



Congresso SID-AMD Regione Emilia-Romagna: "Terapie innovative e Medicina di precisione: verso la "decronicizzazione" del diabete"

Parma, 7 ottobre 2022

III Sessione: Innovazione farmacologica nel diabete tipo 2

Twincretine



Gian Paolo Fadini

Università di Padova

Disclosures

Il prof. Gian Paolo Fadini dichiara di aver ricevuto negli ultimi 2 anni Grant o onorari dalle seguenti aziende portatrici di interesse in ambito sanitario

- Abbott
- AstraZeneca
- Boehringer
- Lilly
- MSD
- Mundipharma
- Novo Nordisk
- Sanofi
- Servier
- Takeda

Agenda

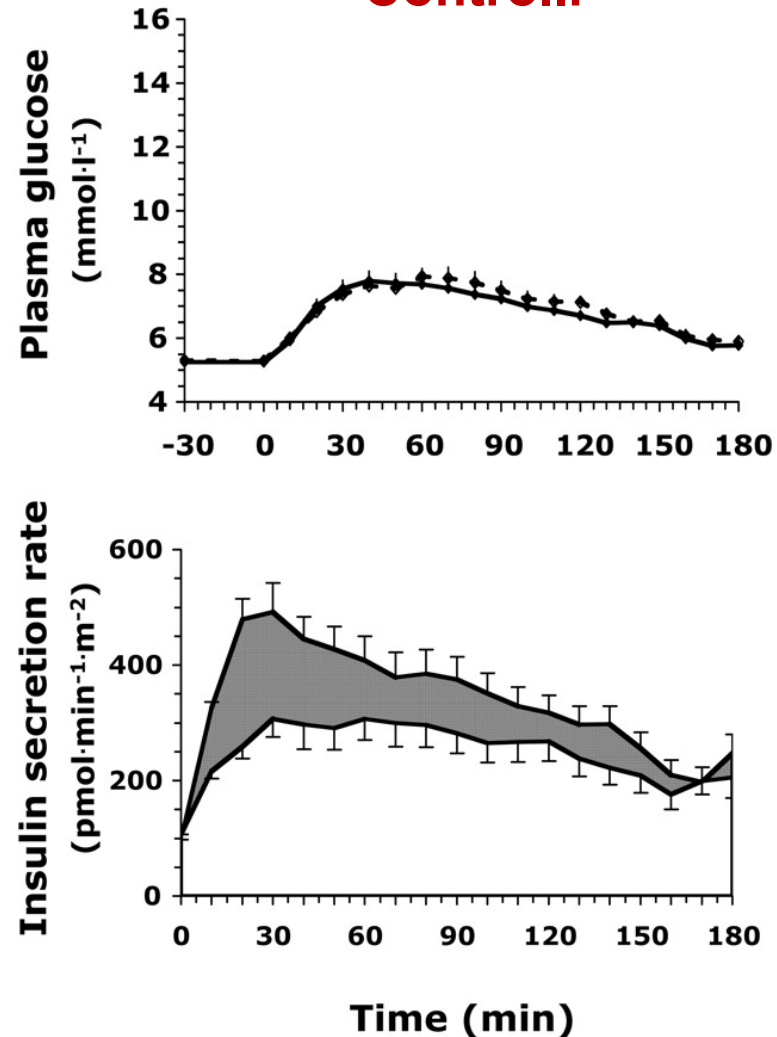
- ✓ Il ruolo del GIP nel sistema incretinico
- ✓ Il difetto incretinico nel T2D
- ✓ L'agonismo duale GLP-1 / GIP
- ✓ Dati clinici su Tirzepatide

Difetto incretinico nel DMT2

Test isoglicemico

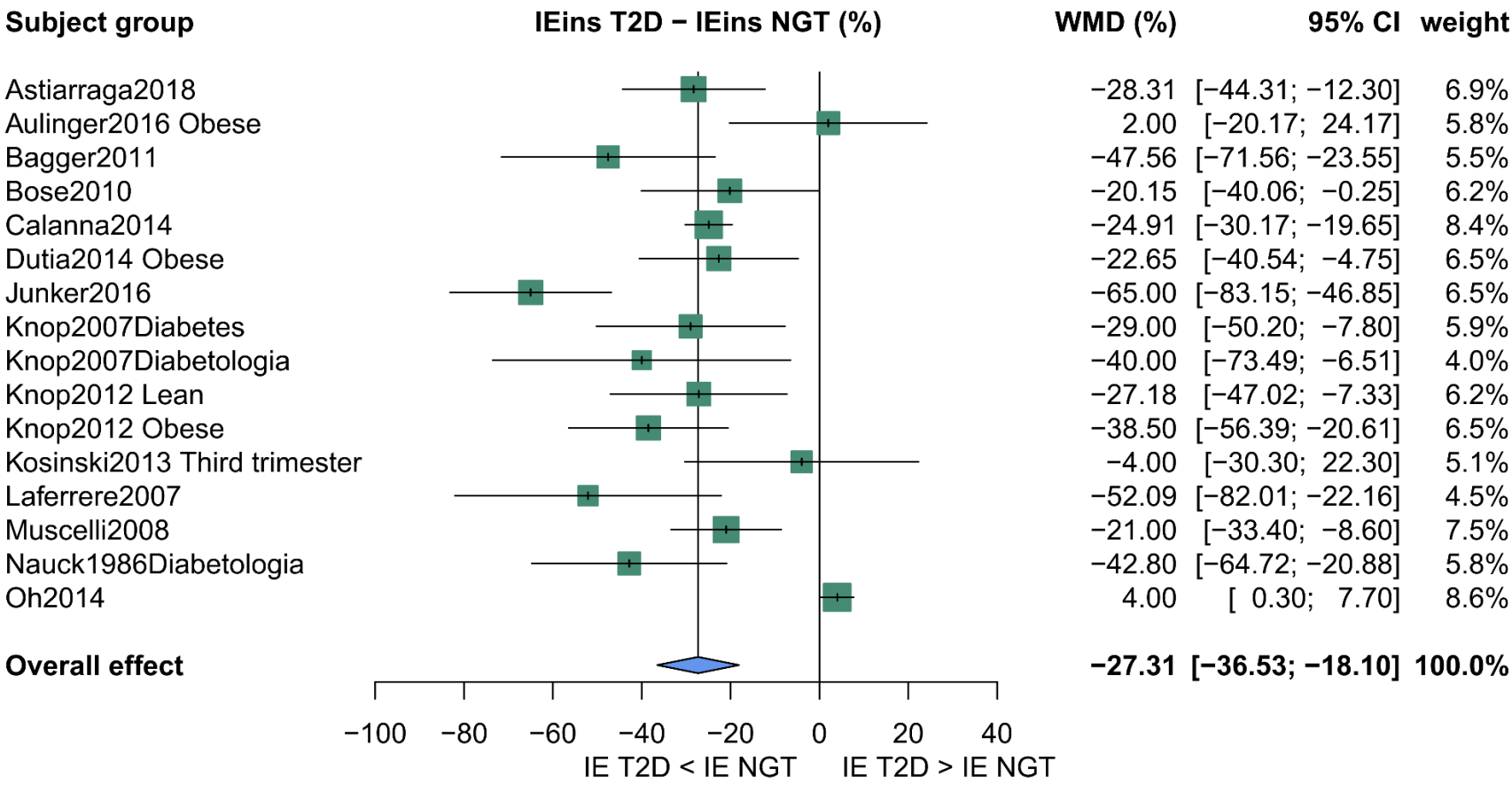
Confronto tra la secrezione di insulina in risposta al carico i.v. e la secrezione insulinica in risposta ad un carico orale isoglicemico

Controlli



Difetto incretinico nel DMT2

Meta-analysis of literature studies



Difetto incretinico nel DMT2

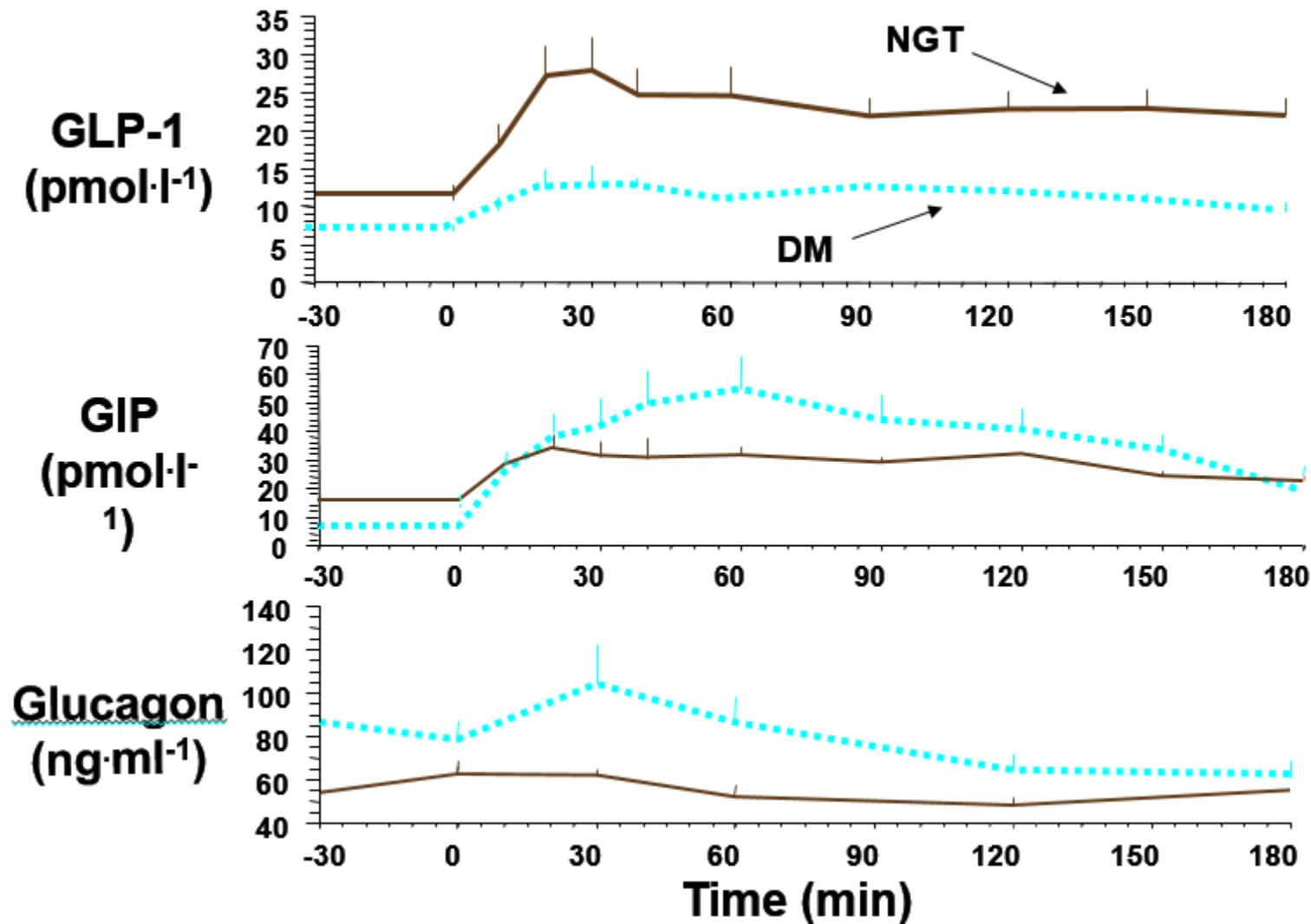
Non è reversibile con il controllo glicemico...

- Thirteen-day treatment with vildagliptin did not improve the incretin defect
Virdali I, et al. J Clin Endocrinol Metab. 2011 Apr;96(4):945-54
- Six-day treatment with metformin +/- sitagliptin did not improve the incretin defect
Virdali I, et al. J Clin Endocrinol Metab. 2011 Apr;96(4):945-54
- Six-week treatment with sitagliptin did not improve the incretin defect
Muscelli E, et al. J Clin Endocrinol Metab 2012;97:2818-26

... ma forse con il controllo del peso

Bariatric surgery (biliopancreatic diversion) improved the incretin effect
Novaes FS, et al. J Clin Endocrinol Metab 2015;100:1984-88

