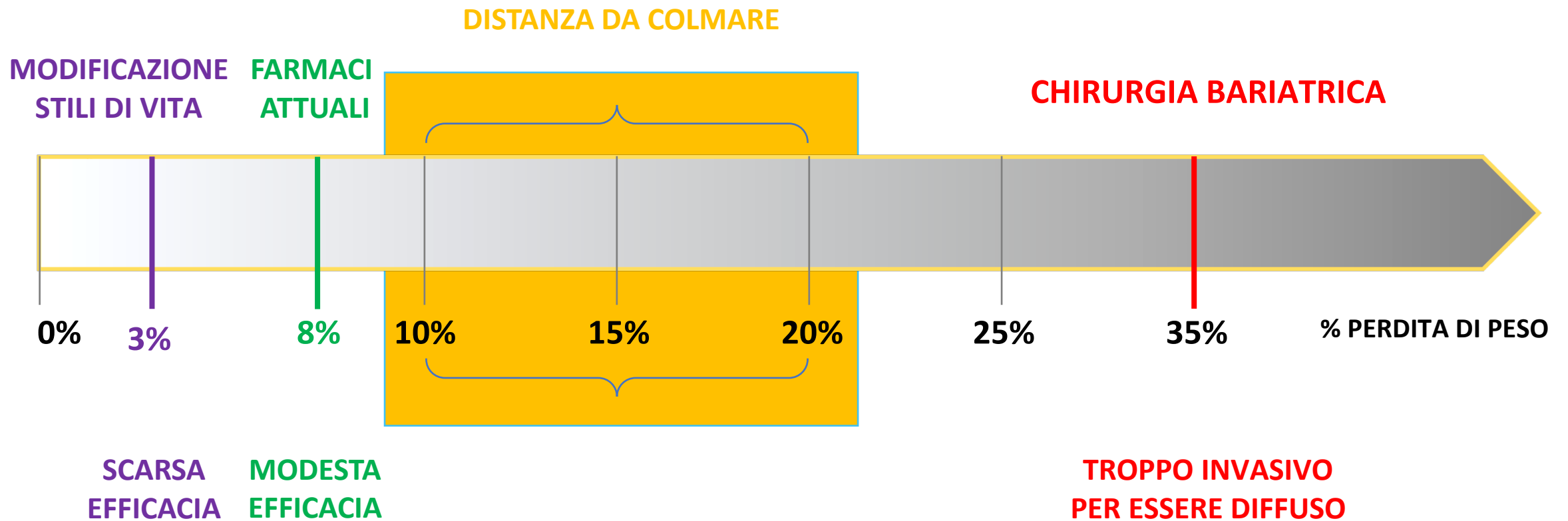
NALTREXONE/BUPROPIONE RP

- Antagonista recettore μ oppioidi/Antidepressivo atipico, 4 compresse al giorno
- Azione centrale (nucleo arcuato e circuito dopaminergico meso-limbico)
- «Emotional hunger»

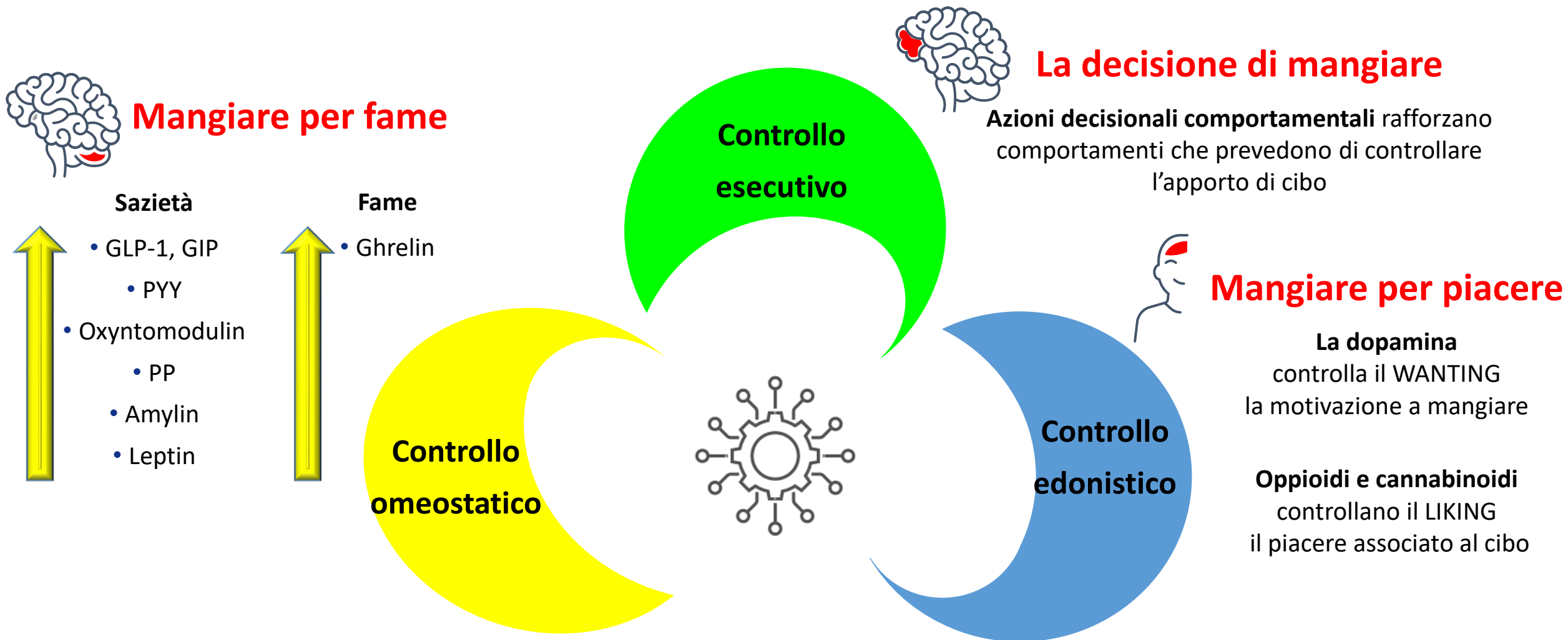
LIRAGLUTIDE

- Analogo GLP-1 (Glucagon-like Peptide-1), 1 iniezione sottocutanea 3 mg al giorno
- Azione periferica (rallentamento svuotamento gastrico) e centrale (nucleo arcuato e aree deputate al controllo edonico)
- «Hungry gut»

Il controllo o la remissione di molte comorbidità legate all'obesità richiedono un calo ponderale ben superiore al 5%



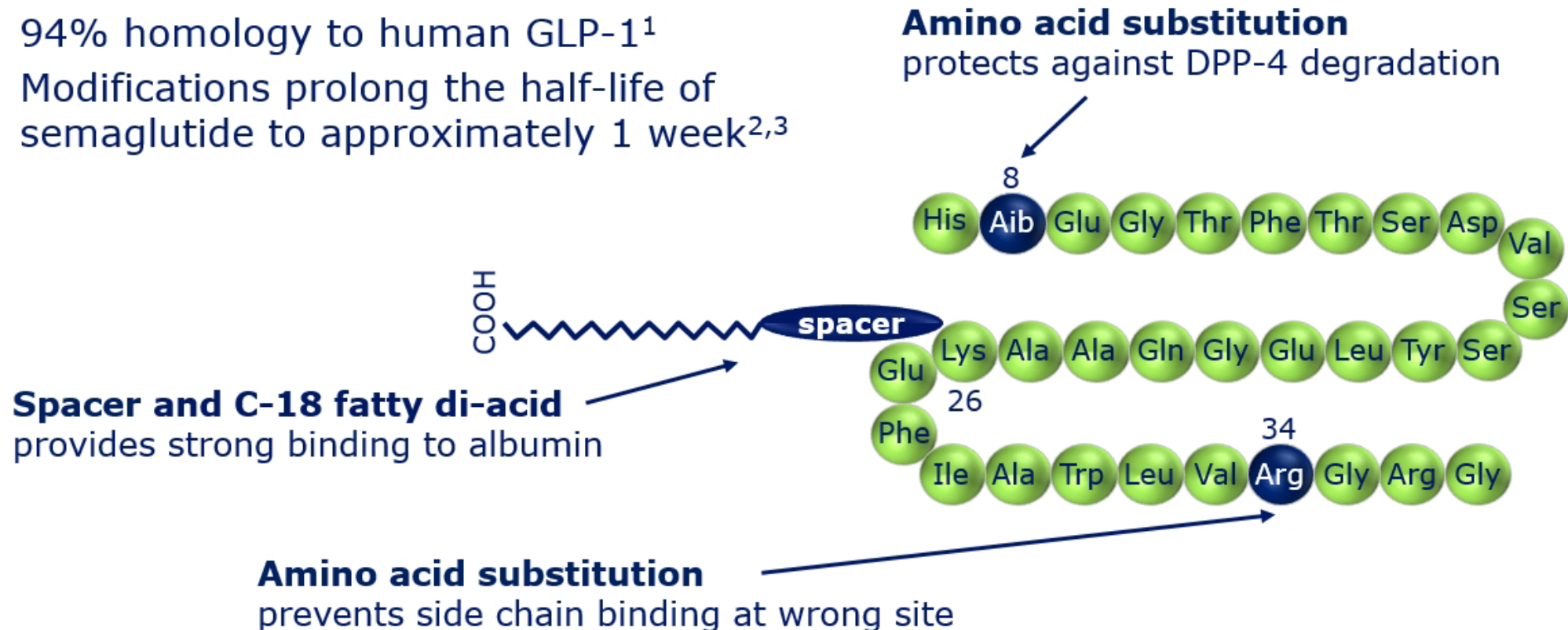
La farmacologia dell'obesità oggi: il ruolo del cervello nella regolazione del comportamento alimentare



Semaglutide

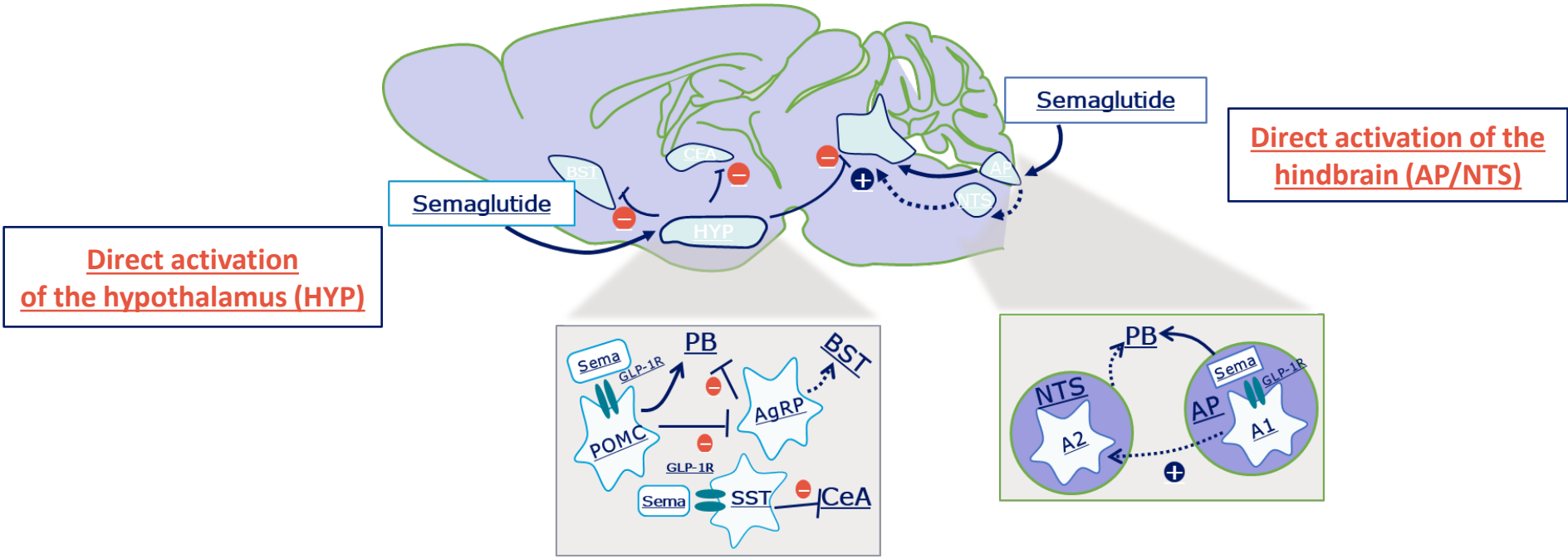


- 94% homology to human GLP-1¹
- Modifications prolong the half-life of semaglutide to approximately 1 week^{2,3}



DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.
1. Lau J et al. J Med Chem 2015;58:7370-80; 2. Kapitza C et al. J Clin Pharmacol 2015;55:497-504; 3. Marbury TC et al. Clin Pharmacokinet 2017; DOI: 10.1007/s40262-017-0528-2.

Semaglutide

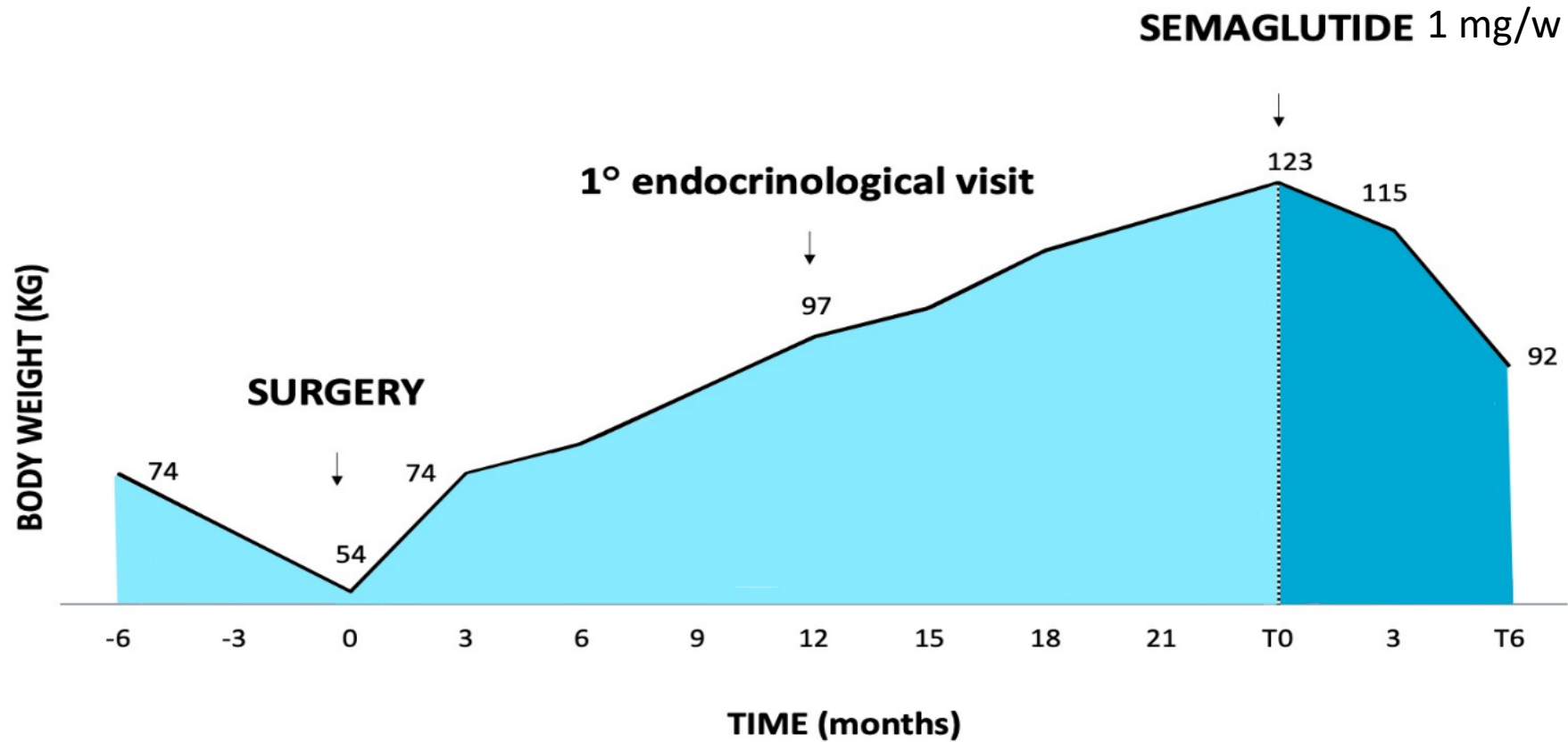


Semaglutide induces a secondary neuronal response in the PB, either directly through GLP-1R stimulation of AP–PB projections or indirectly through the AP–NTS–PB pathway

A1/A2, noradrenergic cell group 1/2; AgRP, agouti-related peptide; AP, area postrema; ARH, arcuate nucleus; BST, bed nuclei of the stria terminalis; CeA; central amygdala nucleus; GLP-1R, glucagon-like-1 receptor; HYP, hypothalamus; NTS, nucleus tractus solitarius; PB, parabrachial nucleus; POMC, pro-opiomelanocortin; sema, semaglutide; SST, somatostatin.

