OK per GLP-1 RA. Ma insieme a chi?

GIP (e anti-GIP)

Francesco Giorgino, M.D., Ph.D.
Professor of Endocrinology

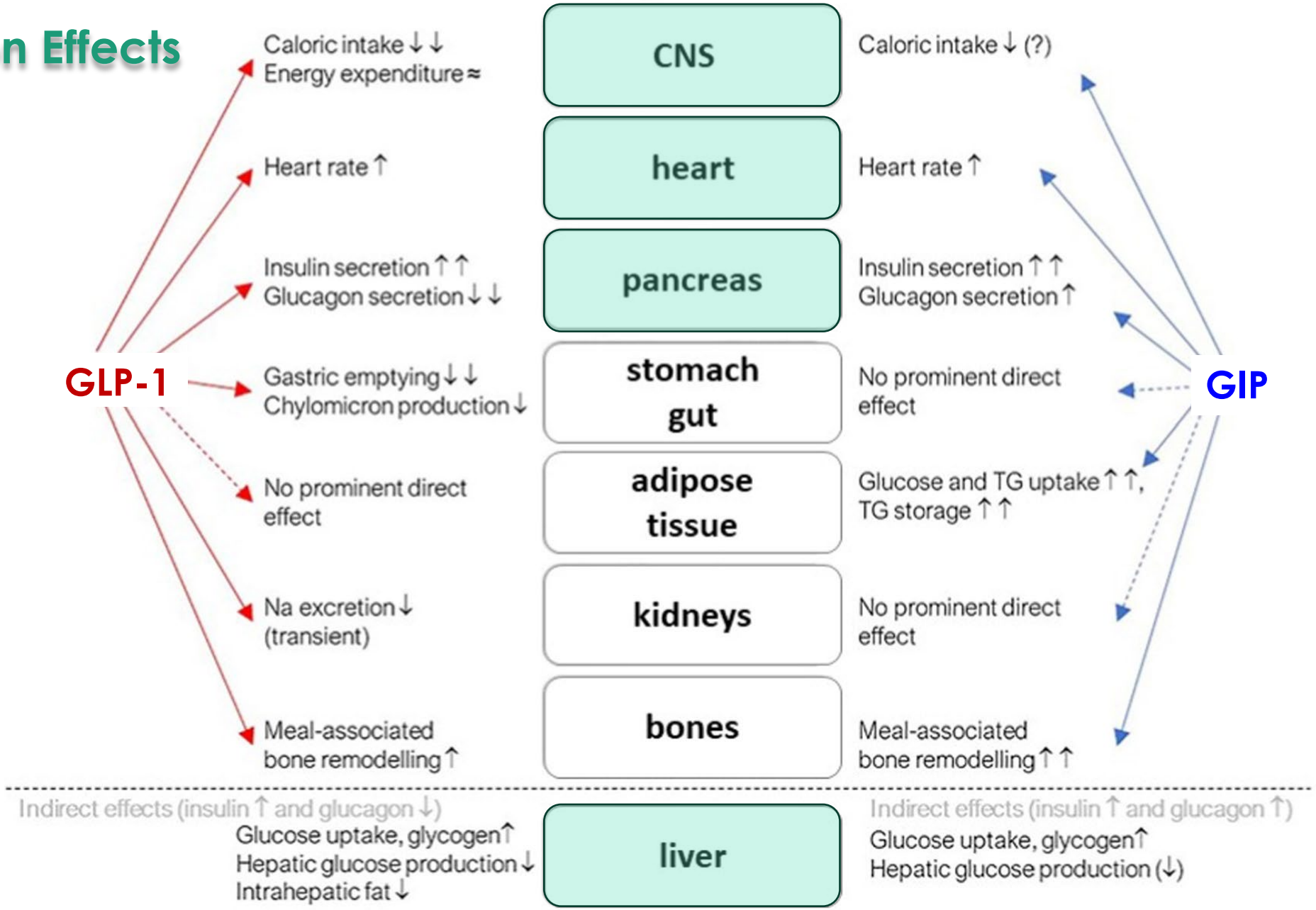
Department of Precision and Regenerative Medicine and Ionian Area
Section of Internal Medicine, Endocrinology,
Andrology and Metabolic Diseases

UNIVERSITÀ
DEGLI STUDI DI BARI
ALDO MORO

Disclosures

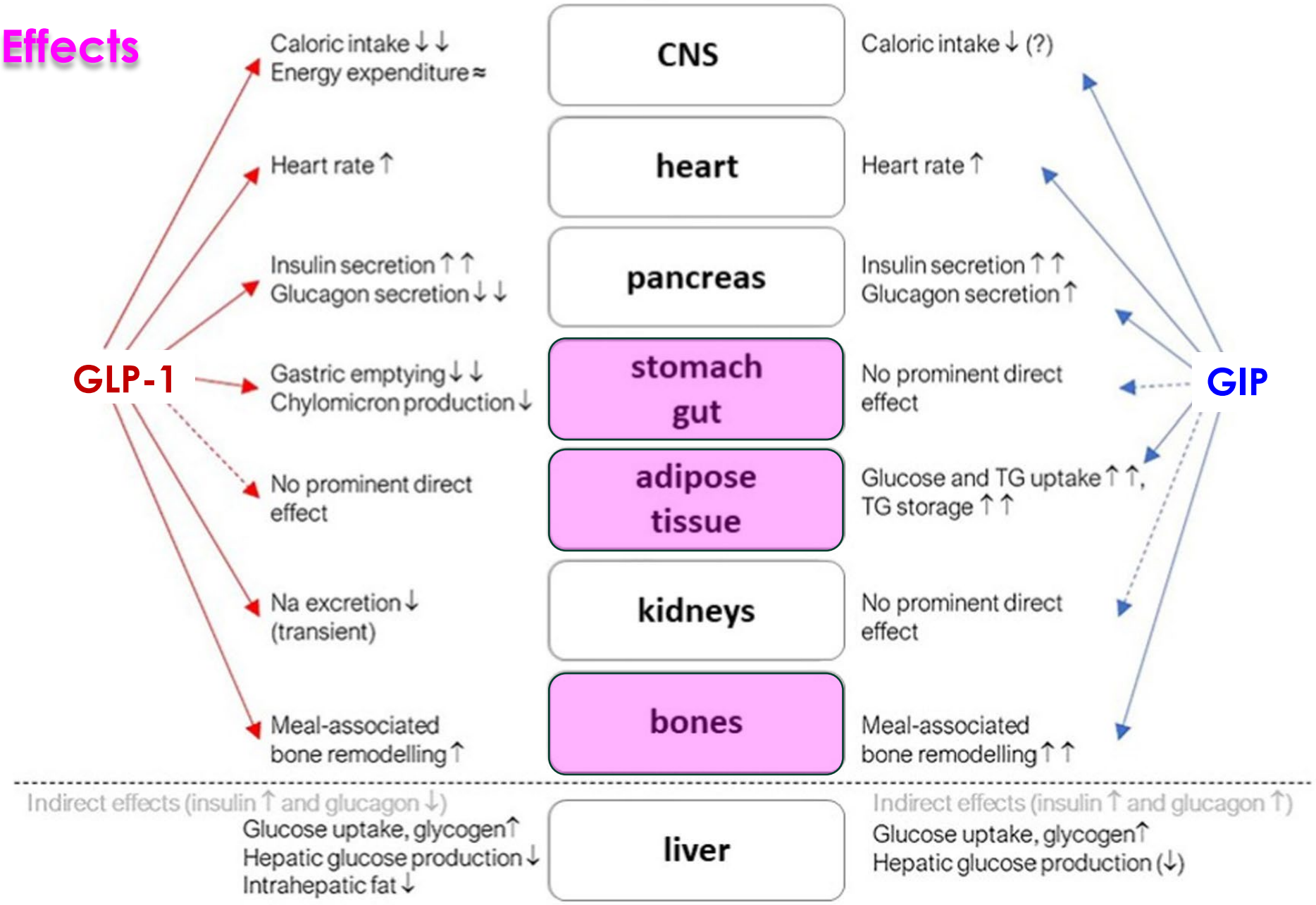
- **Advisory Boards**: AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Lifescan, Merck Sharp & Dohme, Medimmune, Medtronic, NovoNordisk, Roche Diabetes Care, Sanofi
- **Other Boards**: Senior Vice-President of the European Association for the Study of Diabetes (EASD)/European Foundation for the Study of Diabetes (EFSD)
- **Consultant**: Eli Lilly, NovoNordisk
- **Lectures, presentations, or educational events**: AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Lifescan, Merck Sharp & Dohme, Medtronic, NovoNordisk, Roche Diabetes Care, Sanofi
- **Research Support**: Eli Lilly, Roche Diabetes Care
- **Receipt of Medical Writing or Support for Statistical Analysis**: AstraZeneca, Eli Lilly, NovoNordisk, Roche Diabetes Care, Sanofi

Common Effects



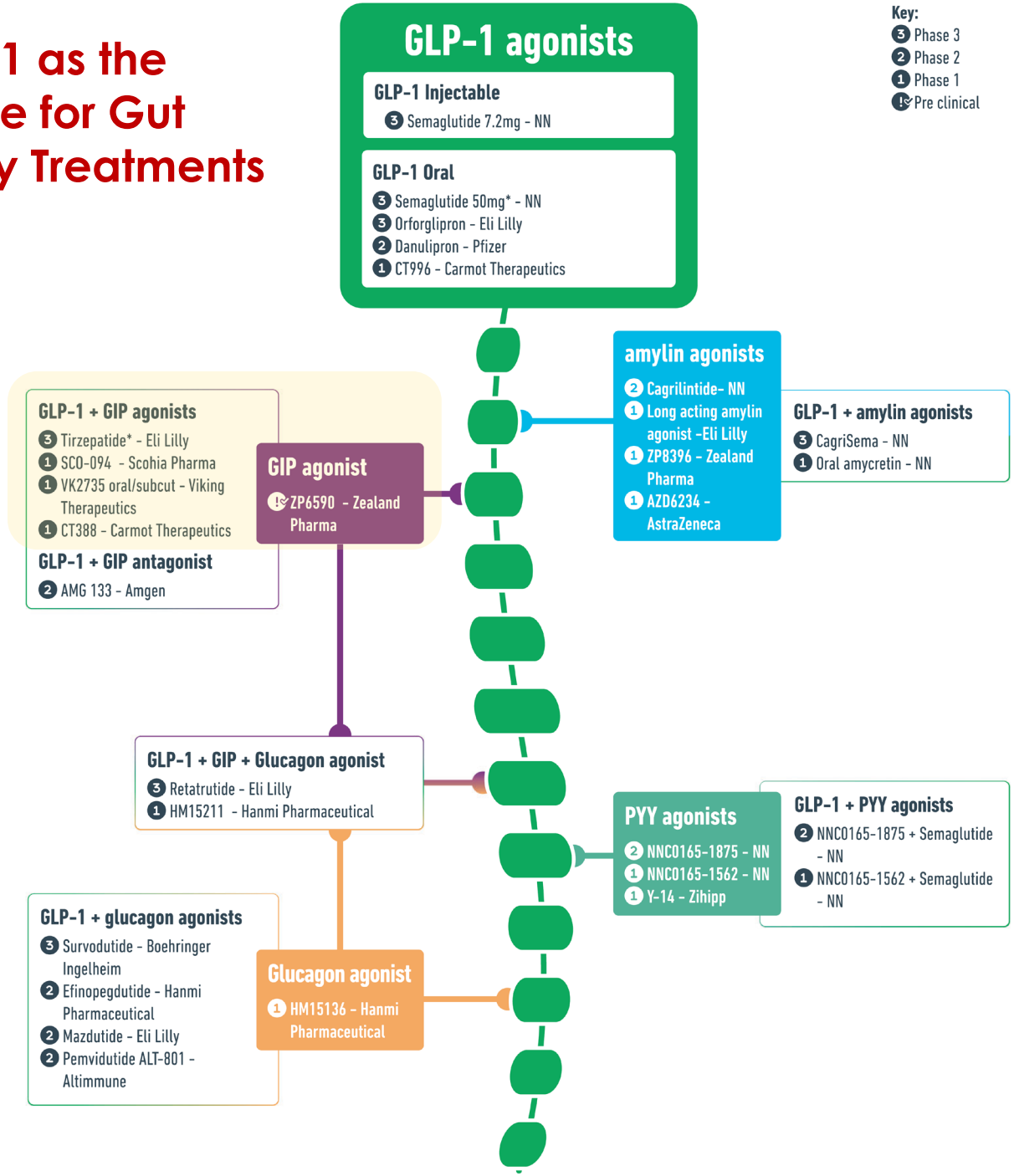
Blüher M, …, Giorgino F, *Endocrinol Diab Metab* 2022

Distinct Effects



Blüher M, …, Giorgino F, *Endocrinol Diab Metab* 2022

Glucagon-like peptide-1 as the Backbone of the Pipeline for Gut Hormone-based Obesity Treatments

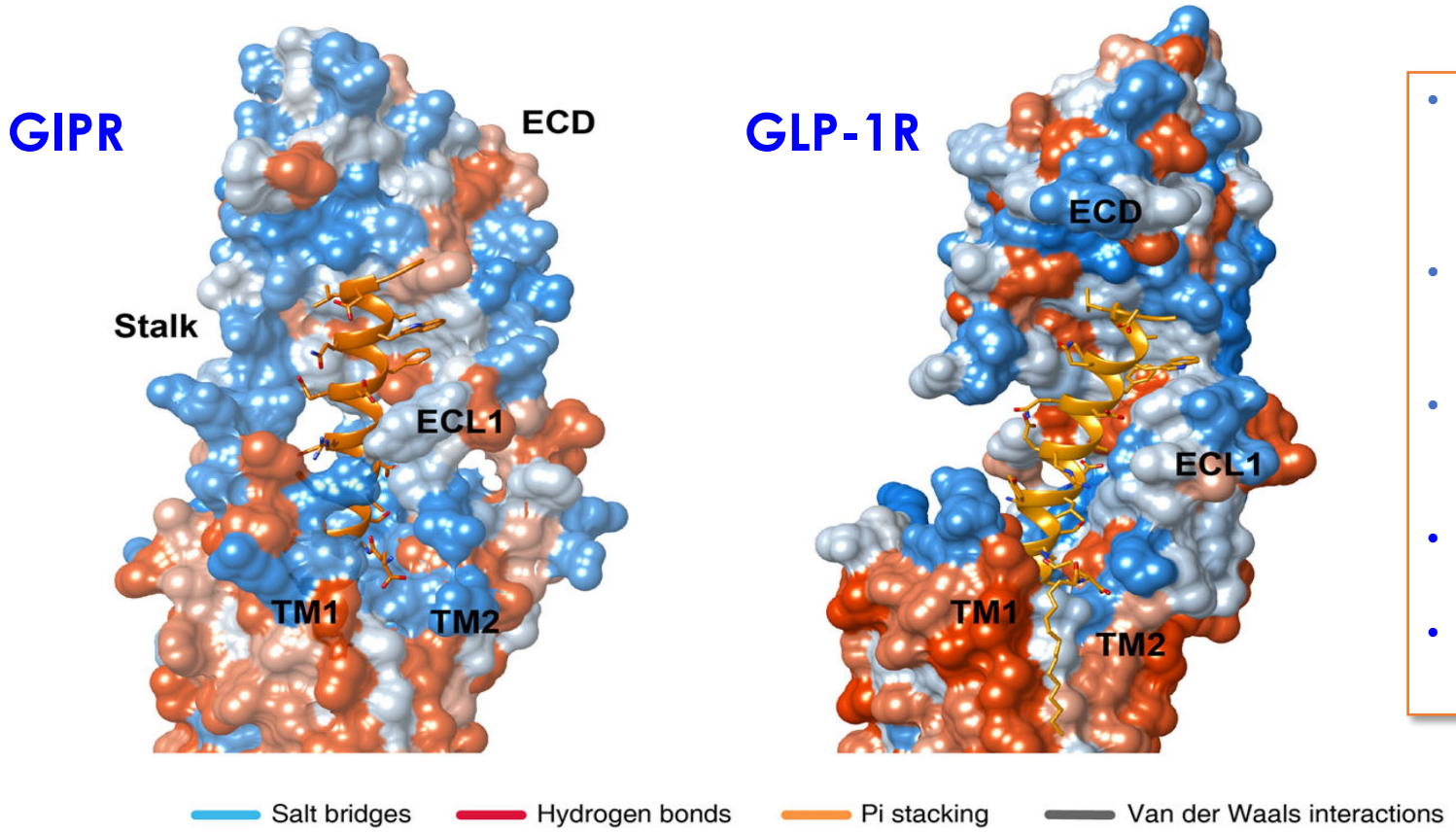


GLP-1 glucagon like peptide-1, GIP glucose-dependent insulinotropic polypeptide, PYY peptide YY, NN: Novo Nordisk, *completed phase 3 trials for obesity.

