CONGRESSO REGIONALE
SID-AMD MARCHE 2025

SID Società Italiana di Diabetologia

AMD MARCHE ASSOCIAZIONE MEDICI DIABETOLOGI

LA CURA DELLA PERSONA CON DIABETE NELL' ERA DELL' INTELLIGENZA ARTIFICIALE

TRAGUARDI, SFIDE E NUOVI ORIZZONTI

RESPONSABILE SCIENTIFICO Paola Canibus

JESI (AN) | 11 ottobre 2025
Hotel Federico II

Nuove terapie in diabetologia: i multiagonisti recettoriali GIP/GLP-1

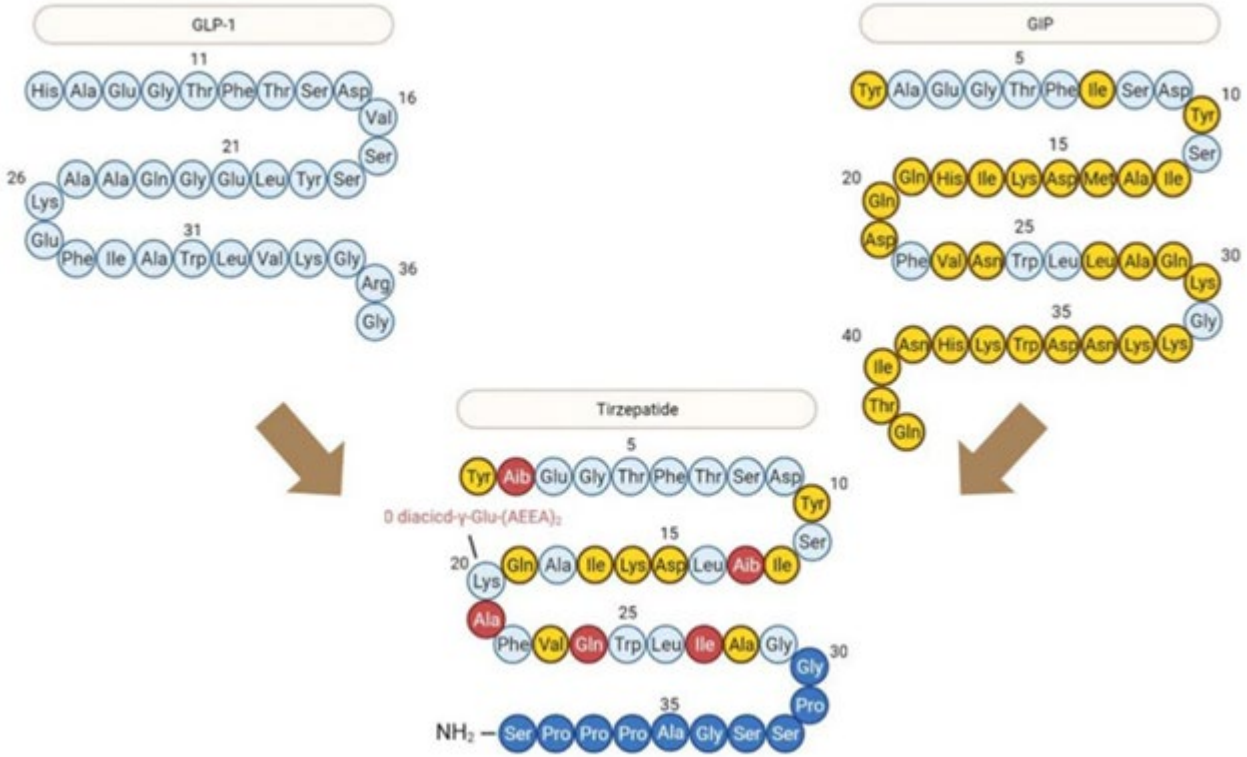
Vanessa Ronconi

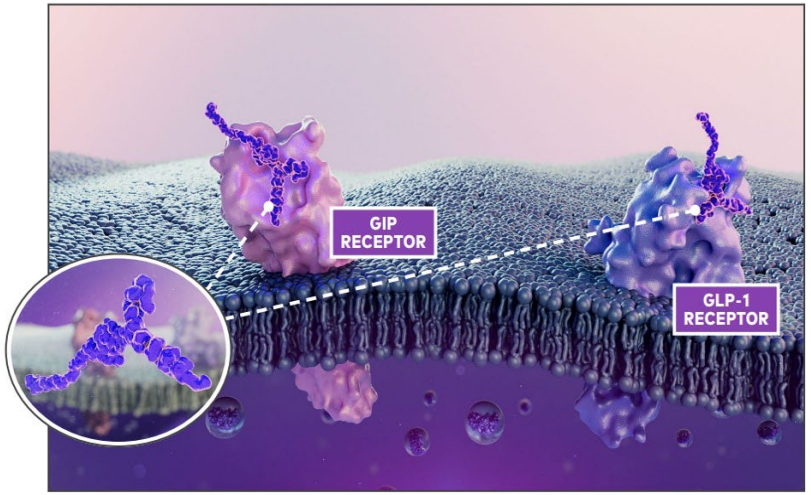
La Dr.ssa Vanessa Ronconi dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

GLP-1 RA e GIP agonista: TIRZEPATIDE

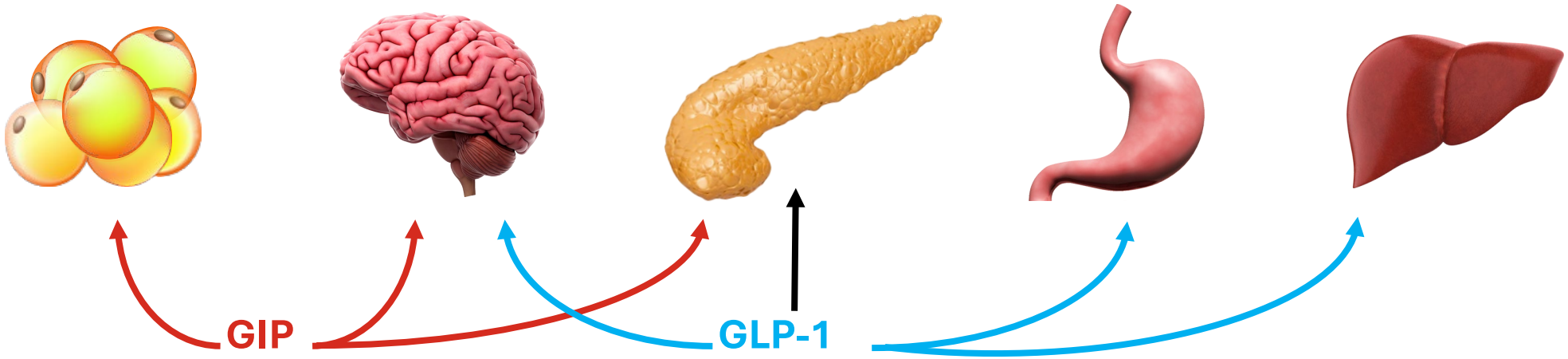
- È un **peptide** con struttura basata sulla sequenza nativa del GIP, modificata per legare sia i recettori del GIP che del GLP-1. È il primo della sua classe terapeutica
- Il peso molecolare di **Tirzepatide** è di 4,8 kD (Dulaglutide 63 kD, Semaglutide 4,11 kD)
- Ha un'emivita media di 5 giorni (116,7 ore) , permettendo di avere una posologia settimanale





È una **singola molecola**, un coagonista con due target farmacologici

EFFETTI FISIOLOGICI DEGLI AGONISTI GIP E GLP-1



Tessuto adiposo:
- ↑ Sensibilità insulinica
- Miglioramento del metabolismo lipidico