Adapted from Gabery S et al. JCI Insight 2020

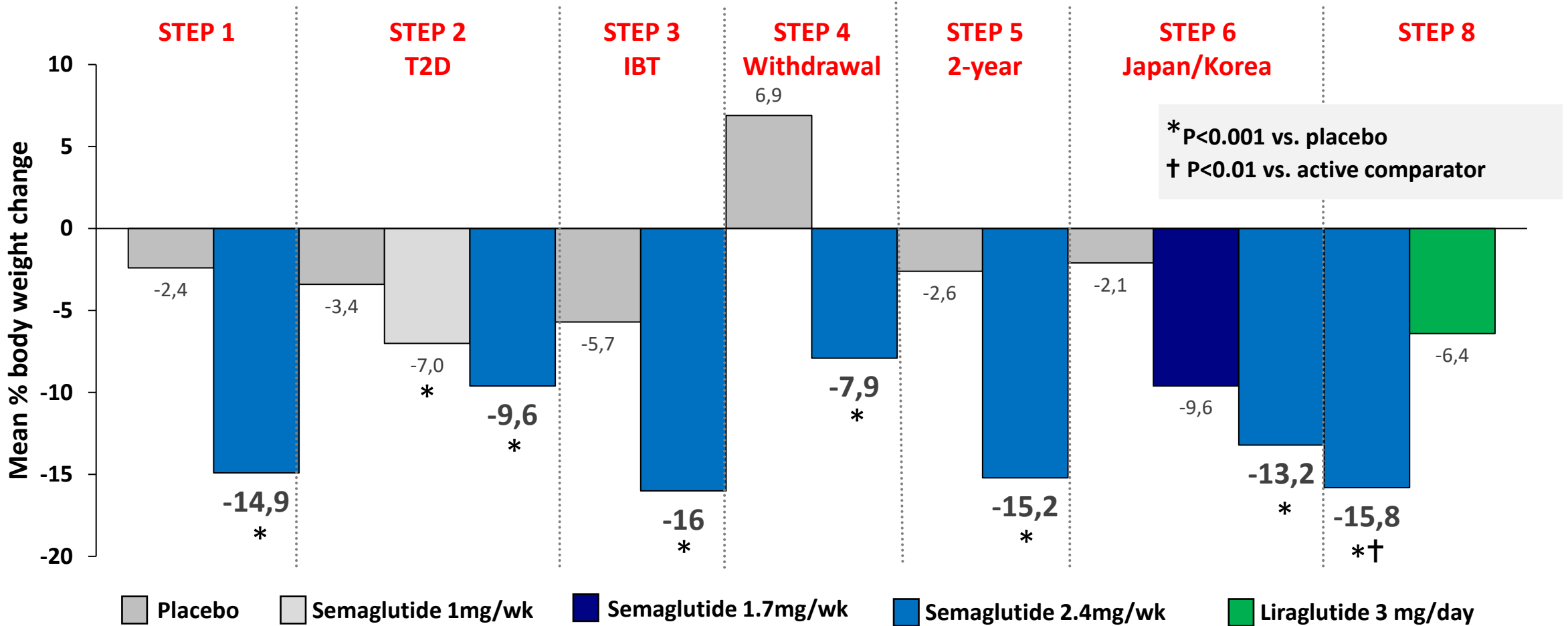
SEMAGLUTIDE PER IL TRATTAMENTO DELL'OBESITA' IPOTALAMICA: DATI ESPORATIVI



Sciacovelli C and Garelli S JCEM Case Reports 2024

I nuovi farmaci nella terapia dell'obesità

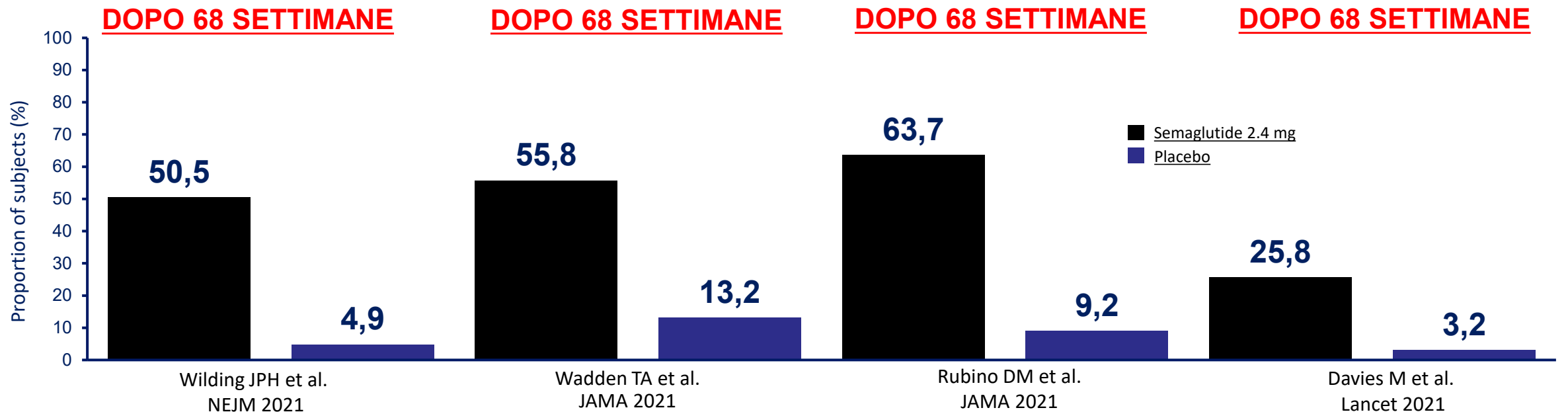
Semaglutide: risultati del programma STEP



Wilding JPH et al. NEJM 2021; Wadden TA et al. JAMA 2021; Rubino DM et al. JAMA. 2021; Davies M et al. Lancet 2021; Kadowaki T et al. Lancet D&E 2022; Rubino DM et al. JAMA 2022, Gravey WT et al. Nature Med 2022

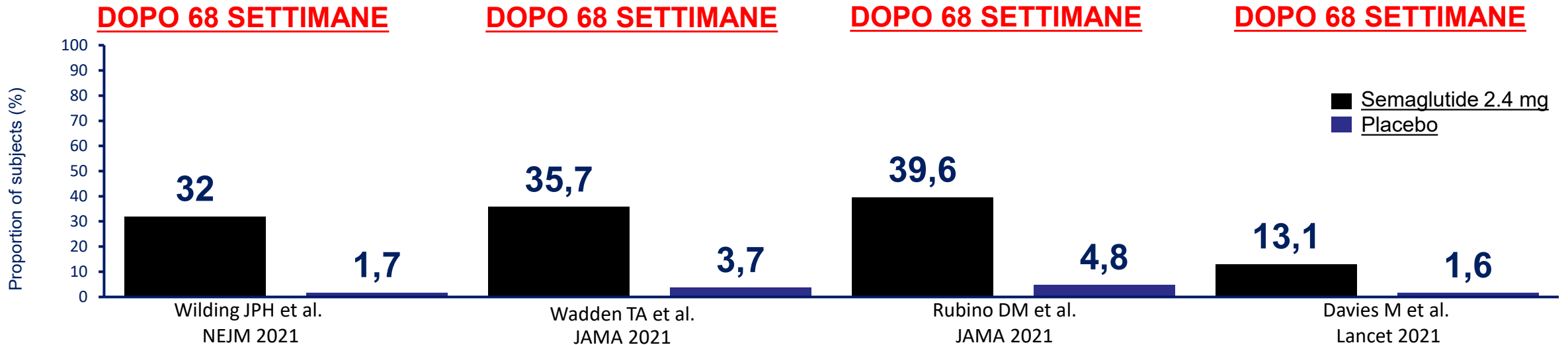
STEP 1–4: % di soggetti che perdono $\geq 15\%$ del peso corporeo

	STEP 1	STEP 3	STEP 4	STEP 2
	Weight management	Weight management with IBT	Sustained weight management	Weight management in T2D
PESO IN PARTENZA	105.3 kg	105.8 kg	107.2 kg	99.8 kg