Melson E, et al, *Int J Obes* 2024

Surface Representations of the Receptors for GIP and GLP-1

Tirzepatide

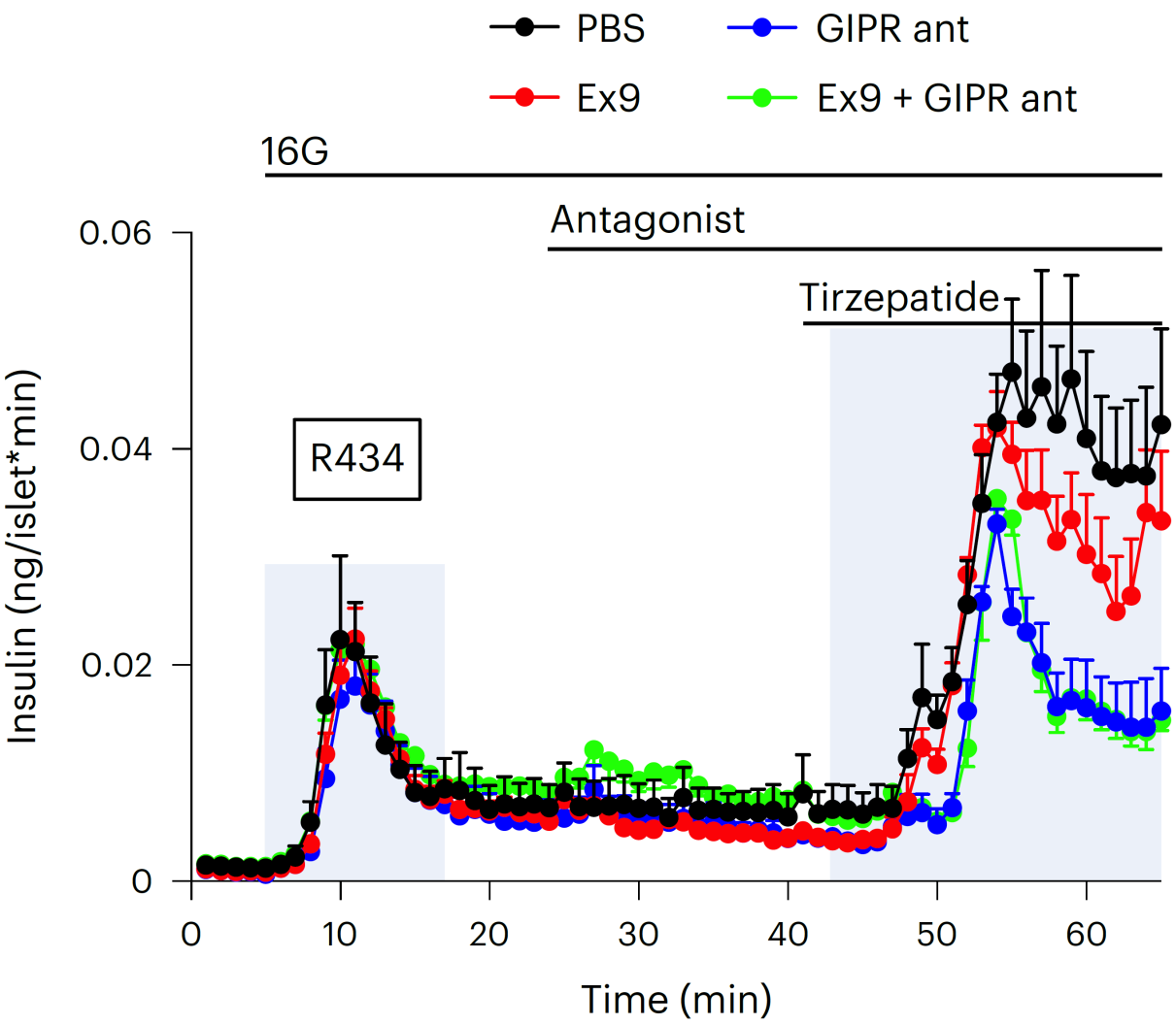


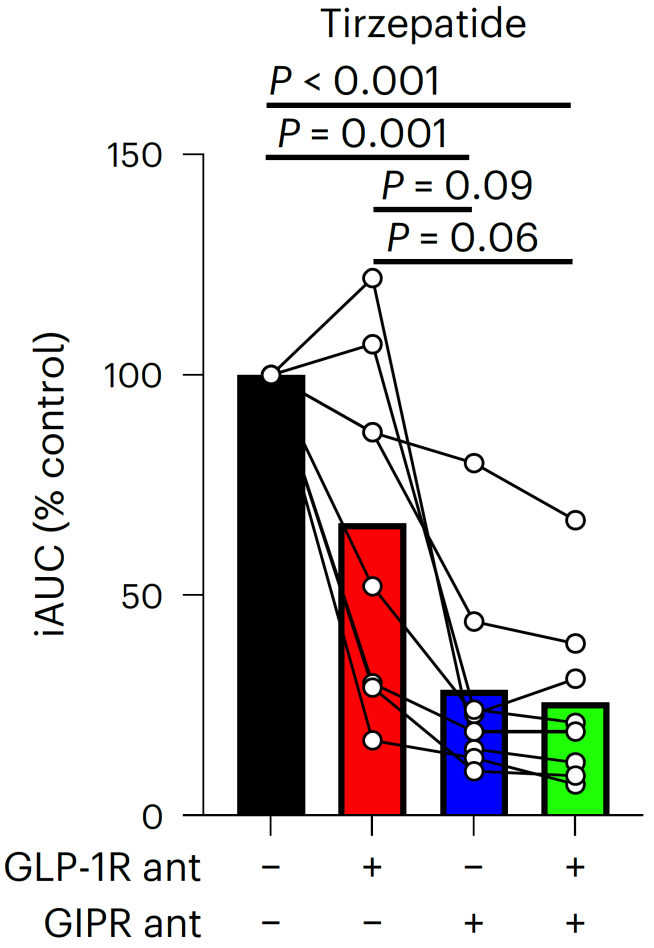
- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIPR and GLP-1R
- Tirzepatide is a 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- Tirzepatide has a mean half-life of approximately 5 days (116.7 hours), enabling once-weekly dosing
- More active on GIPR vs GLP-1R for production of cAMP
- Less GLP-1R downregulation vs GLP-1

Most hydrophilic regions in white, most hydrophobic regions in orange to red. ECD, extracellular domain; ECL, extracellular loop; GCGR, glucagon receptor; TM, transmembrane domain.

Zhao F et al. *Nat Comm* 2023

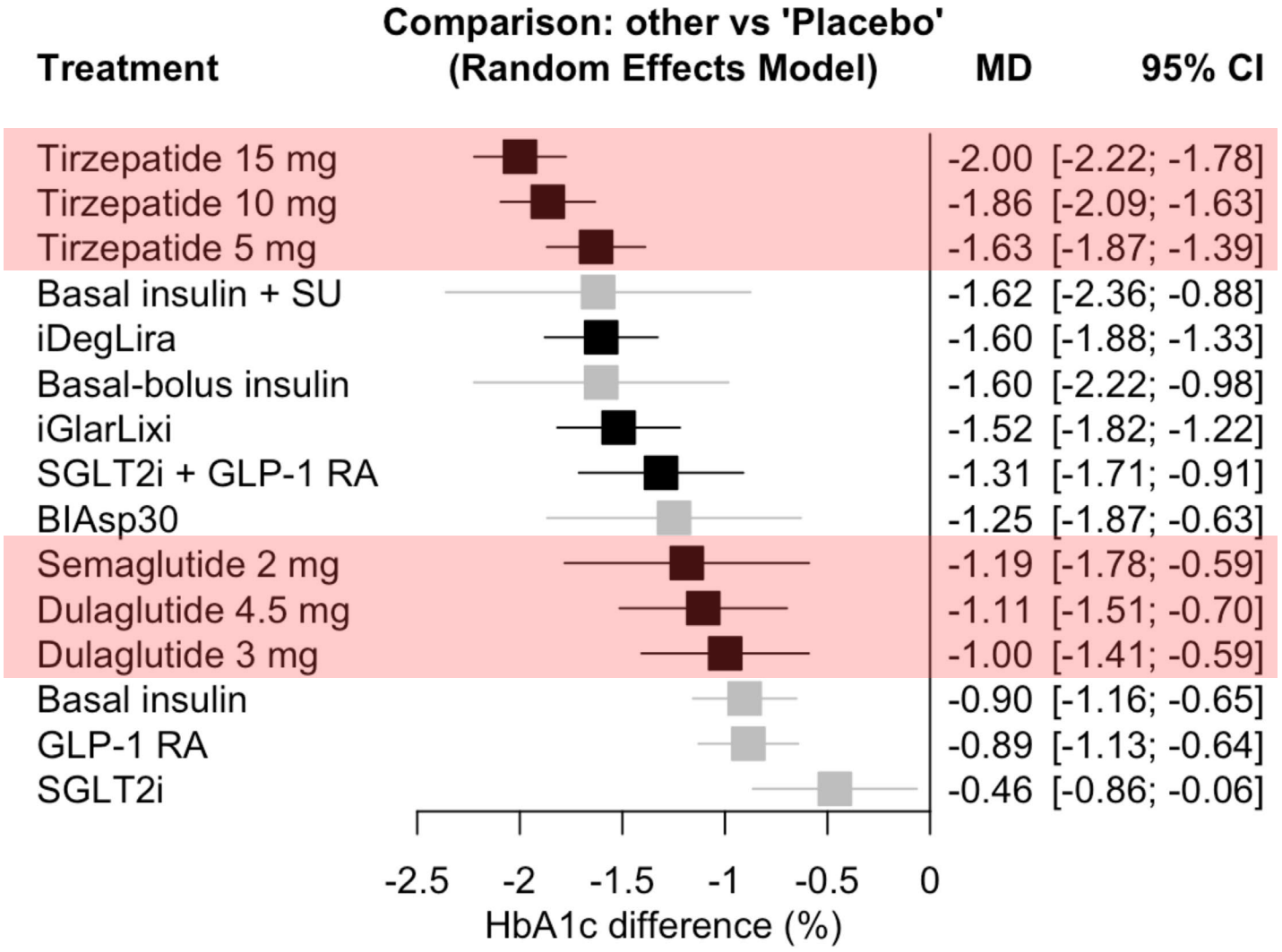
The Incretin Co-agonist Tirzepatide Requires GIPR for Insulin Secretion from Human Islets





Kimberley EI et al, *Nat Metab* 2023

Change from Baseline in HbA1c Compared with Placebo: A Network Meta-analysis of 40 Trials (26,490 patients)



↑ Insulin secretion
↑ Insulin sensitivity
↓ Glucagon levels

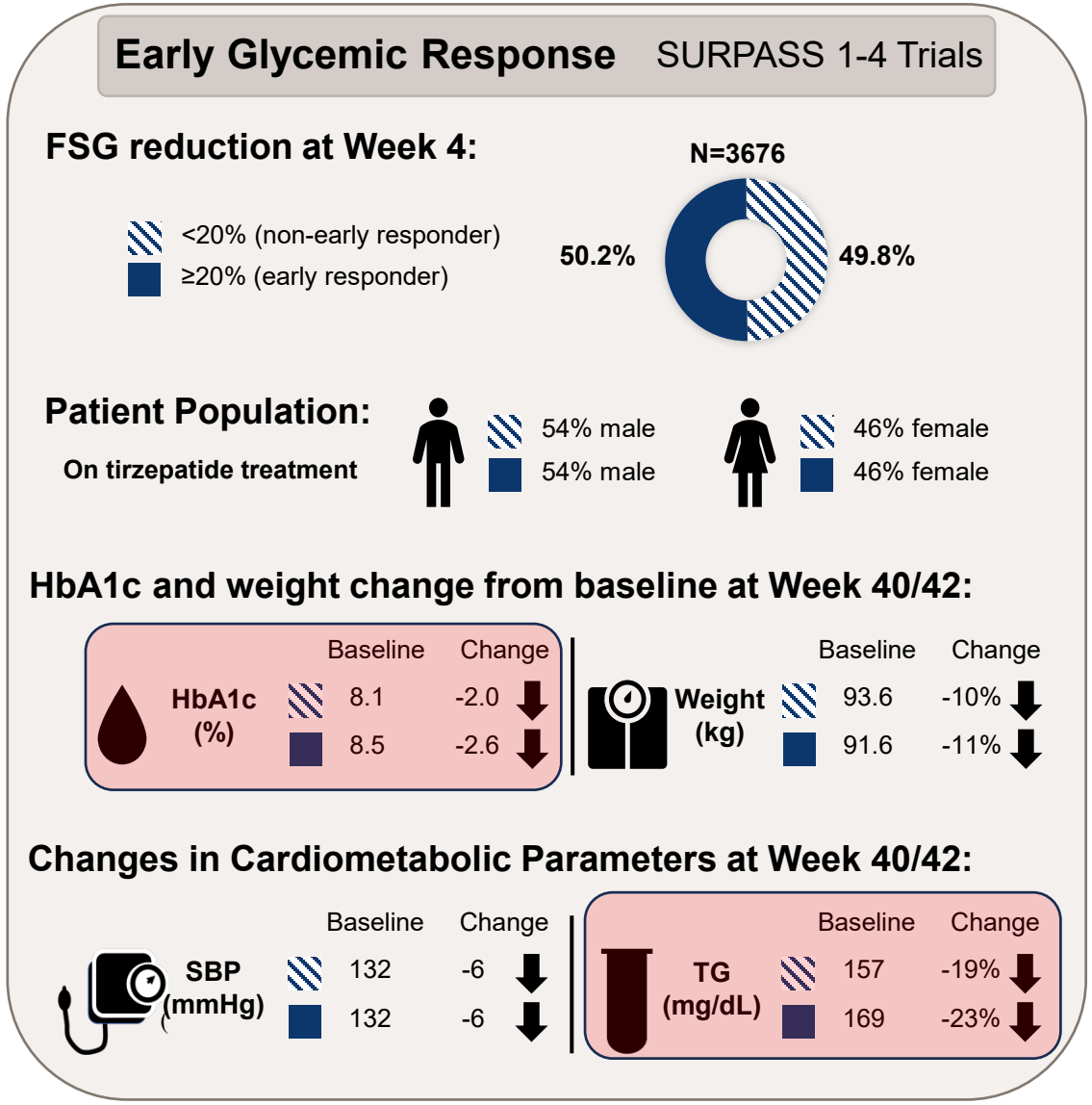
Treatments are presented according to their effect estimate compared with placebo. Effect sizes are presented as mean difference (MD) and 95% confidence intervals (CI).