SNC:
- ↓ Appetito
- ↑ Sazietà
- ↓ Nausea

Insula pancreatica:
- ↑ Secrezione insulinica
- ↑ Secrezione di glucagone

SNC:
- ↓ Appetito
- ↑ Sazietà

Insula pancreatica :
- ↑ Secrezione insulinica
- ↓ Secrezione di glucagone

Stomaco:
- Rallentamento svuotamento gastrico

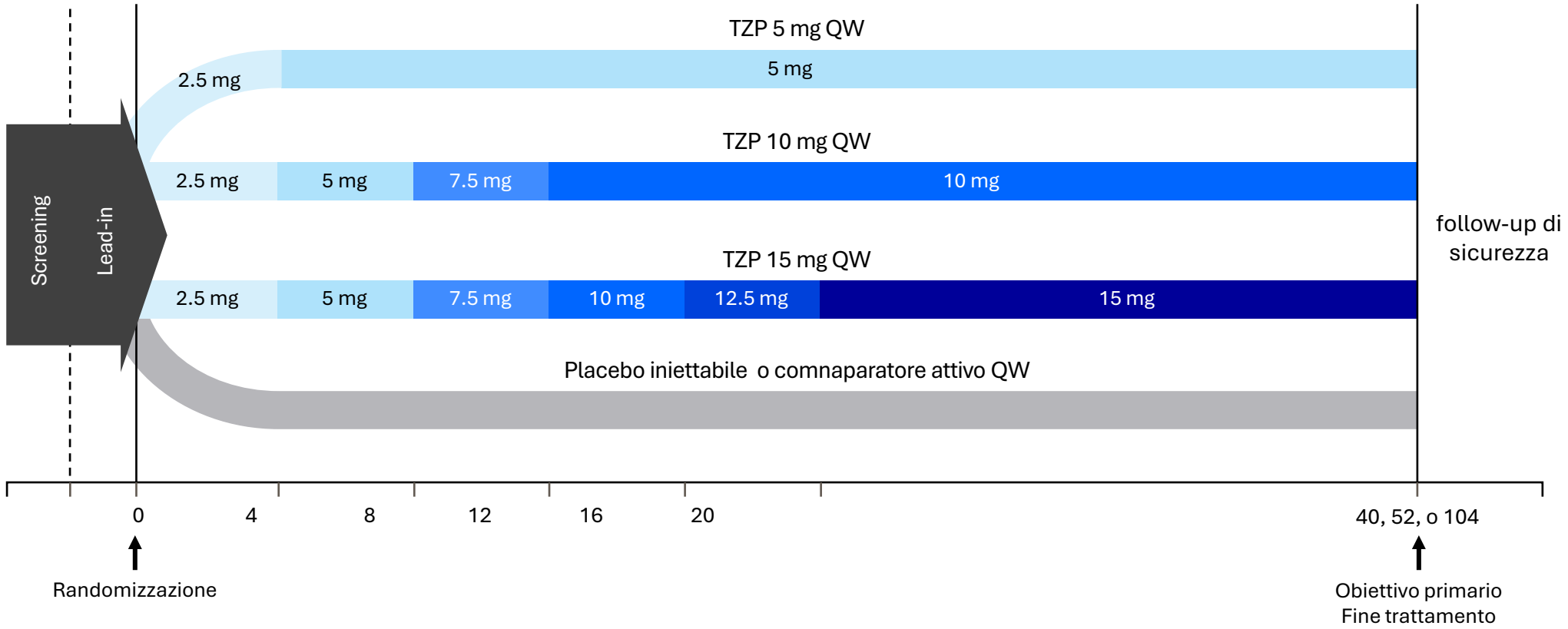
Fegato:
- ↓ Gluconeogenesi

Modificato da :1 Hædersdal S, et al. *Nat Rev Endocrinol.* 2023;19(6):321-335. 2. Hammoud R, Drucker DJ. *Nat Rev Endocrinol.* 2023;19(4):201-216

TIRZEPATIDE NEL DM2:PROGRAMMA SURPASS

Monotherapy	2-Drug Combination	2-3 Drug Combinations	2-4 Drug Combinations	Combination With Insulin
SURPASS-1 **vs placebo**[1]	**SURPASS-2** **vs semaglutide**[2] Add-on to metformin	**SURPASS-3** **vs insulin degludec**[3] Add-on to metformin with or without SGLT2i	**SURPASS-4** **vs insulin glargine**[4] Add-on to ≥1 and ≤3 oral antidiabetic medications (metformin, SGLT2i, or SU)	**SURPASS-5** **vs placebo**[5] Both with insulin glargine with or without metformin **SURPASS-6** **vs insulin lispro**[6] **(TID)** Both with insulin glargine with or without metformin
Mean T2D duration 4.7 years Mean age=54.1 years N=478	Mean T2D duration 8.6 years Mean age=56.6 years N=1878	Mean T2D duration 8.4 years Mean age=57.4 years N=1437	Mean T2D duration 11.8 years Mean age=63.6 years N=1995	Mean T2D duration 13.3 years Mean age=60.6 years N=475

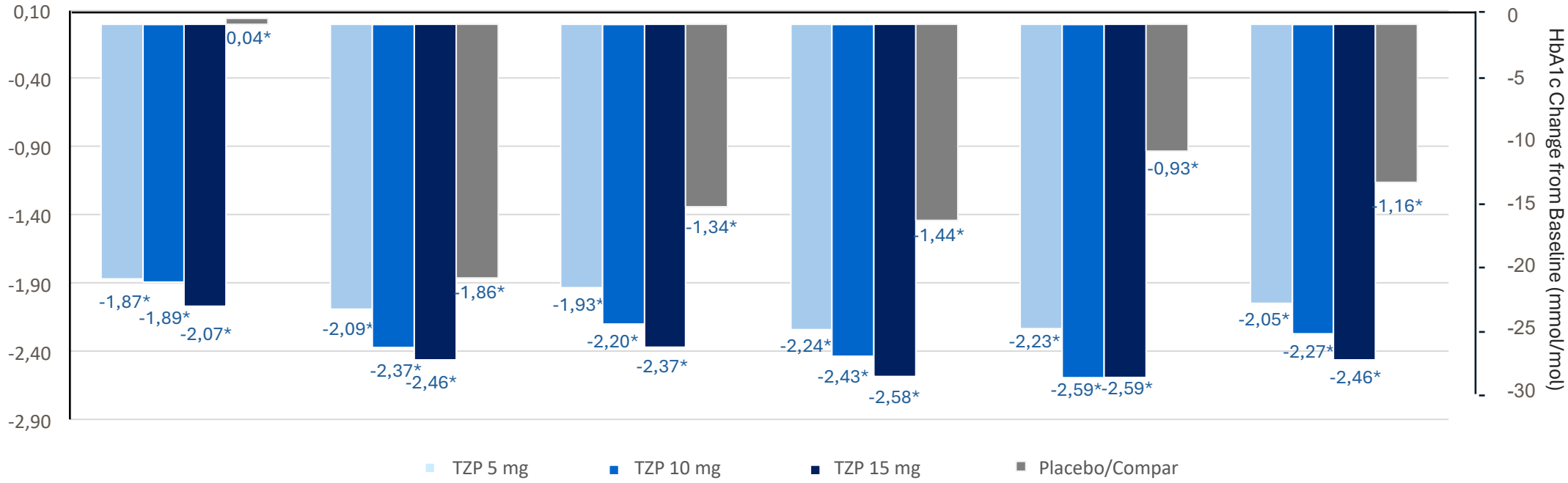
SURPASS: DISEGNO GENERALE DEGLI STUDI



Obiettivo primario: Superiorità e/o non inferiorità di TZP 5 mg e/o 10 mg e/o 15 mg vs. placebo o comparatore attivo per la **variazione media HbA1c** rispetto al basale dopo 40 o 52 settimane di terapia

RIDUZIONE DI GLICATA E POSOLOGIA TZP

Study	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]	SURPASS-6[6]
Duration	40 Weeks	40 Weeks	52 Weeks	52 Weeks	40 Weeks	52 Weeks
Baseline HbA1c	7.9%	8.3%	8.2%	8.5%	8.3%	8.8%
N	478	1879	1444	2002	475	1425



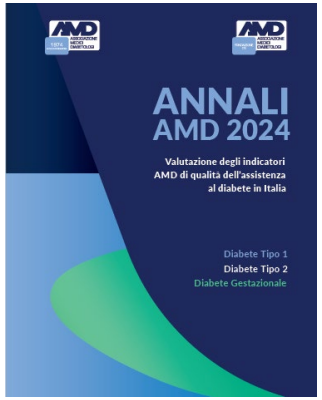
Superiority vs.	Placebo	SEMA 1 mg	Insulin degludec	Insulin glargine	Placebo	Insulin lispro
Background therapy	Monotherapy	Add-on to MET	Add-on to MET or MET + SGLT2i	Add-on to MET, SGLT2i, or SU	Add-on to insulin glargine ± MET	Add-on to insulin glargine ± MET

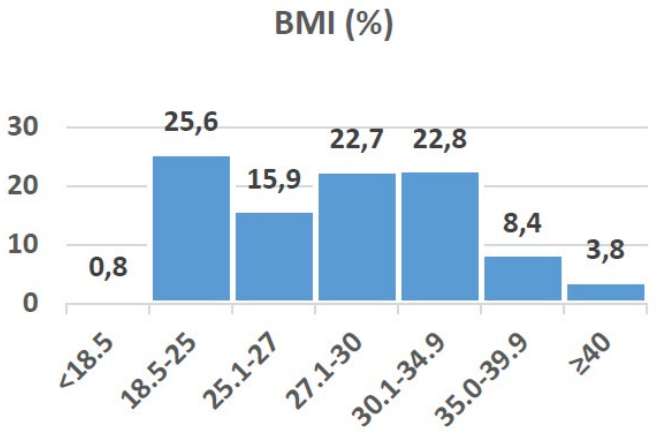
Diabetes Care Volume 48, Supplement 1, January 2025 S167

8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes–2025

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2025;48(Suppl. 1):S167–S180 | https://doi.org/10.2337/dc25-S008





8.15 When choosing glucose-lowering medications for people with type 2 diabetes and overweight or obesity, prioritize medications with beneficial effect on weight. **B**

8.16 Weight management pharmacotherapy should be considered for people with diabetes and overweight or obesity along with lifestyle changes. Potential benefits and risks must be considered. **A**