Difetto incretinico nel DMT2



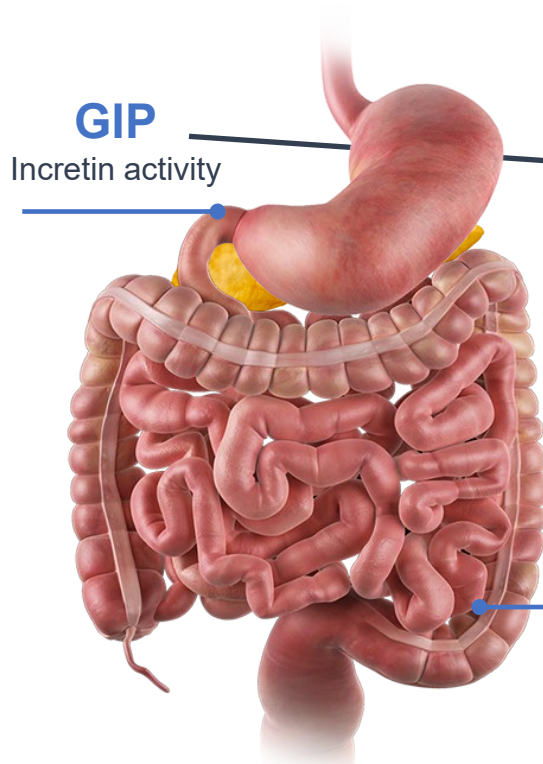
GIP e GLP-1

Discovery:
Early 1970s

Secreted by:
Duodenal K cells

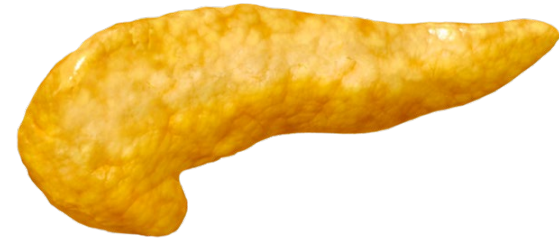
Stimulated by:
Nutrient load in the
gut

GIP
Incretin activity



GLP-1
Incretin activity

Increased glucose-dependent
insulin secretion helps regulate
PPG clearance



Discovery:
Early 1980s

Secreted by:
Distal ileal and Colonic L cells

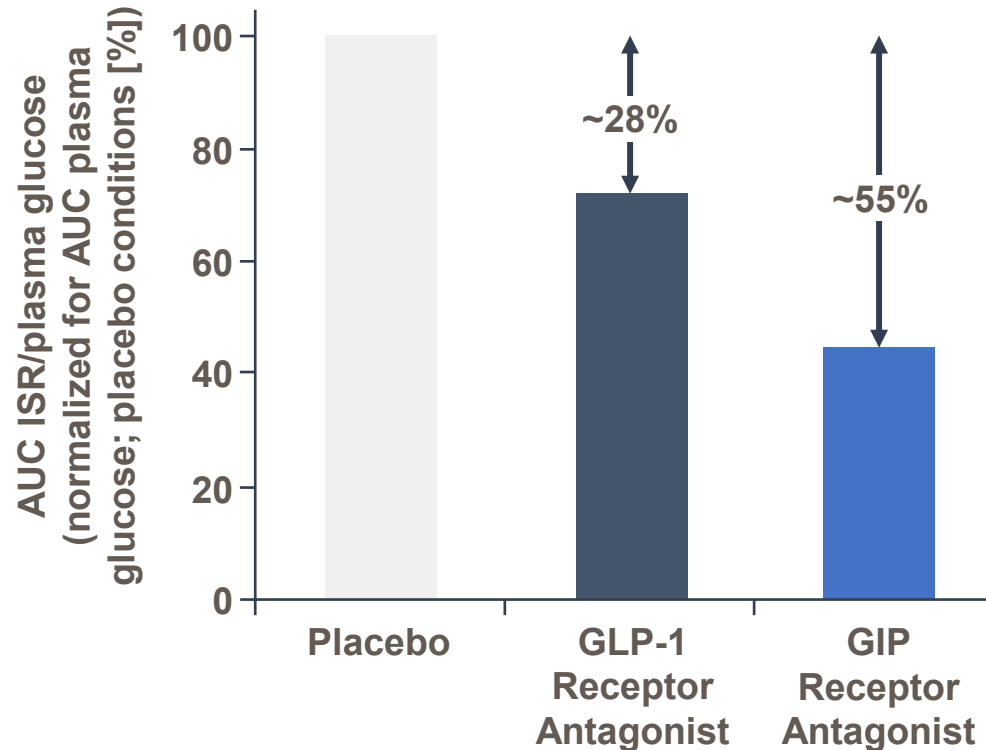
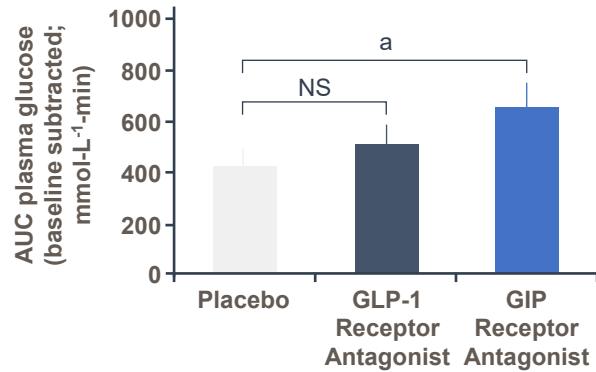
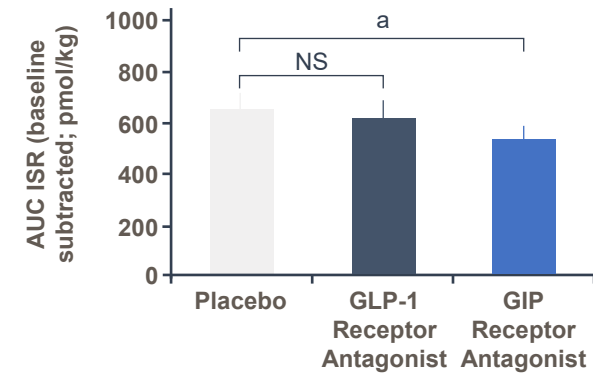
Stimulated by:
Nutrient load in the gut

IV = intravenous.

1. Aronoff SL, et al. *Diabetes Spectr.* 2004;17(3):183-190. 2. Brown JC. *Can J Biochem.* 1971;49(2):255-261. 3. Brown JC, Dryburgh JR. *Can J Biochem.* 1971;49(8):867-872. 4. Kim W, Egan JM. *Pharmacol Rev.* 2008;60(4):470-512. 5. Lund PK. *Regul Pept.* 2005;128(2):93-96.

Importanza relativa di GIP e GLP-1

Selective antagonism of GIP or GLP-1 receptors during oral glucose challenge demonstrates individual contribution of GIP and GLP-1 to insulin secretion/glycemic control in **healthy controls**



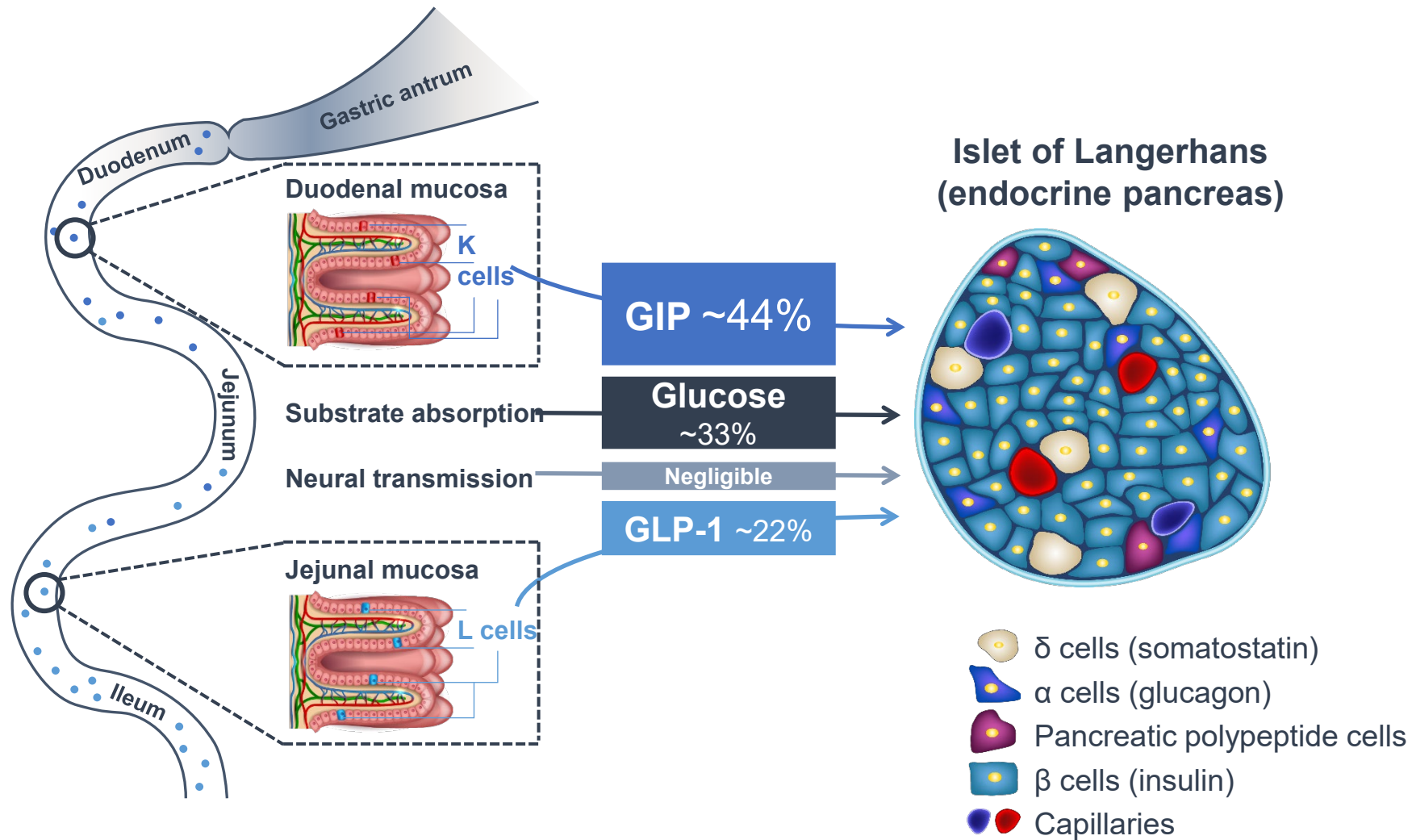
In antagonist studies, GIP generated a more significant effect on insulin-mediated glucose clearance in healthy individuals compared with GLP-1

^a $P < .05$.

AUC = area under the curve; GIPR = glucose-dependent insulintropic polypeptide receptor; GLP-1R = glucagon-like peptide-1 receptor; ISR = insulin secretion rate; NS = not significant.

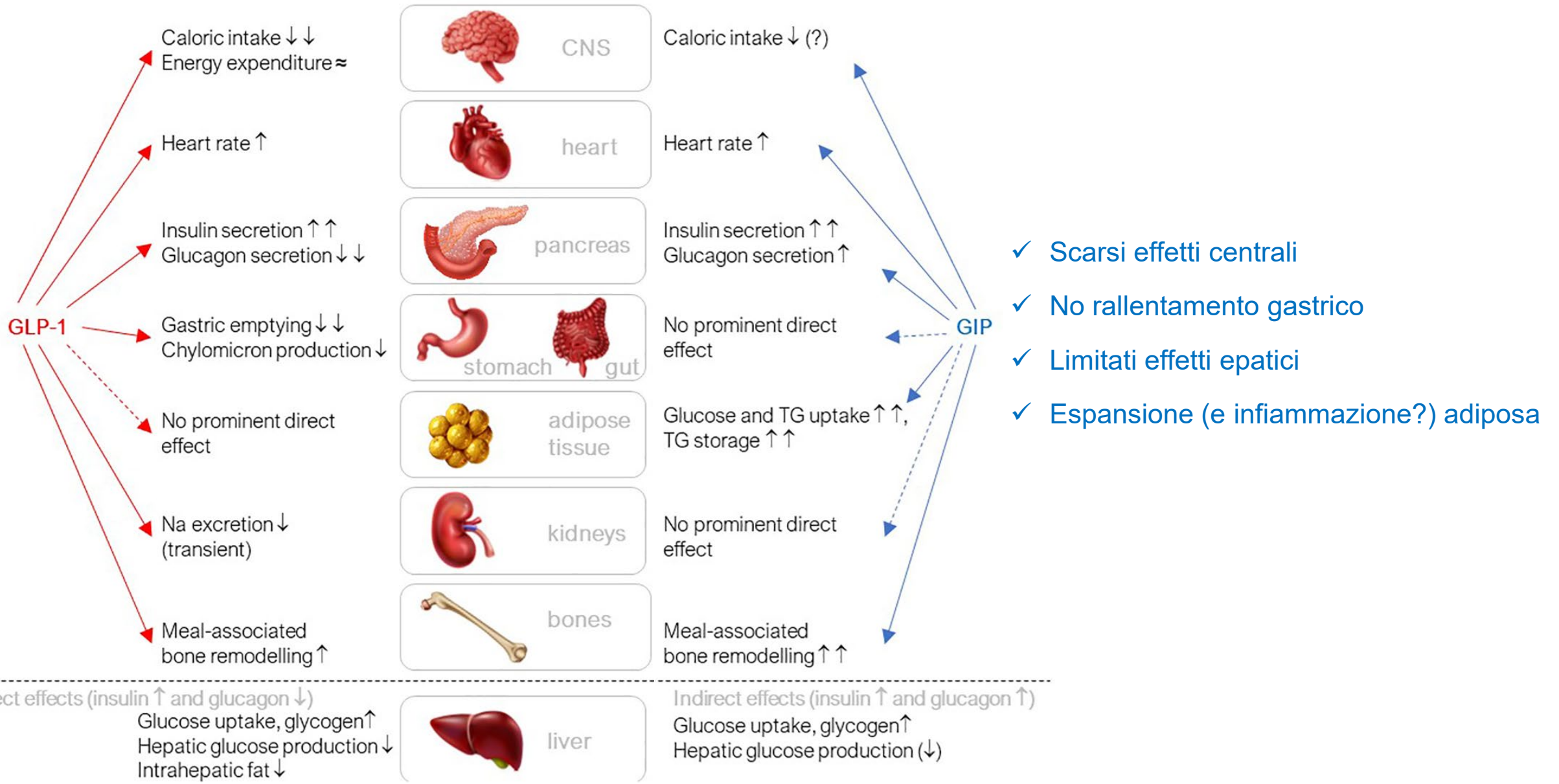
Nauck MA, Meier JJ. *Diabetes*. 2019;68(5):897-900.

Importanza relativa di GIP e GLP-1



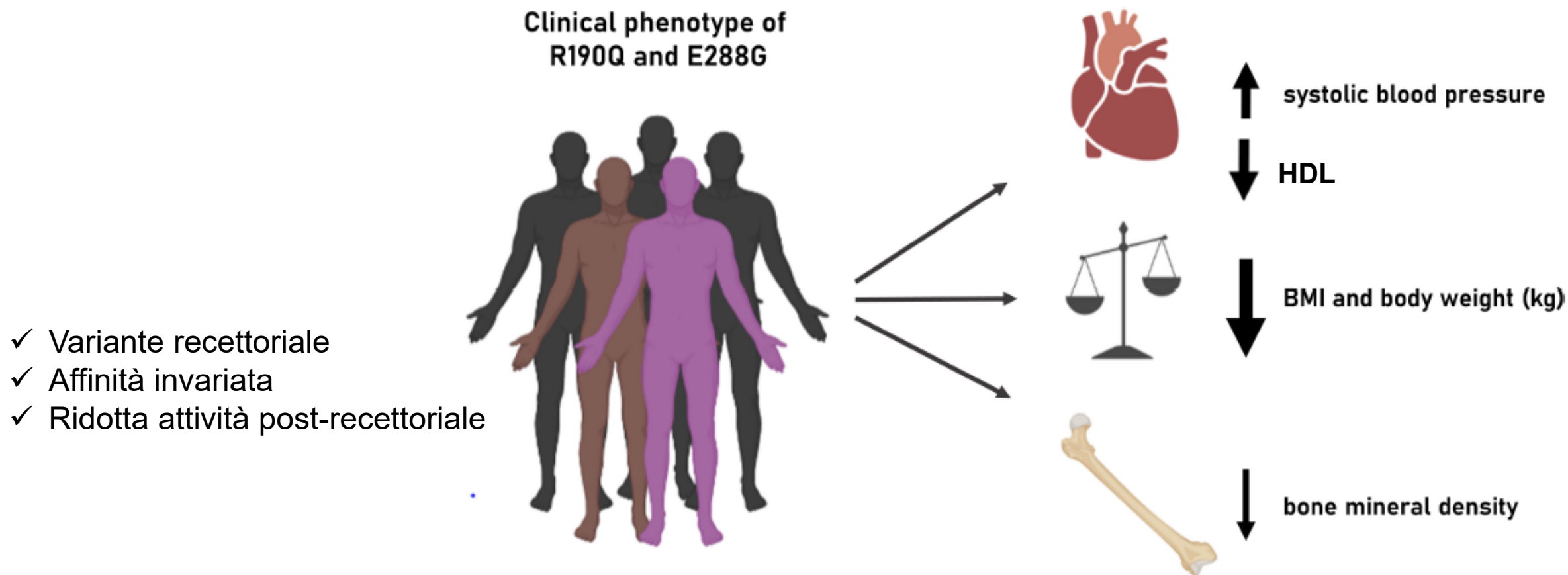
GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; PPG = postprandial glucose.
Nauck MA, Meier JJ. *Diabetes*. 2019;68(5):897-900.

Altri contributi del GIP?