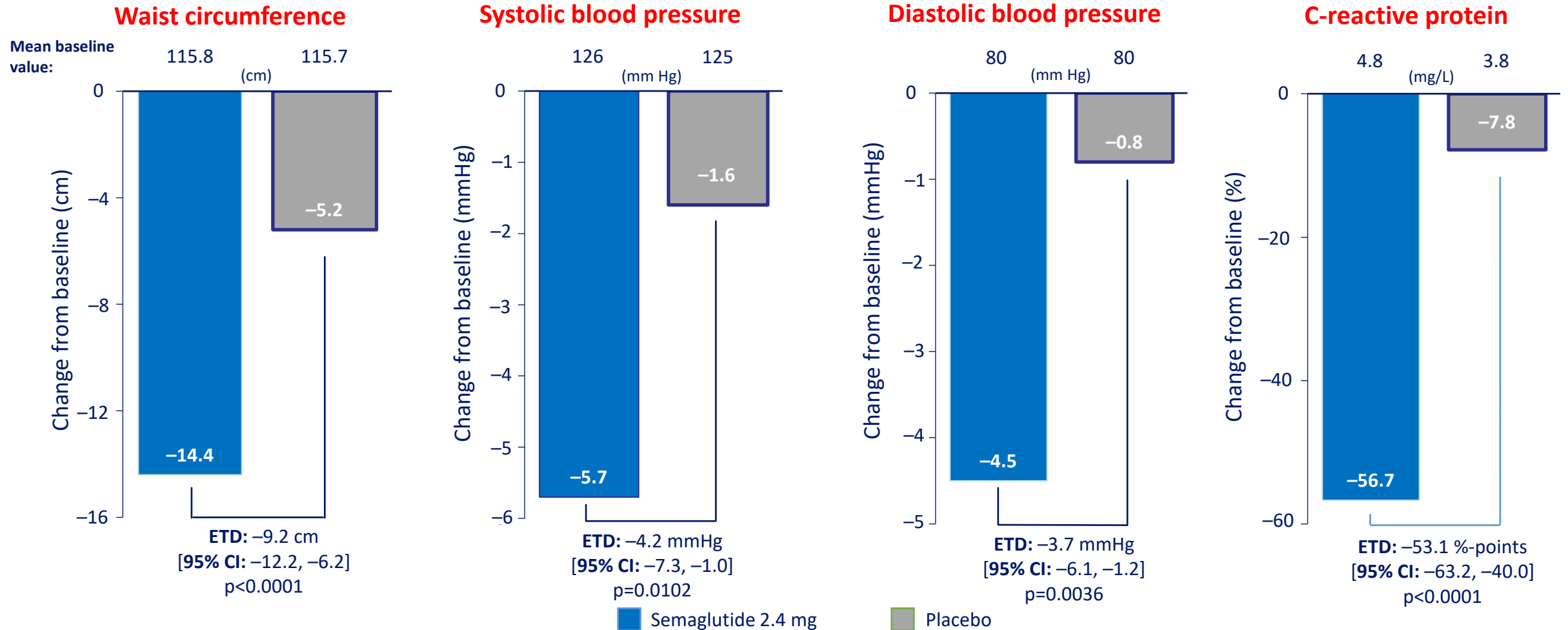


STEP 1–4: % di soggetti che perdono $\geq 20\%$ del peso corporeo

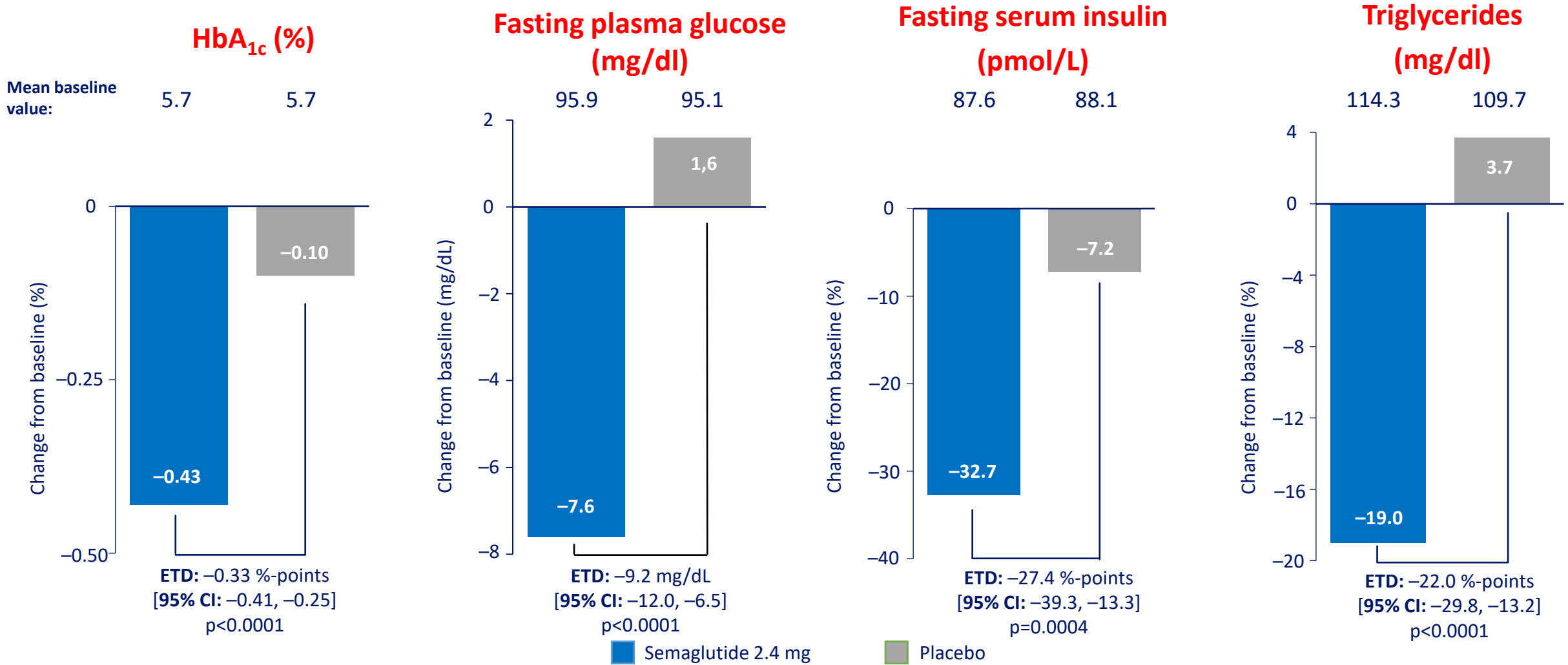
	STEP 1	STEP 3	STEP 4	STEP 2
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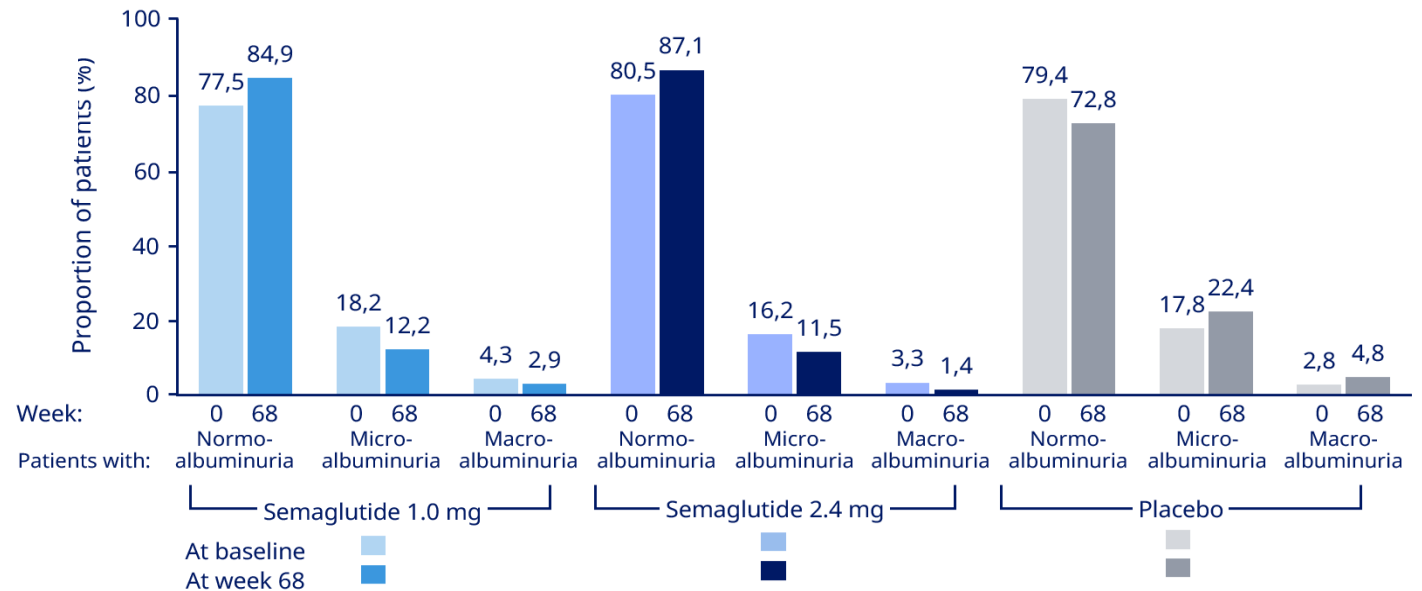
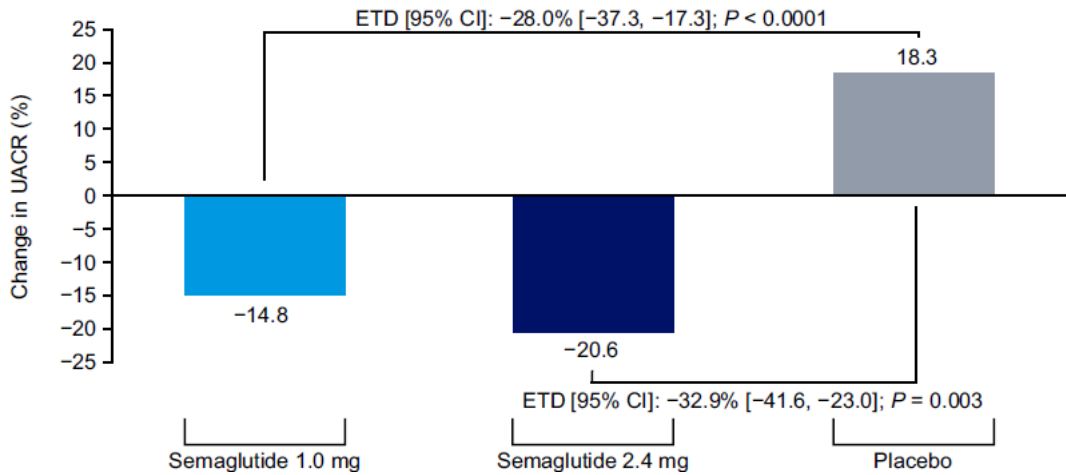
STEP 5: Fattori di rischio cardiovascolare



STEP 5: Fattori di rischio metabolici



Distribuzione dei pazienti rispetto a uACR basale vs 68 settimane (Post-hoc analysis di STEP 1-3)



Studio Select: sicurezza e prevenzione CV

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

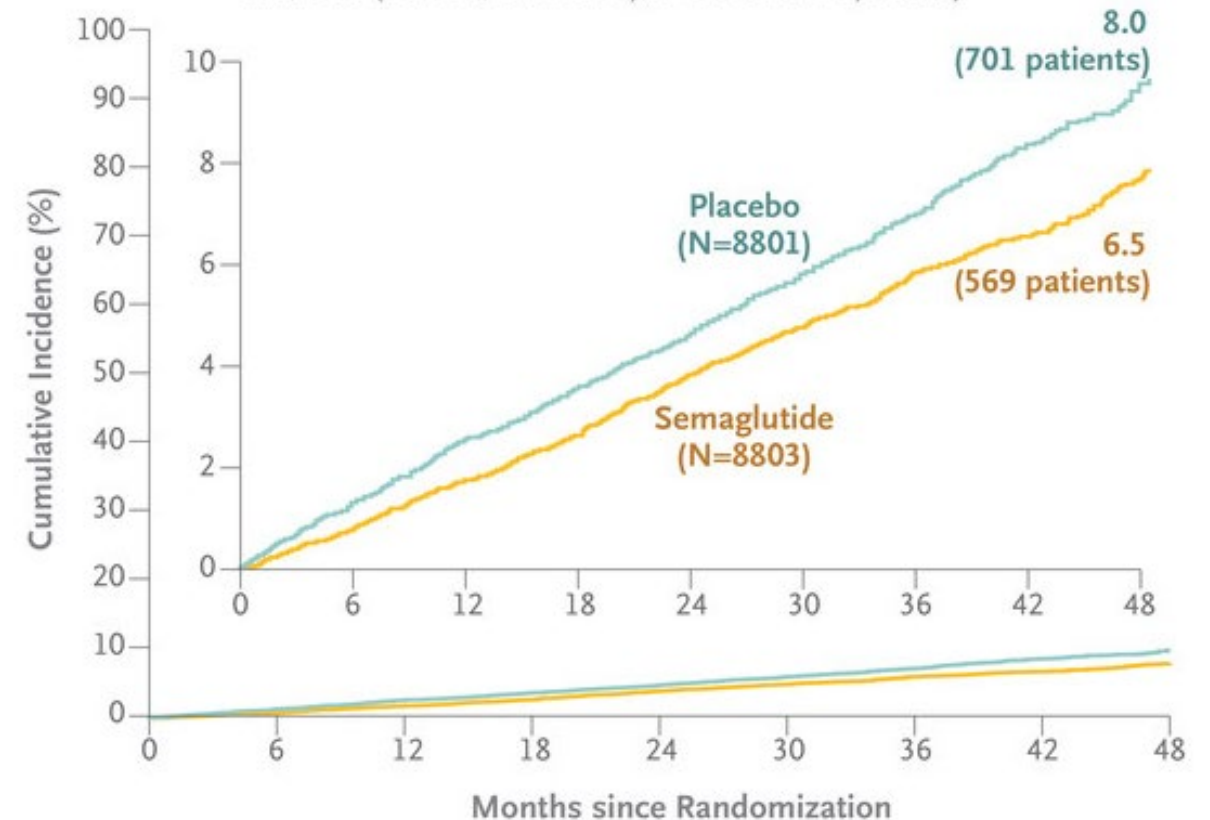
Lincoff AM et al. DOI: 10.1056/NEJMoa2307563

CONCLUSIONS

In patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, once-weekly subcutaneous semaglutide at a dose of 2.4 mg was superior to placebo in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke during a mean follow-up of approximately 40 months.

Death from Cardiovascular Causes, Nonfatal MI, or Nonfatal Stroke

HR, 0.80 (95% CI, 0.72–0.90); P<0.001 for superiority



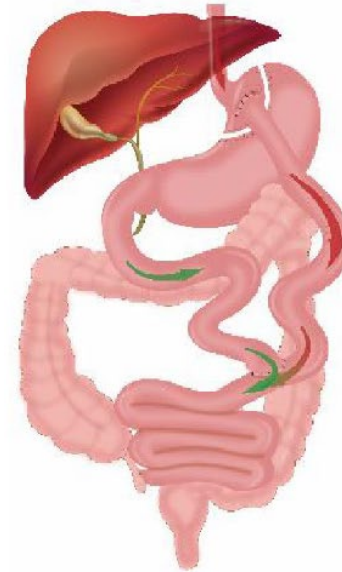
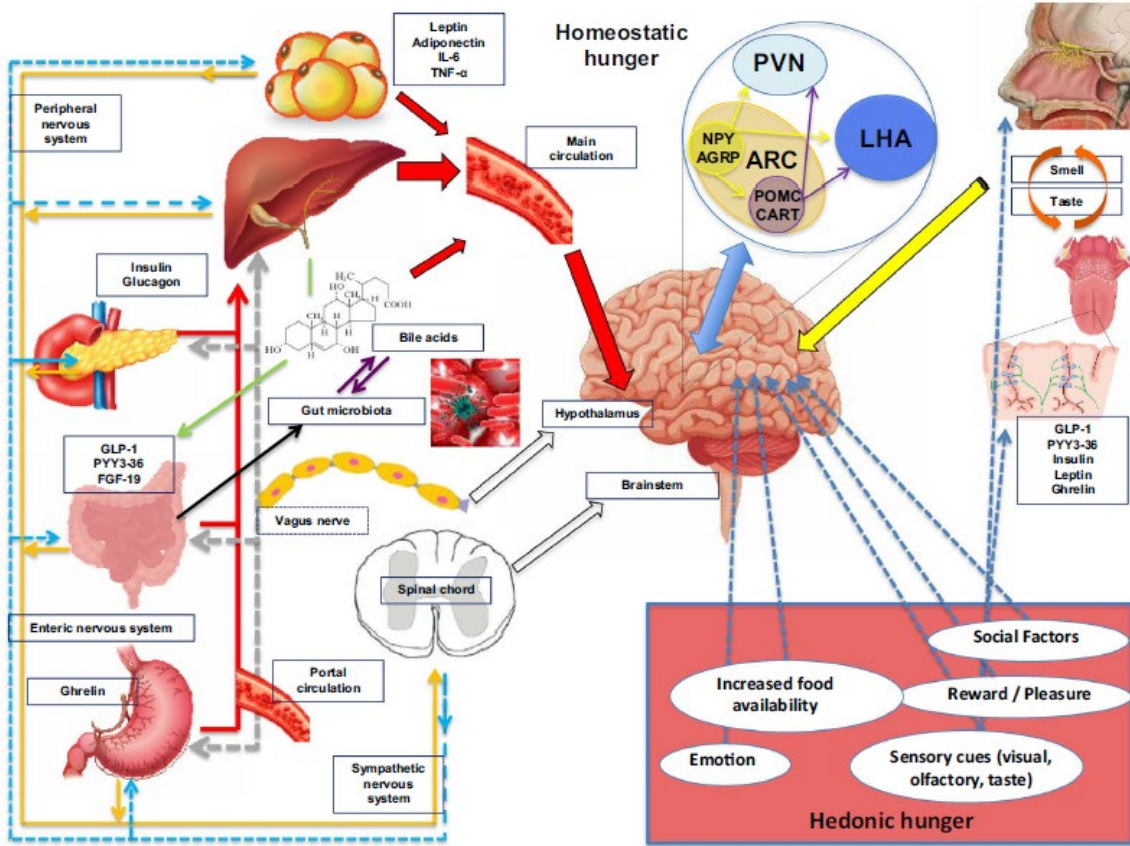
Lincoff AM and SELECT Trial Investigators. N Engl J Med. 2023 Dec

Semaglutide: effetti collaterali

Table 4. Investigator-Reported Adverse Events.^{*,†}

Event	Semaglutide (N = 8803)	Placebo (N = 8801)	P Value [‡]
	<i>no. of patients (%)</i>		
Serious adverse events [‡]	2941 (33.4)	3204 (36.4)	<0.001
Cardiac disorders	1008 (11.5)	1184 (13.5)	<0.001
Infections and infestations	624 (7.1)	738 (8.4)	0.001
Nervous system disorders	444 (5.0)	496 (5.6)	0.08
Surgical and medical procedures	433 (4.9)	548 (6.2)	<0.001
Neoplasms benign, malignant, and unspecified	405 (4.6)	402 (4.6)	0.94
Gastrointestinal disorders	342 (3.9)	323 (3.7)	0.48
Adverse events leading to permanent discontinuation of trial product, irrespective of seriousness [‡]	1461 (16.6)	718 (8.2)	<0.001
Gastrointestinal disorders	880 (10.0)	172 (2.0)	<0.001
Nervous system disorders	124 (1.4)	92 (1.0)	0.03
Metabolism and nutrition disorders	108 (1.2)	27 (0.3)	<0.001
General disorders and administration-site conditions	105 (1.2)	47 (0.5)	<0.001
Neoplasms benign, malignant, and unspecified	80 (0.9)	105 (1.2)	0.07
Infections and infestations	75 (0.9)	84 (1.0)	0.47
Prespecified adverse events of special interest, irrespective of seriousness [§]			
Covid-19–related events	2108 (23.9)	2150 (24.4)	0.46
Malignant neoplasms	422 (4.8)	418 (4.7)	0.92
Gallbladder-related disorders	246 (2.8)	203 (2.3)	0.04
Acute kidney failure	171 (1.9)	200 (2.3)	0.13
Acute pancreatitis [¶]	17 (0.2)	24 (0.3)	0.28