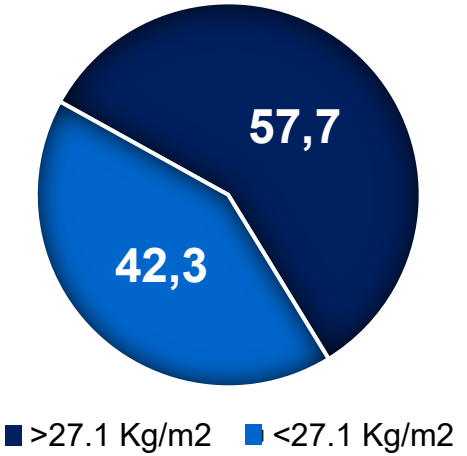
8.17 In people with diabetes and overweight or obesity, the preferred pharmacotherapy should be a glucagon-like peptide 1 receptor agonist or dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist with greater weight loss efficacy (i.e., semaglutide or tirzepatide), especially considering their added weight-independent benefits (e.g., glycemic and cardiometabolic). **A**

La scelta della terapia dovrebbe tenere in conto il controllo del peso

Il **controllo del peso** dovrebbe essere considerato nel trattamento del diabete

Utilizzare preferenzialmente **GLP-1**RA o **GLP-1-GIP** RA

BMI≥ 27.1 Kg/m^2 (57,7%)

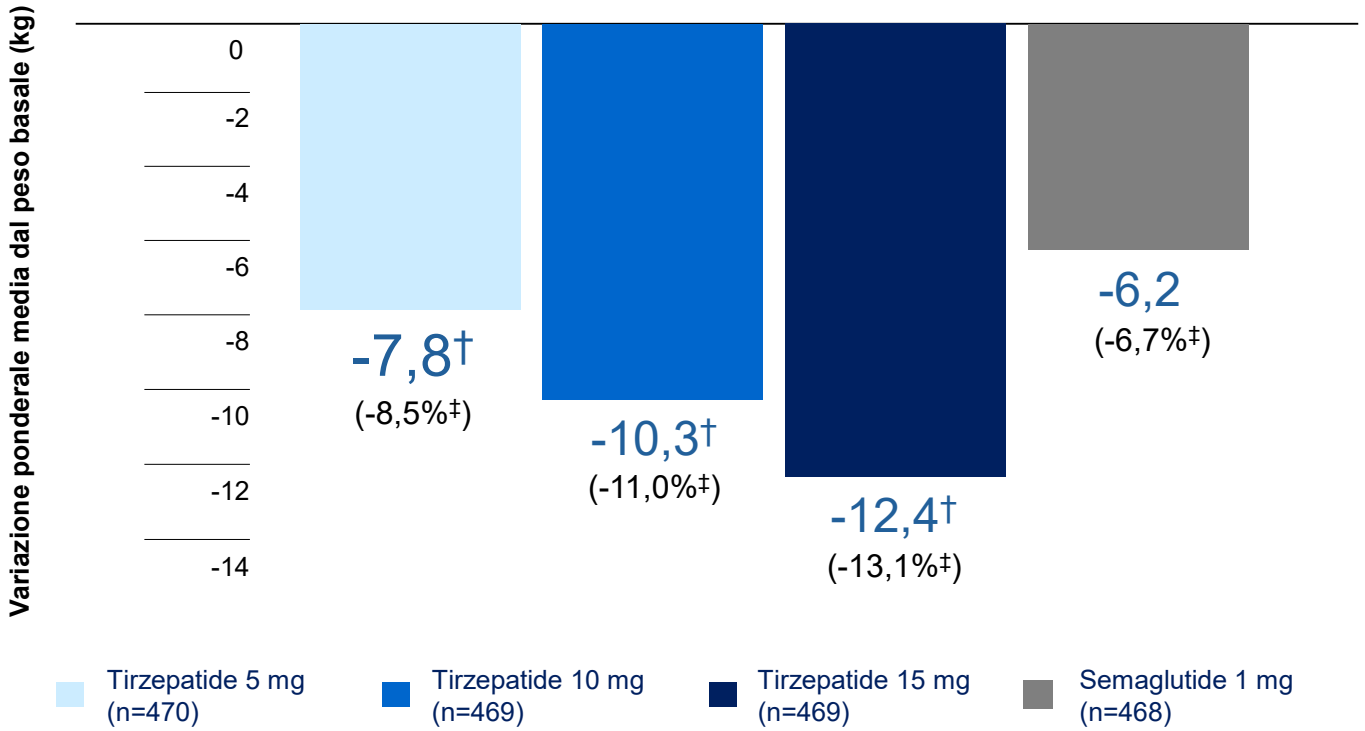


SURPASS: RIDUZIONE DEL PESO

Endpoint secondario principale*

Variazione ponderale media dal basale a 40 settimane

Peso medio generale al basale: 93,7 kg



*Negli studi clinici SURPASS la variazione ponderale era un endpoint secondario.[1]

†p<0,001 vs semaglutide 1 mg per la superiorità, aggiustato per la molteplicità.[1,2] ‡Variazione percentuale dal peso medio al basale del rispettivo braccio di trattamento.

La percentuale di calo ponderale era un calcolo approssimativo della media LS per la variazione dal basale divisa per il valore basale medio.[1]

Estimand di efficacia: analisi MMRM, popolazione mITT (set di analisi di efficacia). I dati presentati sono medie LS. Tirzepatide vs semaglutide 1 mg a 40 settimane.[2]
LS = minimi quadrati; mITT = intent-to-treat modificata; MMRM = modelli misti per misure ripetute.

1. Tirzepatide. Riassunto delle Caratteristiche del Prodotto. 2. Frías JP, et al. N Engl J Med. 2021;385(6):503-515.

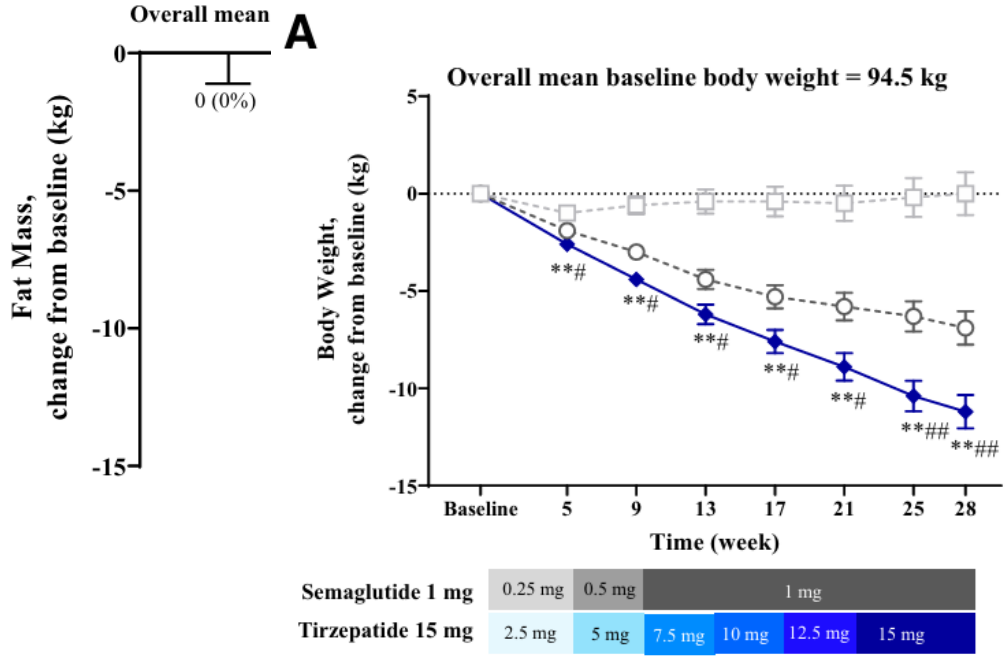
Diabetes Care Volume 46, May 2023

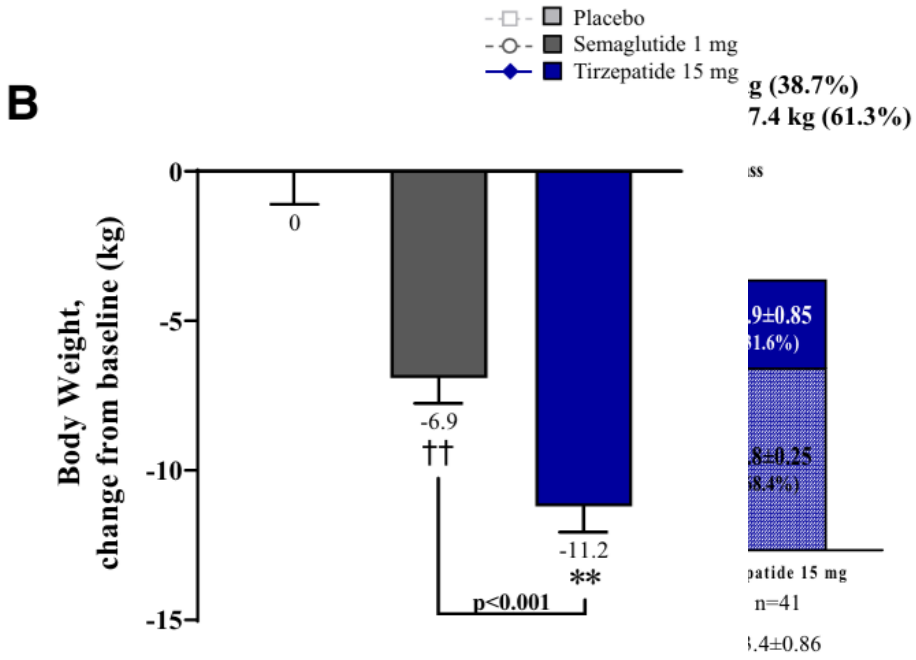
Tirzepatide Reduces Appetite, Energy Intake, and Fat Mass in People With Type 2 Diabetes