Effetti del GLP: un esperimento naturale

Loss of Function Glucose-Dependent Insulinotropic Polypeptide Receptor Variants Are Associated With Alterations in BMI, Bone Strength and Cardiovascular Outcome



GIP a(nta)gonismo



Jonathan E. Campbell^{1,2,3,*}

MOLECULAR
METABOLISM

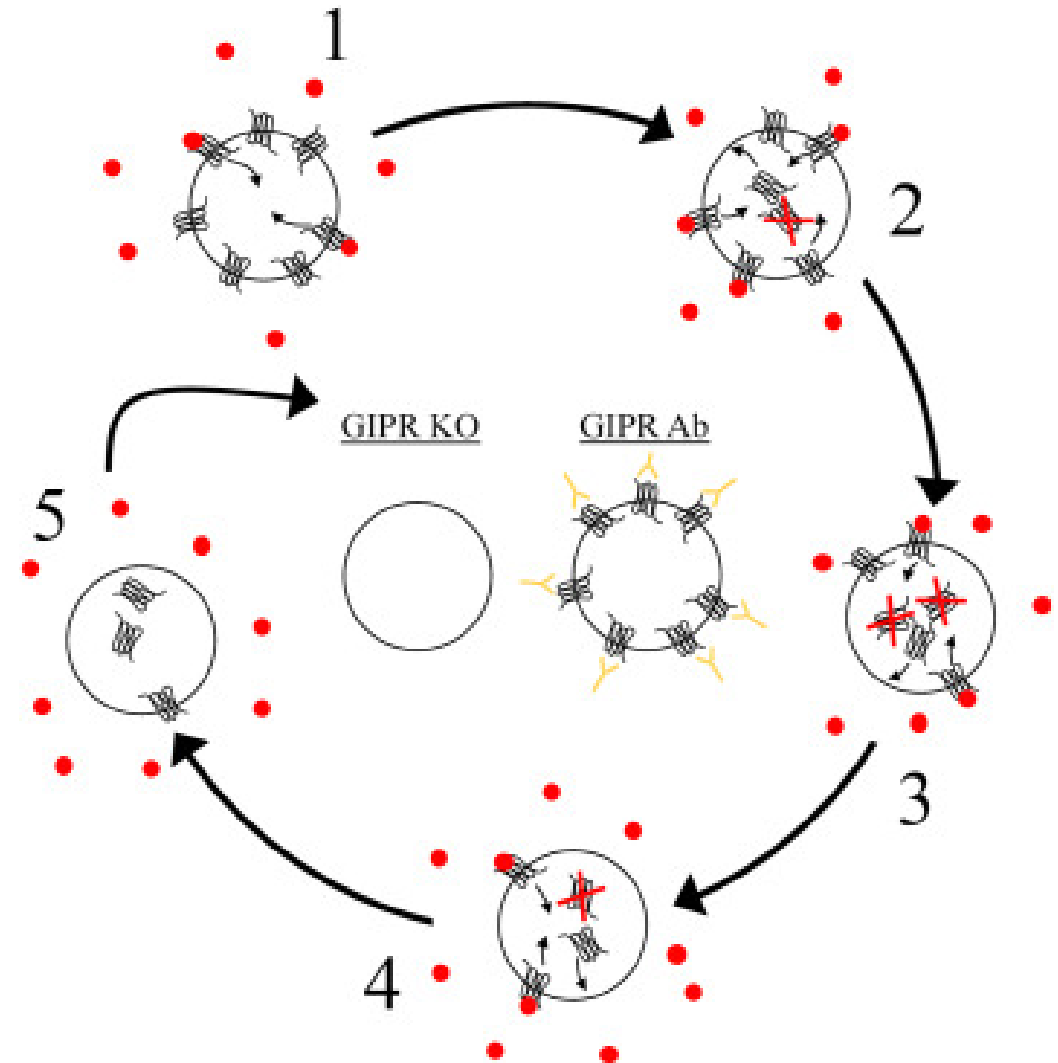
Review

Targeting the GIPR for obesity: To agonize or antagonize? Potential mechanisms

1) Agonism of the GIPR leads to internalization of the number of receptors that is proportional to the concentrations of agonists.

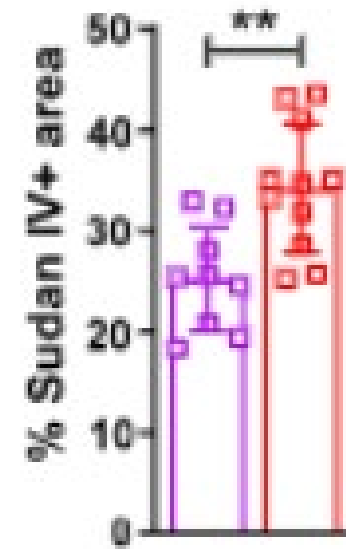
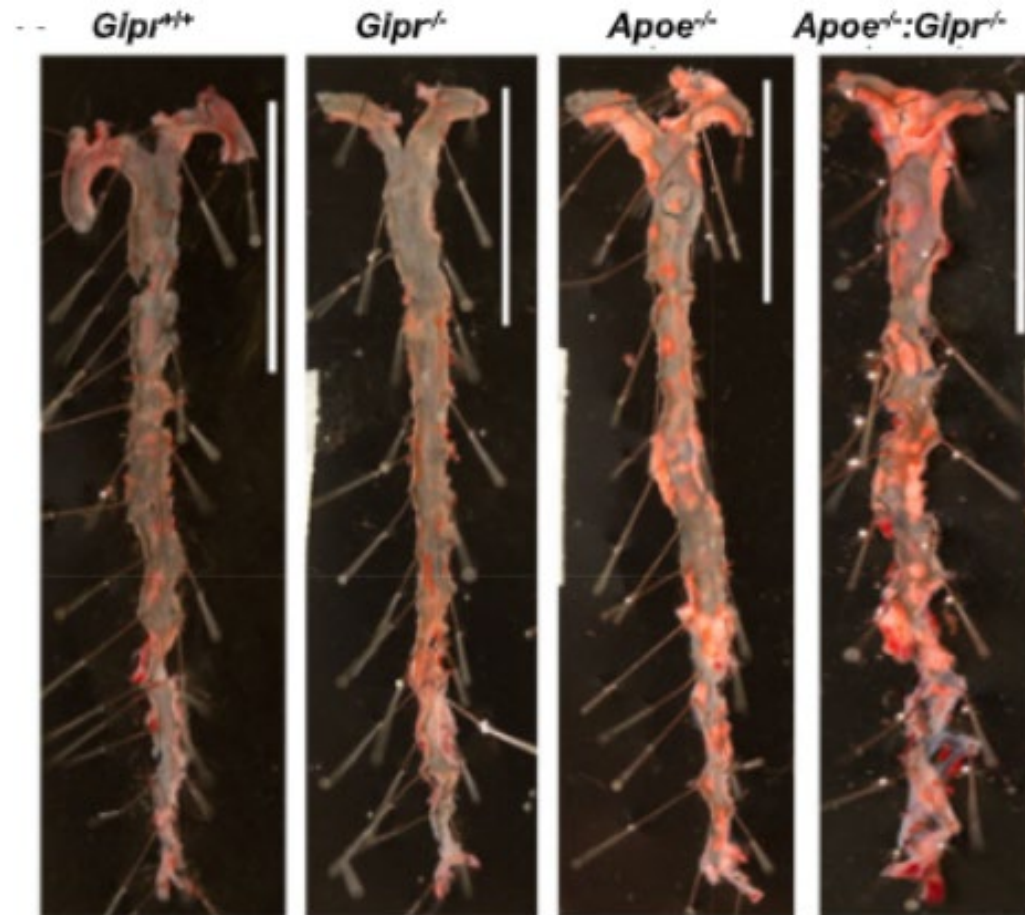
2) Some receptors will recycle back to the membrane, while others will degrade

3–5) Chronic agonism eventually decreases the number of receptors present on the membrane to effectively resemble loss of function



Chronic Agonism Equals Antagonism?

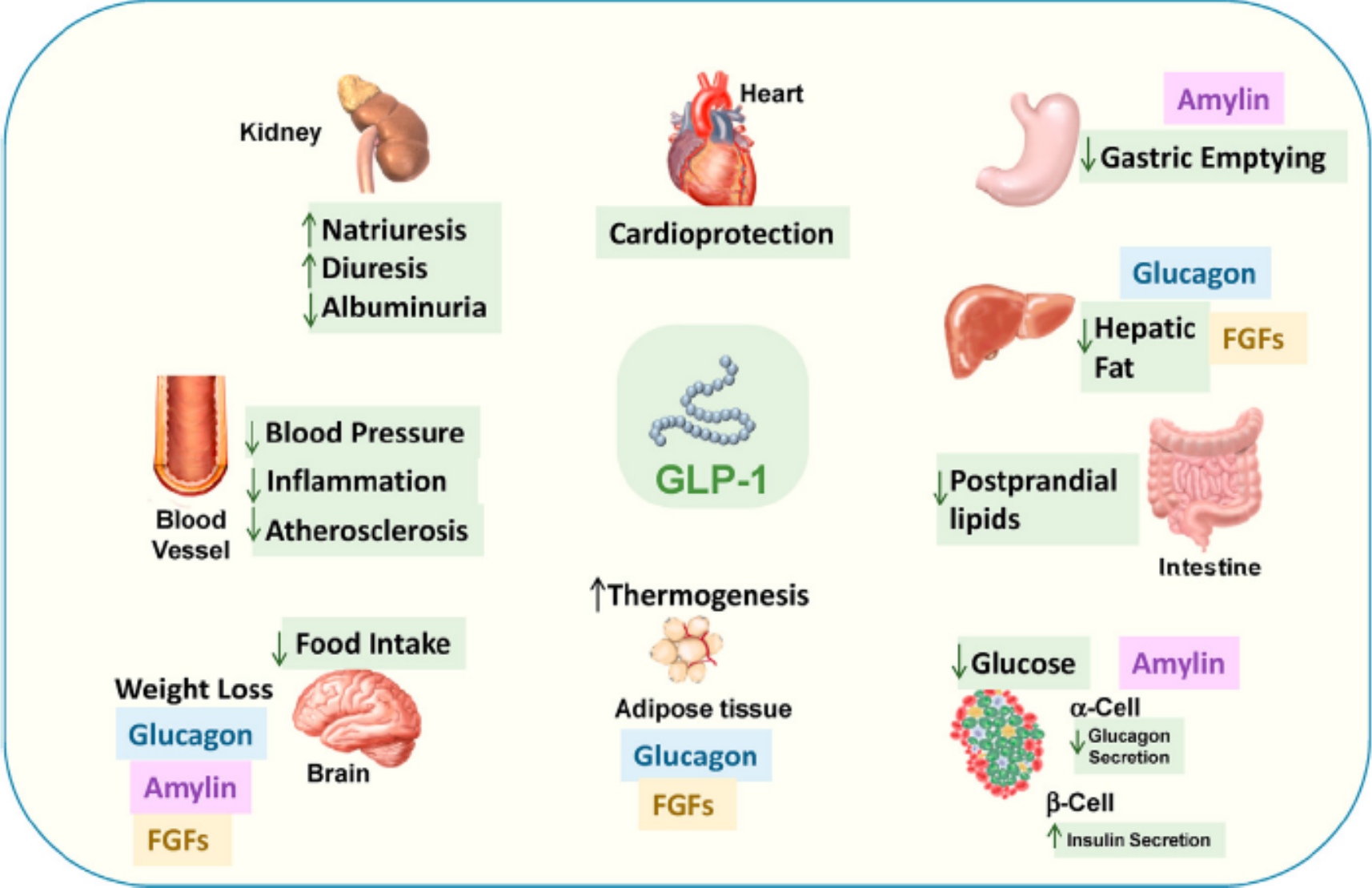
Genetic disruption of the Gpr in Apoe^{-/-} mice promotes atherosclerosis



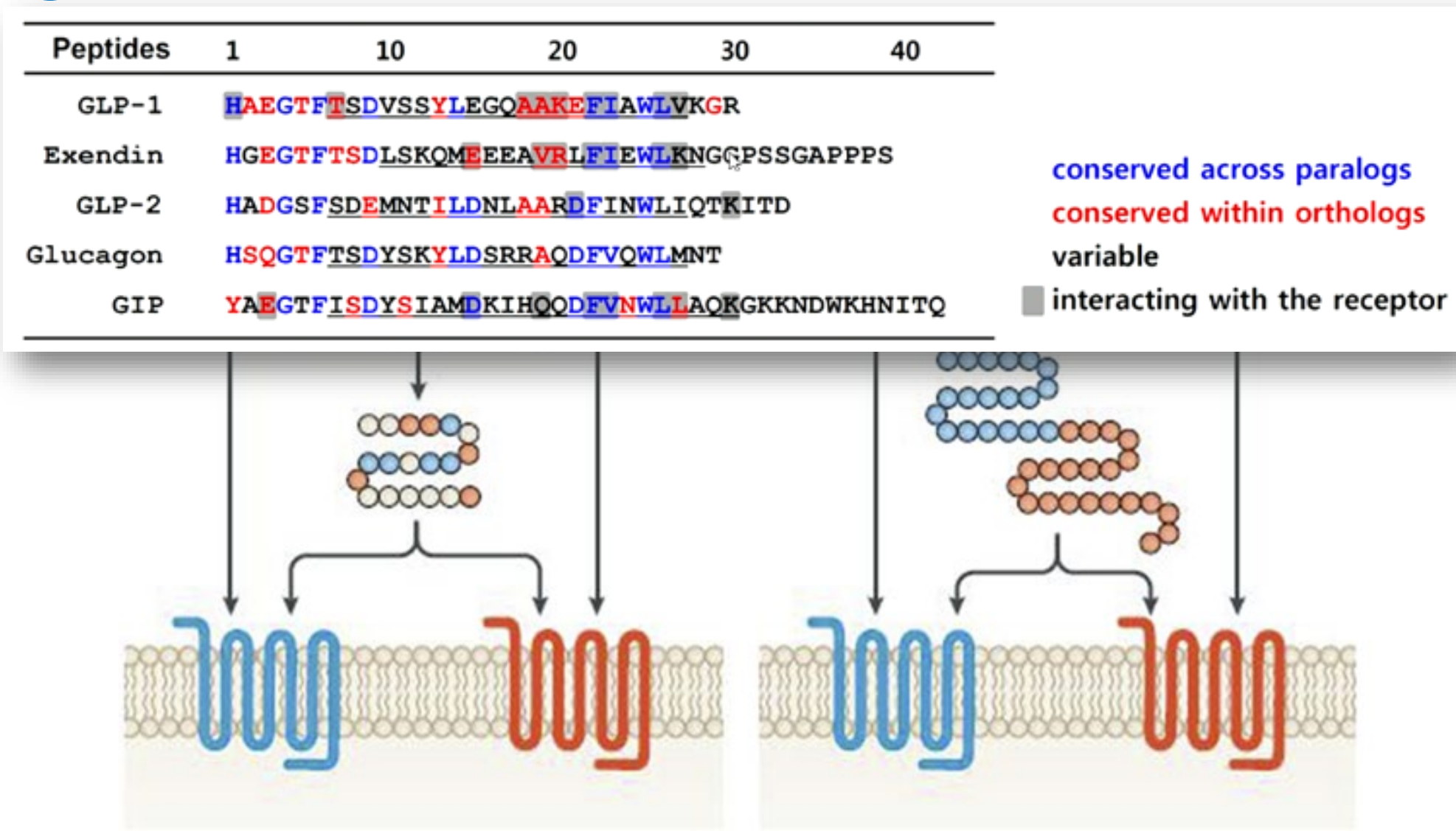
□ *Apoe*^{-/-}

□ *Apoe*^{-/-}:*Gpr*^{-/-}

Spectrum of dual agonists



II co-agonismo

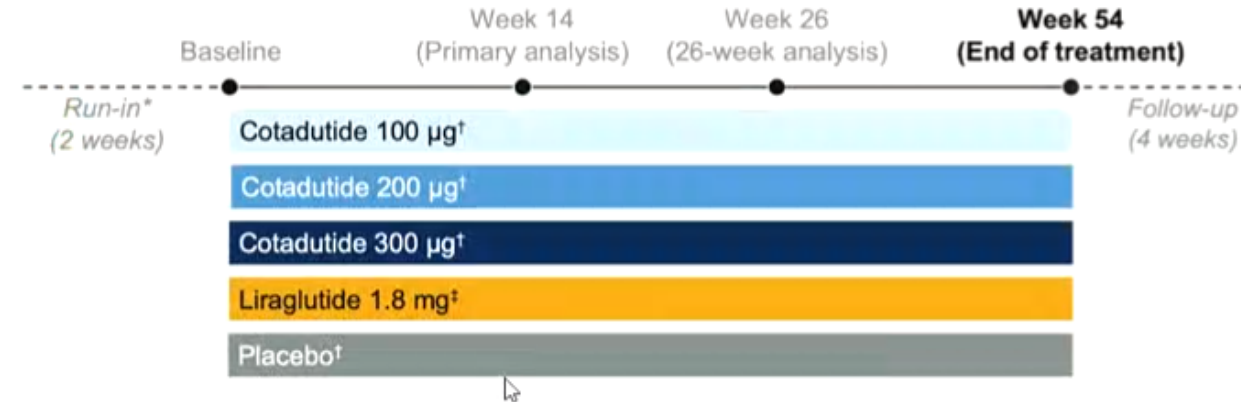


Clinical Validation of dual GLP-1/Glucagon receptor agonists (1)