New GLP-1RA-based treatments are highlighted in black, other treatments in grey.

BIAsp30, biphasic insulin aspart 30/70; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium glucose cotransporter-2 inhibitors, (SGLT-2i); SU, sulfonylurea.

Caruso I, Di Gioia L, Di Molfetta S, et al, *eClinicalMedicine* 2023

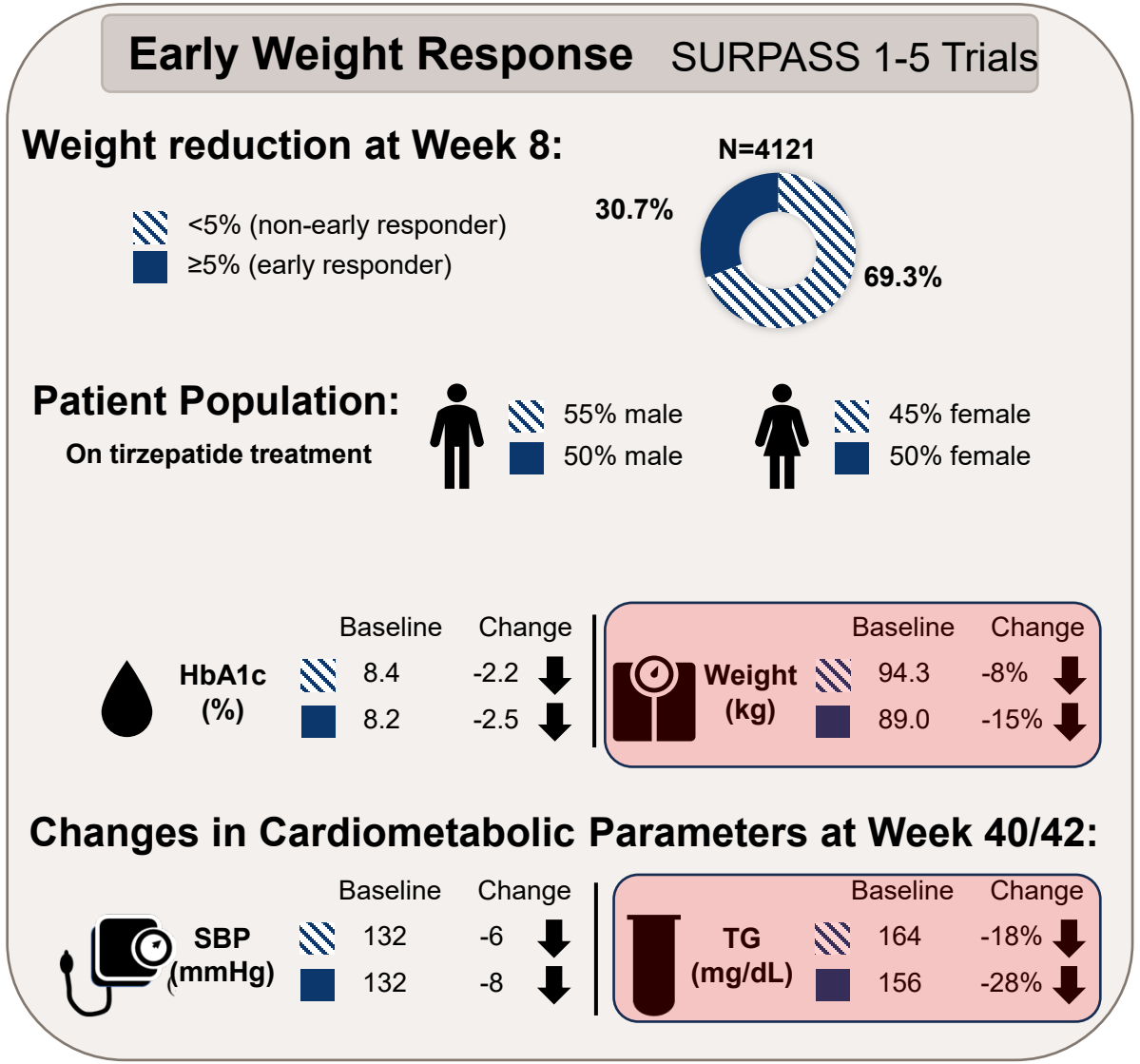
Early Fasting Serum Glucose Reduction With Tirzepatide and Late Metabolic Outcomes in Type 2 Diabetes: A Post Hoc Analysis of the SURPASS Trials



Early glucose response resulted in better longer term metabolic outcomes

Giorgino F et al, *Diabetes Care* 2025

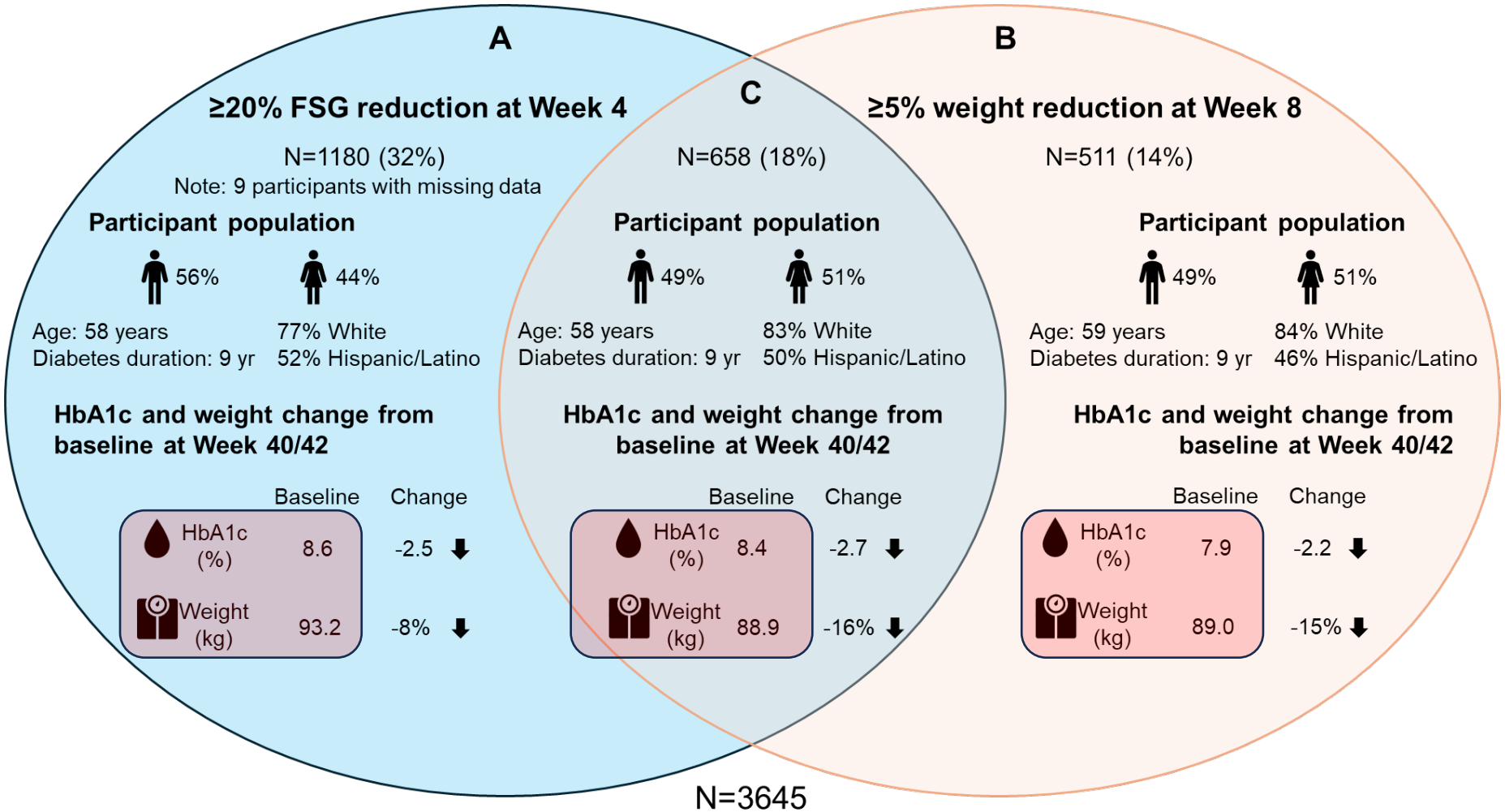
Early Weight Reduction With Tirzepatide and Late Metabolic Outcomes in People With Type 2 Diabetes: A Post Hoc Analysis of the SURPASS Trials



Early weight reduction resulted in better longer term metabolic outcomes

Giorgino F et al, *Diabetes Care* 2025

Venn Diagram of Early responders in (A) Fasting Serum Glucose or (B) Body Weight or (C) Both in Tirzepatide-treated Participants



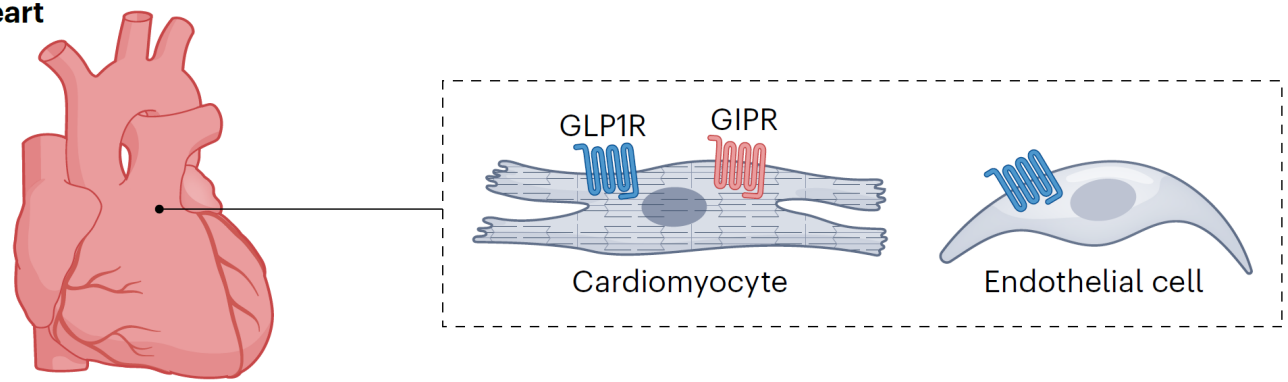
Giorgino F et al, *Diabetes Care* 2025

L'azione del GIP sul rene può rafforzare l'effetto nefroprotettivo del GLP-1RA?

a. No
b. Sì
c. Sì, ma solo nei soggetti obesi
d. Sì, ma solo nei soggetti marcatamente iperglicemici

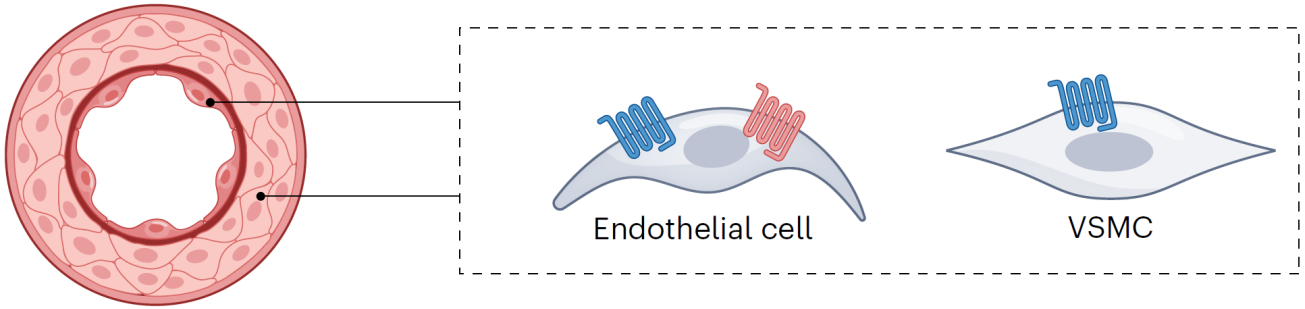
The Actions of GIP and GLP1 in the Cardiovascular and Renal Systems

Heart



↑ Cardioprotection
↑ Myocardial contractility
↑ Heart rate
↑ Glucose uptake

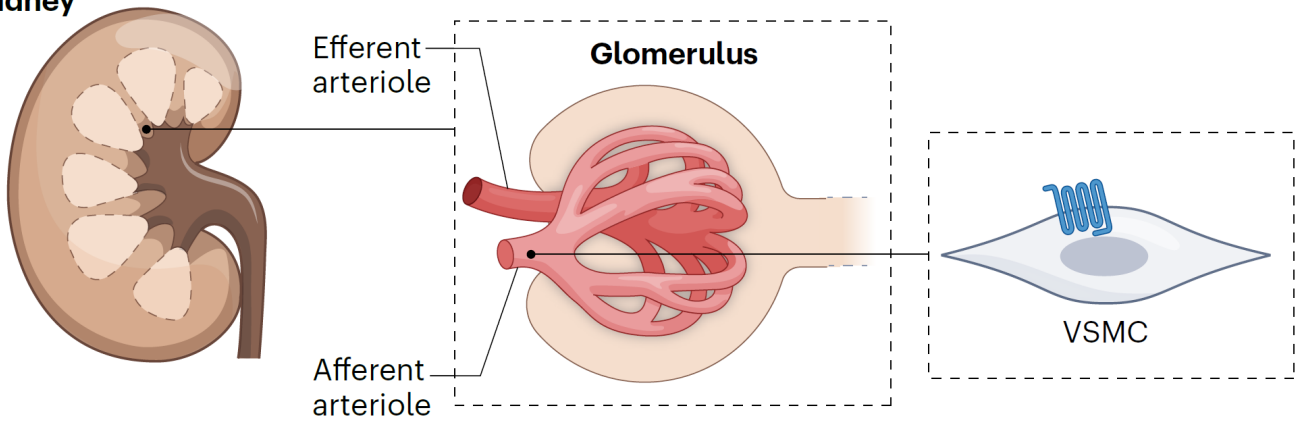
Blood vessel



↑ Vasodilation and NO production
↓ Systemic inflammation
↓ Foam cell formation

↓ Macrophage-driven inflammation
↓ Foam cell formation
↓ VSMC proliferation
↓ Arterial remodelling