Tim Heise,[1] J. Hans DeVries,[1] Shweta Urva,[2] Jing Li,[2] Edward J. Pratt,[2] Melissa K. Thomas,[2] Kieren J. Mather,[2] Chrisanthi A. Karanikas,[2] Julia Dunn,[2] Axel Haupt,[2] Zvonko Milicevic,[2] and Tamer Coskun[2]

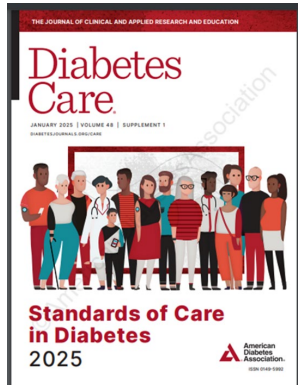
Diabetes Care 2023;46:998–1004 | https://doi.org/10.2337/dc22-1710

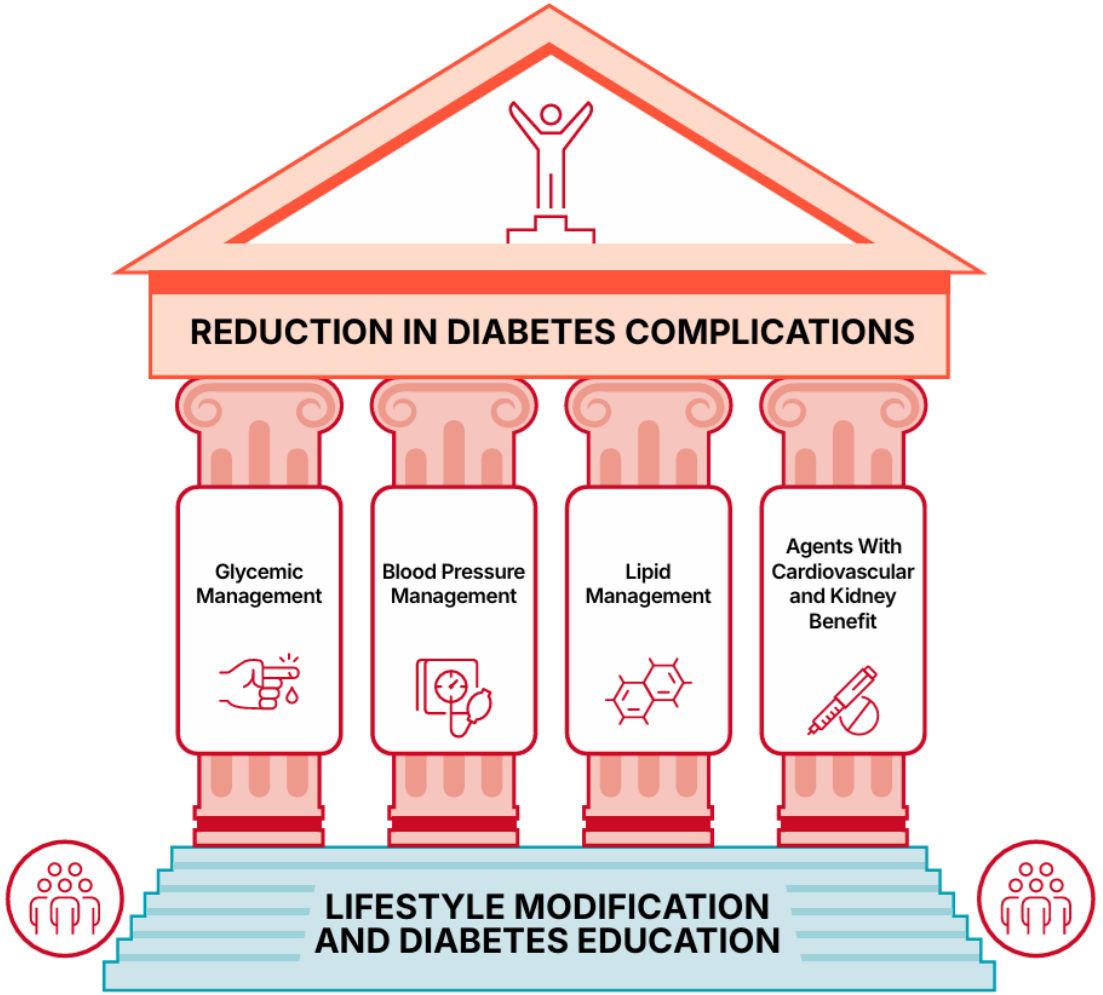
Analisi secondaria di uno studio RCT che ha valutato gli effetti di TZP 15 mg (n=45), semaglutide 1 mg (n=44) e placebo (n=28), dopo 28 settimane di trattamento, su peso e composizione corporea, appetito ed intake calorico.