Dalla mono alla poli-terapia



RYGB



SG

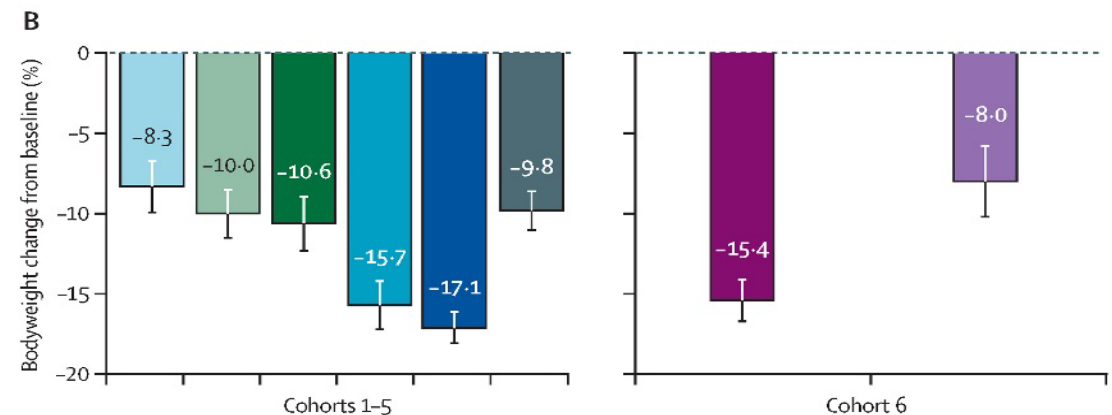
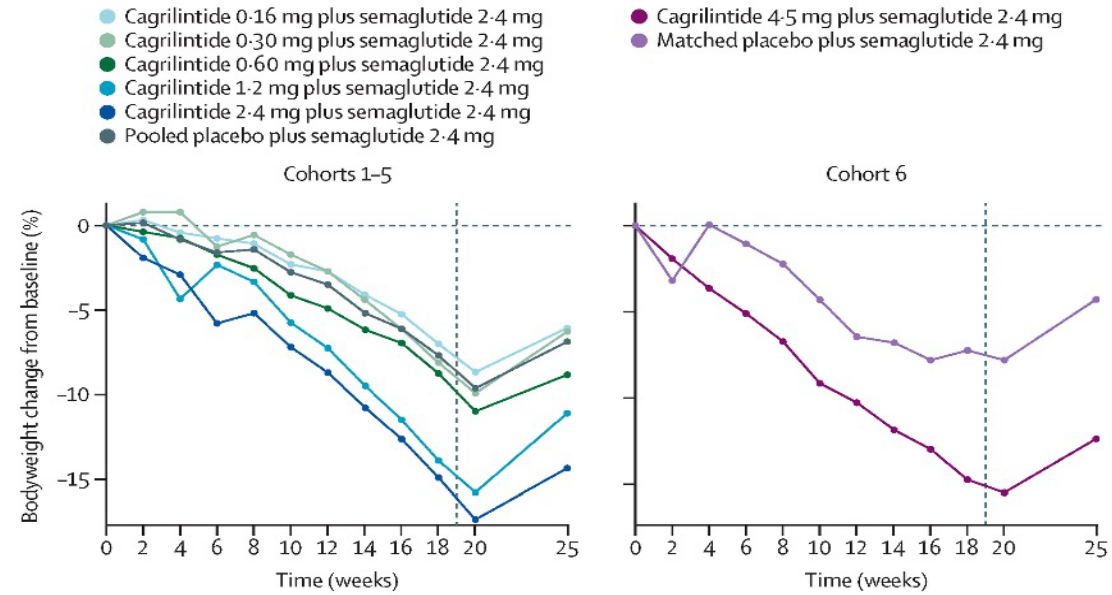
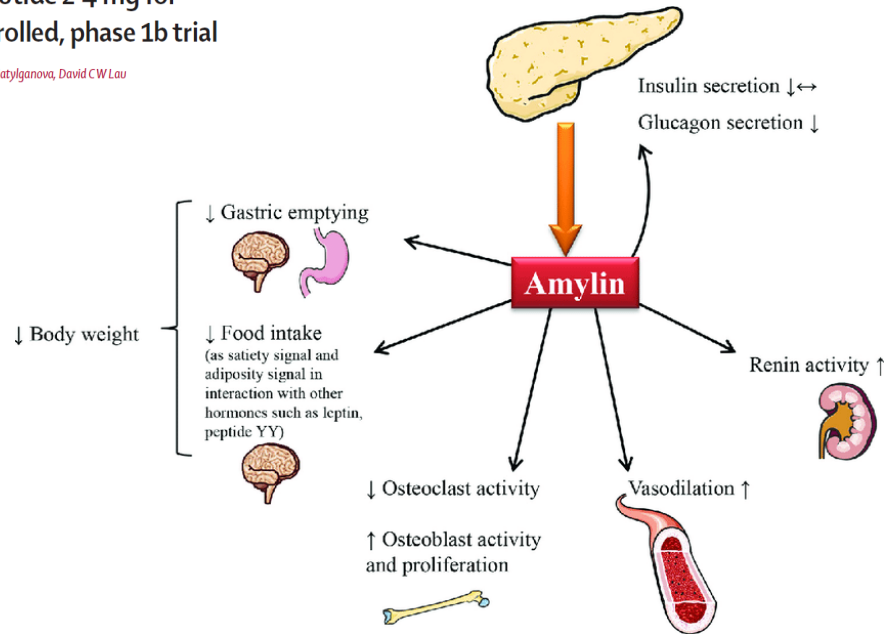
+	Calorie restriction	+
↑	Vagal nerve signaling	↑
+	Taste and smell changes	+
+	Food aversions	+
↓	Ghrelin	↓↓
↑	Bile acid secretion	↑
↑	Intestinal glucose uptake	
+	Fat malabsorption	
↑↑	GLP-1	↑
↑↑	PYY3-36	↑
↓	GIP	
↑	Oxyntomodulin	
↑↑	FGF-19	↑
↑	CCK	↑
↓	Gastrin	↑
↑	Neurotensin	

Tante molecole per un obiettivo o una molecola con molteplici obiettivi?

Associazione cagrilintide + semaglutide

Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2.4 mg for weight management: a randomised, controlled, phase 1b trial

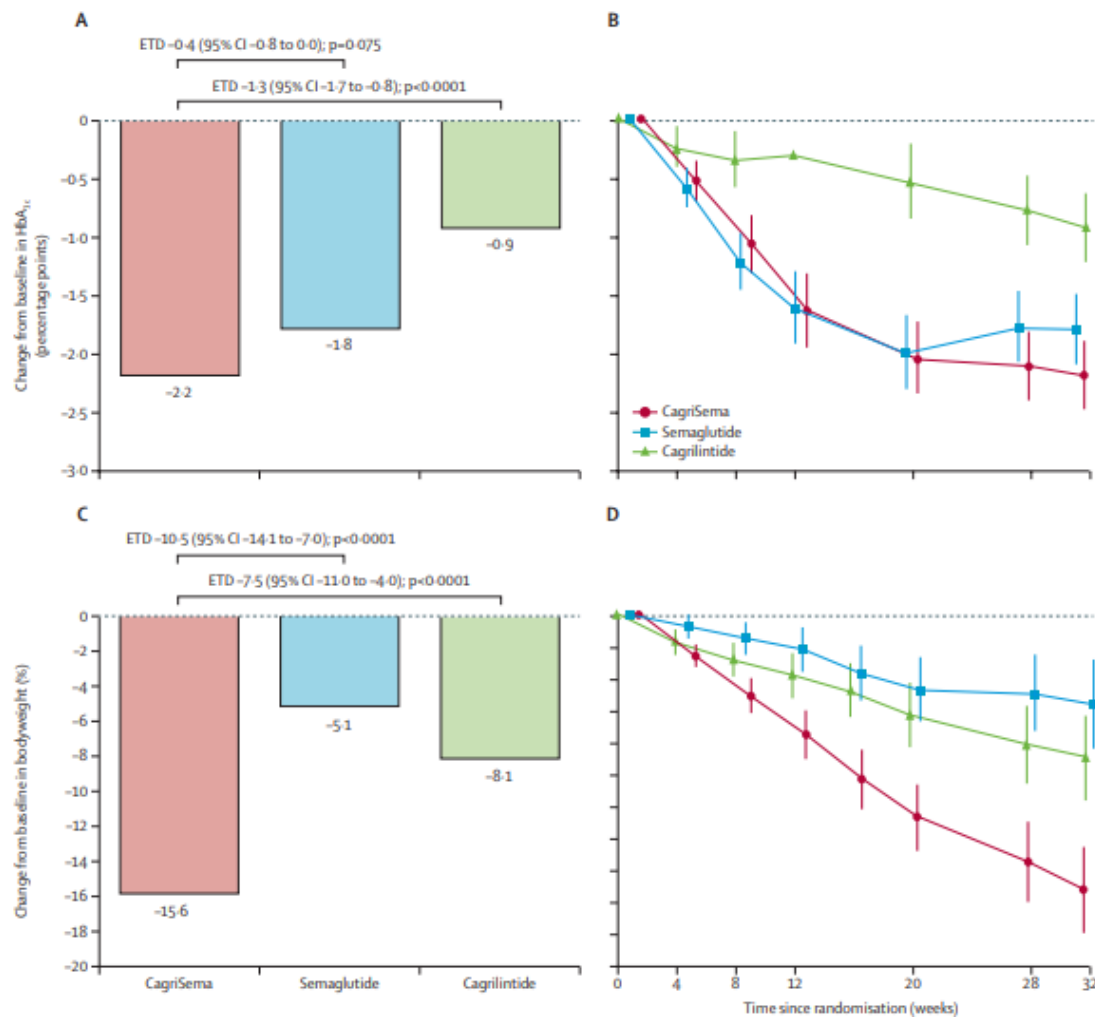
Lone B Enebo, Kasper K Berthelsen, Martin Kankam, Michael T Lund, Domenica M Rubino, Allynal Satyrganova, David CW Lau
Lancet 2021



Association Cagrilintide ow + semaglutide ow is superior to semaglutide + placebo from 1,2 mg cagrilintide on.
The association with semaglutide allows to improve metabolic results, although reducing cagrilintide dose.

➔ REDEFINE phase III trials

Associazione semaglutide + cagrilintide in soggetti diabetici

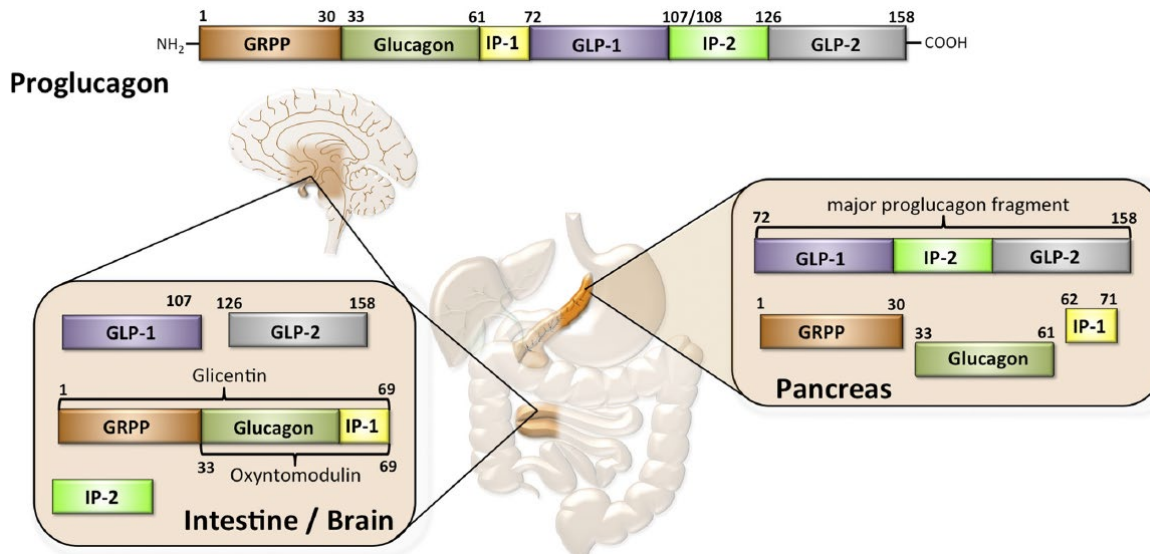


no plateau !

Frias JP et al. Lancet 2023

The «glucagon peptide family»

GLUCAGONE E GLP1: UNA ORIGINE COMUNE

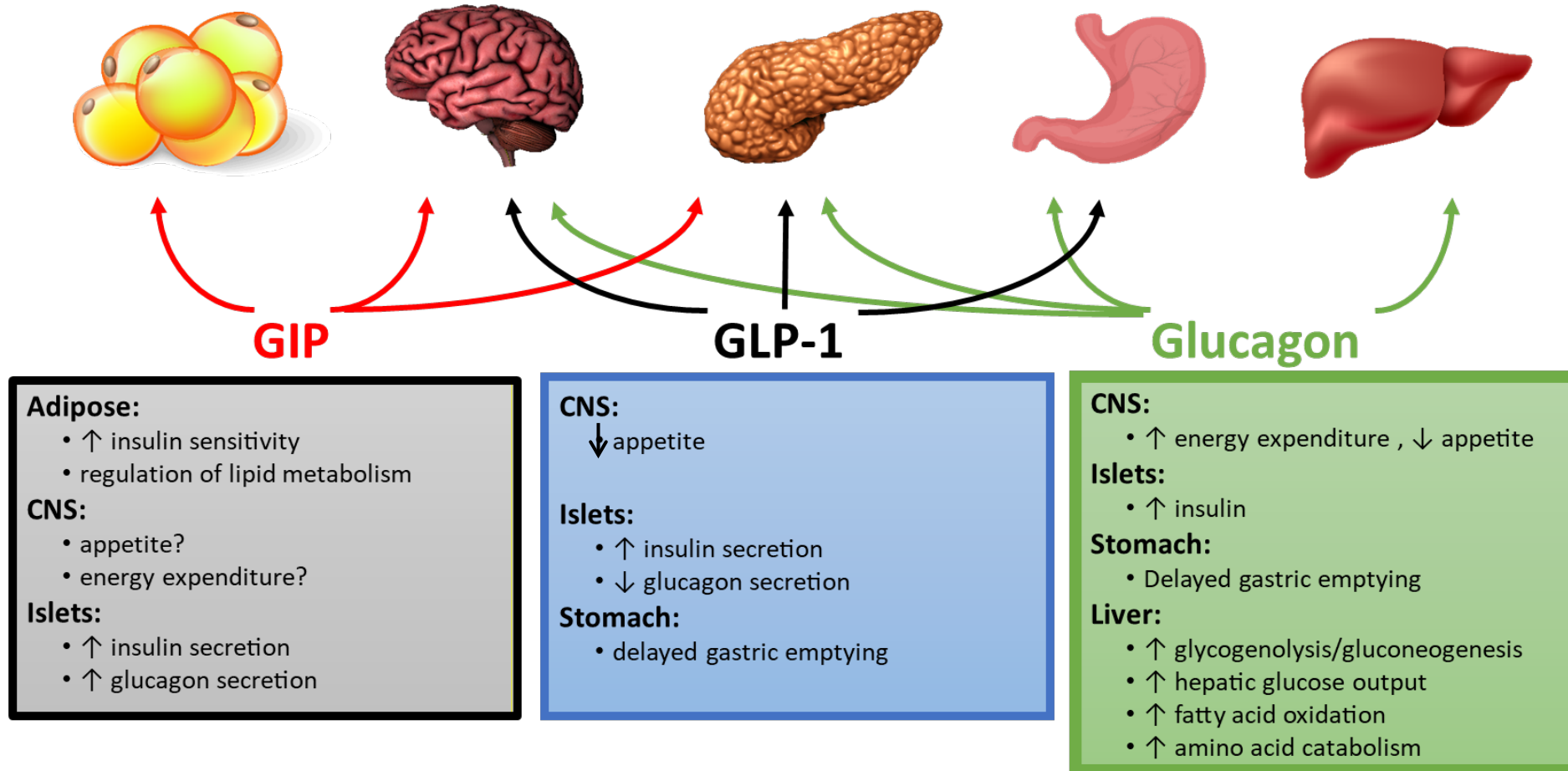


GLP-1 (7-37)	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG
Exendin-4	HGEGTFTSDLKQMEEEAVRLFIEWLKNGGPPS
GIP	YAEGTFI SDYSIAMDKIHQQDFVNWLLAQKGGKNDWKHNI TQ
GLP-2	HADGSFSDEMNTILDNLAARDFINWLIQTKITD
Glucagon	HSQGTFTSDYSKYLDSRRAQDFVQWLMNT
PACAP (1-27)	HSDGI FTDSYSRYRKQMAVKKYLA AVL
	1 5 10 15 20 25 30 35

Underwood CR et al. J Biol Chem 2010.