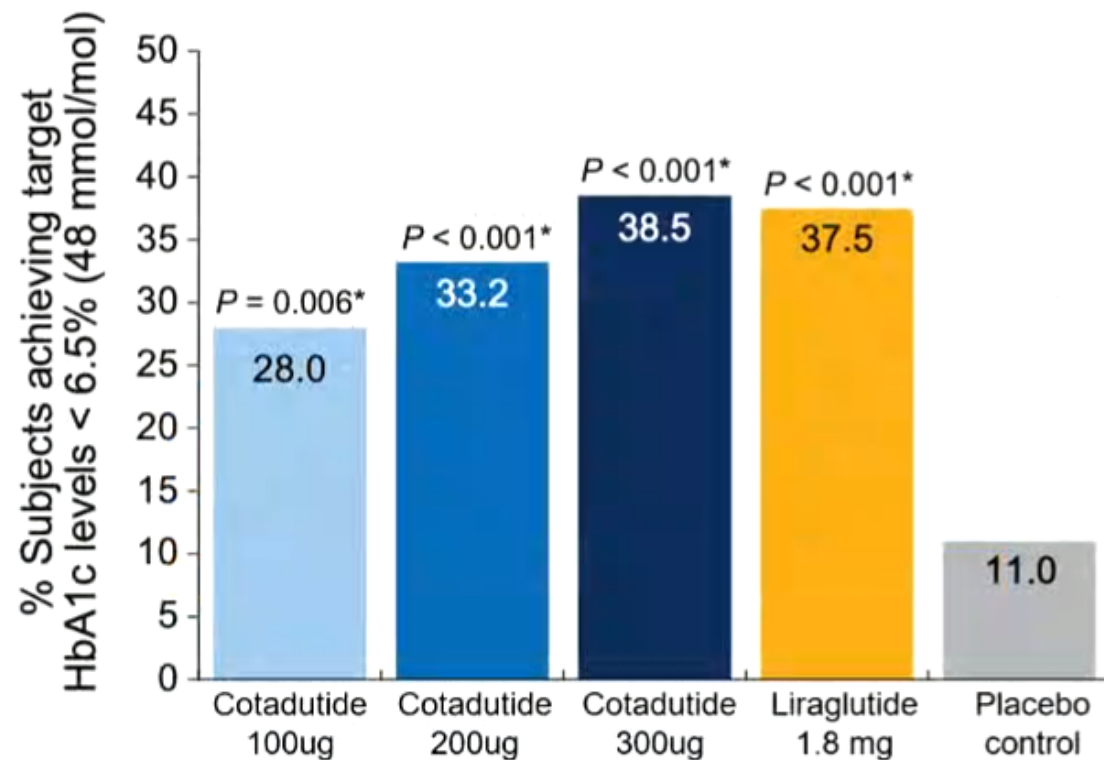
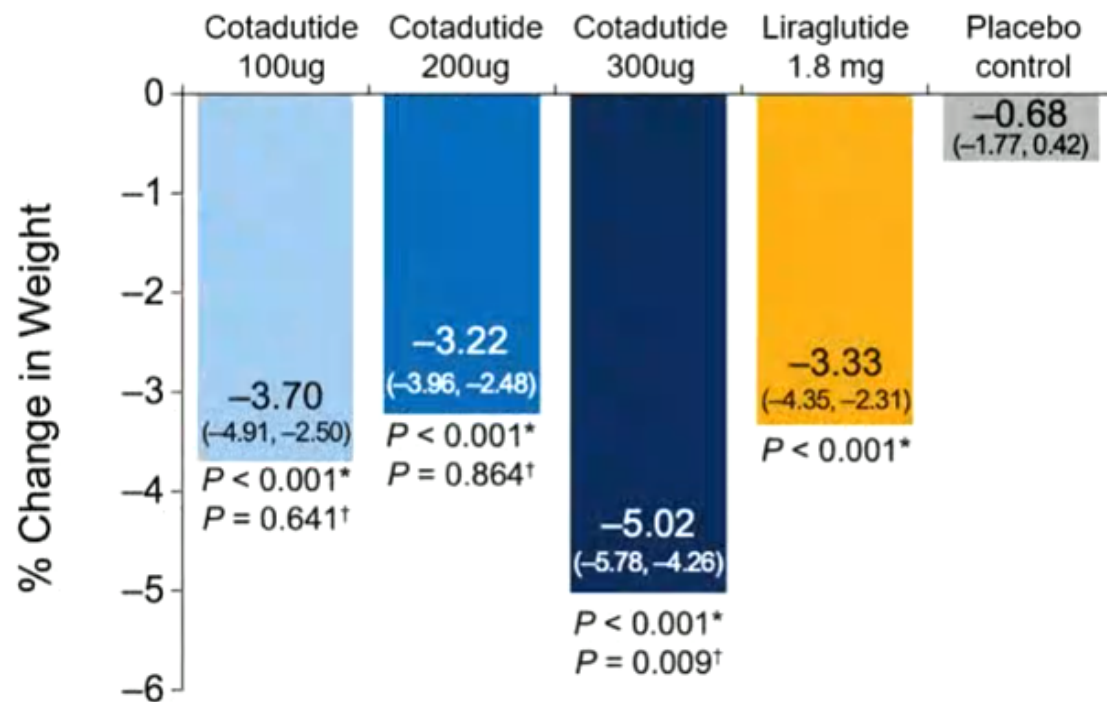
Effects of Cotadutide on Metabolic and Hepatic Parameters in Adults With Overweight or Obesity and Type 2 Diabetes: A 54-Week Randomized Phase 2b Study

Diabetes Care 2021;44:1433–1442 | <https://doi.org/10.2337/dc20-2151>

Rajaa Nahra,¹ Tao Wang,²
Kishore M. Gadde,³ Jan Oscarsson,⁴
Michael Stumvoll,⁵ Lutz Jermutus,⁶
Boaz Hirshberg,⁷ and Philip Ambery⁴



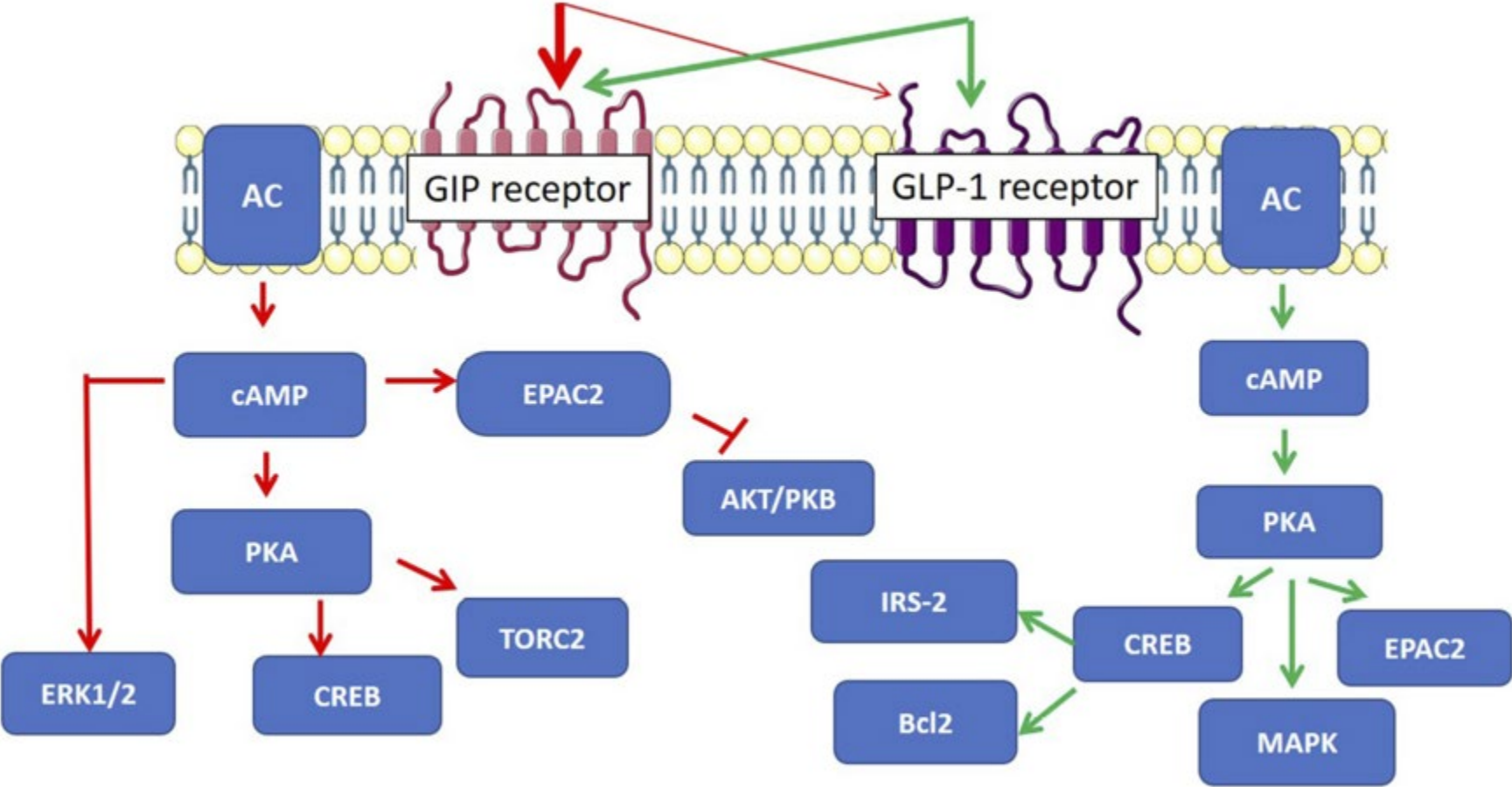
Clinical Validation of dual GLP-1/Glucagon receptor agonists (1): *Body weight & HbA1c*