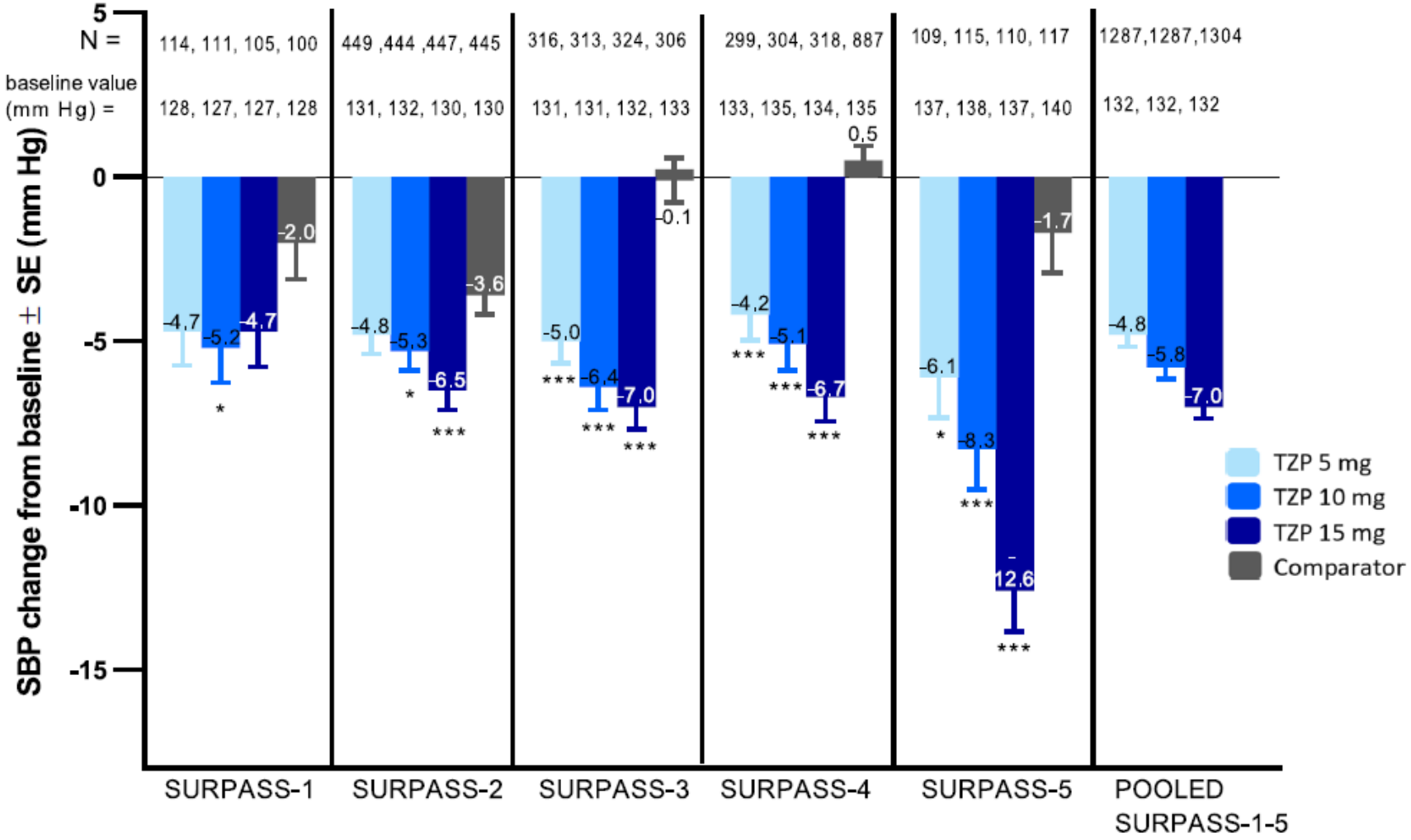


TIRZEPATIDE: OLTRE LA GLICATA ED IL CALO PONDERALE





SURPASS: RIDUZIONE DEI VALORI PRESSORI SISTOLICI

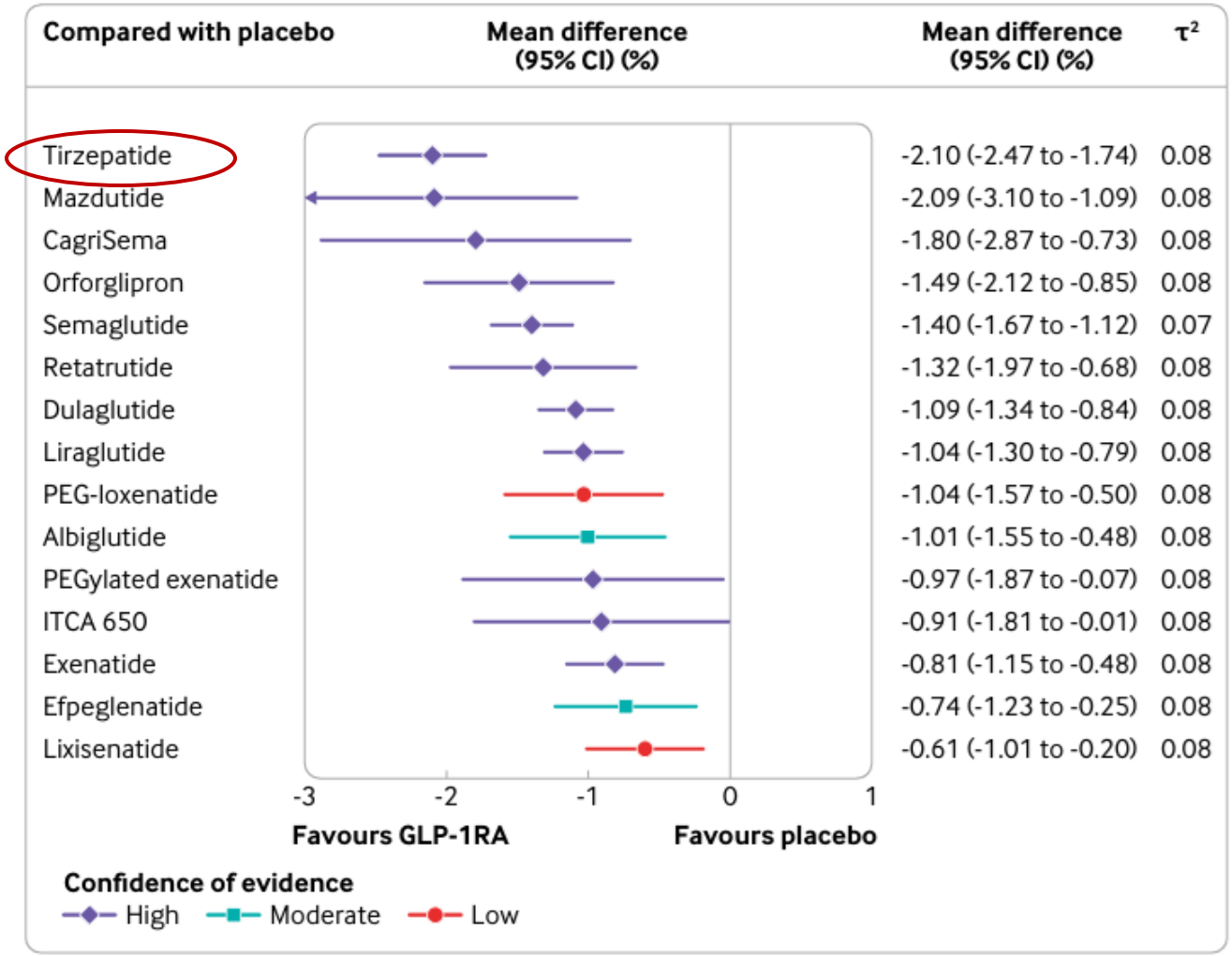


Lingvay et al. *Cardiovascular Diabetology 2023;22:66*

Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis

thebmj | *BMJ* 2024;384:e076410 | doi: 10.1136/bmj-2023-076410

Haiqiang Yao,[1,2] Anqi Zhang,[2] Delong Li,[1,2] Yuqi Wu,[1,2] Chong-Zhi Wang,[3,4] Jin-Yi Wan,[1,2] Chun-Su Yuan[3,4]



Dati estratti da 76 RCT per un totale di 39.246 partecipanti.
Analizzati 15 GLP-1RAs in adulti con DM2.

Forest plot of network effect sizes between GLP-1RAs and placebo for **HbA1c** measured in percentage

. According to the network confidence meta-analysis (CINeMA) framework, the certainty of evidence is visually represented in the forest map, with varying colours indicating different confidence levels. The complete CINeMA assessments are shown in appendix 9. GLP-1RA=glucagon-like peptide-1 receptor agonist; PEG loxenatide=polyethylene glycol loxenatide; ITCA 650=a combination of drug and device containing exenatide in osmotic mini pump

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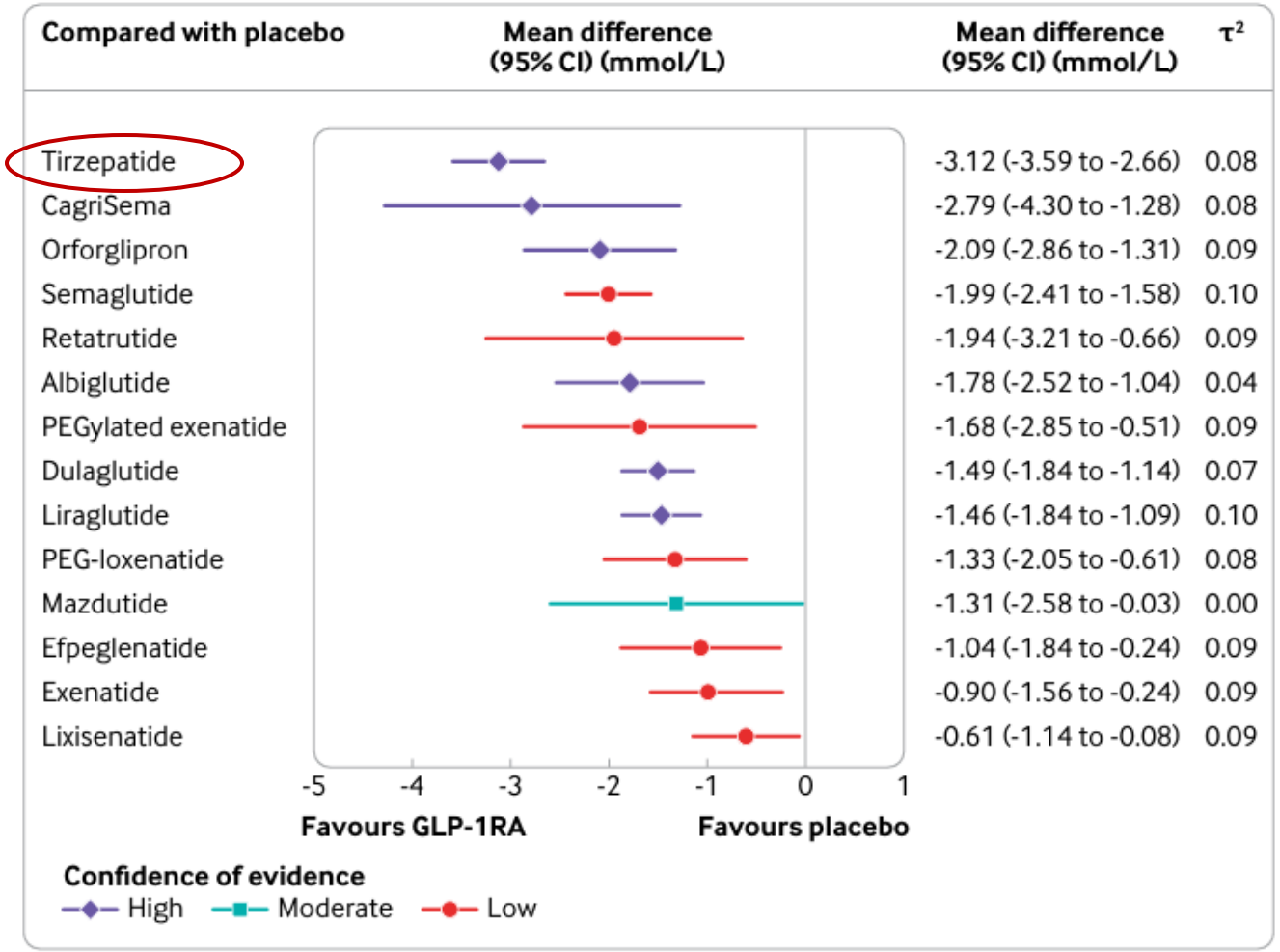

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Forest plot of network effect sizes between GLP-1RAs and placebo for **fasting glucose**