Mueller T et al Physiol Rev 2017

L'interazione tra gli ormoni intestinali ed le funzioni metaboliche



Una molecola con molteplici obiettivi: l'idea delle molecole chimeriche



M. H. Tschöep



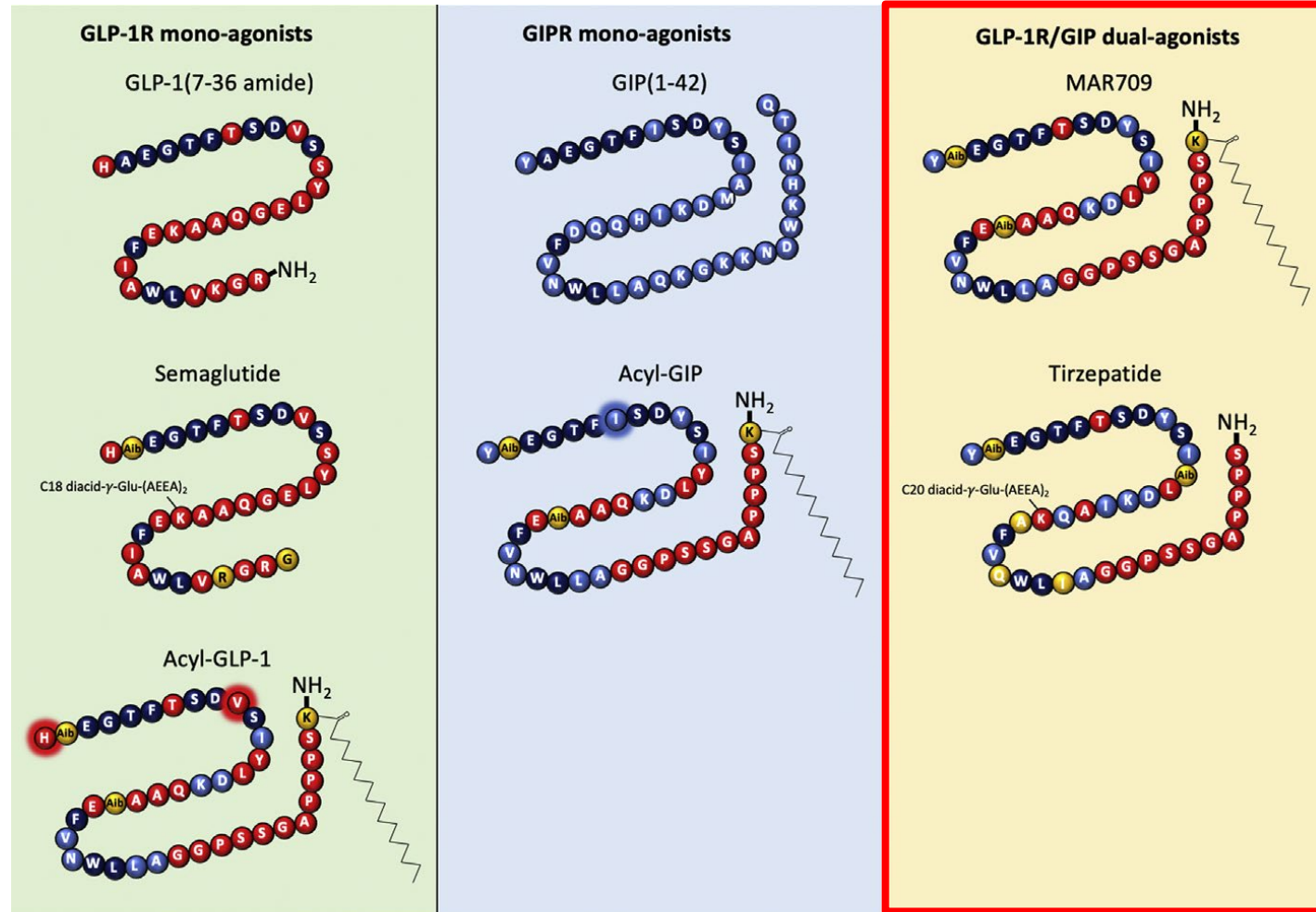
R. D. DiMarchi

The basic idea of unimolecular multi-agonists is that the simultaneous activation of different signaling mechanisms maximizes the metabolic benefits, minimizes adverse effects, and offers a more balanced pharmacokinetic action profile compared to loose co-administration of single hormones.

Brandt SJ et al. Peptides 2018

«TWINCRETINE»

CO-AGONISTA RECETTORIALE GLP-1/GIP: Tirzepatide



Novikoff A. et al Mol Metab 2021

Co-agonismo recettoriale GIP/GLP-1: effetti sistemici

Agonista per il recettore GLP-1

Sistema Nervoso Centrale

- ↑ Sazietà
- ↓ Apporto alimentare
- ↑ Nausea
- ↓ Peso Corporeo

Pancreas

- ↑ Insulina
- ↓ Glucagone

Stomaco

- ↓ Svuotamento gastrico

Sistemico

- ↓ Iperglicemia

Liver

- ↑ Sensibilità insulinica
- ↓ Produzione epatica di glucosio
- ↓ Accumulo ectopico di lipidi

Sistema nervoso centrale

agonista per il recettore GIP

Sistema nervoso centrale

- ↓ Apporto alimentare
- ↓ Nausea
- ↓ Peso corporeo

Pancreas

- ↑ Insulina
- ↑ Glucagone

Tessuto adiposo sottocutaneo

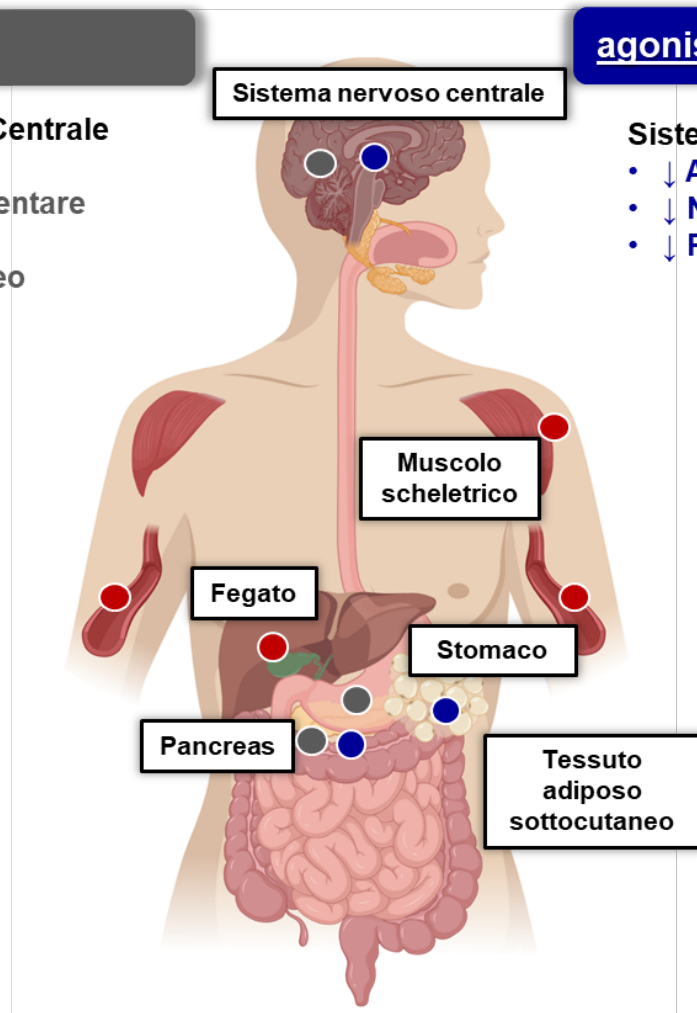
- ↑ Sensibilità insulinica
- ↑ Capacità di accumulo dei lipidi
- ↑ Flusso sanguigno
- ↓ riduzione capacità infiltrative macrofagica

Sistemico

- ↓ iperglicemia, carico postprandiale di TG

Muscolo scheletrico

- ↑ Sensibilità insulinica
- ↓ Accumulo ectopico di lipidi



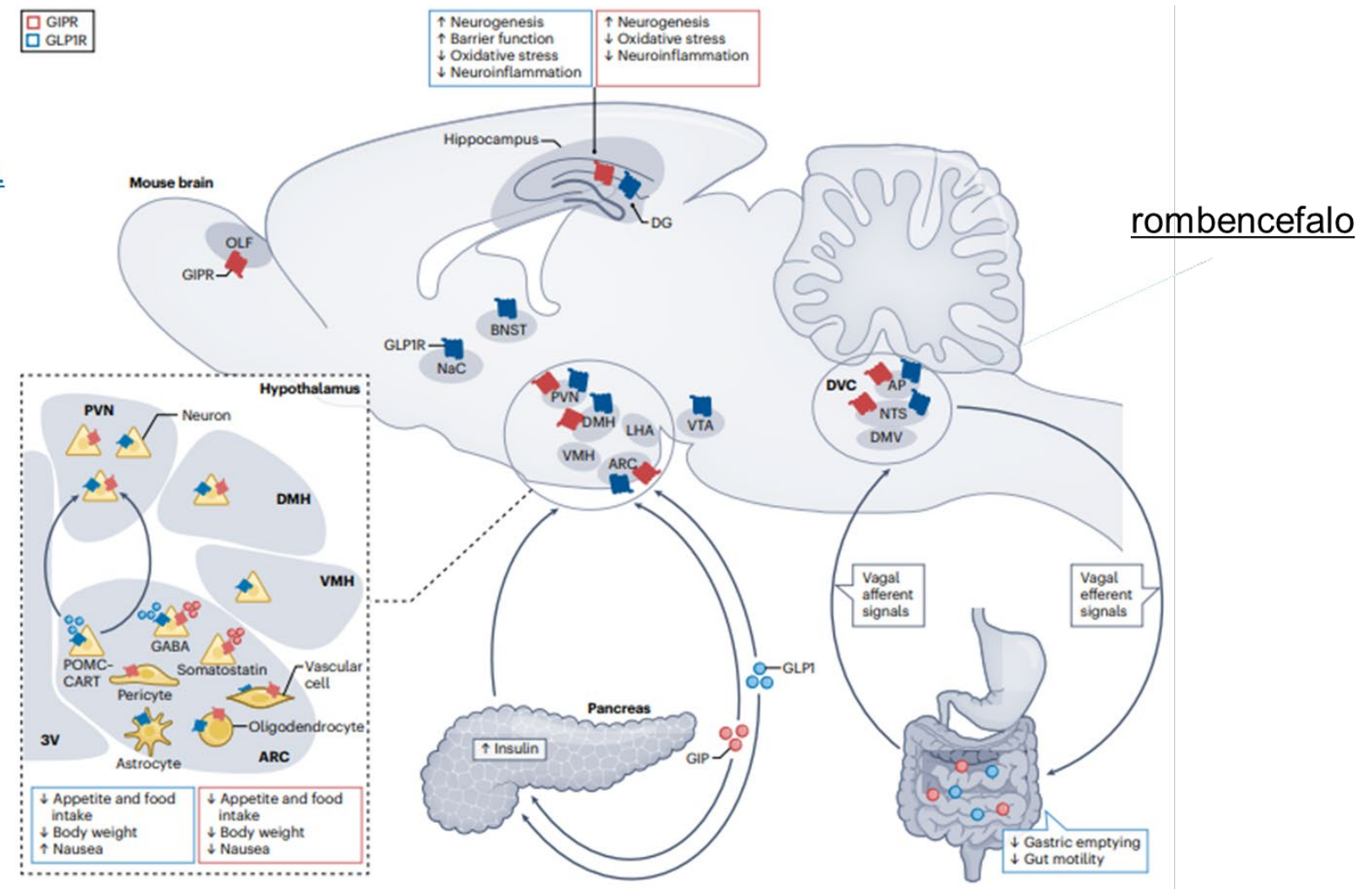
● Agonista del recettore GLP-1

● Agonista del recettore GIP

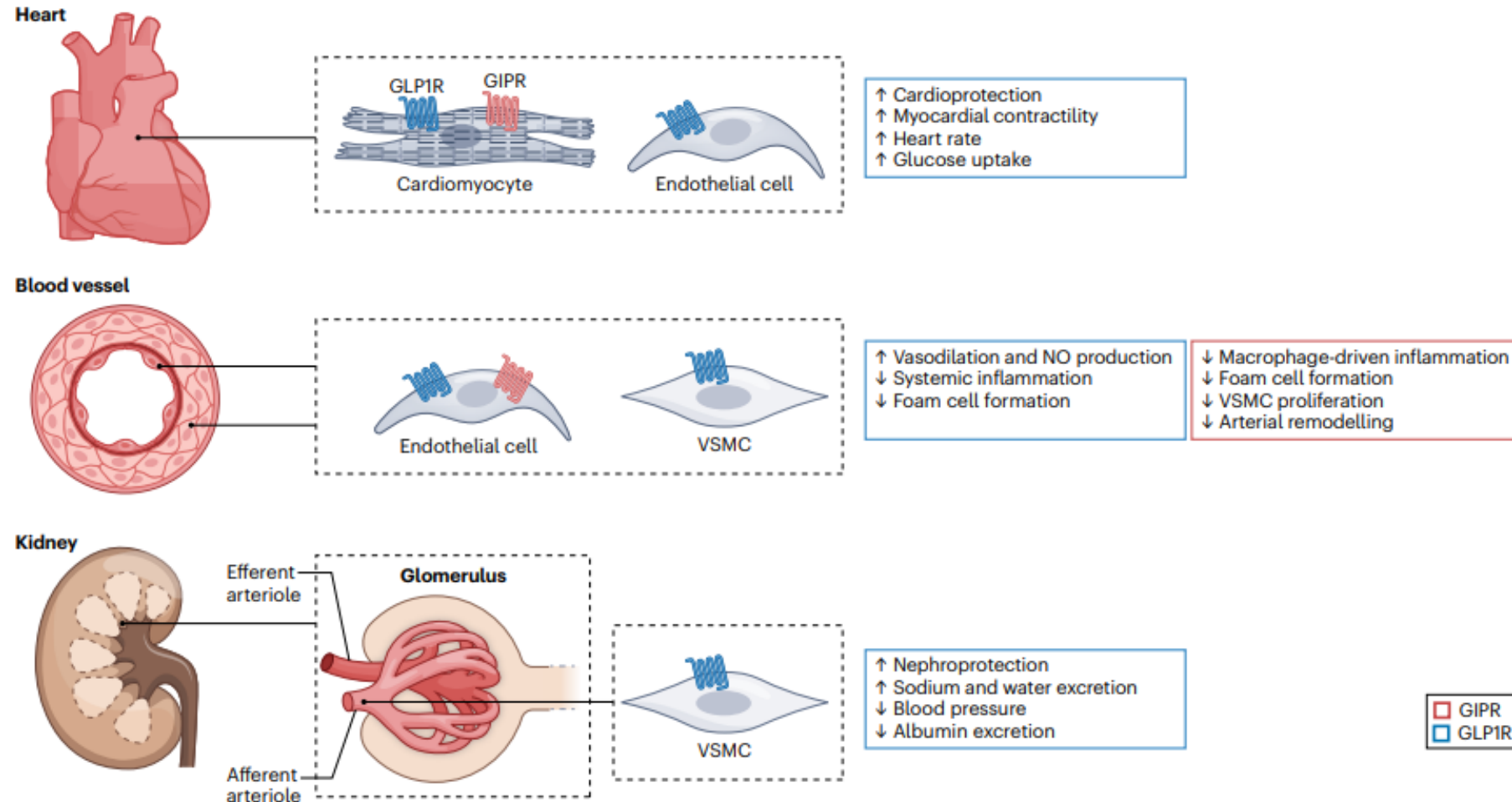
● Azione indiretta

Espressione di recettori di GIP e GLP-1 a livello del SNC

 recettore del GLP1
 recettore del GIP



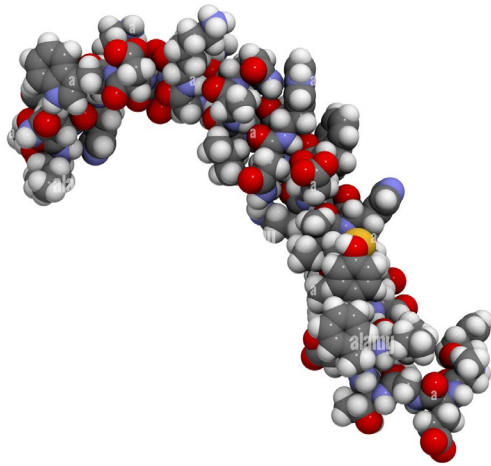
Effetti di GLP-1 e GIP sui sistemi cardiovascolare e renale