Modalità di co-agonismo

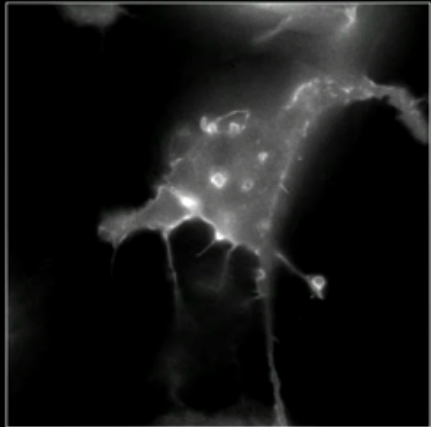
- Bilanciato
- Sbilanciato

Cascata di trasduzione del segnale post-recettoriale

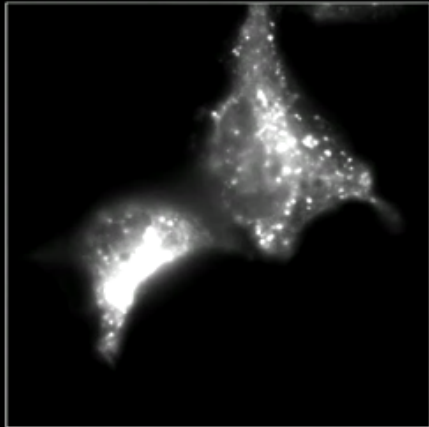


GLP-1/GIP causes faster recycling of the internalized GLP-1R

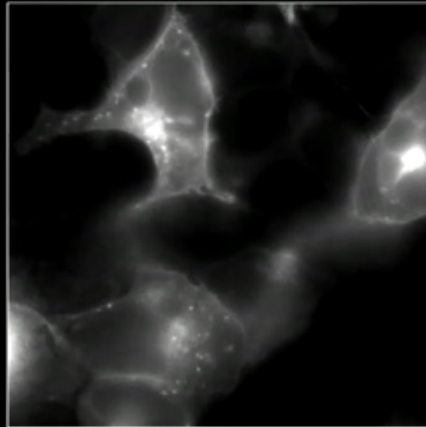
Native GLP-1



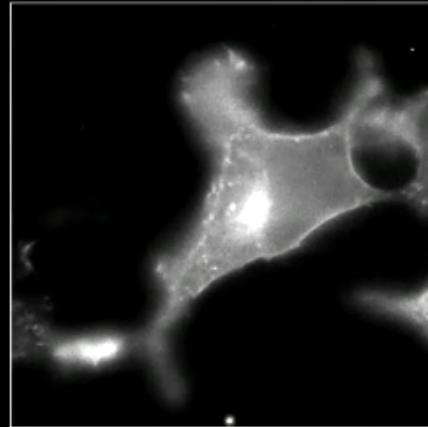
Semaglutide



MAR709



Tirzepatide



Novikoff et al., Mol Metab 2021

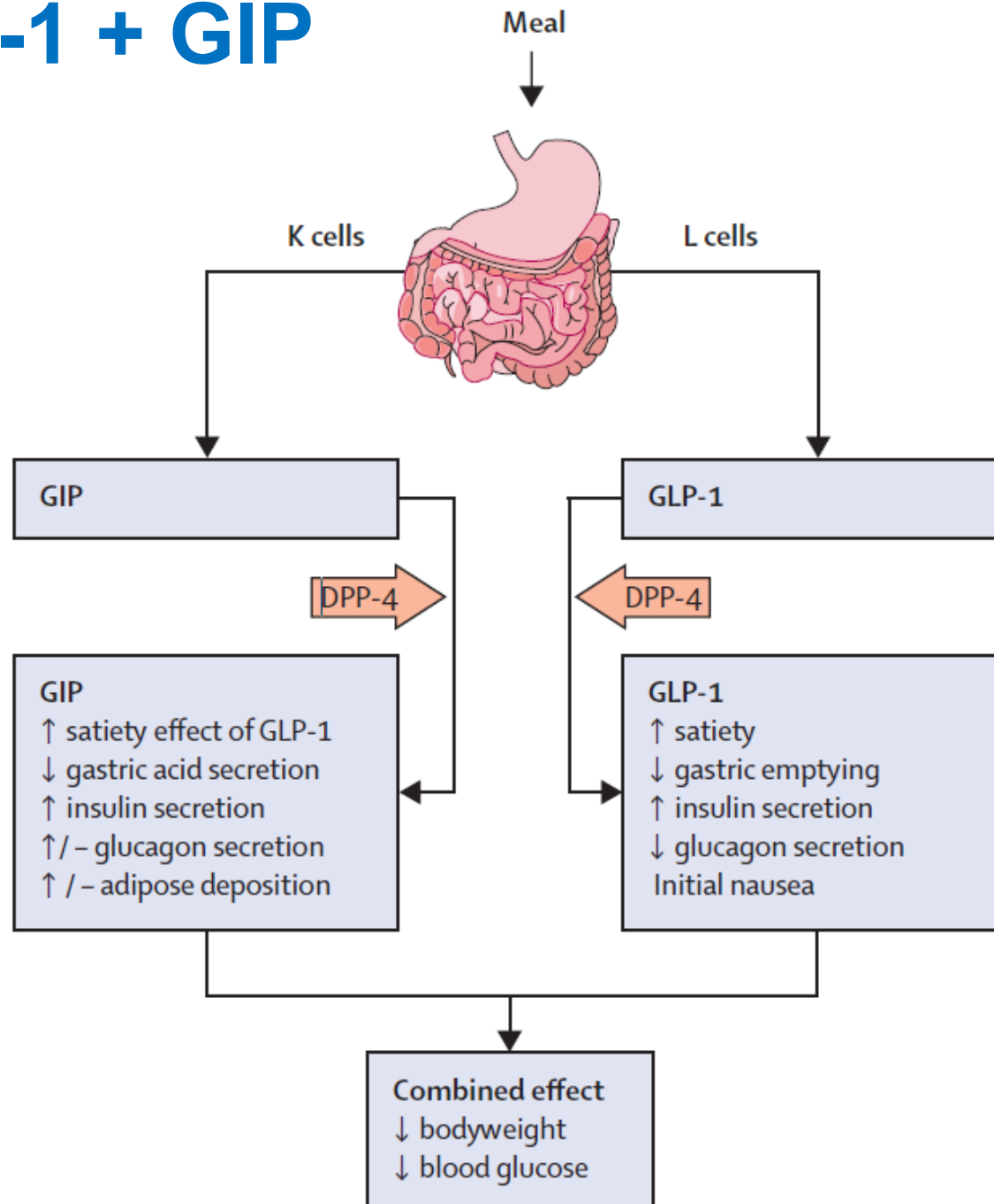


Matthias Tschöp

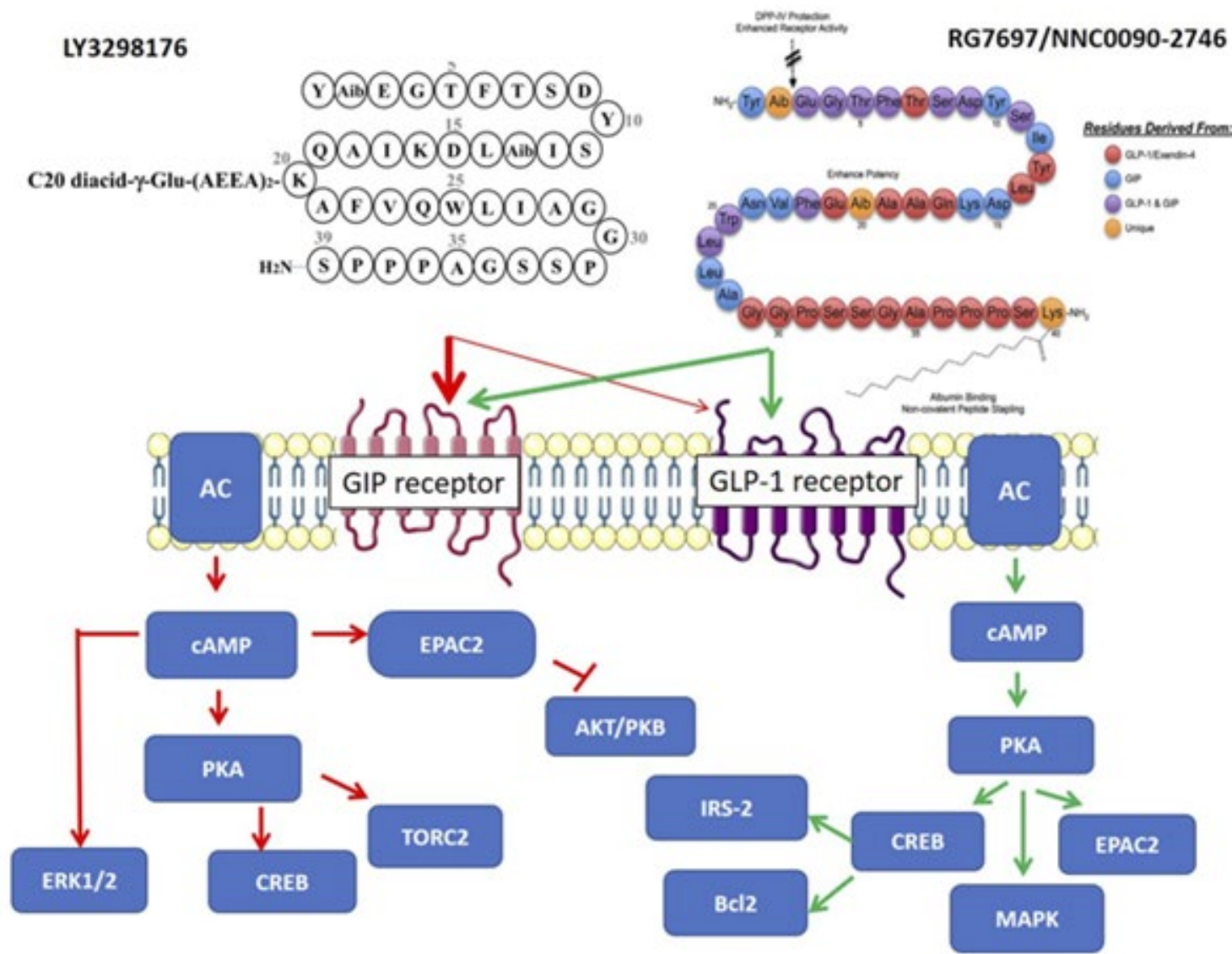
Dual and triple gut hormone co-agonists: From discovery to approval



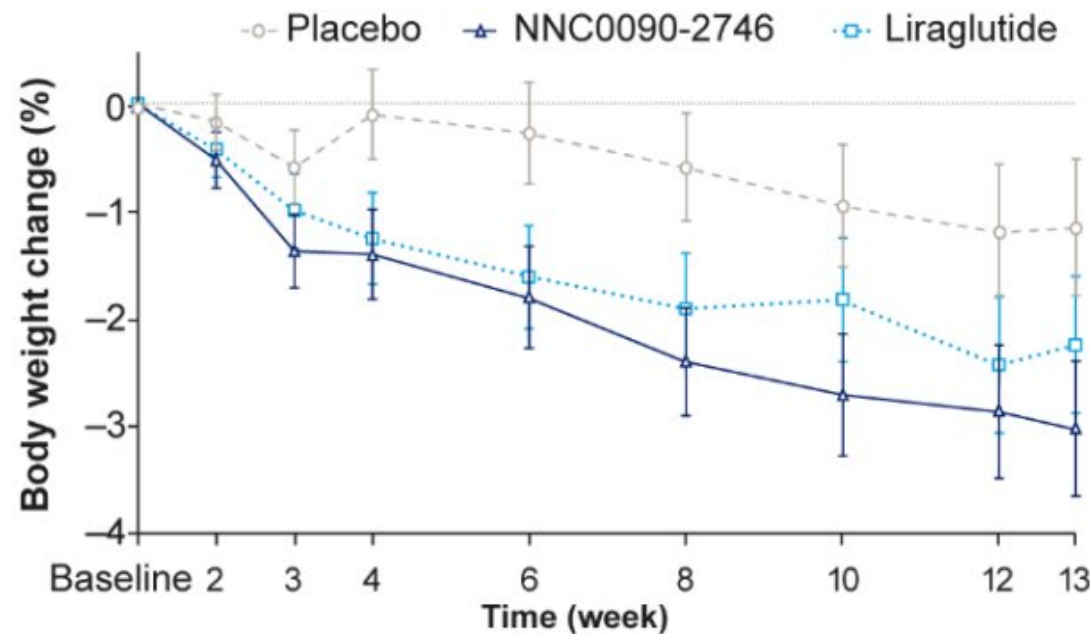
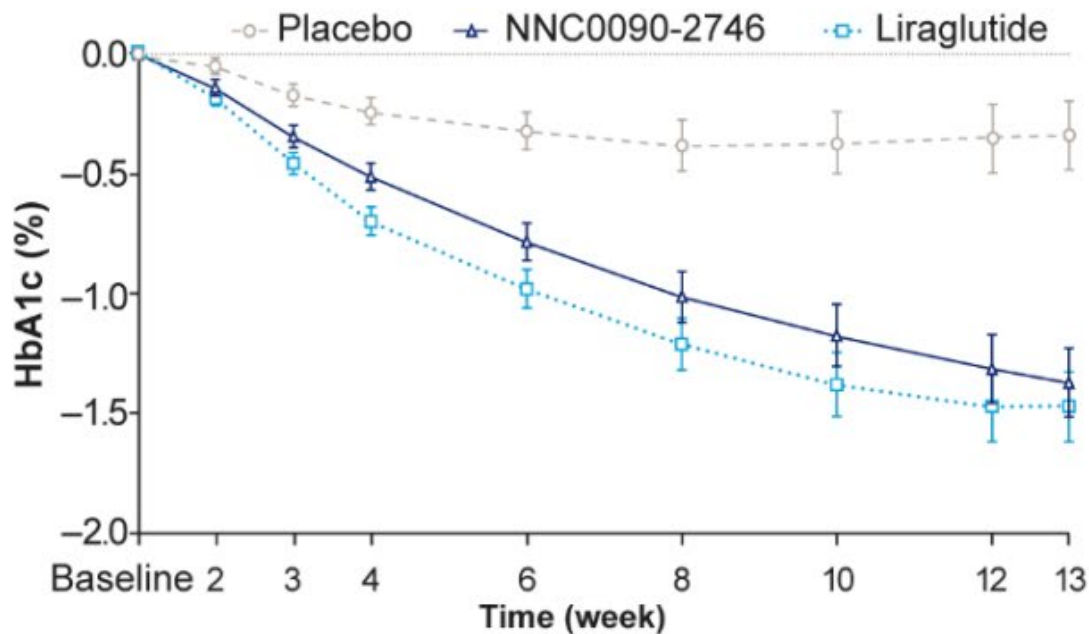
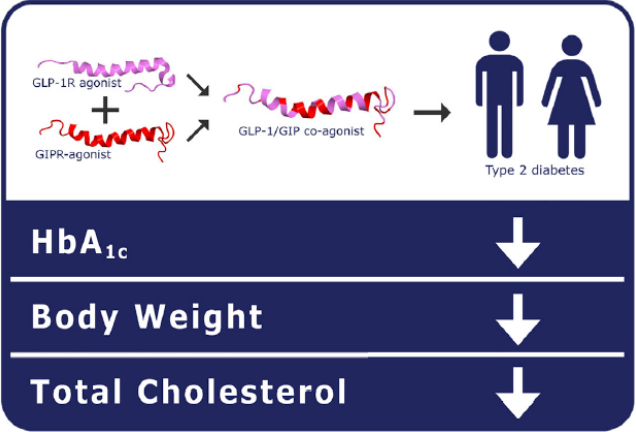
Effetti del GLP-1 + GIP



II co-agonismo



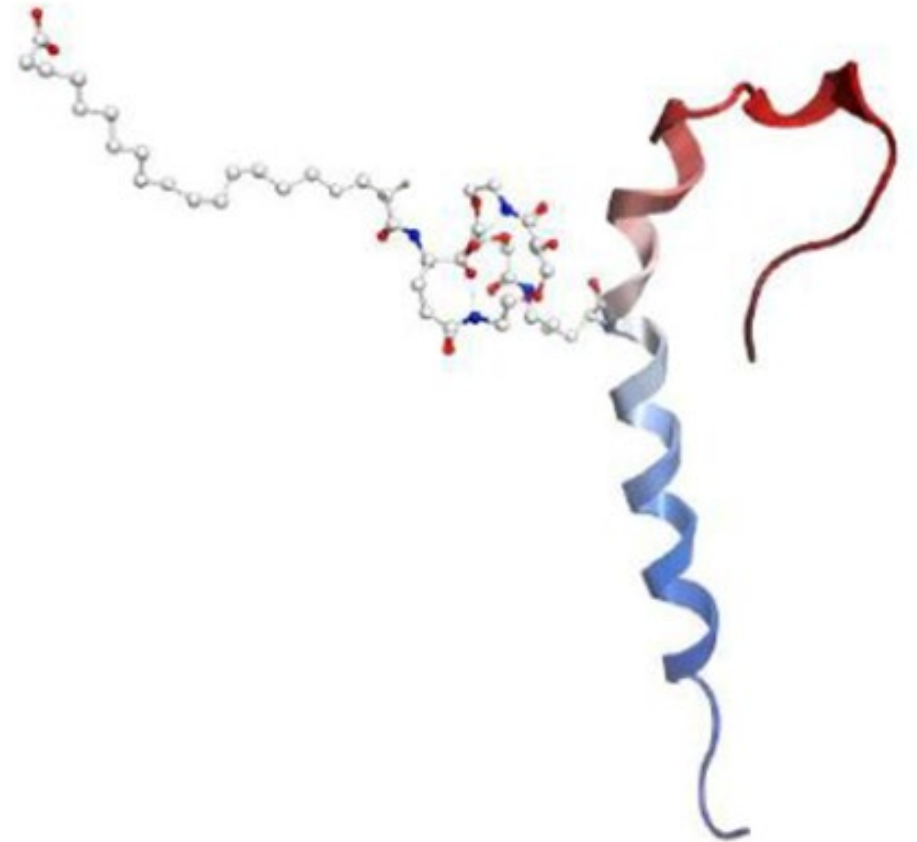
Effetti clinici di un agonista bilanciato



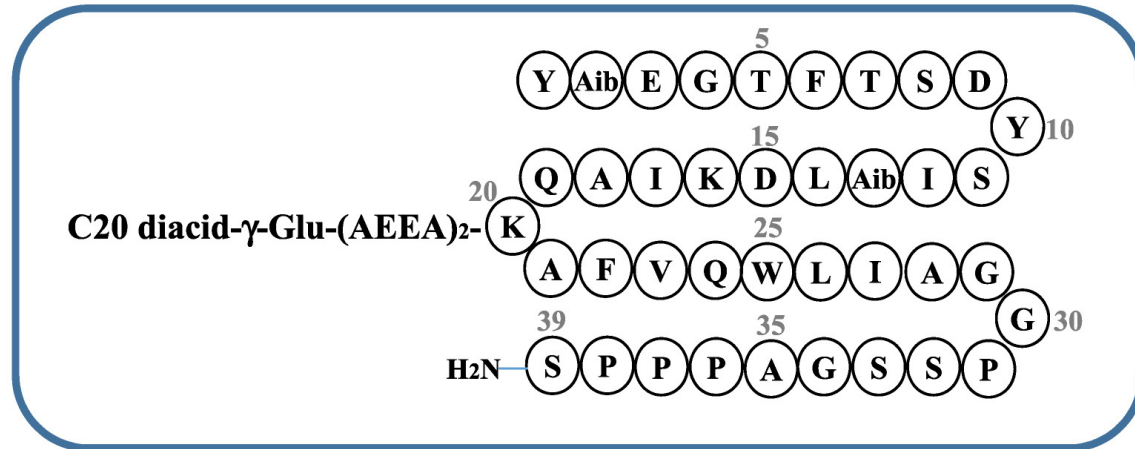
« the reductions in body weight for NNC0090-2746 and liraglutide in this trial were similar »

Tirzepatide

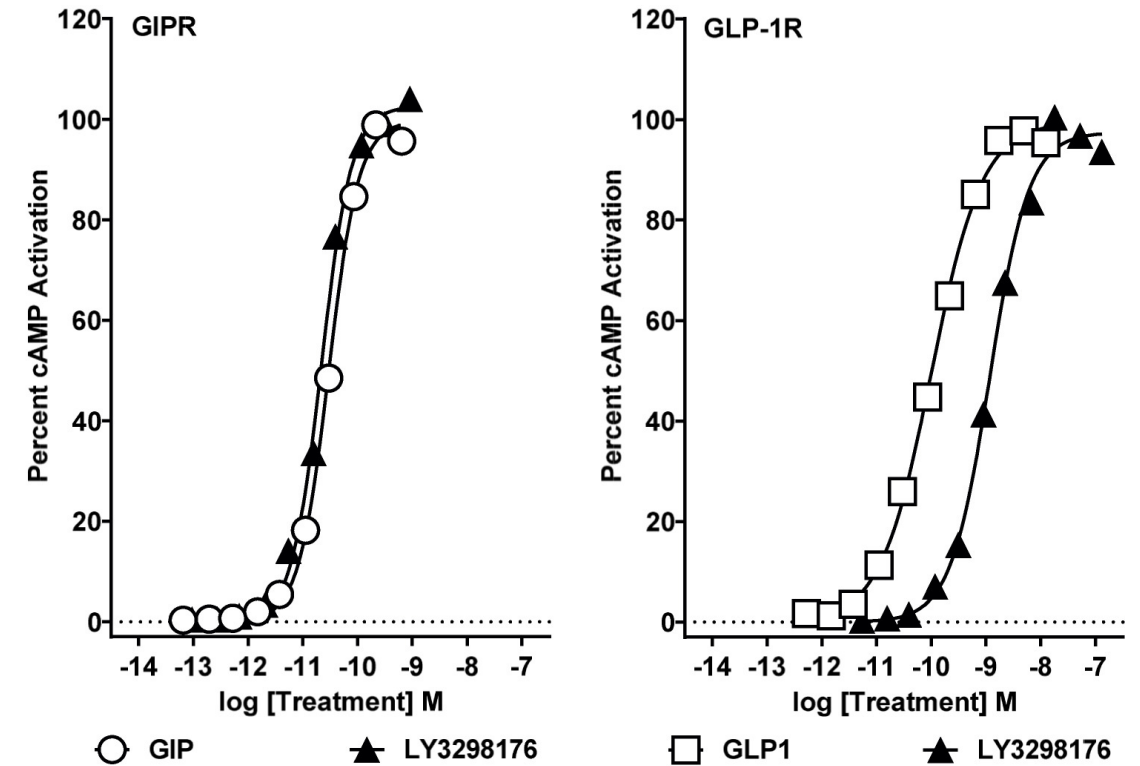
- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIP and GLP-1 receptors
- Tirzepatide is a 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- *In vitro*, it has higher potency to native GIP and is less potent to native GLP-1
- Tirzepatide has a mean half-life of ~5 days, enabling once-weekly dosing