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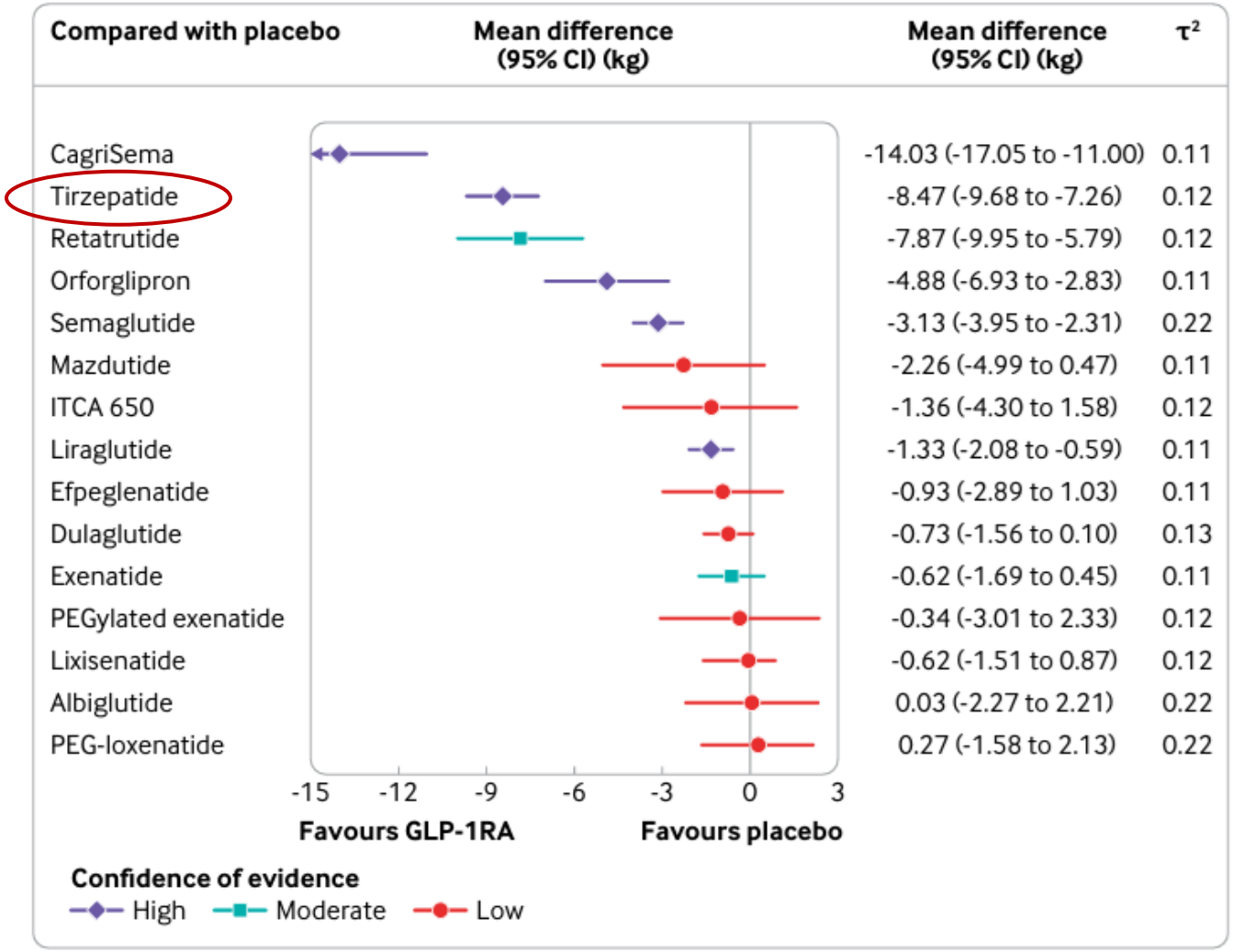

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Forest plot of network effect sizes between GLP-1RAs and placebo for **body weight**

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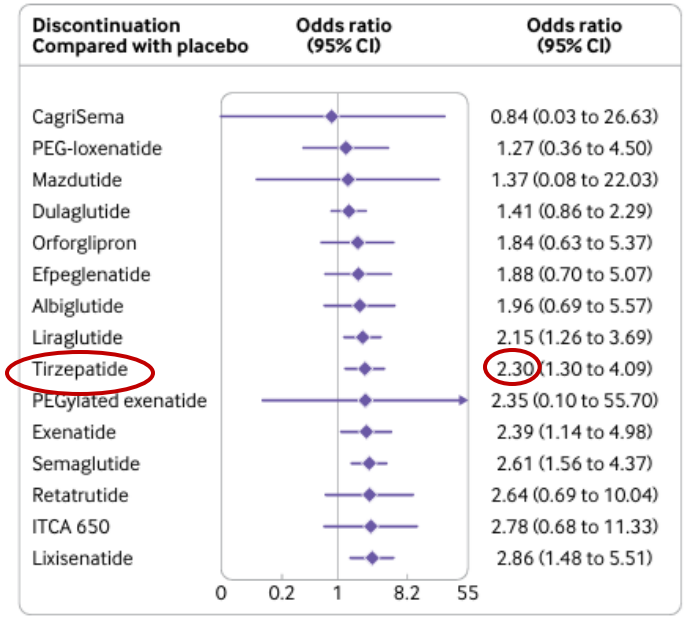

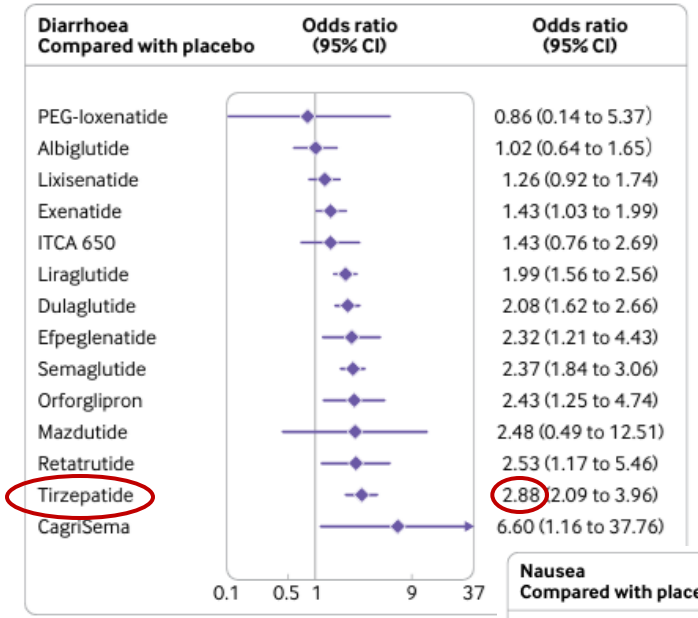

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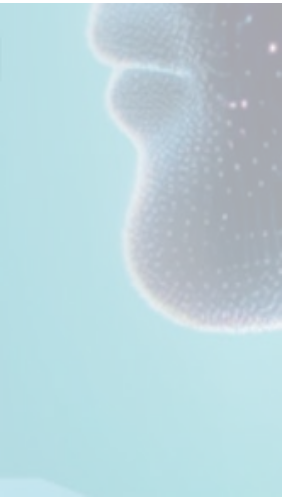