Hammoud R and Drucker DJ Nature Rev Endo 2023

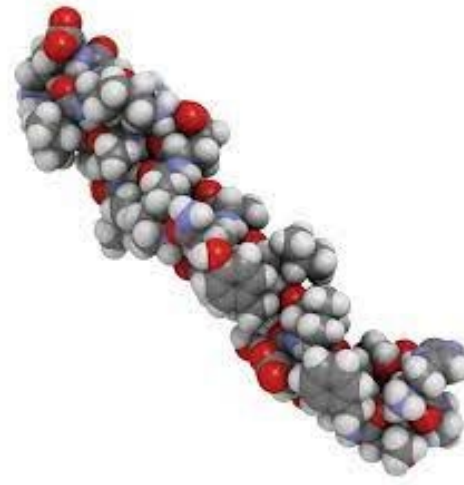
Tirzepatide non è la somma di GIP e GLP-1,
ma è un'unica molecola

GIP



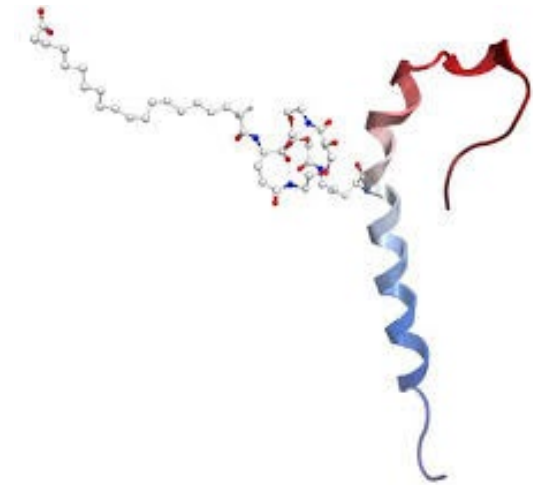
+

GLP-1



≠

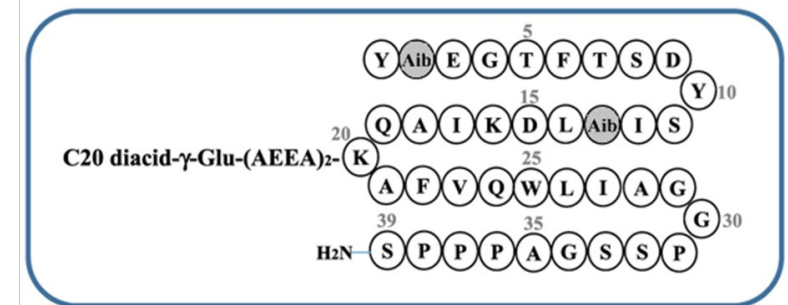
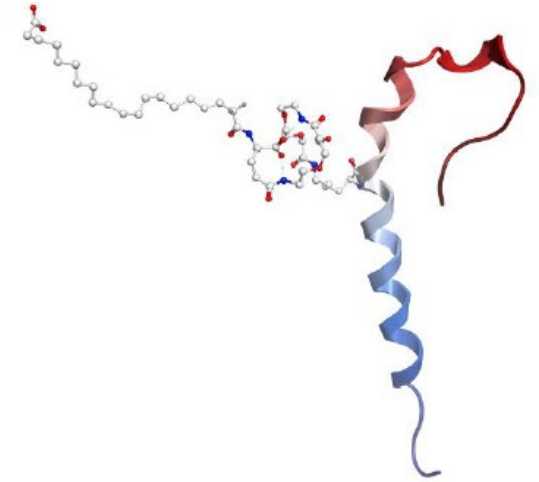
Tirzepatide



Coskun T. et al. Mol Metab 2018

Tirzepatide: agonista dei recettori di GIP e GLP-1

- Tirzepatide è un peptide multifunzionale che si basa sulla sequenza nativa del GIP modificata per permettere di attivare entrambi i recettori per GIP e GLP-1
- Tirzepatide ha una struttura lineare di 39 amino acidi ed incorpora un acido grasso C20 attaccato in posizione 20 alla lisina (aumenta la connessione con albumina prolungandone l'emivita)
- Contiene due residui aminoacidici non codificati in posizione 2 and 13 (Aib, a-amino isobutyric acid)
- *In vitro*, Tirzepatide ha maggiore potenza sul GIPR rispetto al GLP1R
- Tirzepatide possiede un'emivita di ~5 giorni (116.7 h), per tale motivo può avere una somministrazione settimanale
- Il suo peso molecolare è di 4.8 kD (dula 63 kD, sema 4.11 kD)

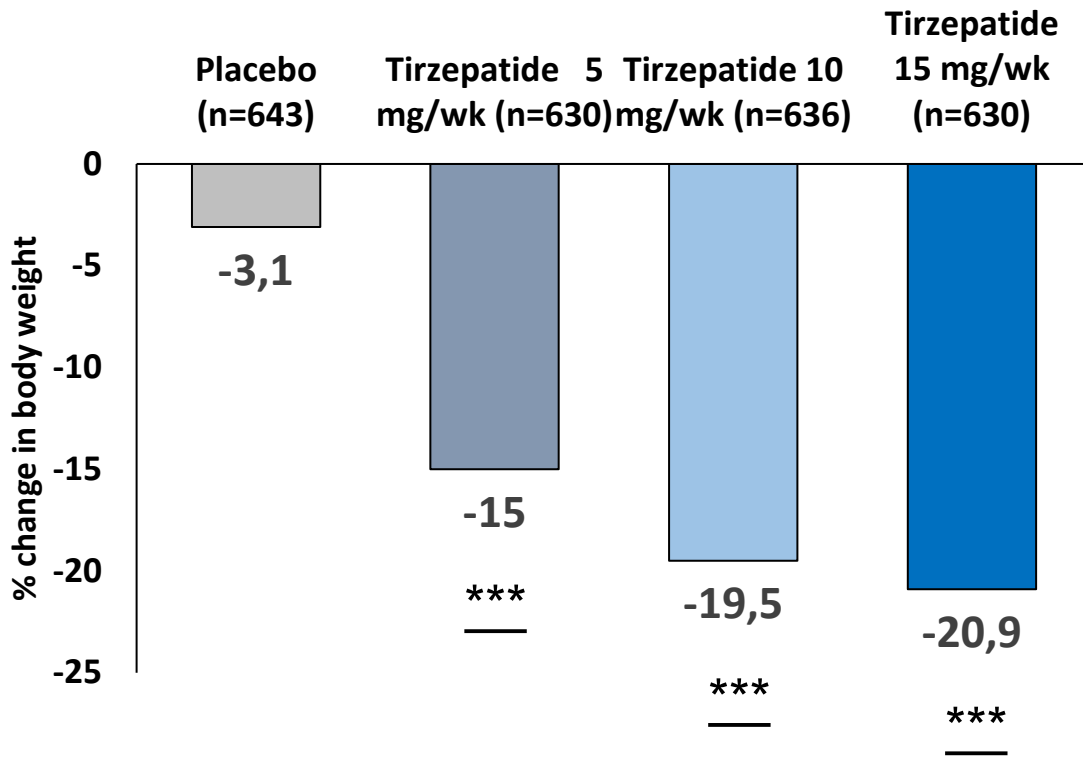


Tirzepatide molecule structure
Shading indicates non-coded amino acids

Coskun T. et al. Mol Metab 2018

Tirzepatide: lo studio SURMOUNT -1

% variazione peso alla 72a sett

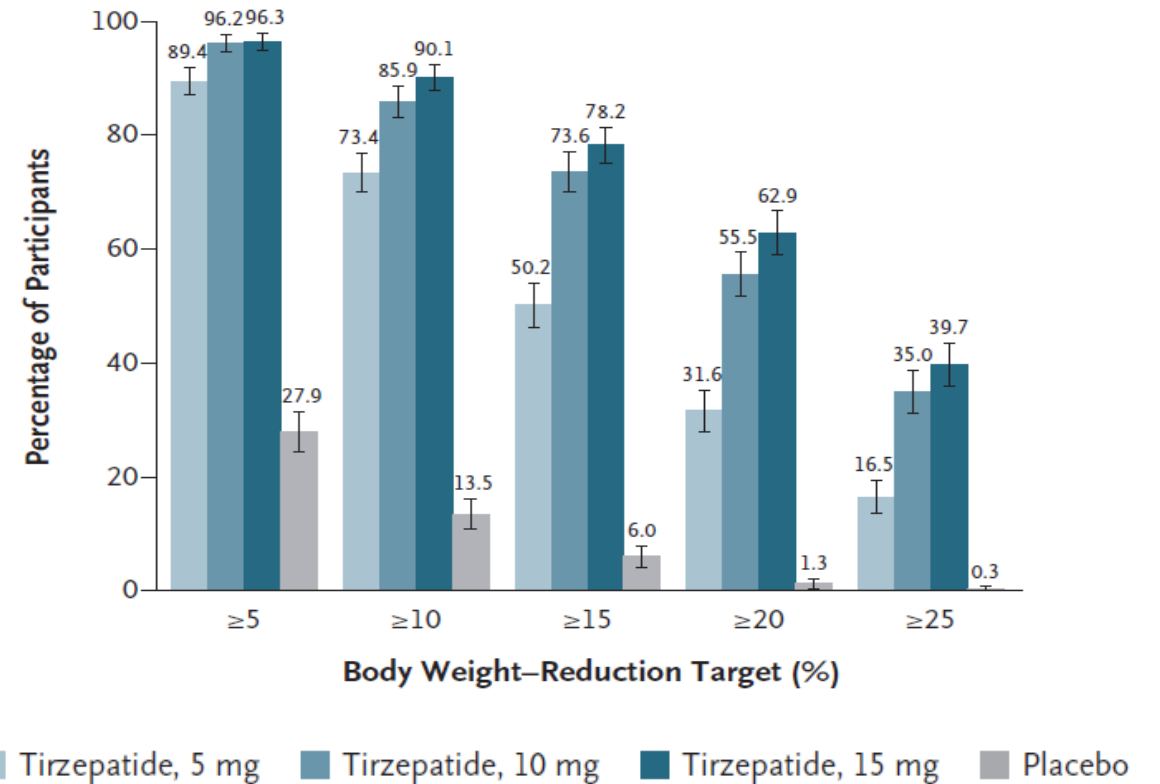


***P<0.001 vs. placebo

Jastreboff AM et al. NEJM 2022

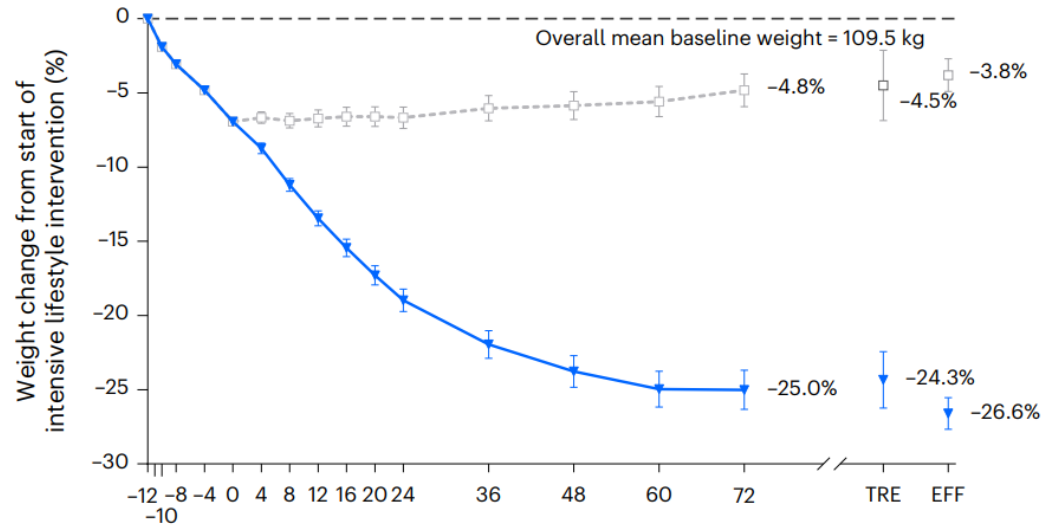
% paz con differente calo ponderale alla 72a sett

D Participants Who Met Weight-Reduction Targets (efficacy estimand)



Implementare la perdita di peso e mantenere i risultati: gli studi SURMOUNT 3 e 4

SURMOUNT-3



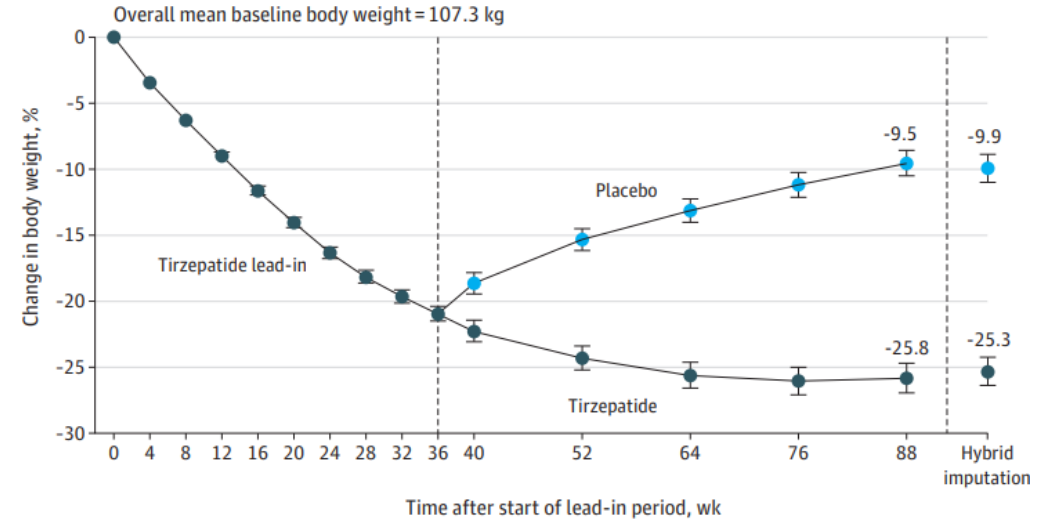
No. of participants

Weeks since randomization

	-12	-8	-4	0	4	8	12	16	20	24	36	48	60	72	TRE	EFF
Tirzepatide MTD	287	287	283	279	279	273	266	261	262	287	284					
Placebo	292	292	288	268	260	242	228	218	223	292	291					