Kidney

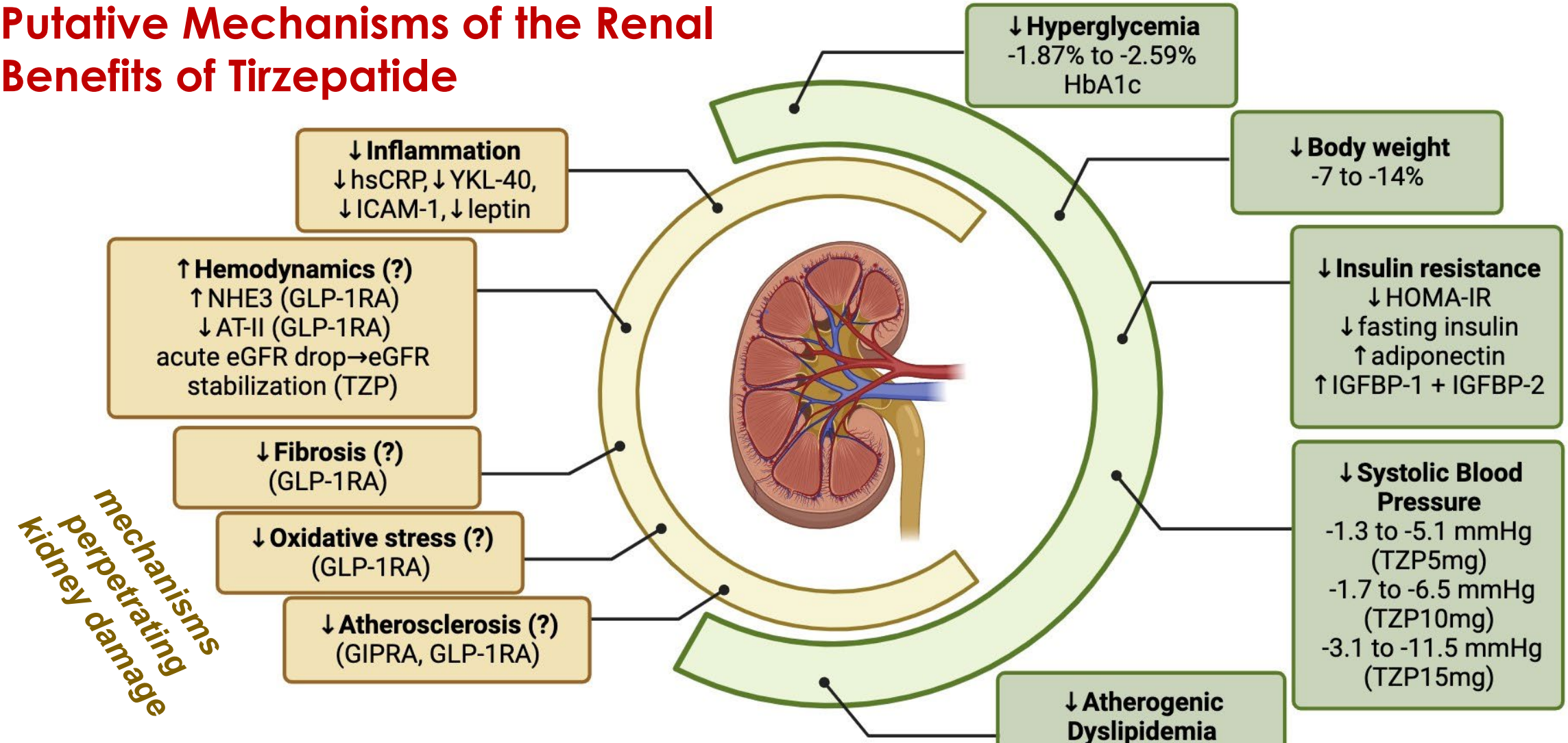


↑ Nephroprotection
↑ Sodium and water excretion
↓ Blood pressure
↓ Albumin excretion

GIPR
GLP1R

Hammoud R & Drucker DJ, *Nat Rev Endocrinol* 2023

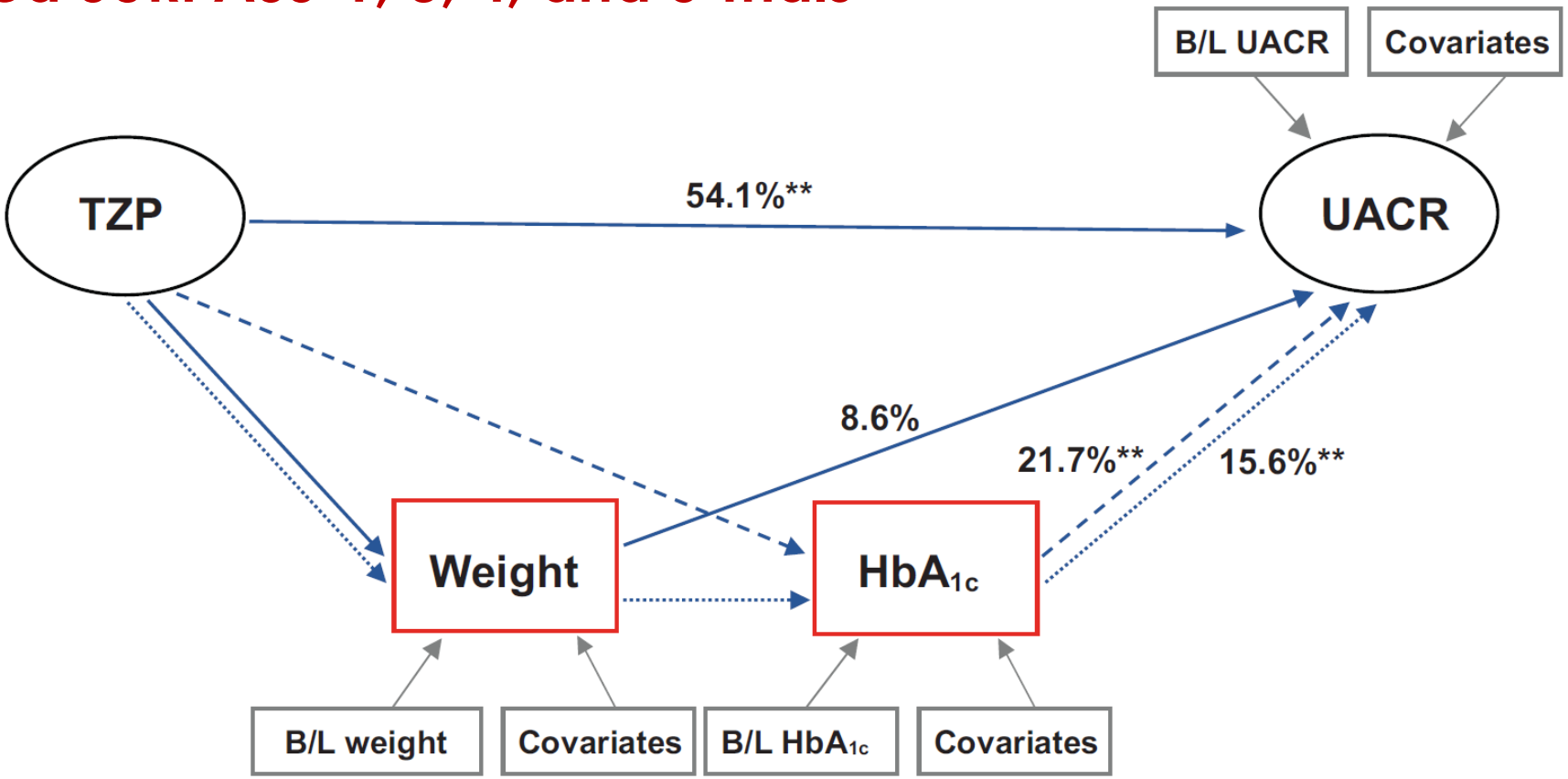
Putative Mechanisms of the Renal Benefits of Tirzepatide



apoB, apolipoprotein B; apoCIII; apolipoprotein CIII; AT-II, angiotensin II; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GIPRA, glucose-dependent insulinotropic polypeptide receptor agonist; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HDL, high density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; hsCRP, high sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule 1; IGFBP-1, insulin growth factor binding protein-1; IGFBP-2, insulin growth factor binding protein-2; LDL, low density lipoprotein cholesterol; NHE3, sodium-hydrogen exchanger 3; TZP, tirzepatide; VLDL, very low density lipoprotein; YKL-40, also known as chitinase-3 like-protein-1.

Caruso I & Giorgino F. *Endocrine* 2024

Mediation Analysis Exploring Potential Effects of Tirzepatide on UACR in the Pooled SURPASS-1, 3, 4, and 5 Trials

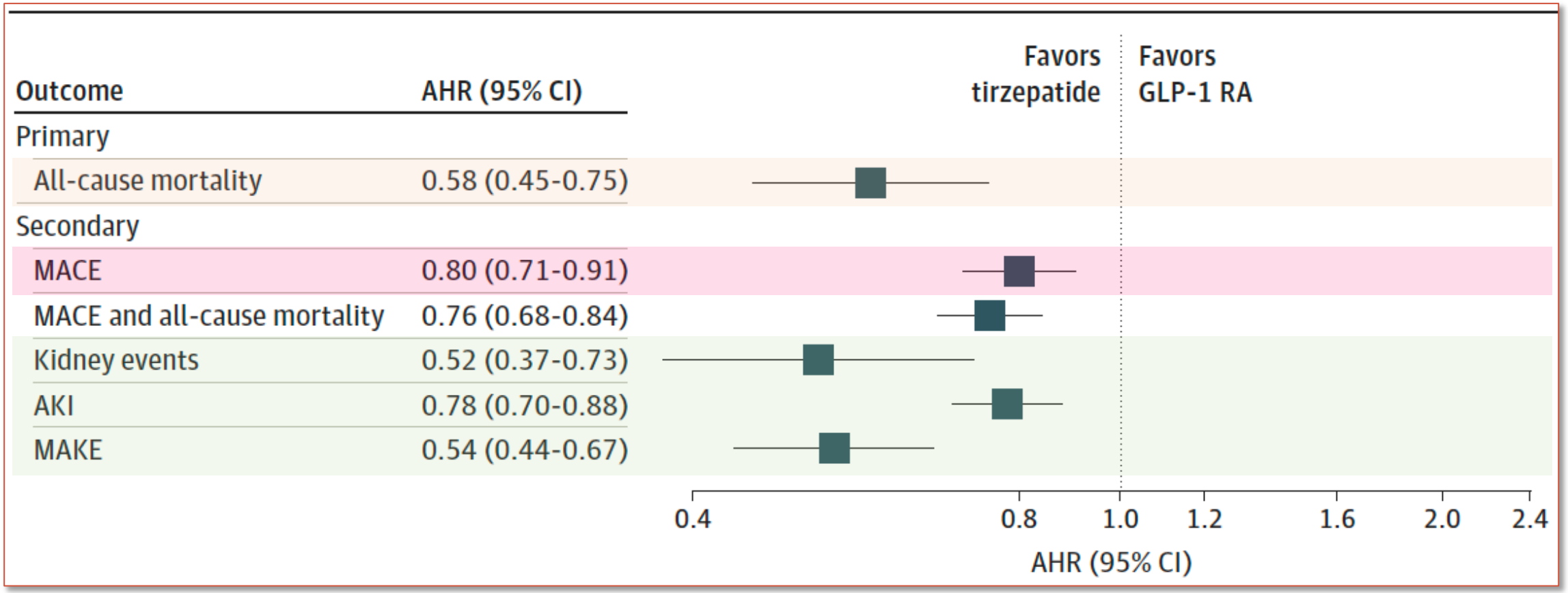


The total potential indirect effect of Tirzepatide was 45.9%.

Indirect paths are denoted by solid, dotted, or dashed lines to depict the full modeled relationship from TZP to change in UACR: Solid lines depict TZP!weight!UACR; dashed lines depict TZP ! HbA! UACR; and dotted lines depict TZP ! weight ! HbA! UACR. Only participants with nonmissing baseline and week 40/42 value of the response variable were included in analysis (n = 2,978). Each analysis model was adjusted for study identifier, sex, country, treatment, and baseline outcome variable and weighted using inverse probability of treatment weights. **P < 0.001. B/L, baseline.

Apperloo et al. *Diabetes Care* 2025

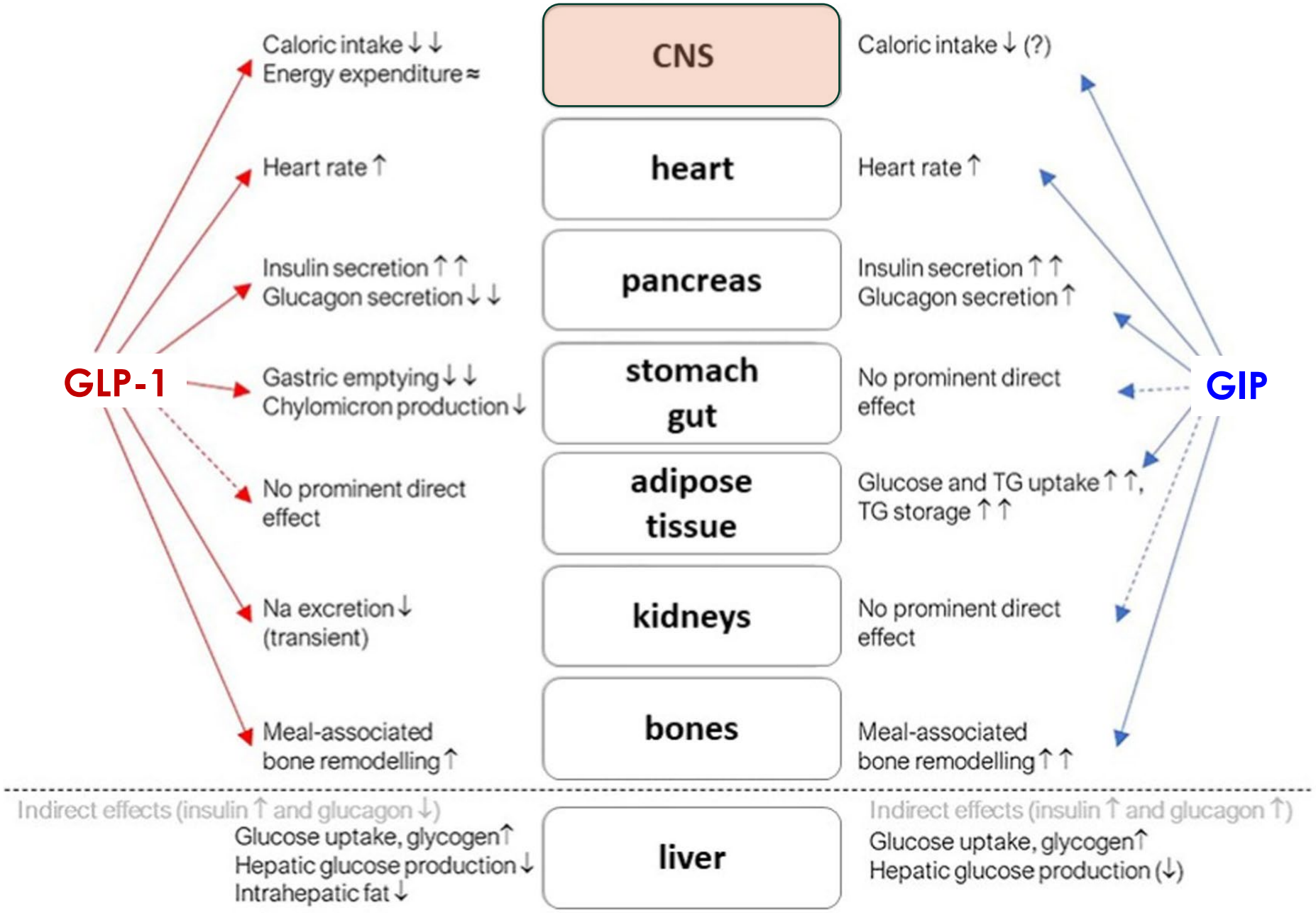
Clinical Outcomes with Tirzepatide or GLP1-RAs in T2D



Retrospective cohort study using the US Collaborative Network of TriNetX data collected on individuals with T2D aged ≥18 years initiating tirzepatide or GLP-1 RA between June 1, 2022, and June 30, 2023; without stage 5 CKD or kidney failure at baseline; and without MI or stroke within 60 days of drug initiation.