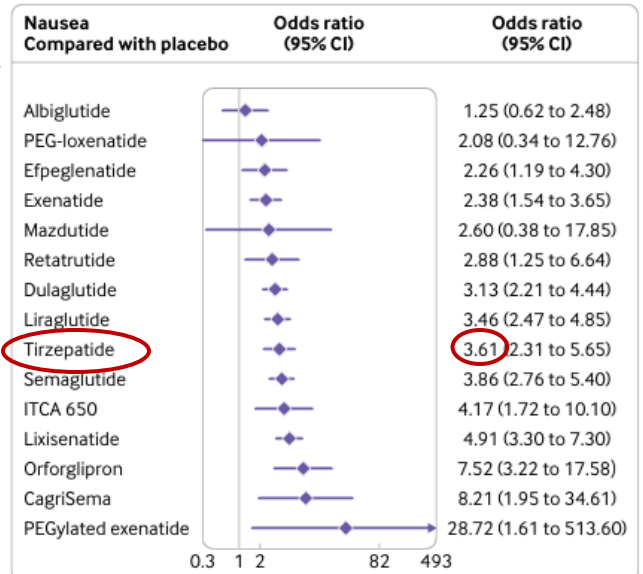

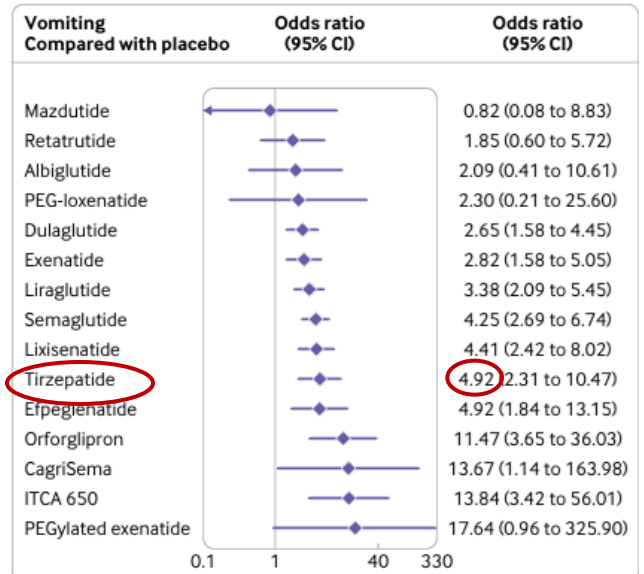

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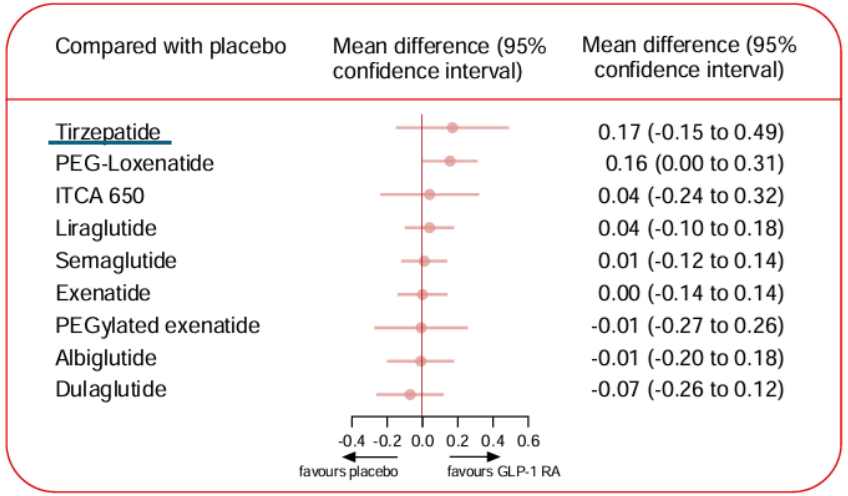
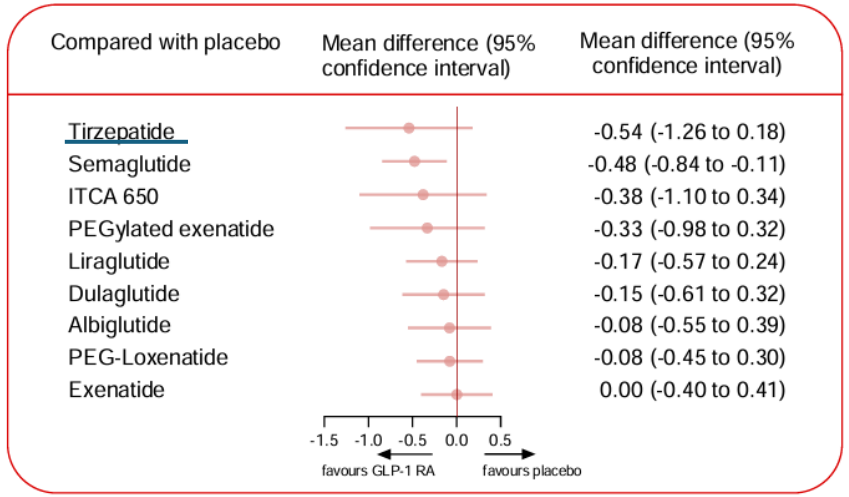
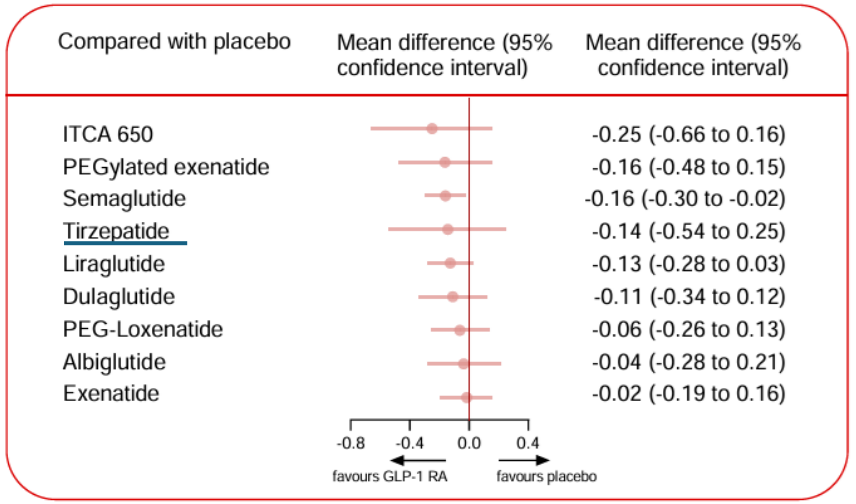
HDL colesterolo



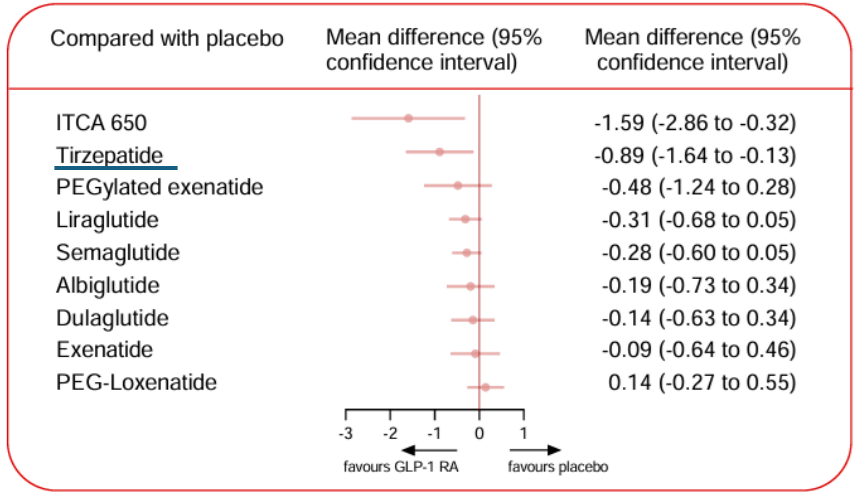
Colesterolo tot



LDL colesterolo



Trigliceridi



Yao H et al. *BMJ 2024* 384:e076410

Nauck and D'Alessio
Cardiovascular Diabetology (2022) 21:169
https://doi.org/10.1186/s12933-022-01604-7