Wadden TA et al. Nature Med 2023

SURMOUNT-4



No. at risk

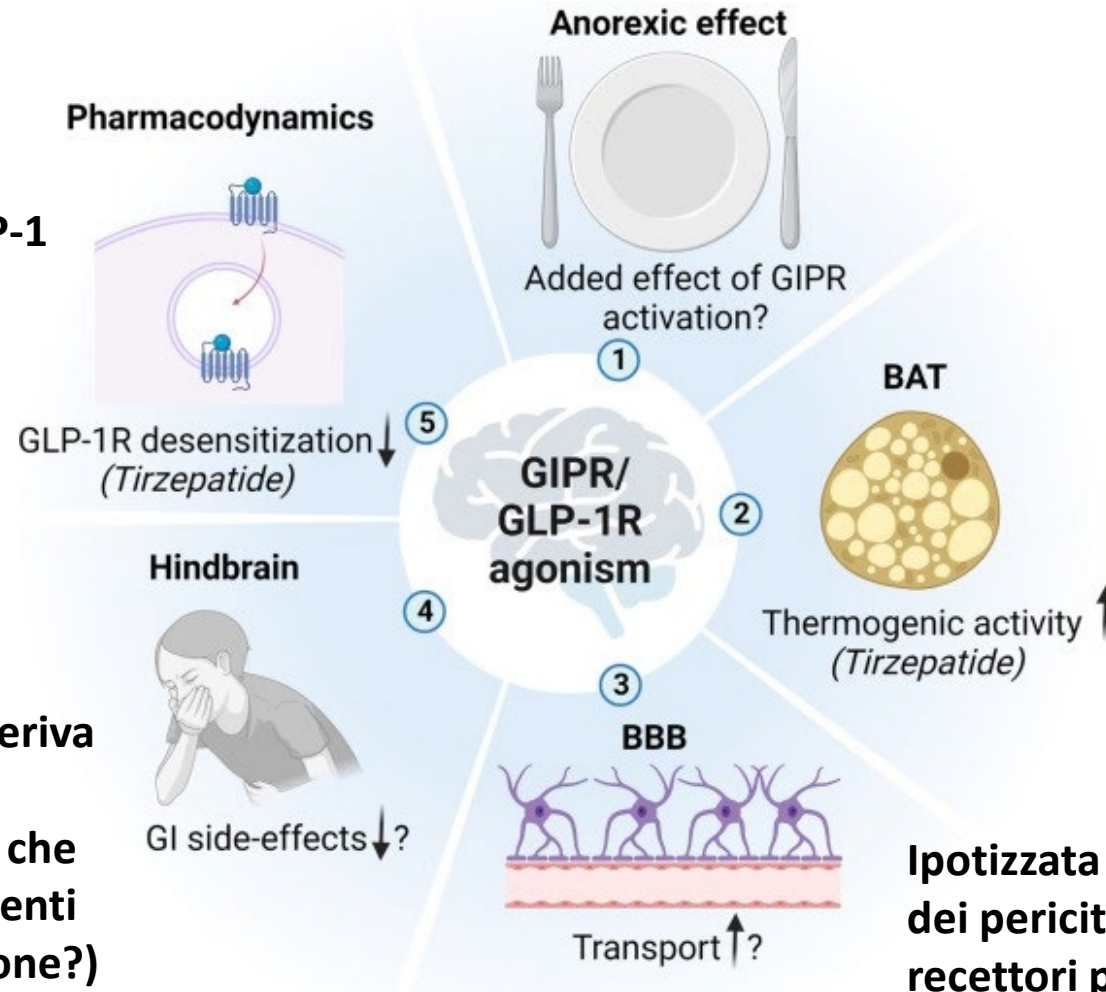
	0	4	8	12	16	20	24	28	32	36	40	52	64	76	88	Hybrid imputation
Tirzepatide lead-in	670	666	669	668	667	667	669	663	659	670						
Tirzepatide										335	333	328	317	310	310	335
Placebo										335	330	317	303	292	289	335

Aronne LJ et al. JAMA 2023

Potenziati effetti sinergici derivanti dall'azione di agonisti di GLP-1 e GIP

Tirzepatide favorisce il re-cycling del recettore del GLP-1 sulla superficie cellulare

Novikoff A. et al Mol Metab 2022
Boer GA et al. Trends Pharmacol Sci. 2023



Tirzepatide nel topo obeso stimola la spesa energetica e contrasta l'adattamento metabolico

Samms et al. Mol Metab. 2022.
Coskun T et al. EASD 56th 2020; Vienna, Austria.
Oral presentation #116.

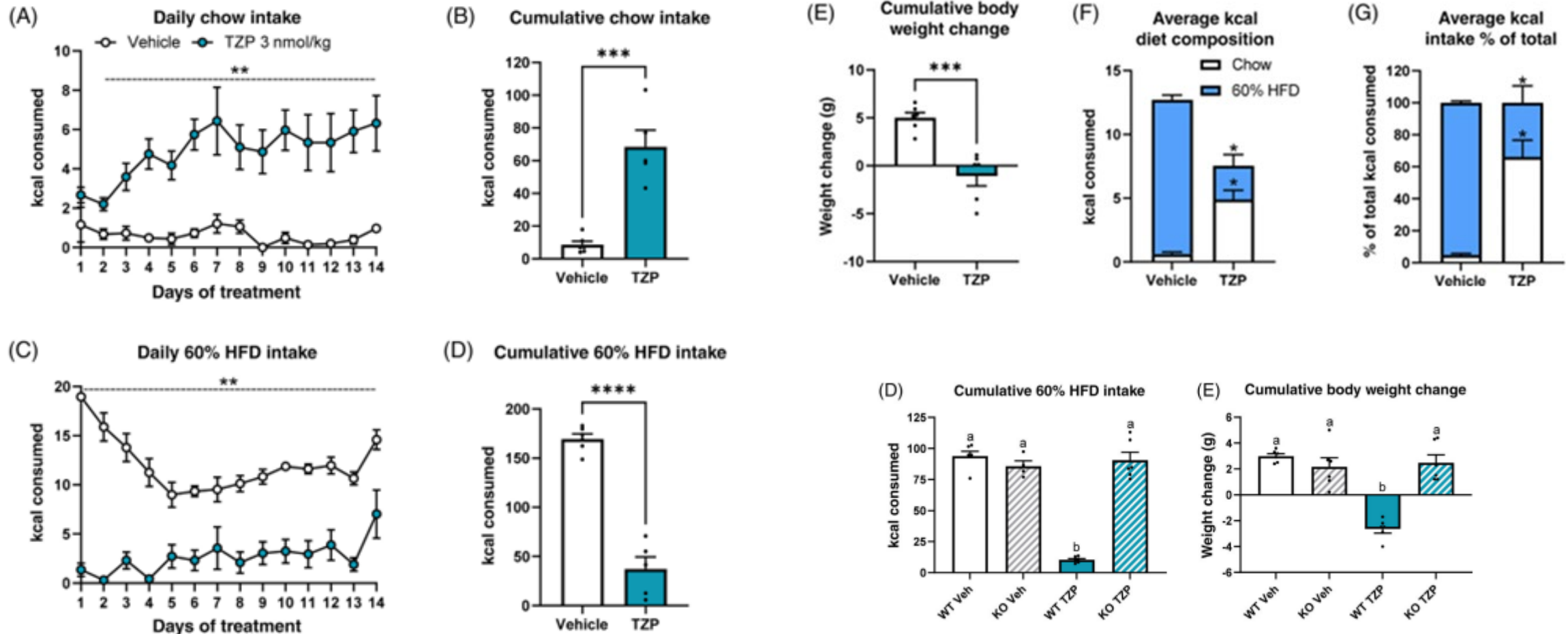
La nausea indotta dal GLP-1 deriva dall'attivazione di recettori localizzati nell'area postrema, che contiene anche cellule esprimenti sia GIPR che GLP-1R (mitigazione?)

Boer GA et al. Trends Pharmacol Sci. 2023

Ipotizzata la presenza di recettori per GIP a livello dei periciti dell'eminenza mediana, oltre ai recettori per GLP-1 a livello dei taniciti

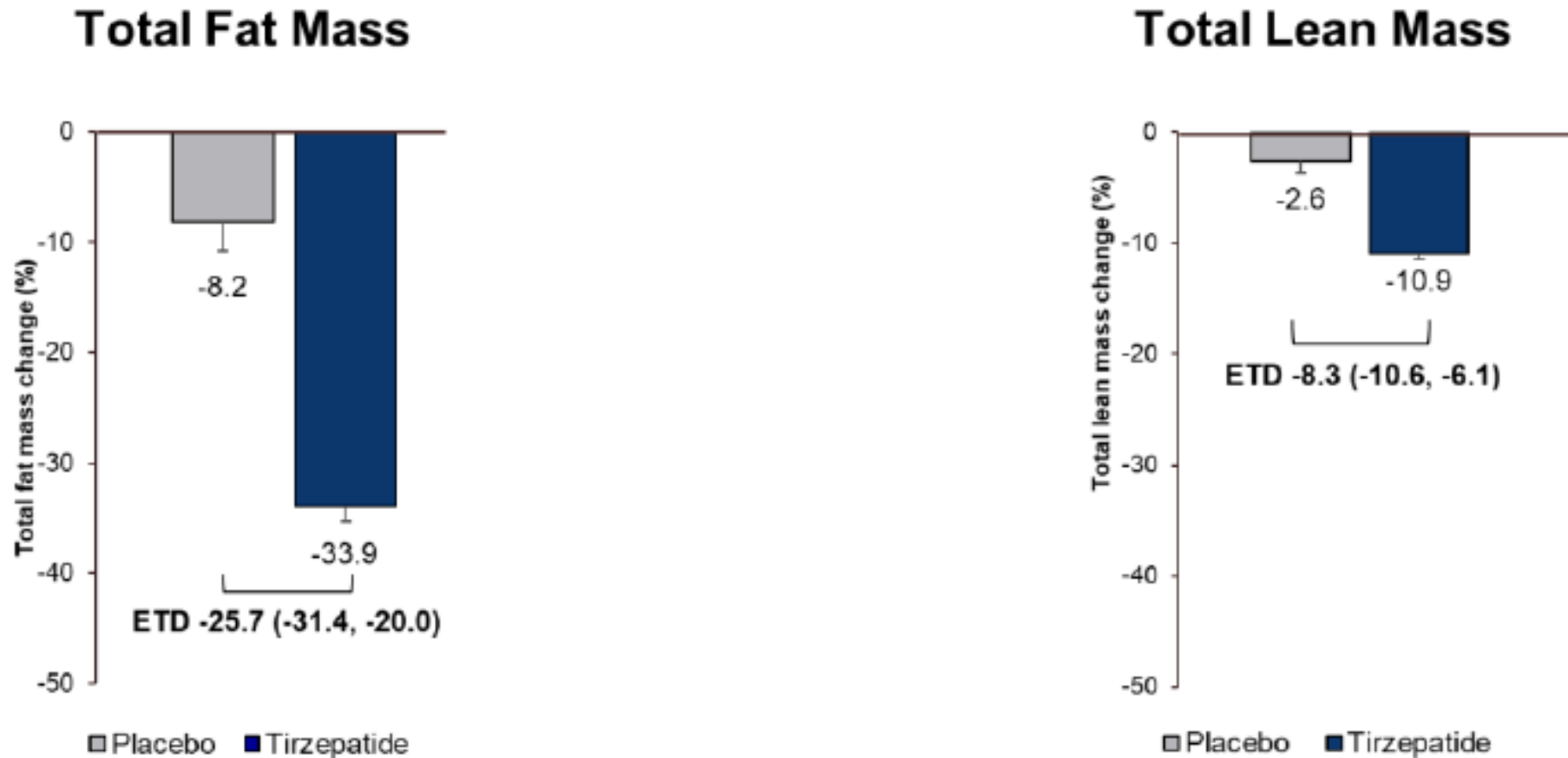
Boer GA et al. Trends Pharmacol Sci. 2023

Tirzepatide riduce l'apporto di cibo palatabile agendo massimalmente sulla preferenza verso un'alimentazione ricca di grassi: studio sui roditori



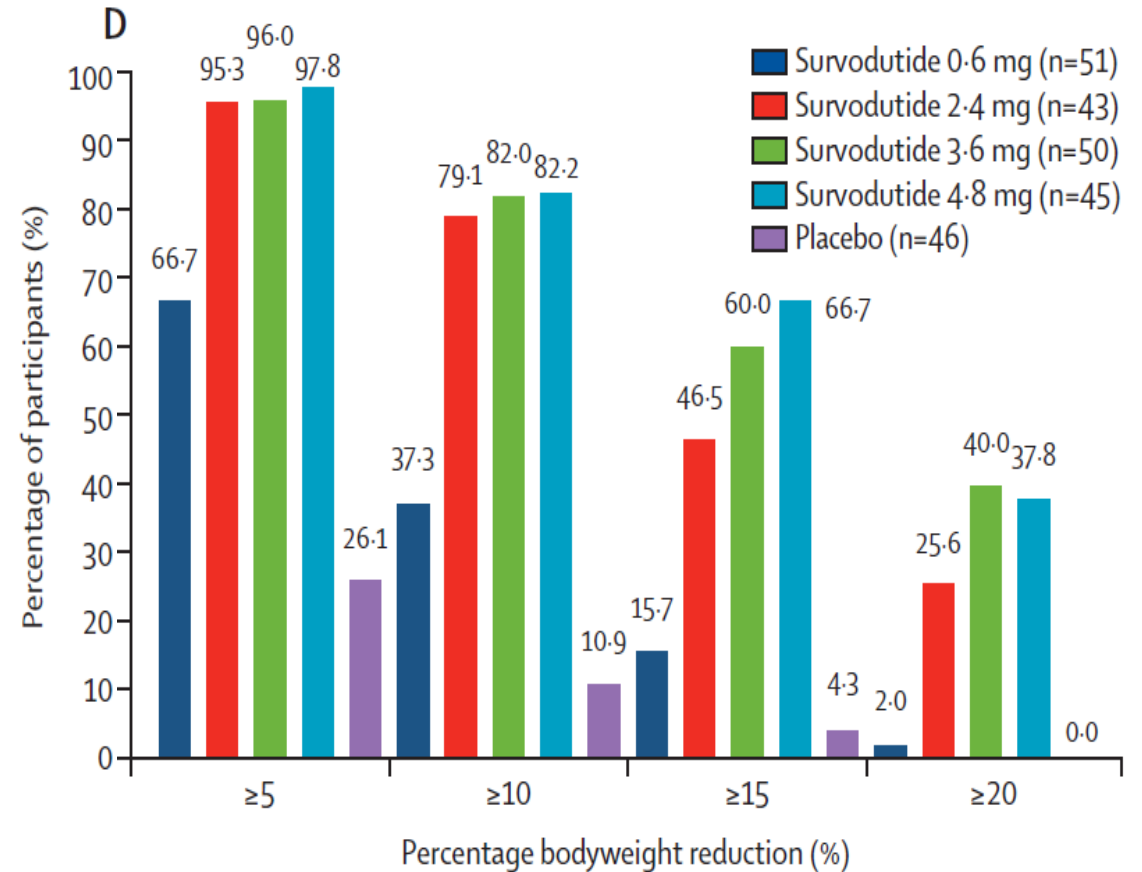
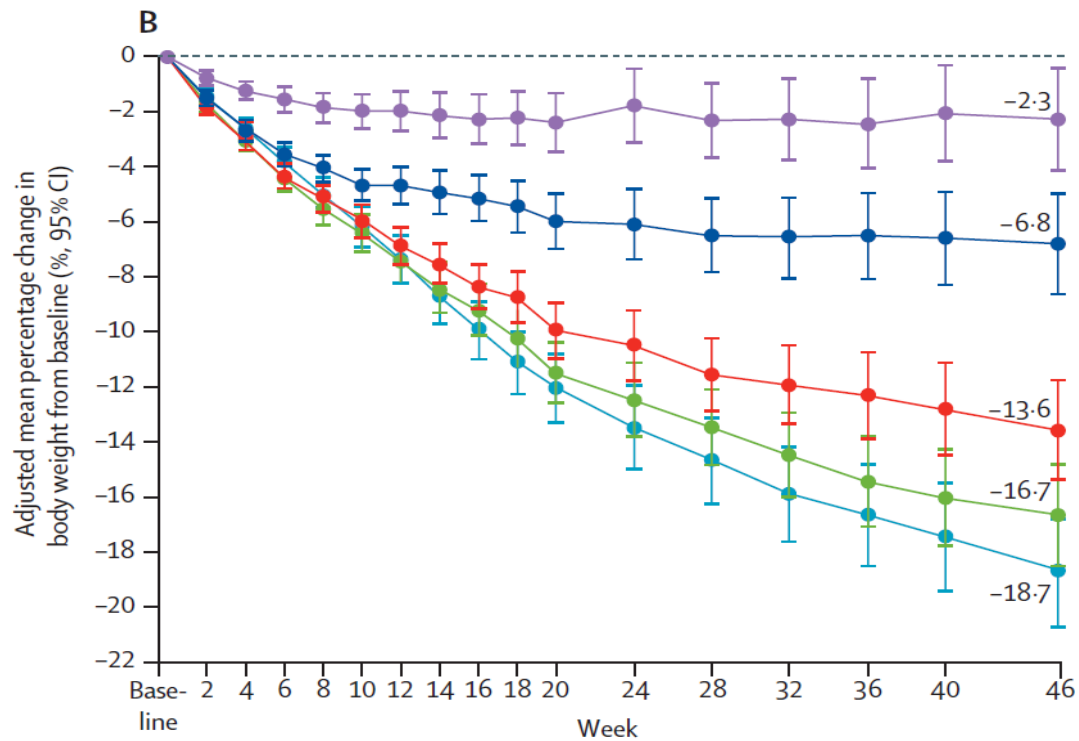
Geisler CE et al Diabetes Obesity Metabolism, 2022