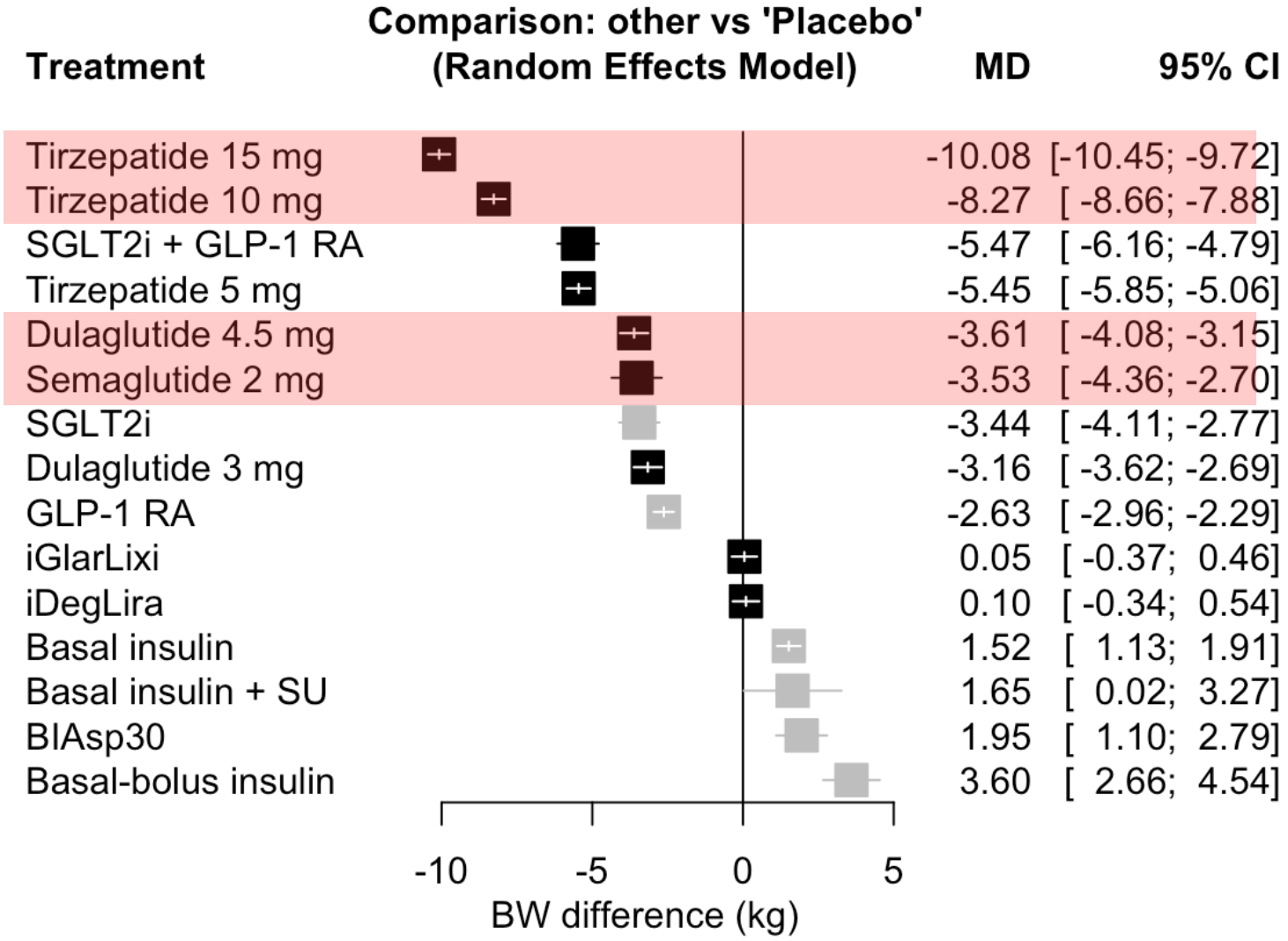
14834 patients with tirzepatide, 125474 with GLP-1 RAs
Median (IQR) follow-up of 10.5 (5.2-15.7) months

Chuang MH et al, *JAMA Netw Open*. 2024



Blüher M, …, Giorgino F, *Endocrinol Diab Metab* 2022

Change from Baseline in Body Weight Compared with Placebo: A Network Meta-analysis of 40 Trials (26,490 patients)



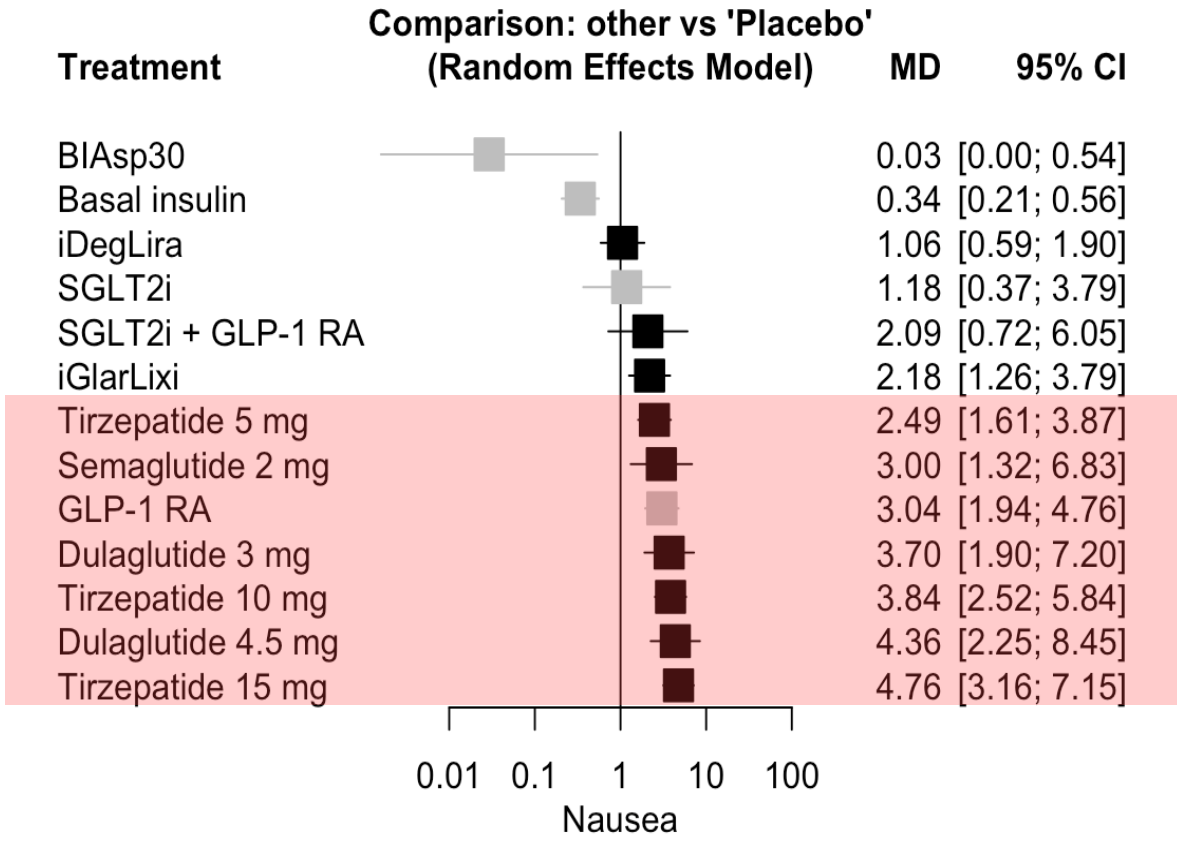
Treatments are presented according to their effect estimate compared with placebo. Effect sizes are presented as mean difference (MD) and 95% confidence intervals (CI).

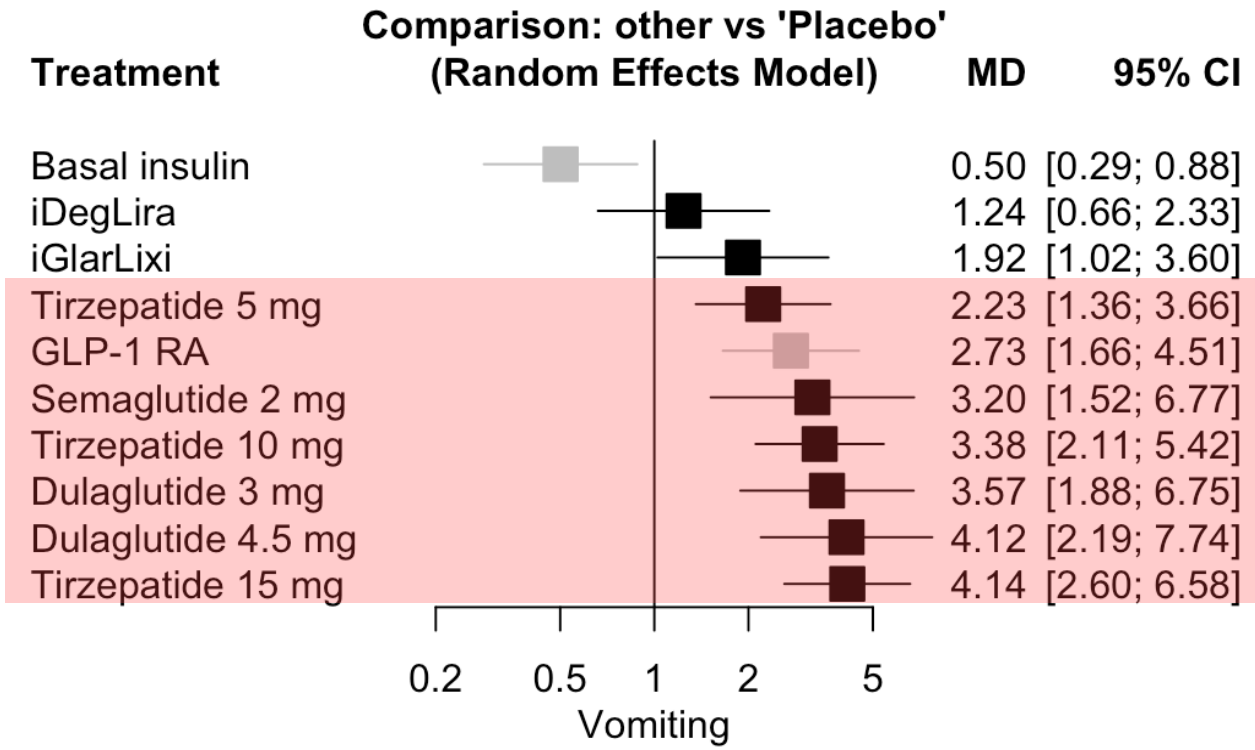
New GLP-1RA-based treatments are highlighted in black, other treatments in grey.

BIAsp30, biphasic insulin aspart 30/70; BW, body weight; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium glucose cotransporter-2 inhibitors, (SGLT-2i); SU, sulfonylurea.

Caruso I, Di Gioia L, Di Molfetta S, et al, *eClinicalMedicine* 2023

Nausea and Vomiting Compared with Placebo: A Network Meta-analysis of 40 Trials (26,490 patients)

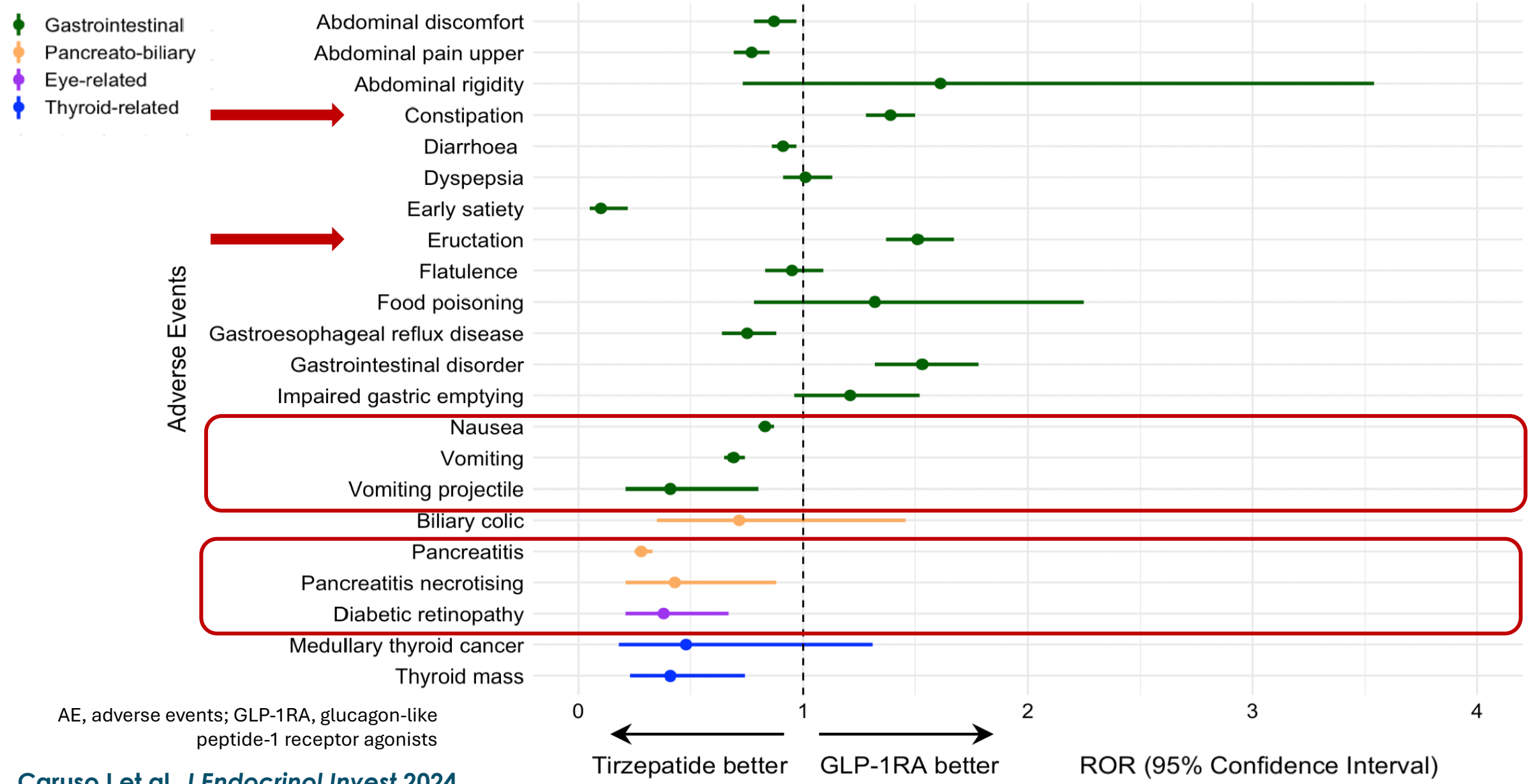




BIAsp30, biphasic insulin aspart 30/70; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium glucose cotransporter-2 inhibitors, (SGLT-2i); SU, sulfonylurea.