Tirzepatide – effetti GIP e GLP-1



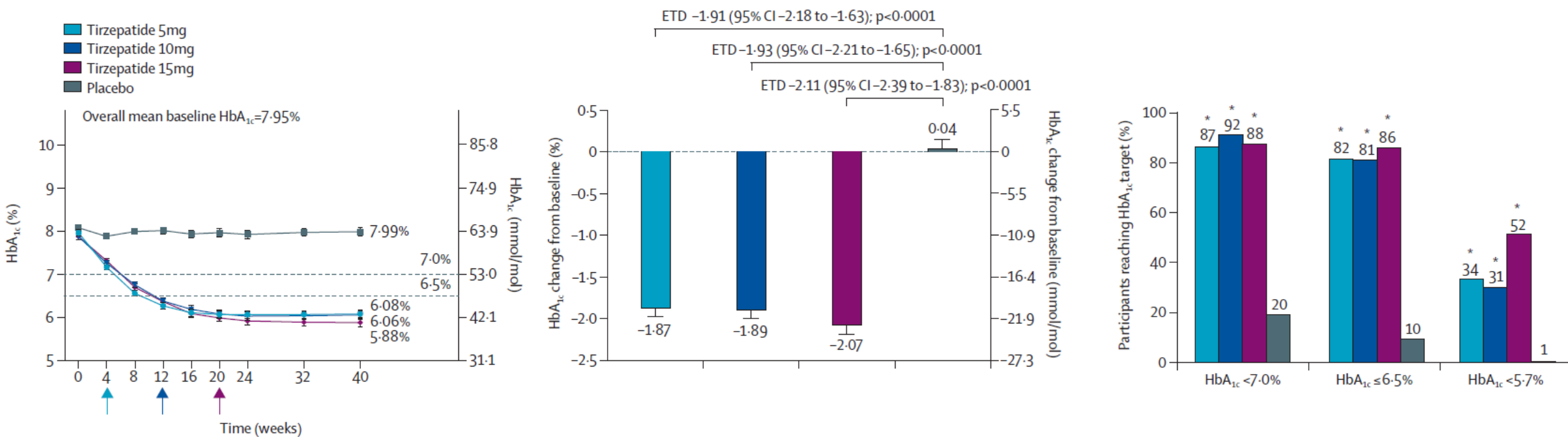
Recombinant human receptor expression



TZP is more active on the GIP than on the GLP-1 receptor

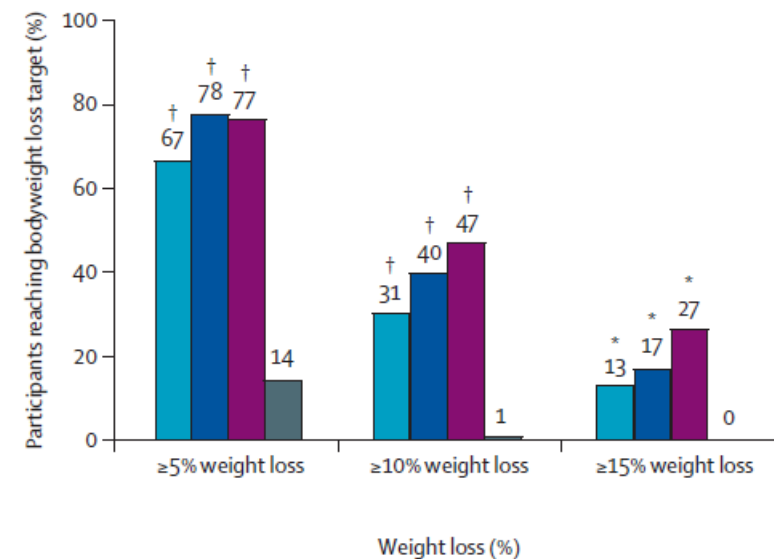
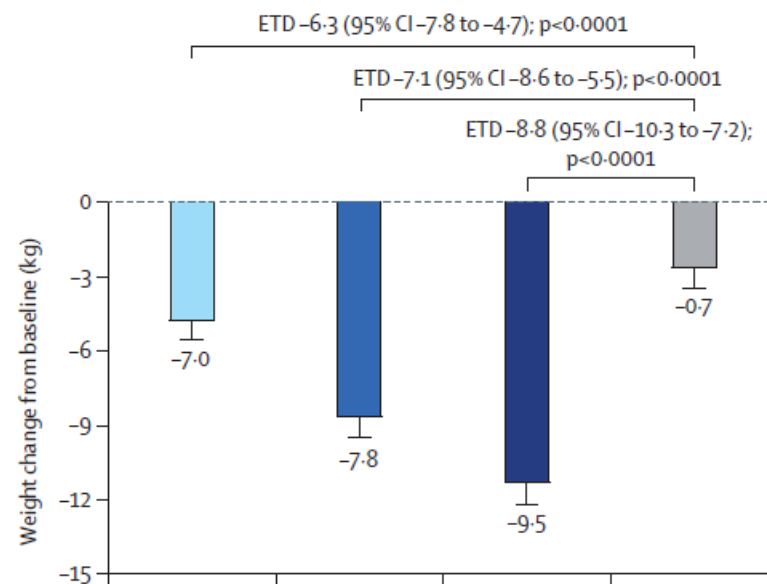
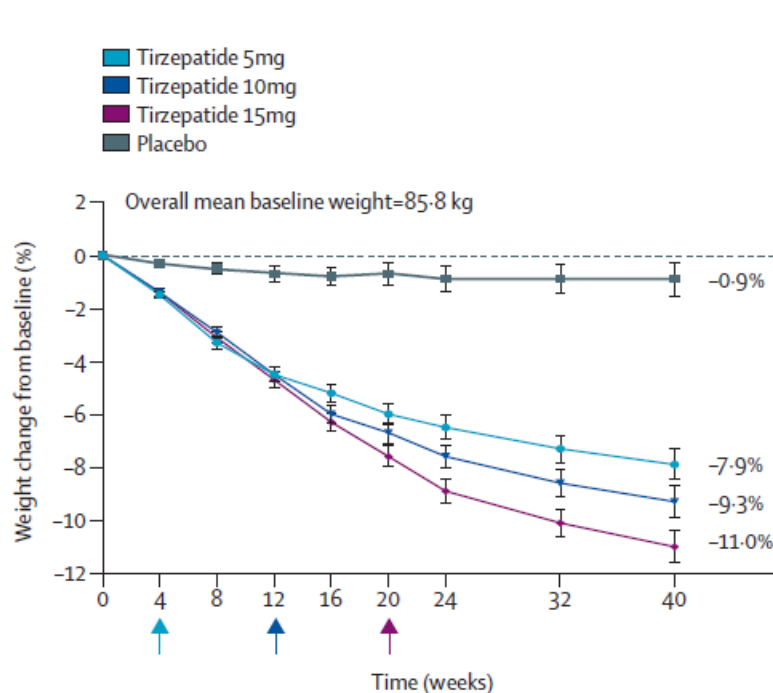
Tirzepatide – studio di fase 3

Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial



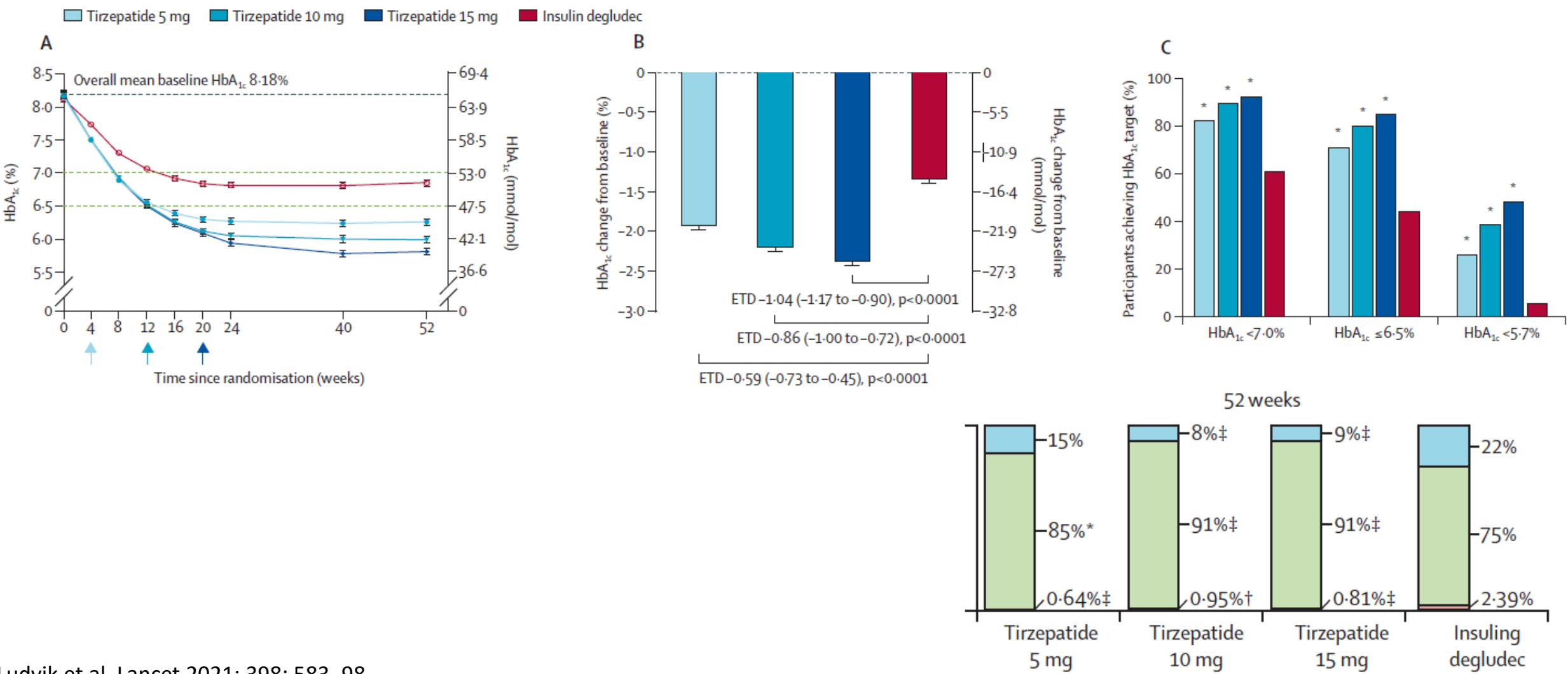
Tirzepatide – studio di fase 3

Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial



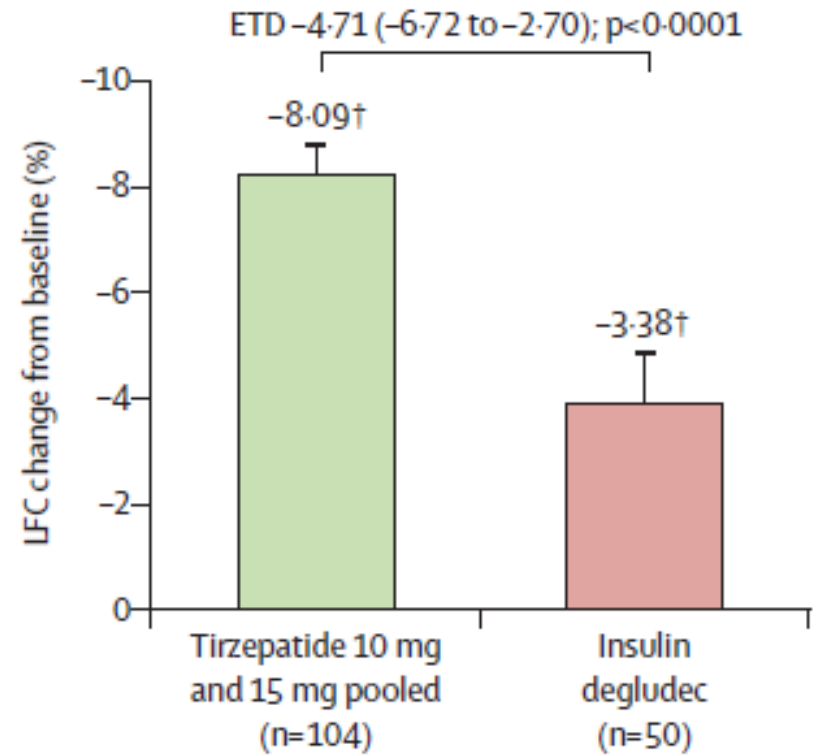
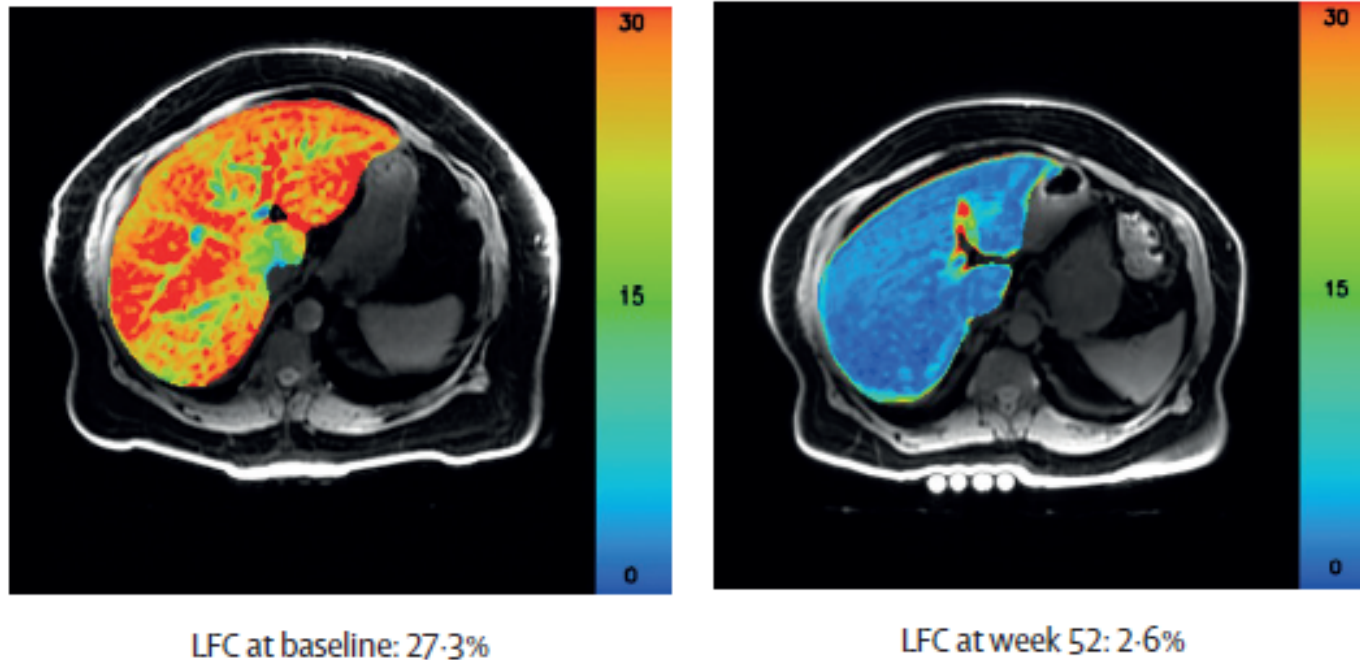
Tirzepatide – studio di fase 3