Tirzepatide: effetti sulla composizione corporea



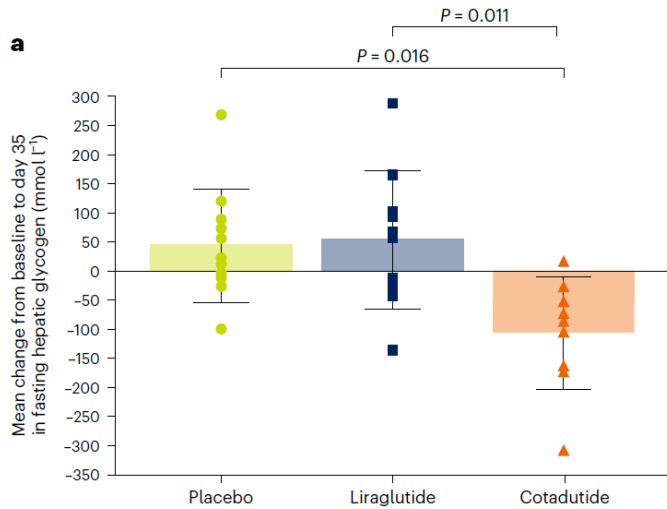
Jasterboff AM et al. NEJM 2022

CO-AGONISMO GLP-1/Glucagone: risultati dello studio di fase 2 con SORVODUTIDE

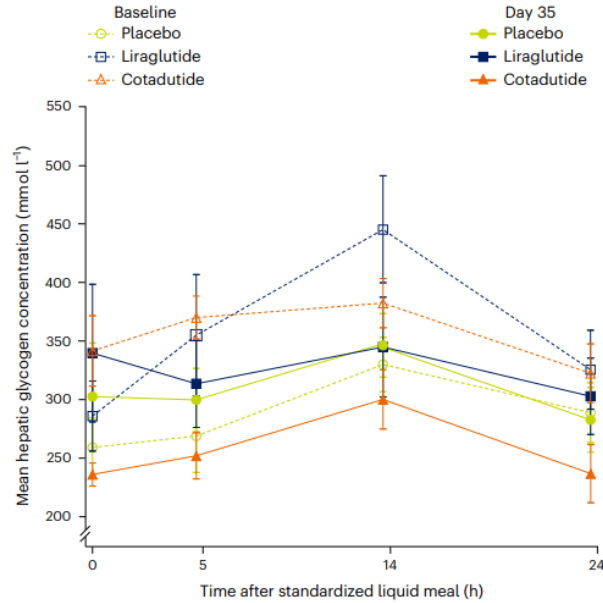


Il co-agonismo GLP-1R e GLC-R potenzia la glicogenolisi epatica

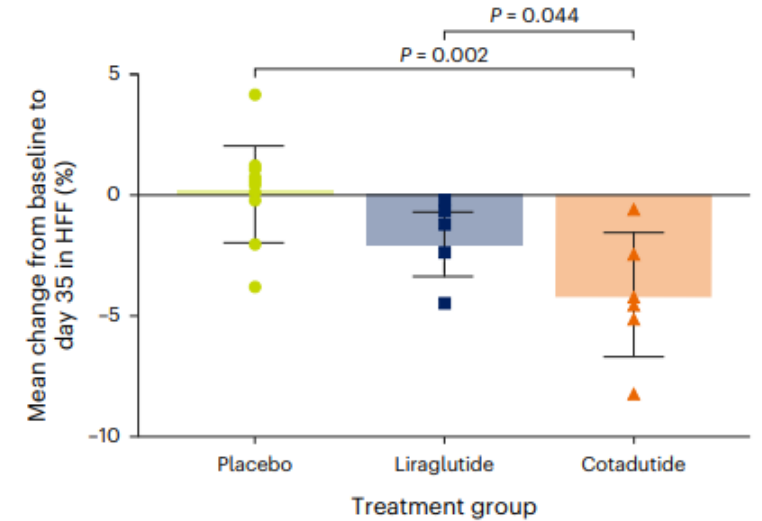
FASTING HEPATIC GLYCOGEN



POST-PRANDIAL HEPATIC GLYCOGEN



HEPATIC FAT FRACTION



GLP-1R are not expressed in liver

similar reductions of body weight and fasting glucose were observed in cotadutide and liraglutide groups, greater than in placebo.

Cotadutide promotes greater reductions in liver glycogen and hepatic fat fraction compared with both placebo and liraglutide

Retatrutide (TRI-AGONISTA: GLP-1/GIP/Glucagone)

VERDE – EFFETTO SPECIFICO DEL **GLUCAGONE**

BLU – EFFETTO **AUMENTATO RISPETTO AL DUAL AGONIST (GIP-GLP1)**

NERO – EFFETTO SIMILE AL DUAL AGONIST (GIP-GLP-1)

Obesity

- **Appetite & food intake** ↓
- **Energy expenditure** ↑

Diabetes

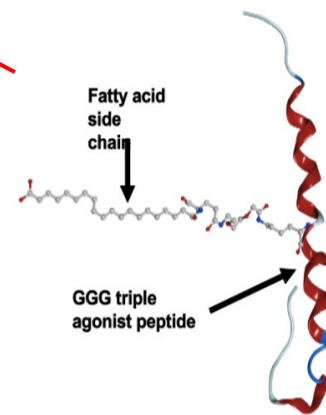
- **Insulin secretion** ↑
- **Insulin sensitivity** ↑
- **Gluconeogenesis** ↑

Hyperlipidemia

- **Liver FFA oxidation** ↑
- **Lipoprotein synthesis** ↓
- **Lipoprotein degradation** ↑

GIP/GLP-1/GCG Tri-agonista

LY3437943



NASH

- **Liver fat clearance** ↑

CKD

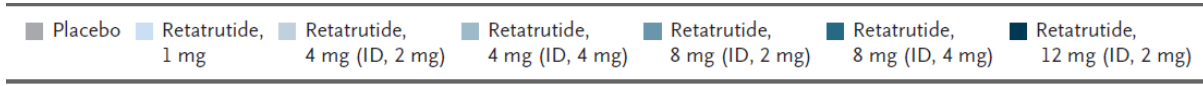
- **Kidney fat clearance** ↑
- **Lipotoxicity** ↓
- **Electrolyte handling**
- **Urea excretion**

Heart Failure

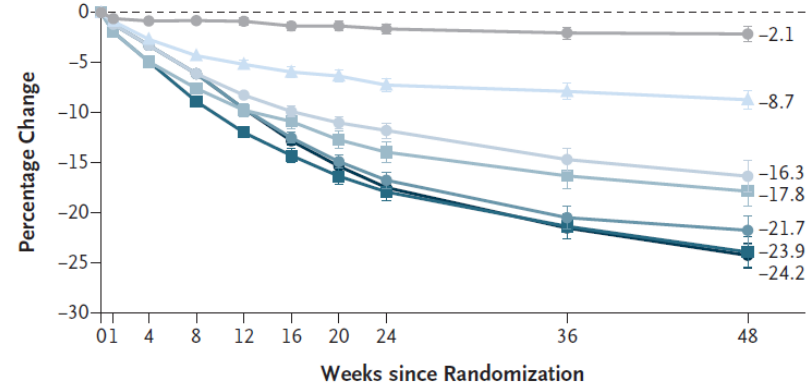
- **Epicardial fat clearance** ↑
- **Blood volume** ↓
- **Blood pressure** ↓

1. Adeva-Andany MM et al. Metabolic effects of glucagon in humans. *J Clin Transl Endocrinol.* 2019:45-53. 2. Bankir L et al. Glucagon actions on the kidney revisited: possible role in potassium homeostasis. *Am J Physiol Renal Physiol.* 2016:F469-F486. 3. Rix I et al. Glucagon physiology. 2015. 4. Kleinert M et al. Glucagon regulation of energy expenditure. *Int J Mol Sci.* 2019:5407. 5. Campbell JE, Newgard CB. Mechanisms controlling pancreatic islet cell function in insulin secretion. *Nature Rev Mol Cell Biol.* 2021:142-158.

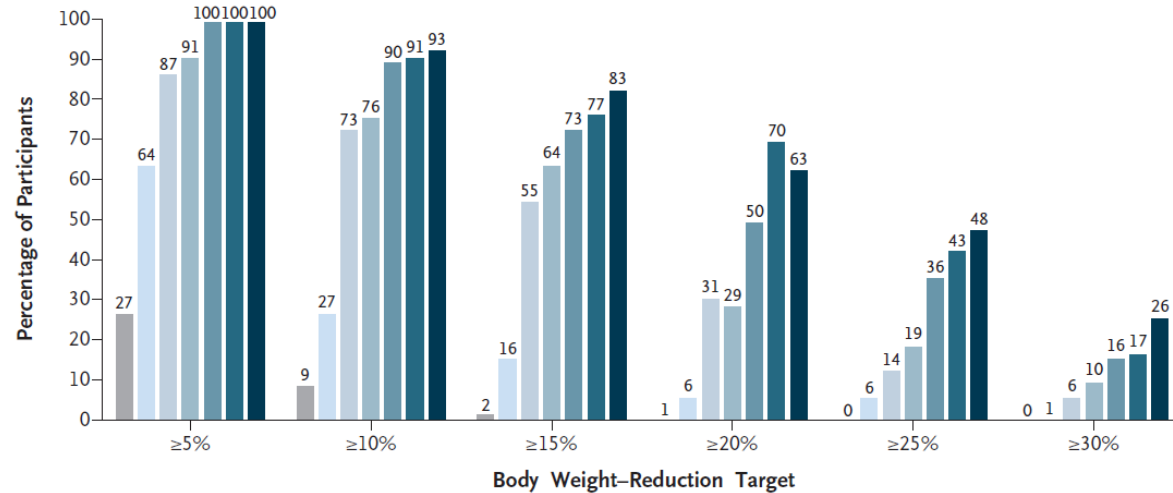
Retatrutide: effetti sul peso



A Changes in Body Weight

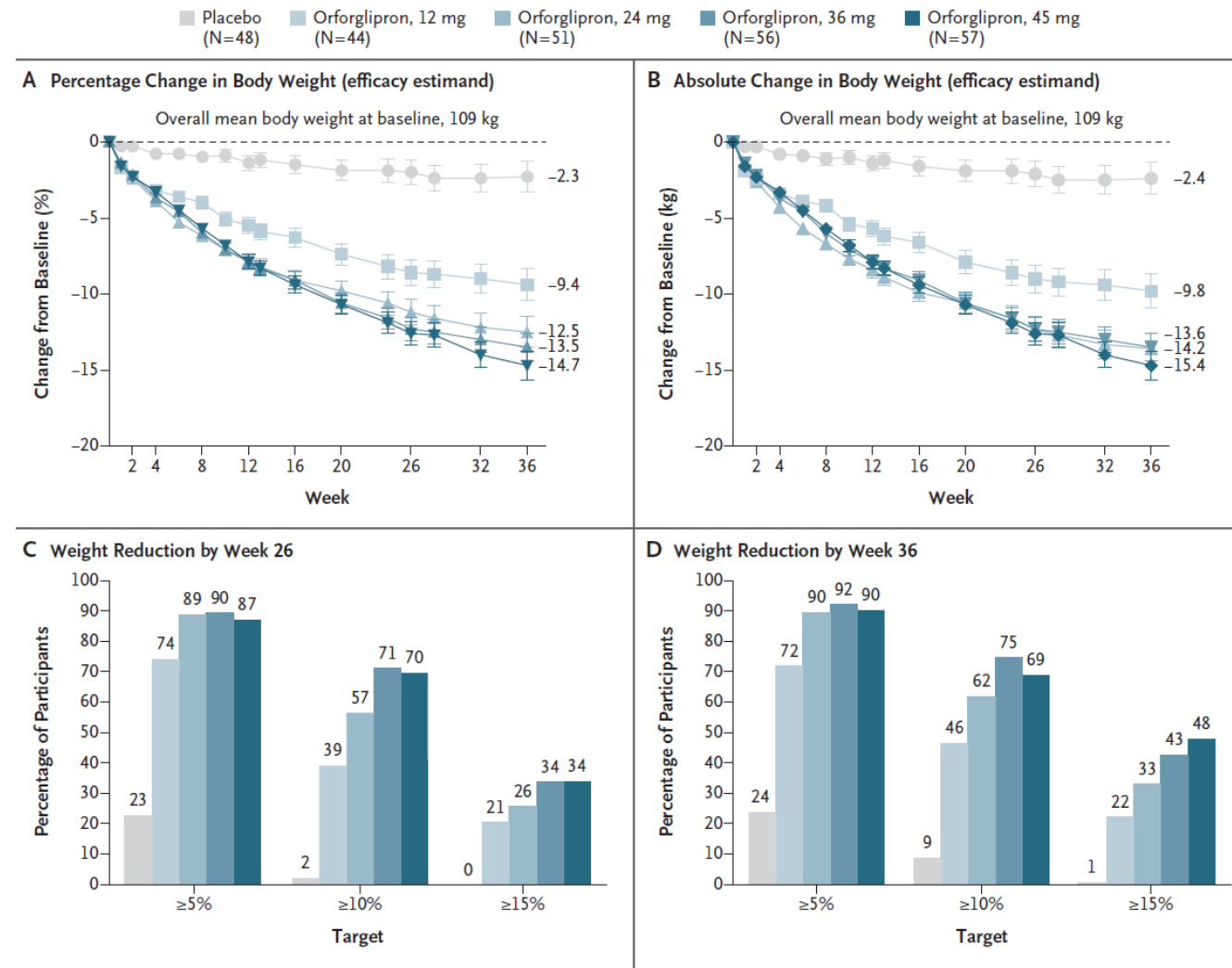


B Attainment of Weight-Reduction Targets



Jasterboff AM et al. NEJM 2023

ORFORGLIPRON: GLP-1RA orale giornaliero in adulti con obesità



Wharton S et al. NEJM 2023

Take home messages

Il trattamento farmacologico dell'obesità e delle sue complicanze oggi può contare su un crescente spettro di molecole derivanti dall'interazione cervello-intestino

I benefici dei farmaci disponibili stanno riducendo il gap presente in passato tra trattamento dietetico-comportamentale e chirurgia bariatrica, soprattutto in campo di protezione cardio e cerebrovascolare

L'efficacia dei farmaci coinvolge una quota sempre maggiore di pazienti, analogamente a quanto descritto nel campo della chirurgia bariatrica

Ad oggi il limite maggiore all'impiego delle terapie farmacologiche risiede nella non rimborsabilità, che ne limita l'accessibilità a molti pazienti

Sarà necessaria una maggiore educazione al trattamento farmacologico, vigilando al tempo stesso su usi «scomposti» della farmacoterapia.

**S.I.C.O.B.
EVENTI**



**SICOB CONVEGNO EMILIA-ROMAGNA
CESENA 19 - 20 Aprile 2024**

**PRESIDENTE: A.M. SCHETTINO
RESP. SCIENTIFICI: S. CARIANI, V. CORSO, A. LUCCHI**

**Dall'Alimento alla Chirurgia:
il Trattamento Integrato
dell'Obesità**

Grazie