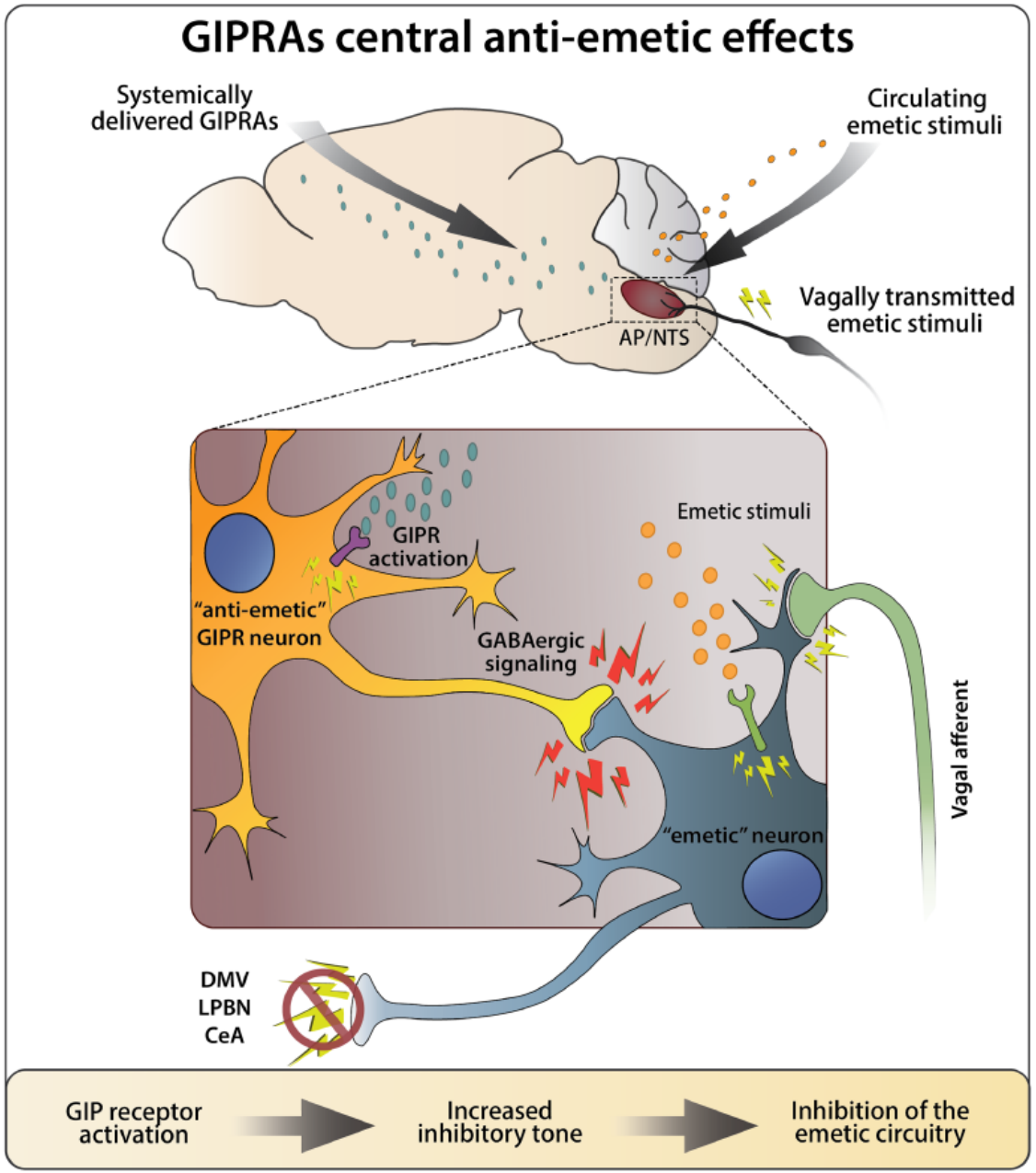
Caruso I, Di Gioia L, Di Molfetta S, et al, *eClinicalMedicine* 2023

FAERS Database: Tirzepatide vs. GLP-1RA on selected AE



AE, adverse events; GLP-1RA, glucagon-like peptide-1 receptor agonists

Caruso I et al, *J Endocrinol Invest* 2024



Borner T, et al., *Am J Physiol Endocrinol Metab*. 2024

Tirzepatide reduces fat, calorie intake, and appetite in people with type 2 diabetes

Adults with type 2 diabetes were randomized across three groups and monitored for 28 weeks

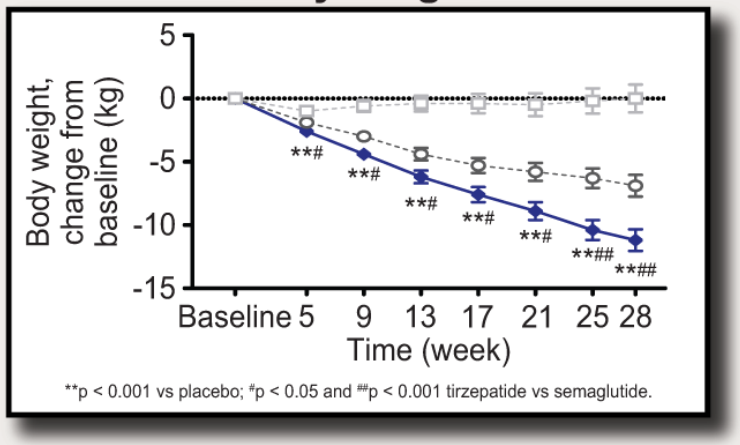
Placebo
(n = 28)

Semaglutide 1 mg
(n = 45)

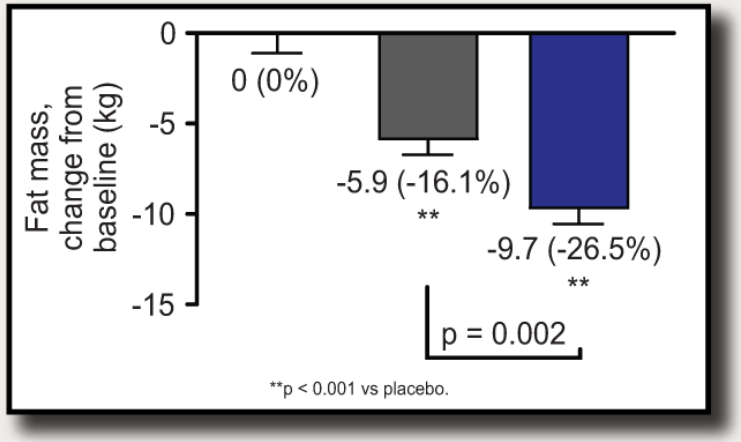
Tirzepatide 15 mg
(n = 48)

Tirzepatide led to significant improvements over semaglutide and placebo on body weight and fat mass.

Body weight

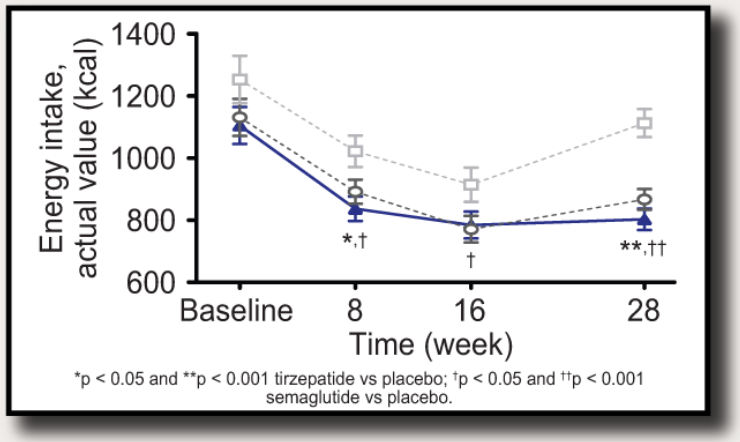


Fat mass

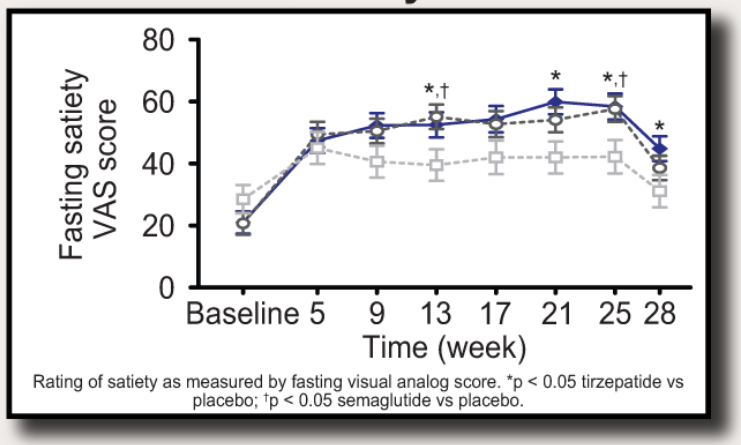


Tirzepatide and semaglutide similarly reduced fasting appetite and energy intake during *ad libitum* lunch.

Calorie intake

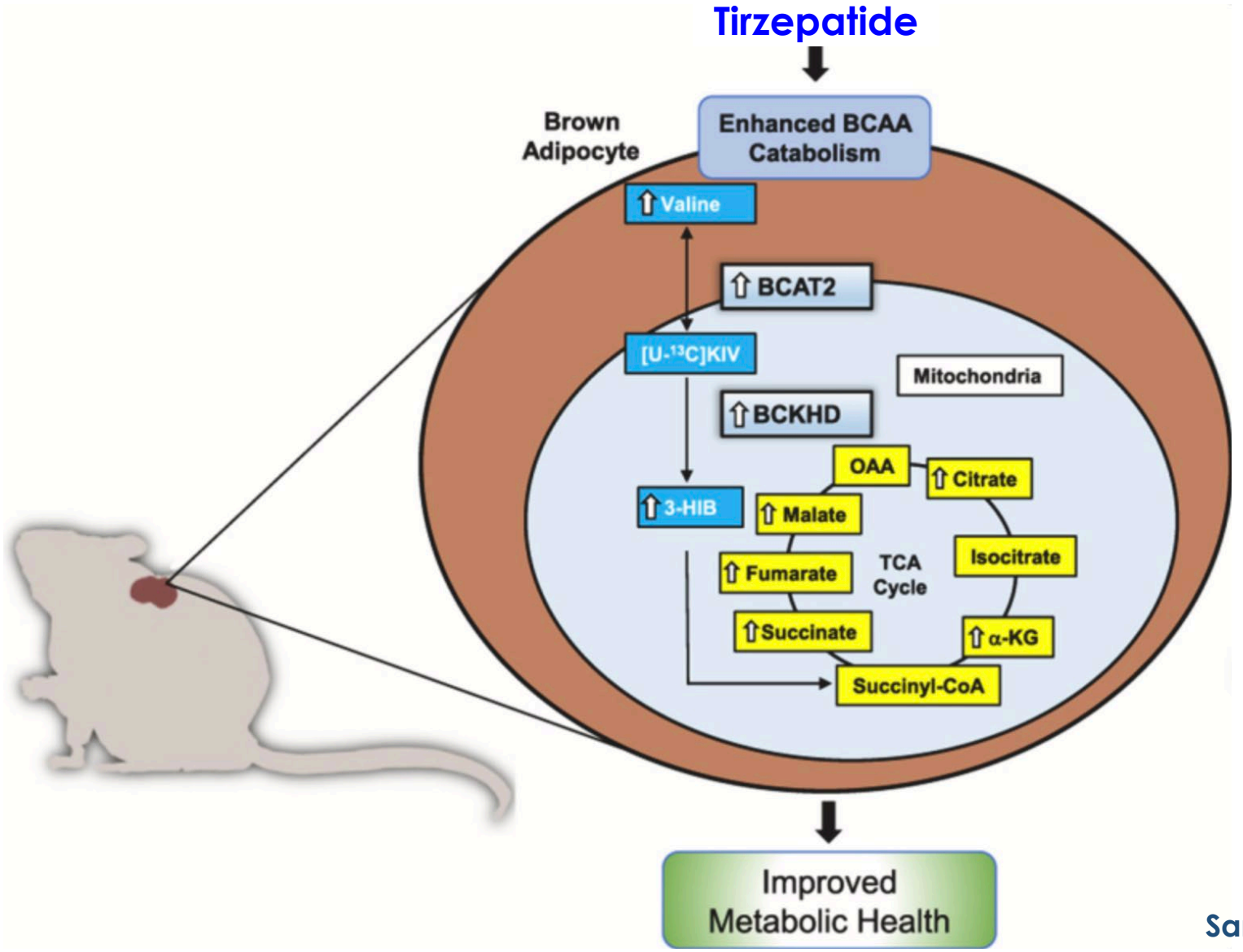


Satiety



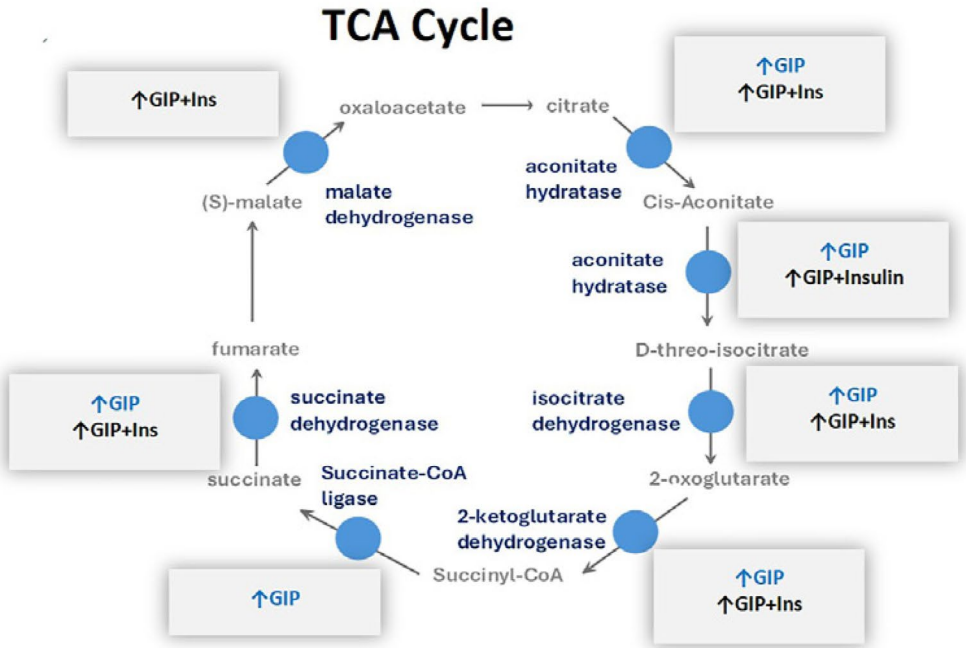
Heise T, et al, *Diabetes Care* 2023

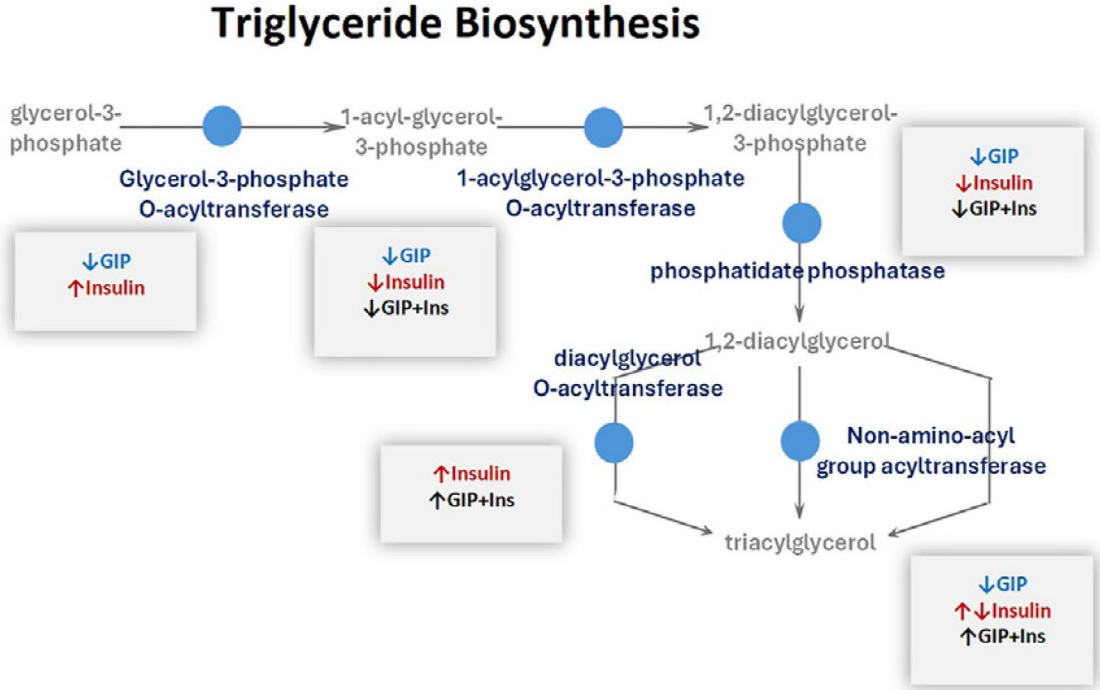
Tirzepatide Induced a Thermogenic-like Amino Acid Profile in Brown Adipose Tissue