Once-weekly tirzepatide versus once-daily insulin **degludec** as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (**SURPASS-3**)



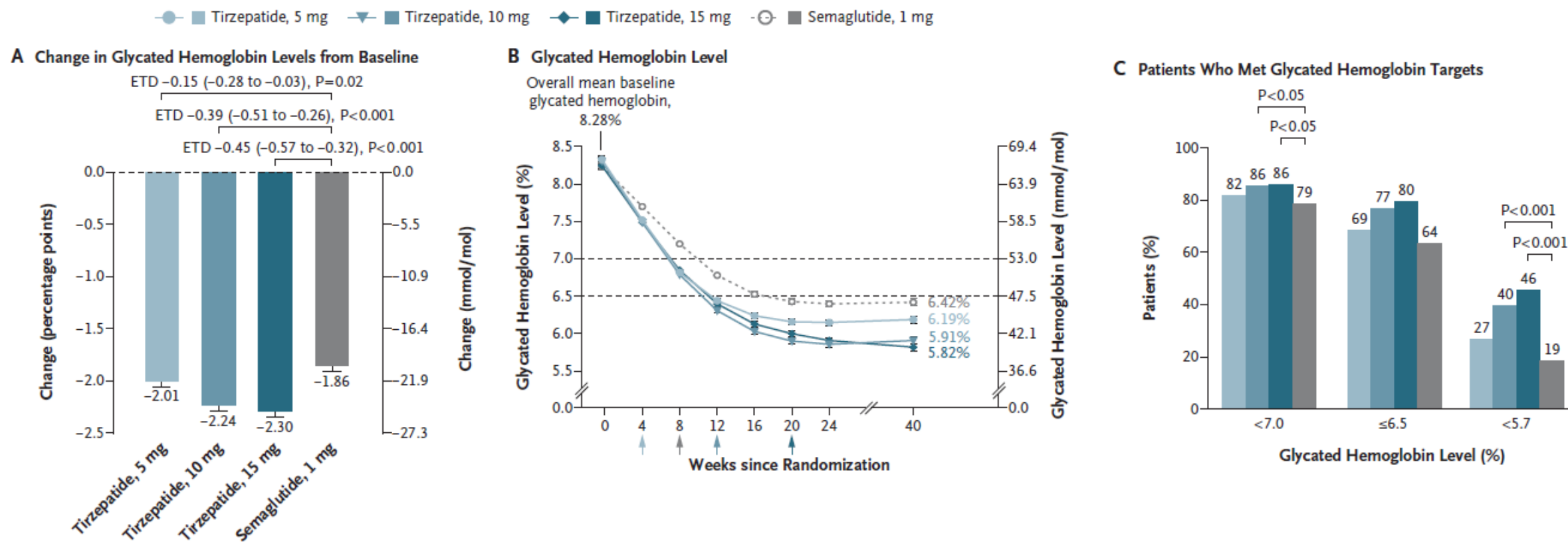
Tirzepatide – studio di fase 3

Once-weekly tirzepatide versus once-daily insulin **degludec** as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (**SURPASS-3**)



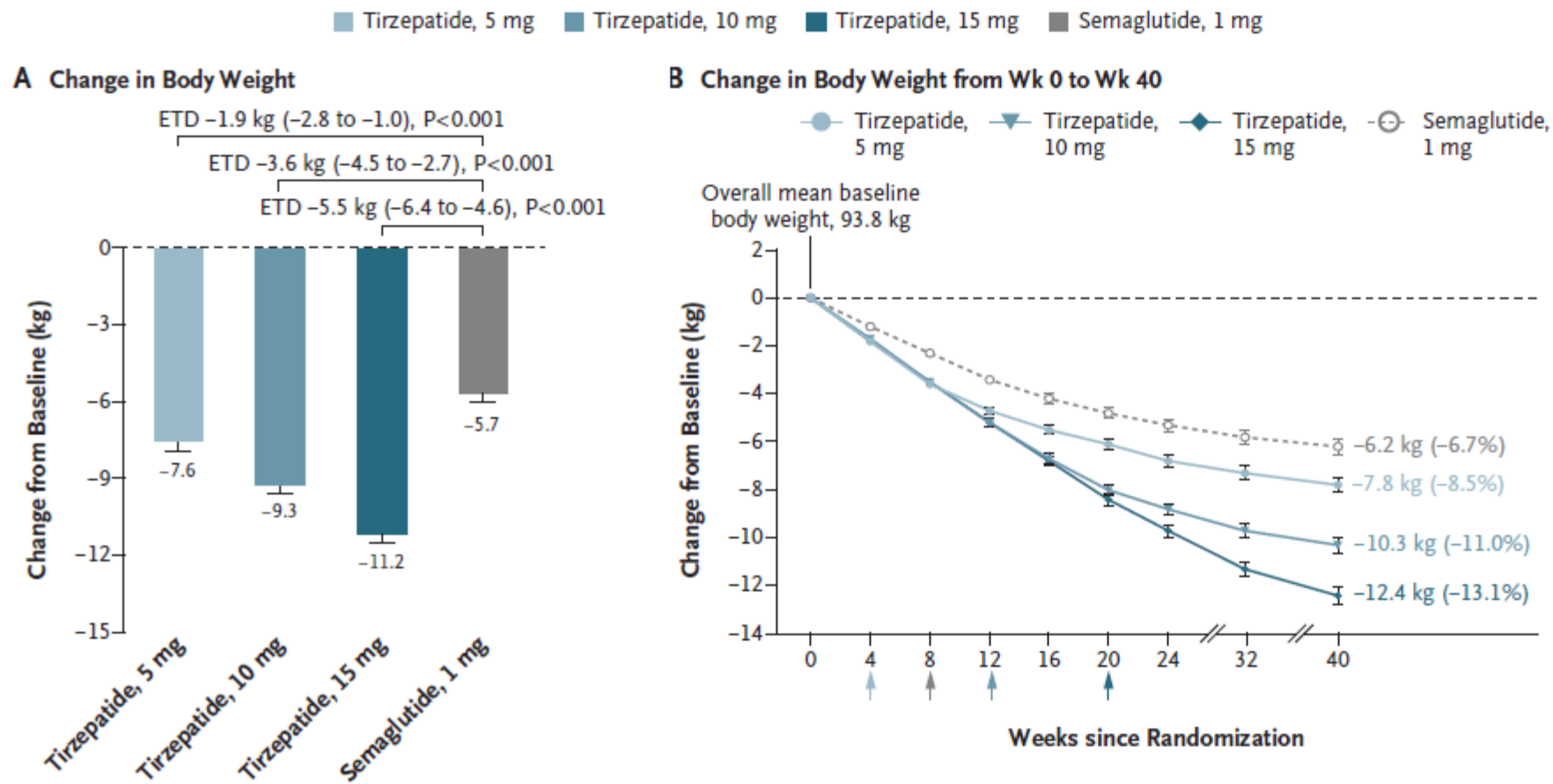
Tirzepatide – studio di fase 3

Tirzepatide versus **Semaglutide** Once Weekly in Patients with Type 2 Diabetes
SURPASS-2



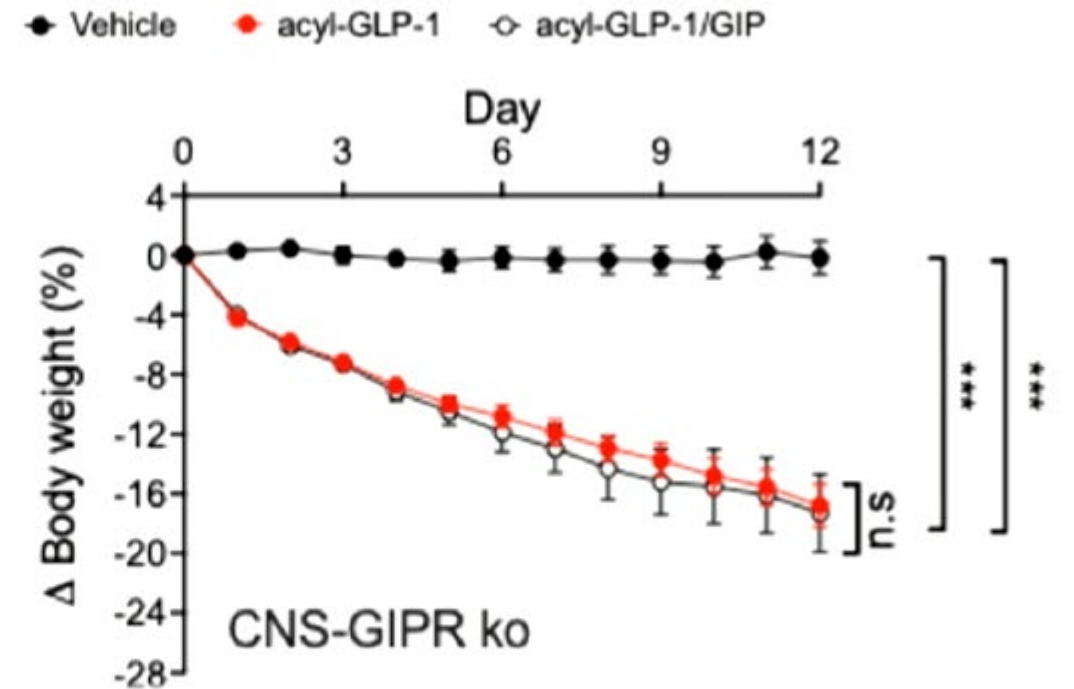
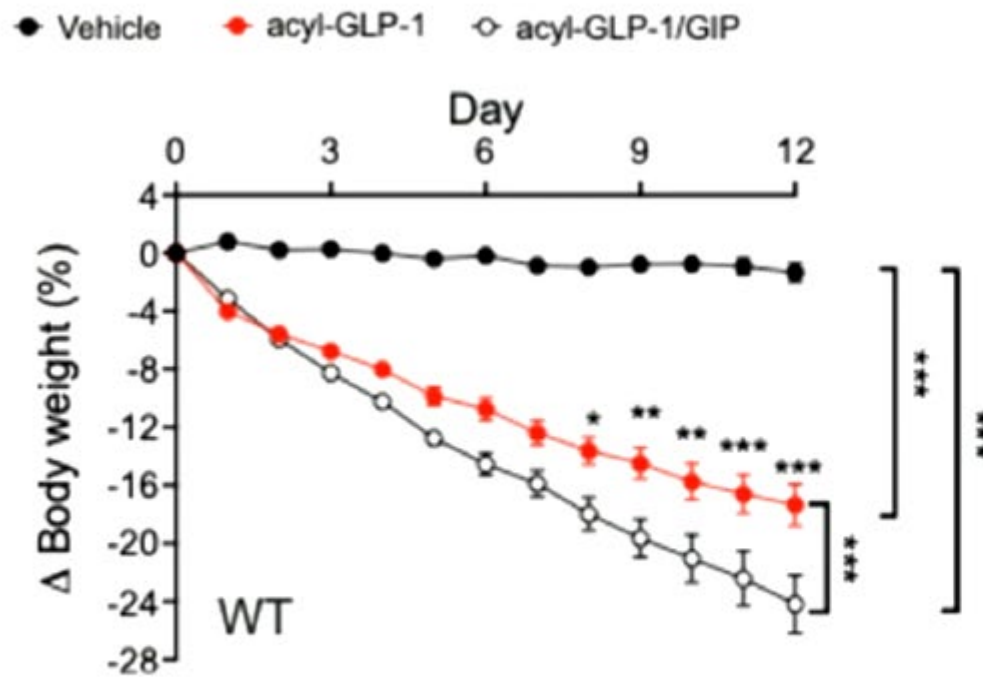
Tirzepatide – studio di fase 3

Tirzepatide versus **Semaglutide** Once Weekly in Patients with Type 2 Diabetes
SURPASS-2