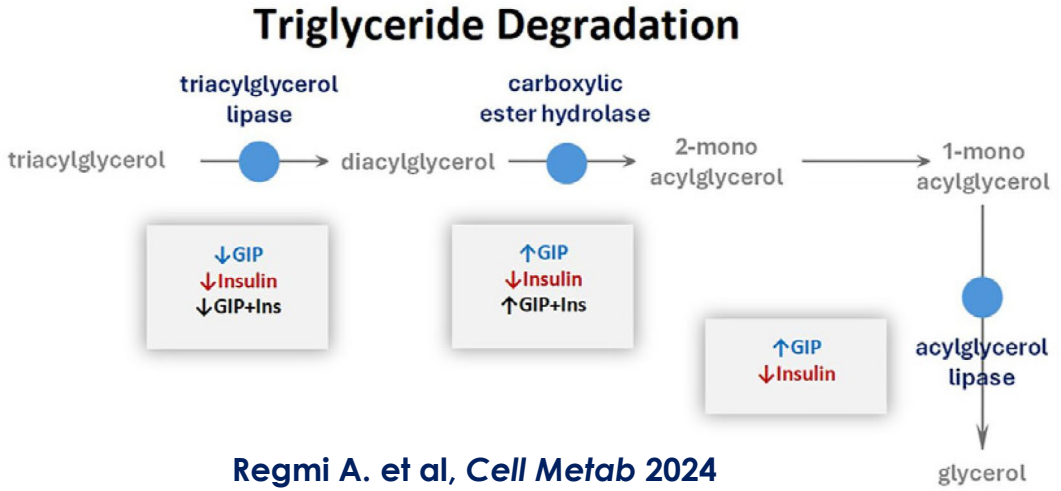


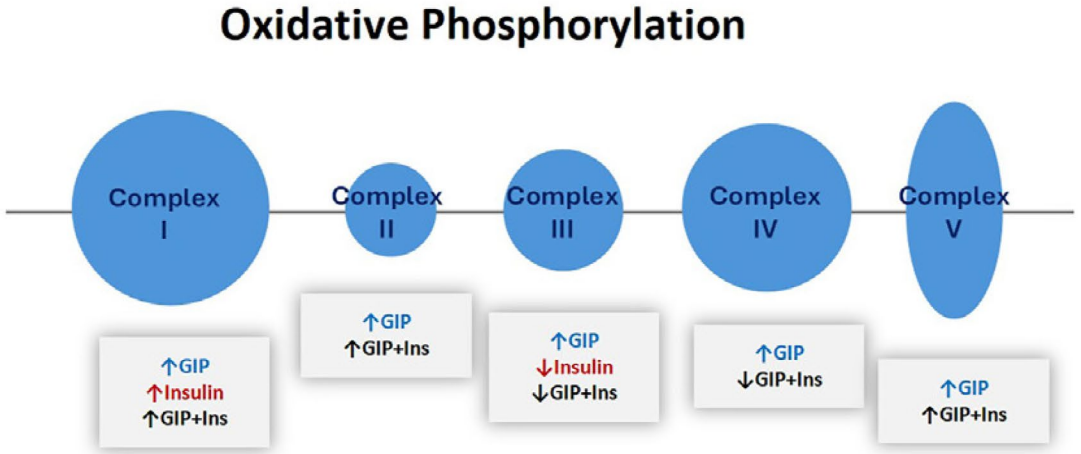
Samms RJ, et al, *Mol Metab* 2022

Tirzepatide and GIP Regulate Adipocyte Transcriptional Metabolic Pathways both Overlapping and Distinct from Insulin Signaling



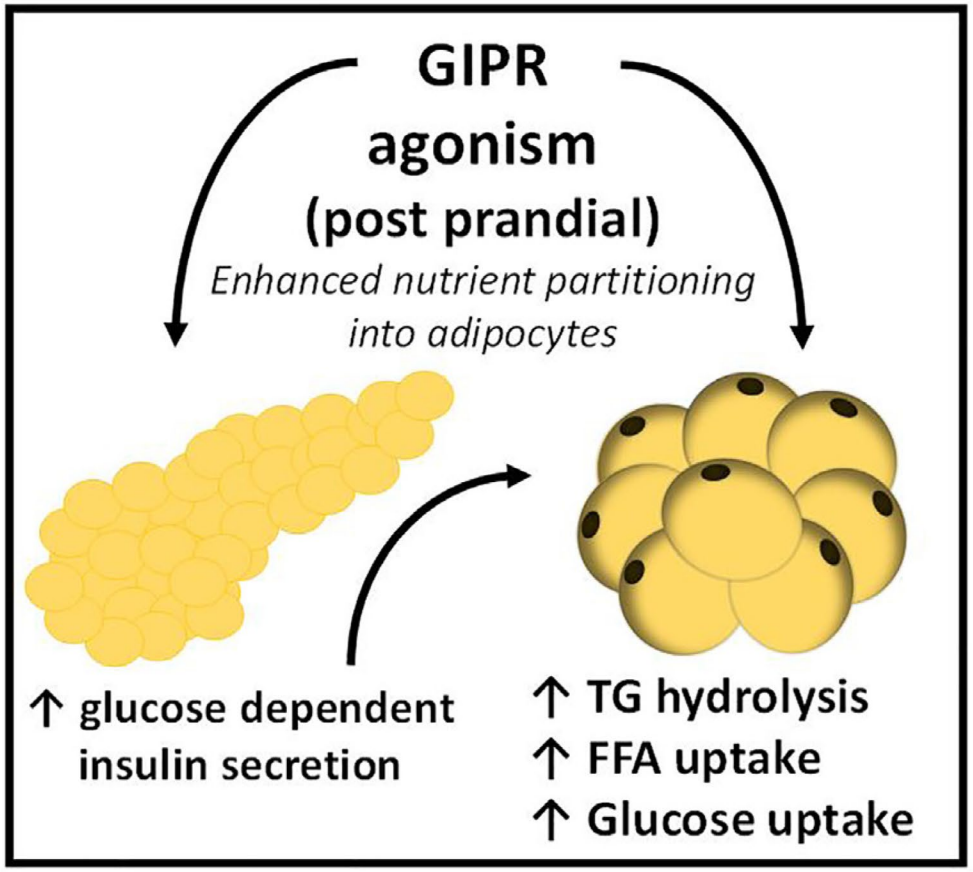




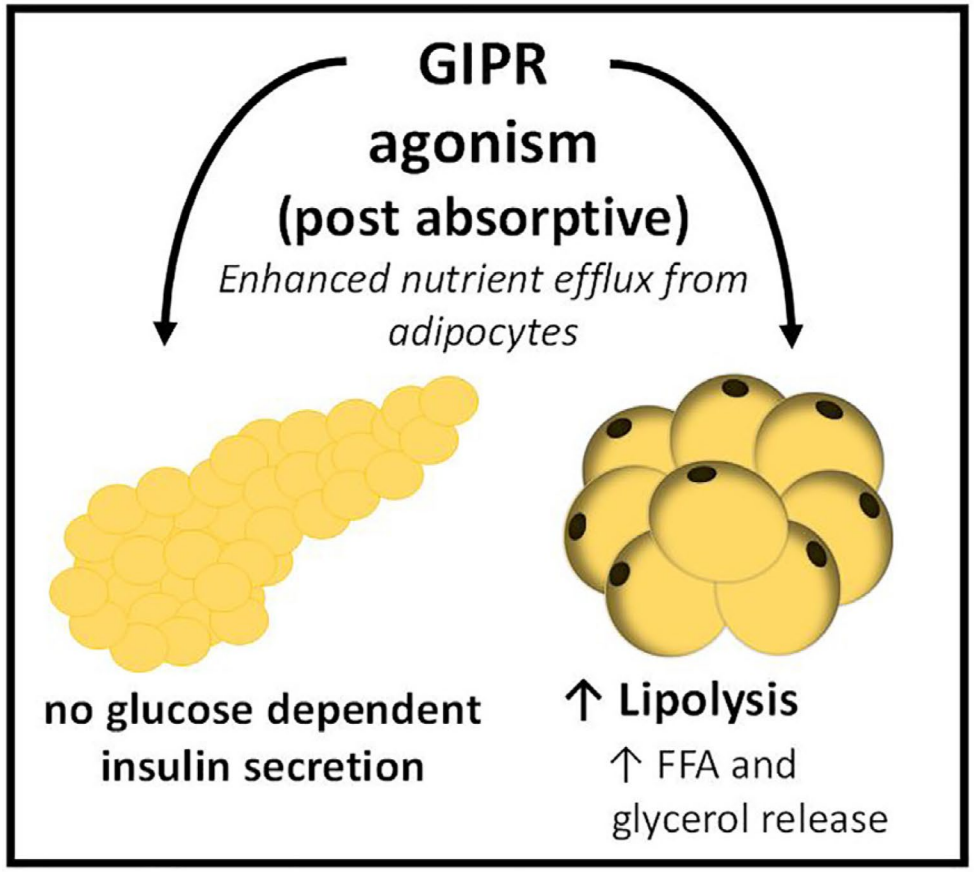


Regmi A. et al, *Cell Metab* 2024

Fasted and Fed Effects of Long-acting GIPR Agonism by Tirzepatide Regulating Adipose Tissue Function



Long-acting GIPR agonism regulation of plasma lipids and glucose under post-prandial/hyperglycemic conditions



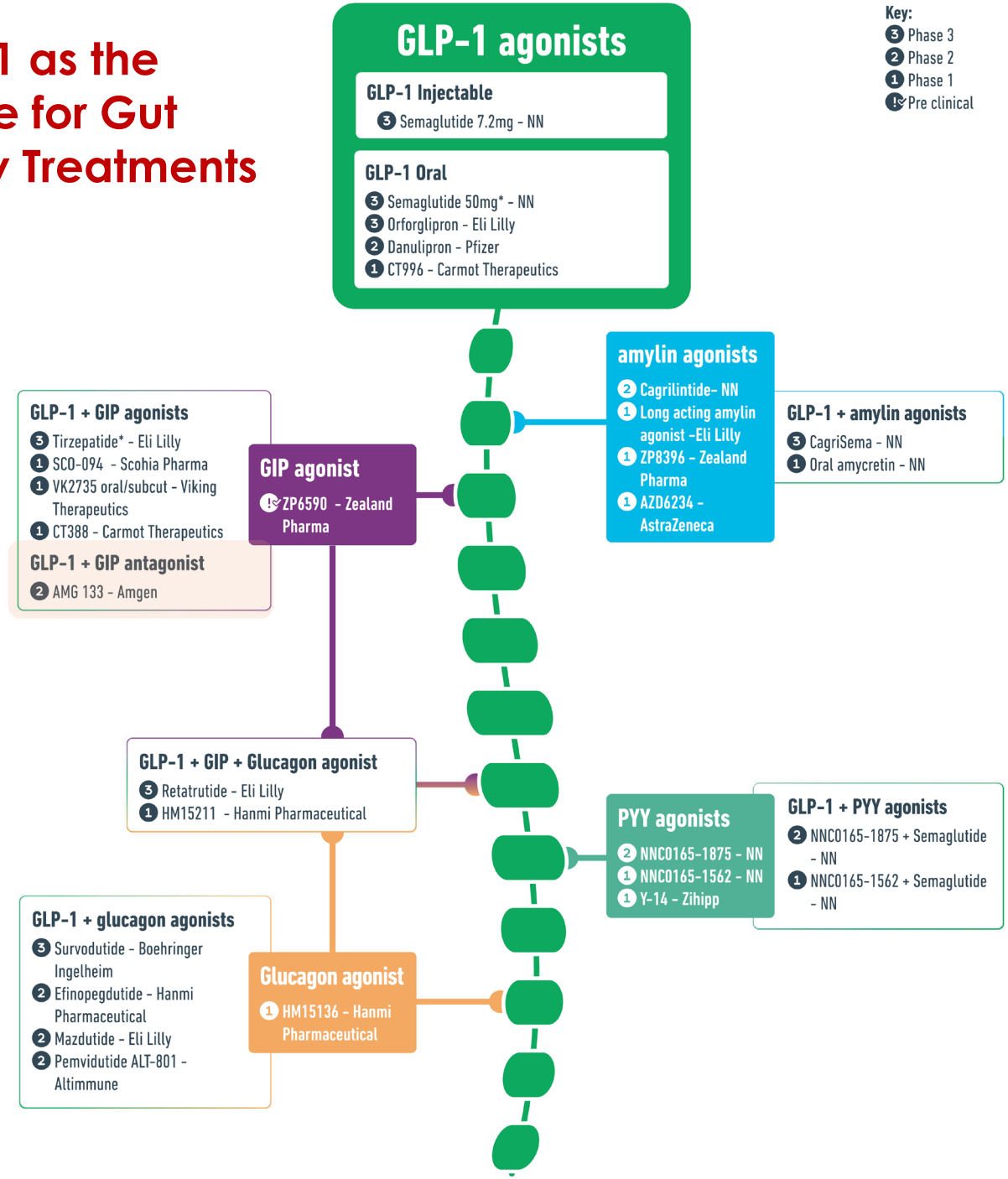
Long-acting GIPR agonism regulation of plasma lipid metabolism under postabsorptive/fasted conditions

Regmi A. et al, *Cell Metab* 2024

Potrebbe essere utile bloccare il recettore del GIP?

a. Sì
b. No
c. No, potrebbe anzi avere effetti metabolici negativi
d. Sì, ma solo in presenza di un agonista del GLP-1R

Glucagon-like peptide-1 as the Backbone of the Pipeline for Gut Hormone-based Obesity Treatments



GLP-1 glucagon like peptide-1, GIP glucose-dependent insulinotropic polypeptide, PYY peptide YY, NN: Novo Nordisk, *completed phase 3 trials for obesity.

Melson E, et al, *Int J Obes* 2024

Rationale for Antagonizing GIP Receptor

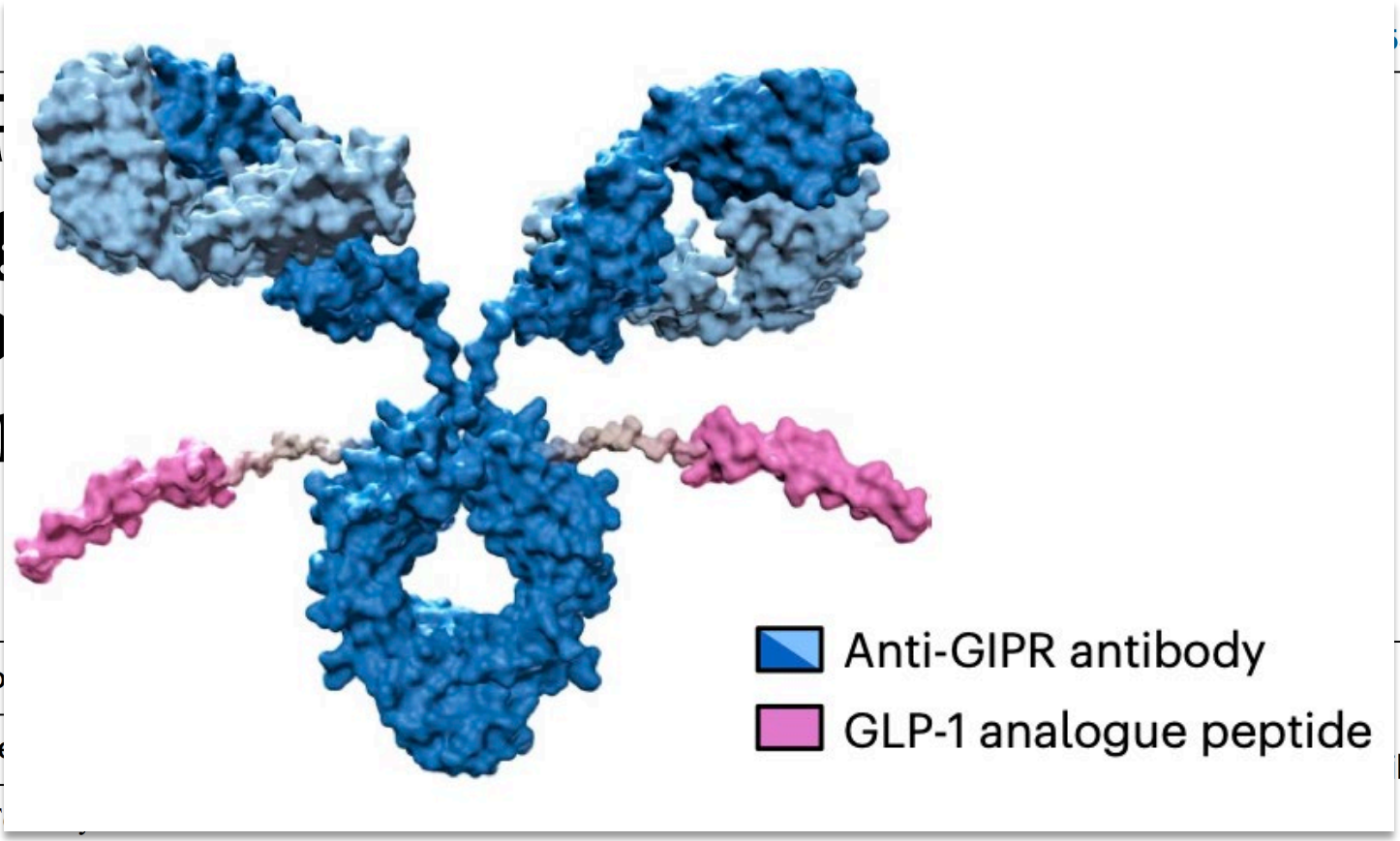
- Genome-wide association studies in humans show that the *GIPR* locus contributes to body weight regulation **(Berndt S I et al, *Nat Genet* 2013; Saxena R et al, *Nat. Genet* 2010; Speliotes EK et al, *Nat Genet* 2010)**
- GIP/GIPR knockout mice are protected from diet-induced obesity (DIO) **(Althage MC et al, *J Biol Chem* 2008; Miyawaki K et al, *Nat Med* 2002)**
- Pharmacological inhibition of GIPR with anti-GIPR antibodies prevented body weight gain in DIO mice and obese cynomolgus monkeys **(Killion EA et al, *Sci Transl Med* 2018)**
- Bispecific molecules that antagonize GIPR and agonize GLP-1R pathways led to decreases in body weight and improvements in metabolic parameters in obese mice and monkeys **(Lu SC et al, *Cell Rep Med* 2021)**

nature metabolism

Article

5-023-00966-w

A GIP
analog
impro
precli



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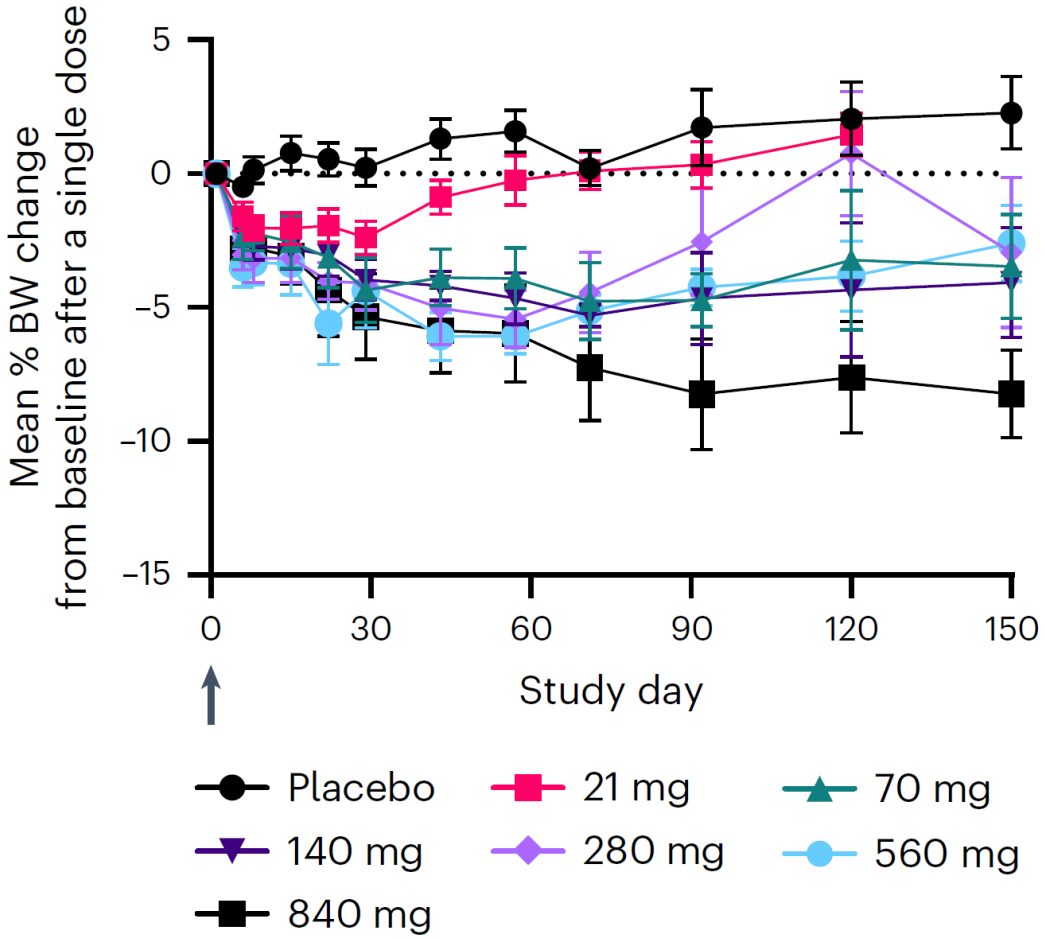
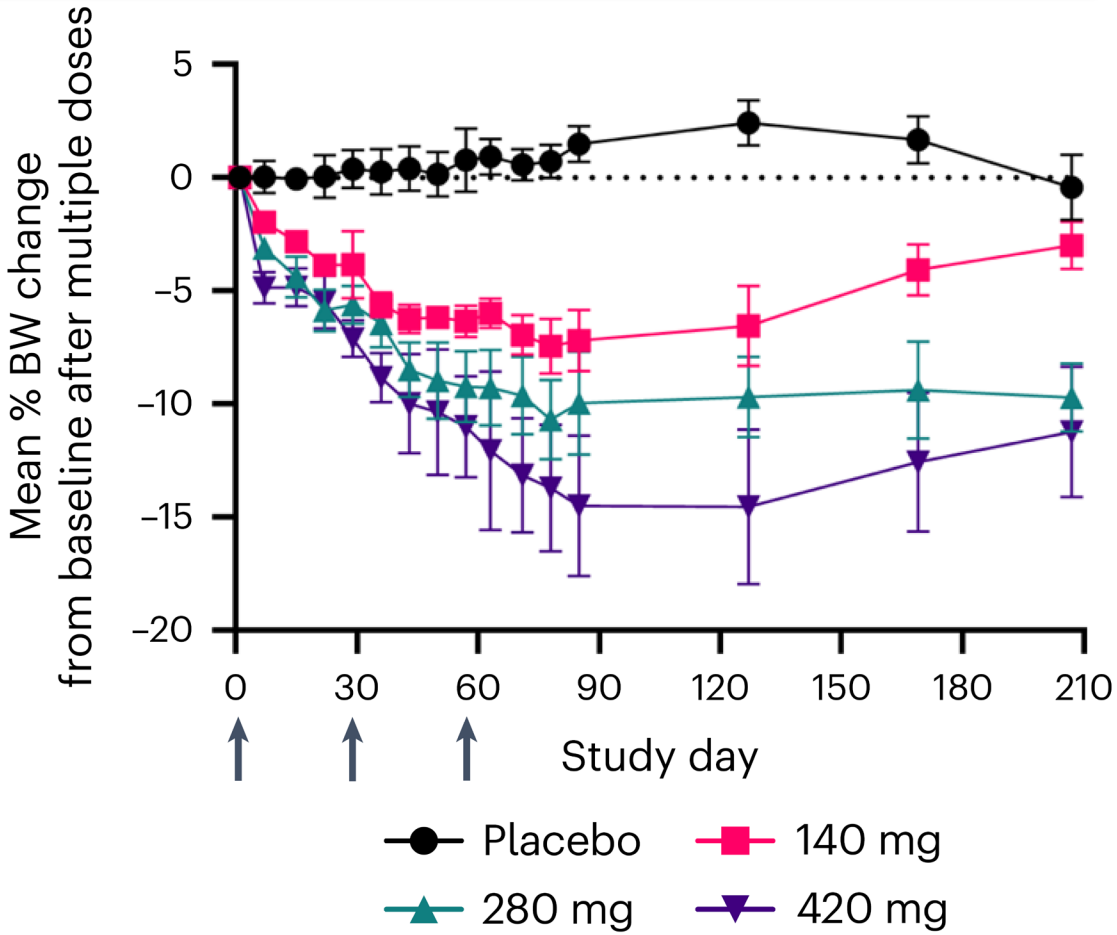
Rajneet K. Oberoi[6], Jane R. Parnes[6], Narimon Honarpour[6], Joel Neutel[7] & Jennifer L. Strande[6]

AMG 133 (Maridebart Cafraglutide) Reduces Body Weight in Humans

single doses,
***n* = 6–7 for AMG 133 and *n* = 12 for placebo**



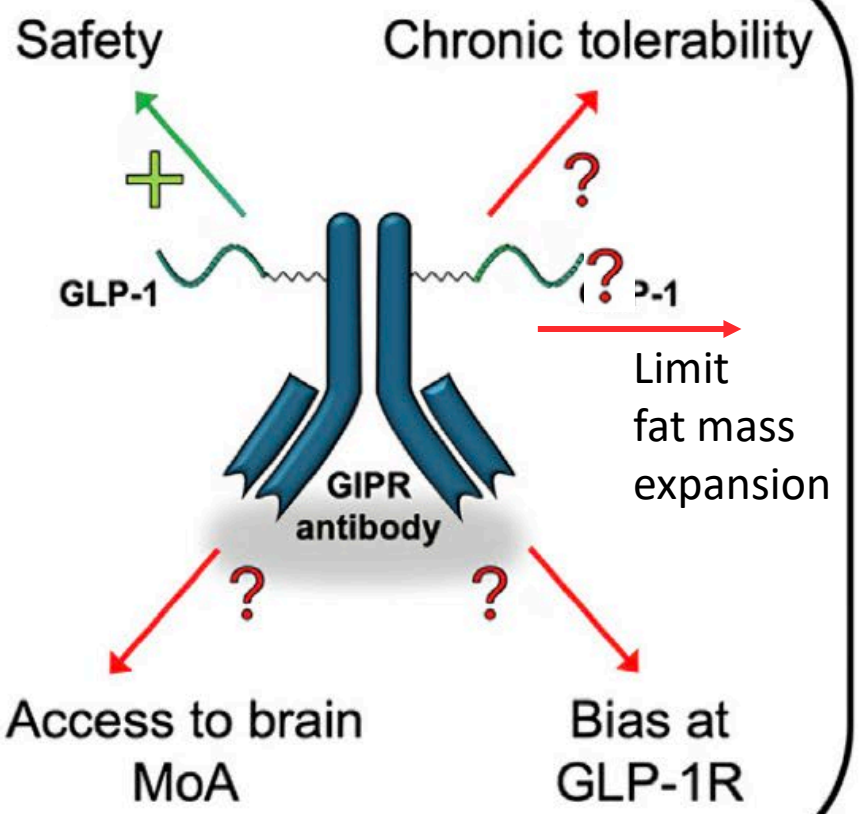
multiple doses,
***n* = 6–8 for AMG 133 and *n* = 6 for placebo**



Véniant MM, et al, *Nat Metab* 2024

To Agonize or Antagonize GIPR within GLP-1R Co-agonism for Body Weight Reduction?

Drug	Semaglutide (2.4 mg)	Tirzepatide (15 mg)	Retatrutide (8 mg)	AMG 133 (420 mg)
Targets	GLP-1R Ag.	GLP-1R/GIPR Dual Ag.	GLP-1R/ GIPR/GcgR Triple Ag.	GLP-1R Ag. / GIPR Ant.
Δ% BW (week 12-13)	-6%	-8%	-12%	-14%
Δ% BW (end of trial)	-15% *68 weeks*	-23% *72 weeks*	-24% *48 weeks*	-14% *12 weeks*
Target dosage achieved (at week 12)	No	No	No	Yes
Clinical trial phase	3	3	3	1
Participant criteria	Obesity w/o T2D	Obesity w/o T2D	Obesity w/o T2D	Obesity w/o T2D



modified from **Novikoff A, et al, *Trends Endocrinol Metab* 2024**

How GIP May Add in the Treatment of Diabetes and Obesity

- Essential component of glucose-dependent insulin secretion → **increased contribution to glucose-lowering effect**
- Potential direct effects and indirect effects on cardiovascular and renal cells → **further reduction of cardiovascular and renal events (?)**
- Reduction of GLP-1RA-induced gastrointestinal side effects → **improved efficacy/tolerability profile**
- Very promising results also when GIPR is blocked → **importance of GIP system in physiology and pharmacology**

GIPR, glucose-dependent insulinotropic peptide receptor; GLP-1RA, glucagon-like peptide 1 receptor agonists.