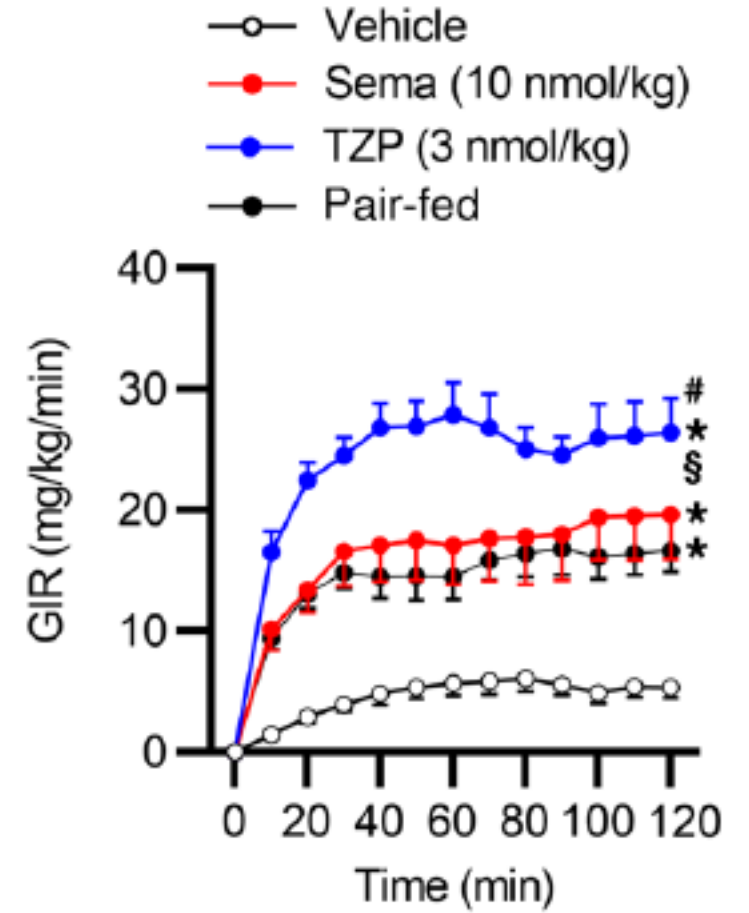
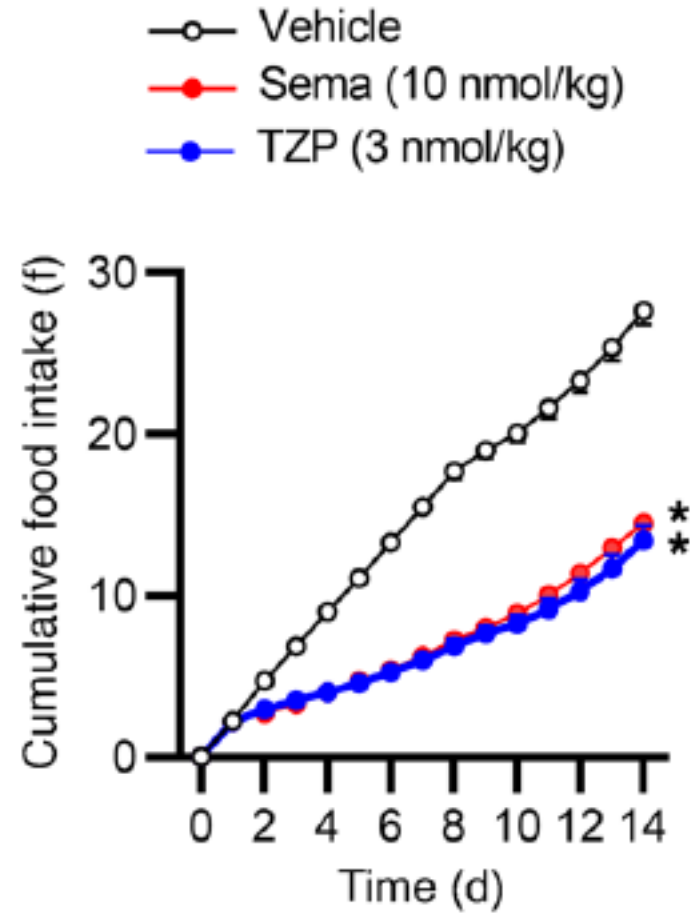
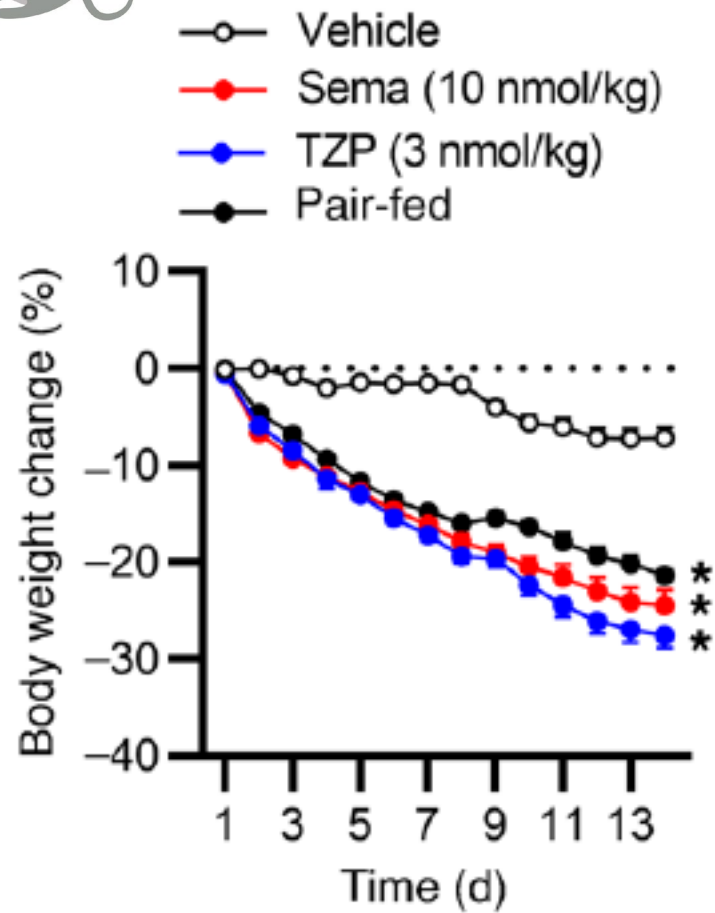
GIPR nel SNC ed effetto dell'agonista

GIPR/GLPR sul peso

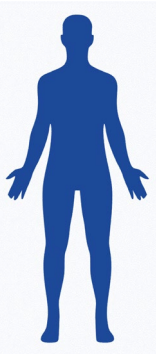


Nestin-cre mediated CNS-GIPR ko

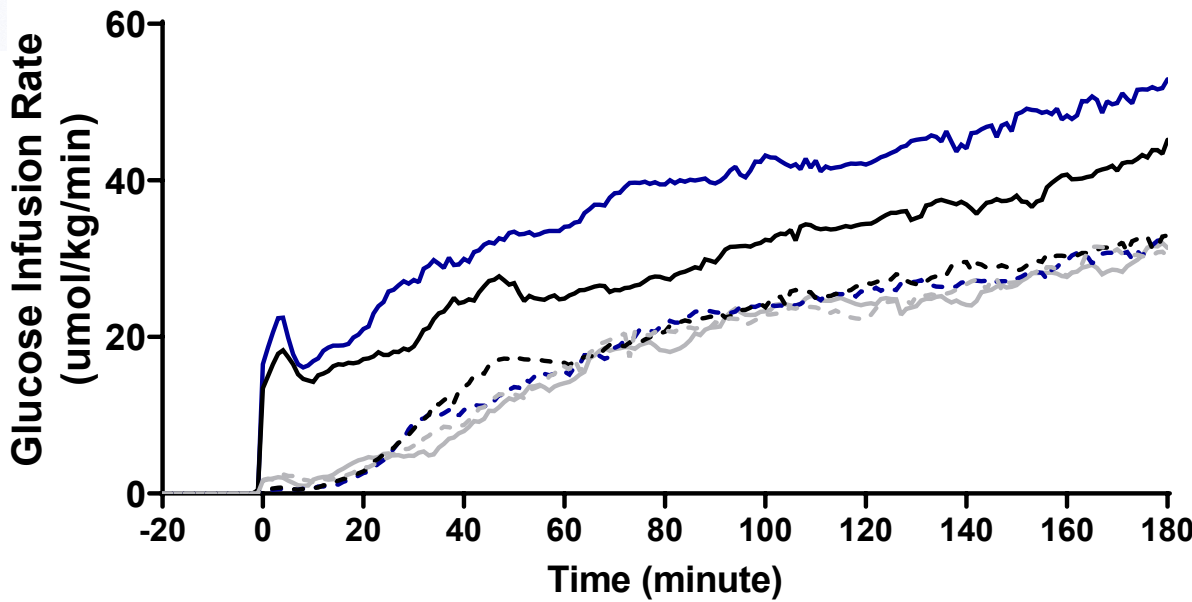
Tirzepatide – effetto insulino-sensibilizzante?



Tirzepatide – effetto insulino-sensibilizzante

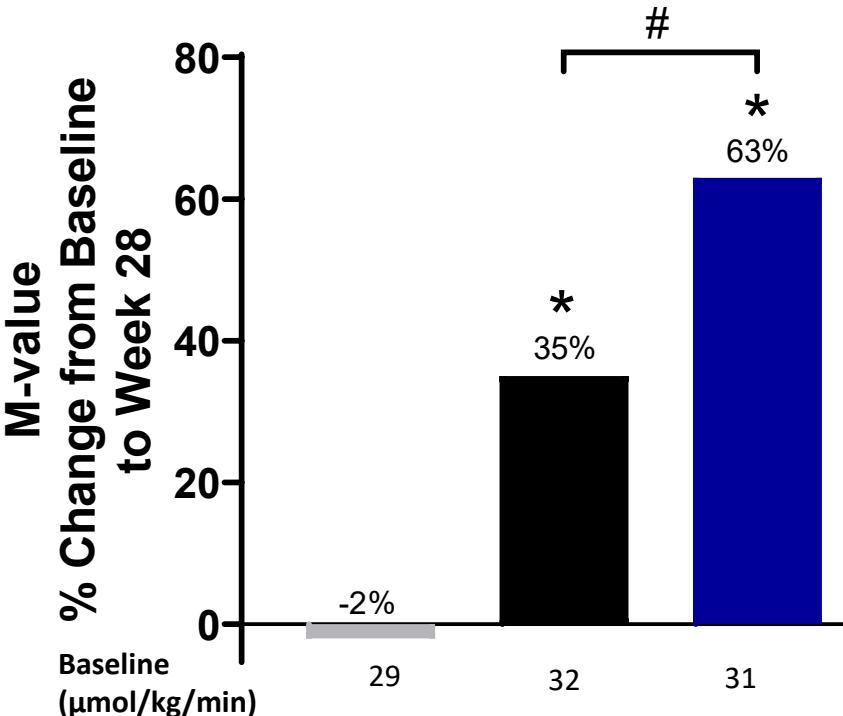


Glucose Infusion Rate

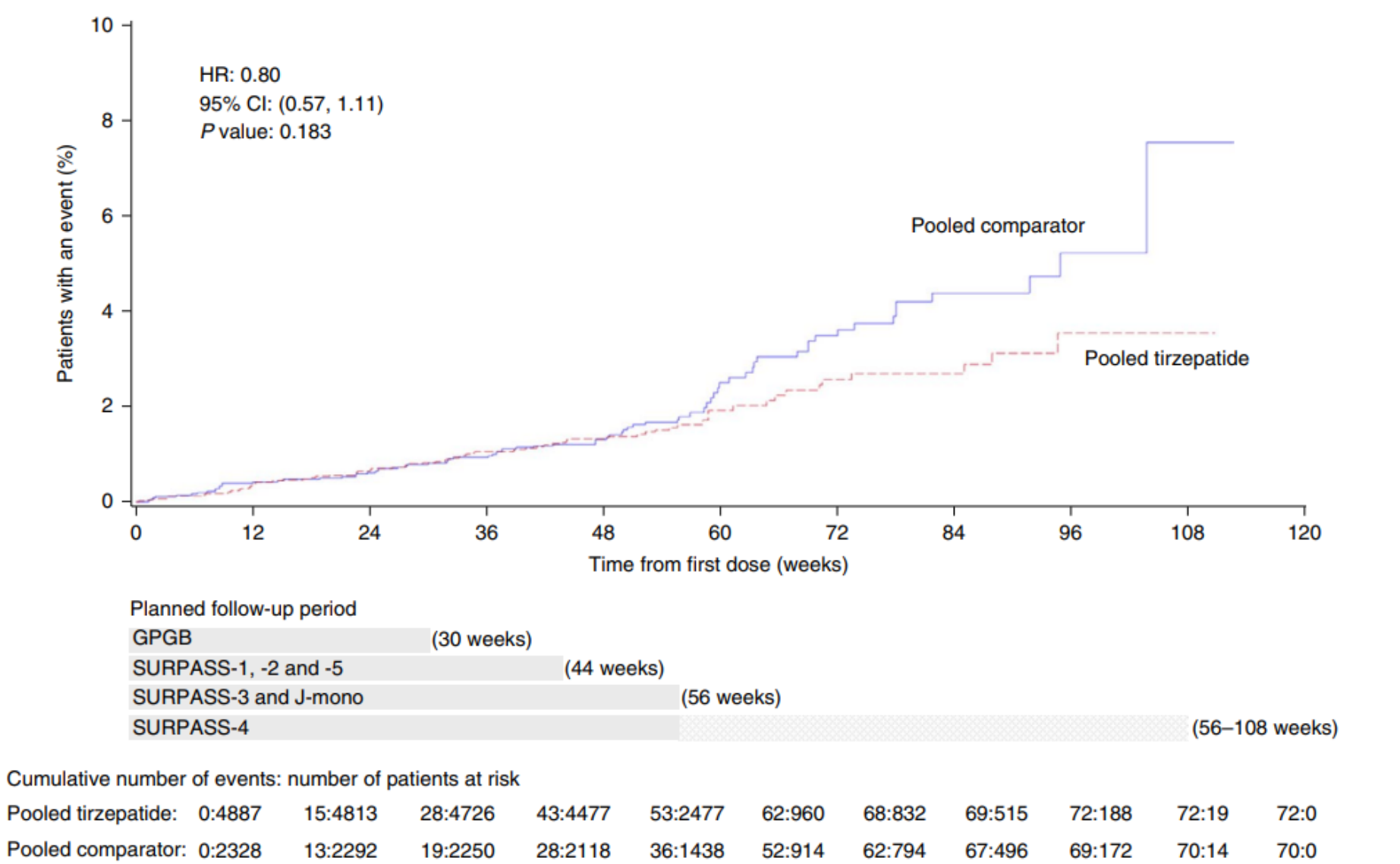


■ Placebo ■ Semaglutide 1.0mg ■ Tirzepatide 15mg
Dashed: baseline Solid: Week 28

Whole-body Insulin Sensitivity

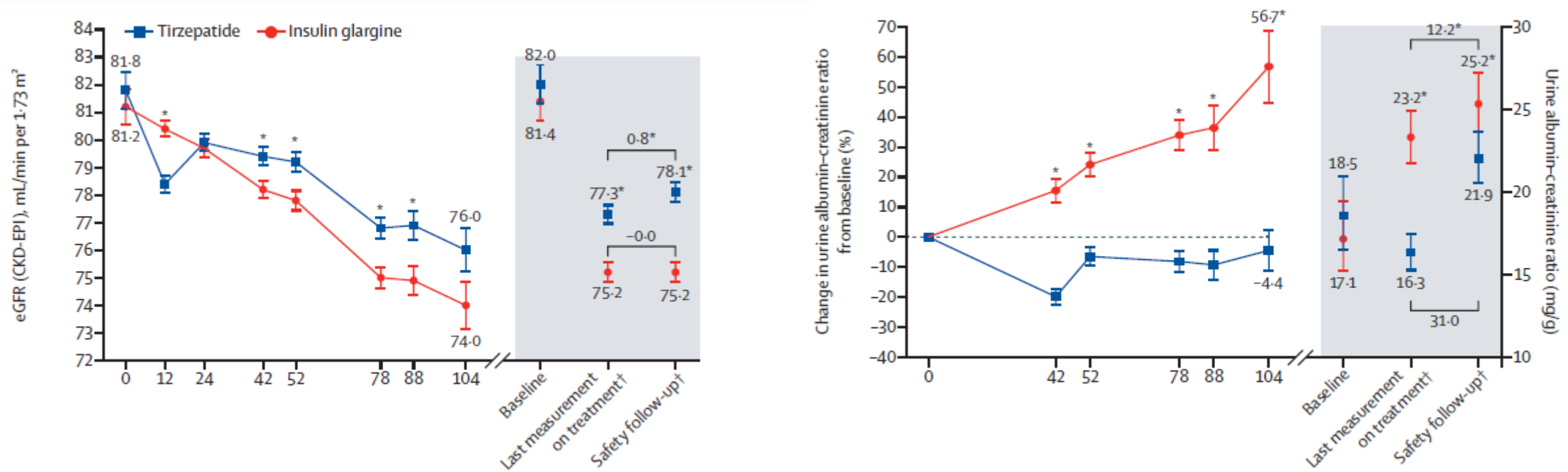


Tirzepatide – eventi cardiovascolari



Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial

Hiddo J L Heerspink, Naveed Sattar, Imre Pavo, Axel Haupt, Kevin L Duffin, Zhengyu Yang, Russell J Wiese, Katherine R Tuttle, David Z I Cherney

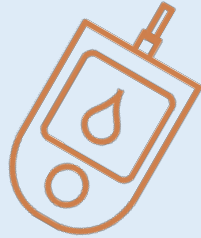
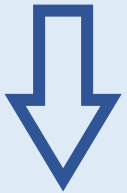


Significantly lower occurrence of the composite kidney endpoint
HR 0.58 (95% CI 0.43 to 0.80)

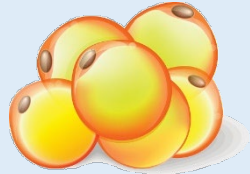
Twinciretin (TZP)



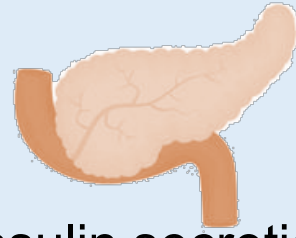
Weight



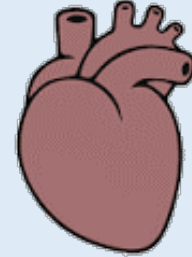
Glycemia



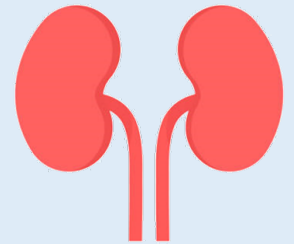
Weight



Insulin secretion
/ sensitivity



CV protection?



Renal
protection?