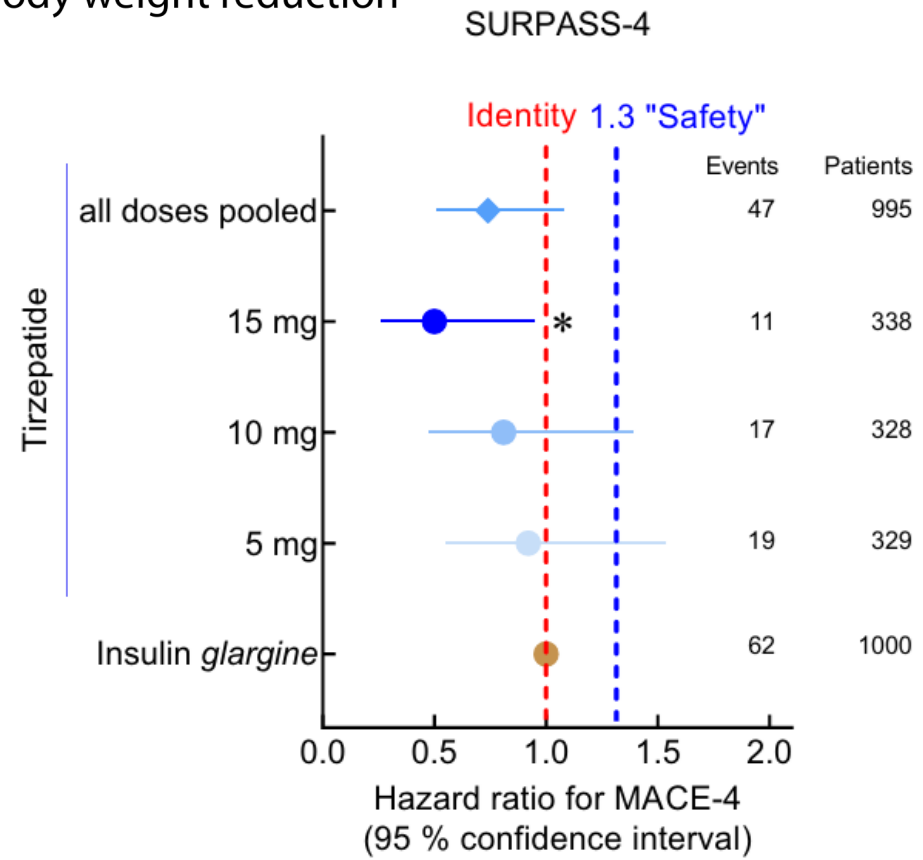
Cardiovascular Diabetology

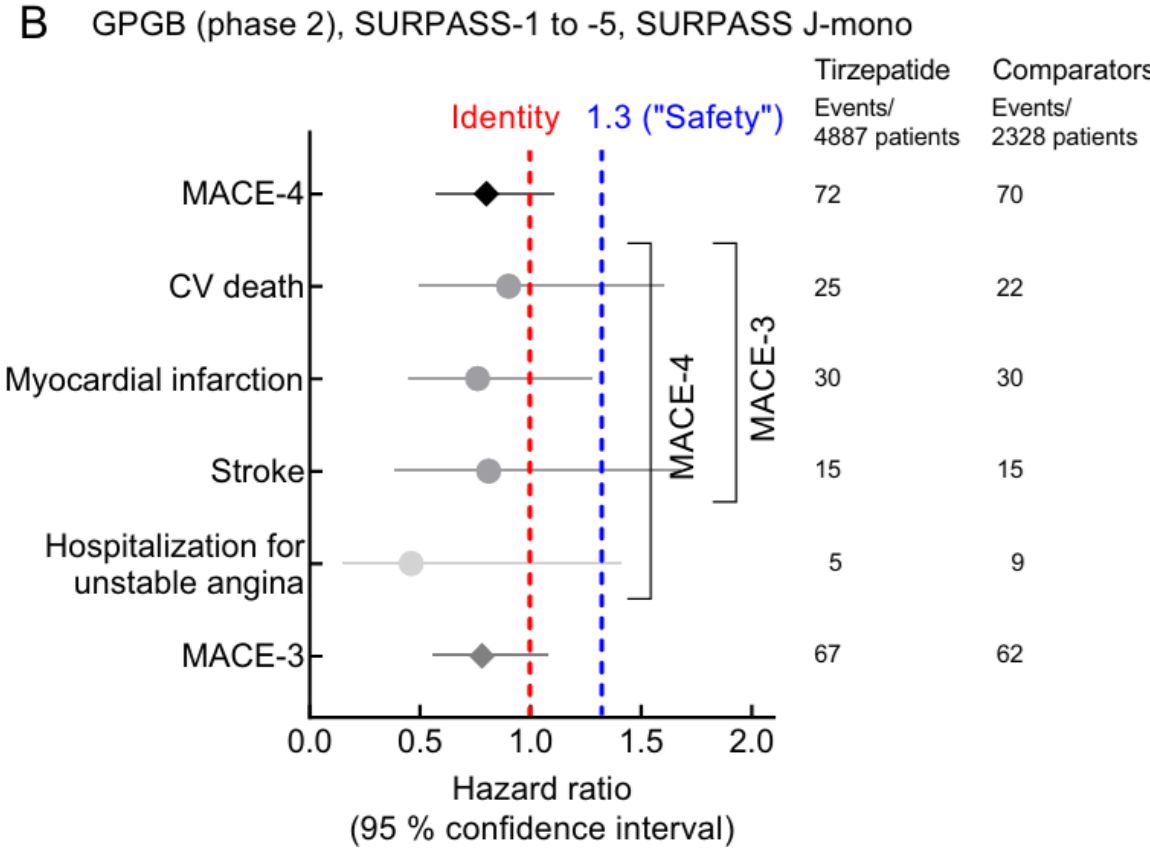
SURPASS e SICUREZZA CARDIOVASCOLARE

REVIEW Open Access

Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight reduction

Michael A. Nauck[1*] and David A. D'Alessio[2]





MACE-4 (IMA non fatale, ictus non fatale, morte CV, ospedalizzazione per angina) tendon ad essere ridotti in un period di osservazione di 2 anni, sebbene con un basso numero di eventi. Per nessuno degli eventi (MACE-4, o single componenti) si è osservato un hazard ratio > 1.0 vs comparatore in tutto il programma di studi SURPASS, con limite superiore dell'inetrvallo di confidenza per MACE < 1,3 soddisfacendo i criteri di sicurezza CV.

SURPASS-CVOT: DISEGNO DELLO STUDIO

- ✓ E' l'unico trial event-driven, RCT cardiovascolare di confronto testa a testa tra due comparatori, tirzepatide alla massima dose tollerata (5 mg,10 mg, 15 mg) e dulaglutide 1,5 mg.
- ✓ Farmaci aggiungi alla standard of care in pazienti con ASCVD conclamata.
- ✓ Condotto in 640 Centri ed in 30 Paesi su 13,299 persone con DM2.
- ✓ La randomizzazione è stata condotta 1:1 in base al Pese di origine ed all'utilizzo di SGLT2i. Follow up 4 anni circa.
- ✓ **Endpoint composito primario:** non inferiorità per tempo del primo evento tra morte CV, IMA e ictus (MACE 3).

Comparison of tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease: SURPASS-CVOT design and baseline characteristics

Stephen J. Nicholls, MBBS, PhD[a], Deepak L Bhatt, MD[b], John B Buse, MD[c], Stefano Del Prato, MD[d], Steven E Kahn, MBChB[e], A Michael Lincoff, MD[f], Darren K McGuire, MD, MHSc[g], Michael A Nauck, MD[h], Steven E Nissen, MD[f], Naveed Sattar, MD[i], Bernard Zinman, MD[j], Sophia Zoungas, MBBS PhD[a,k], Jan Basile, MD[l], Amy Bartee, DNP[m], Debra Miller, RN[m], Hiroshi Nishiyama, PhD[m], Imre Pavo, MD[m], Govinda Weerakkody, PhD[m], Russell J Wiese, PhD[m], and David D'Alessio, MD[n], on behalf of the SURPASS-CVOT investigators *Melbourne, Australia; New York, NY; Chapel Hill, NC; Pisa, Italy; Seattle, WA; Cleveland, OH; Dallas, TX; Bochum, Germany; United Kingdom; ON, Canada; Melbourne, Australia; Charleston, SC; Indianapolis, IN; Durham, NC*

Endpoint secondari:

- ✓ singole componenti del MACE 3;
- ✓ Un'estensione dell'endpoint primario che include rivascolarizzazione cardiaca e ospedalizzazione per angina instabile;
- ✓ mortalità per tutte le cause;
- ✓ scompenso cardiaco che abbia richiesto la ospedalizzazione e/o visita urgente per scompenso cardiaco.
- ✓ Declino della funzione renale, HbA1c, peso corporeo.

Table I. SURPASS-CVOT eligibility criteria.

Key inclusion criteria
Men or women ≥40 Y old with type 2 diabetes (HbA1c ≥7% and ≤10.5%) and BMI ≥25kg/m^2
Established atherosclerotic cardiovascular disease, including ≥1 of the following
1. Coronary artery disease with any of the following:
a. Documented history of myocardial infarction
b. ≥50% stenosis in ≥1 major coronary arteries determined by invasive angiography
c. ≥50% stenosis in 2 or more major coronary arteries, determined by computed tomography coronary angiography
d. History of surgical or percutaneous coronary revascularization procedure
2. Cerebrovascular disease (any of the following):
a. Documented history of ischemic stroke
b. Carotid arterial disease with ≥50% stenosis, documented by carotid ultrasound, MRI, or angiography
c. History of carotid stenting or surgical revascularization
3. Peripheral arterial disease with either of the following:
a. Intermittent claudication and ankle-brachial index <0.9
b. Prior nontraumatic amputation or peripheral vascular procedure (eg, stenting or surgical revascularization), due to peripheral arterial ischemia

SURPASS-CVOT: DISEGNO DELLO STUDIO

Table II. Baseline clinical characteristics in SURPASS-CVOT.

	SURPASS-CVOT ($N = 13,299$)
Age, years	64.1 ± 8.8
Sex, female	3849 (28.9)
Geography	
North America	1955 (14.7)
South America	3833 (28.8)
Europe	6149 (46.2)
Asia-Pacific	1,362 (10.2)
Weight, kg	92.5 ± 18.8
BMI, kg/m^2	32.6 ± 5.5
History	
Coronary artery disease	8,649 (65.0)
Myocardial infarction	6,288 (47.3)
Coronary revascularization procedure	7,630 (57.4)
Stroke	2,541 (19.1)
Peripheral artery disease	3,369 (25.3)
Hypertension	11,986 (90.1)
Dyslipidemia	1,1406 (85.8)
Current tobacco use	1,978 (14.9)
Diabetes duration, years	14.7 ± 8.8
Systolic blood pressure, mm Hg	135.0 ± 15.7
Diastolic blood pressure, mm Hg	77.7 ± 9.7
HbA1c, %	8.4 ± 0.9
eGFR (CKD-EPI), mL/Min/1.73 m^2	76.5 ± 21.3
<60 mL/Min/1.73 m^2	3,029 (22.8)
UACR, mg/g	22.0 (9.0, 83.0)
Microalbuminuria	4,179 (32.0)
Macroalbuminuria	1,503 (11.5)

Data are mean ± SD, n (%), or median (interquartile range).
Percentage is based on number of participants with nonmissing measurement at baseline.
BMI, body mass index; *CKD-EPI*, chronic kidney disease-epidemiology; *eGFR*, estimated glomerular filtration rate; *HbA1c*, glycated hemoglobin A1c; *SD*, standard deviation; *UACR*, urine albumin-creatinine ratio.

Terapie:

- ✓ Il 97.3% dei partecipanti utilizzava terapia farmacologica al basale: metformina (81.1%), insulina (46.7%), SGLT-2 inibitori (30.6%), sulfaniluree (20.5%).
- ✓ L'uso e/o il dosaggio di sulfaniluree, insuline rapide e inibitori DPPIV è stato ridotto o sospeso prima della randomizzazione.

SURPASS-CVOT: RISULTATI

	Tirzepatide	Dulaglutide
Endpoint primario		
MACE 3	HR=0,92 95.3% CI :0.83-1.01 p non inferiorità = 0.003 p superiorità=0.086	
Endpoint secondari		
Morte per tutte le cause	HR=0,84 95.0% CI :0.75- 0.94 p=0.002	
Variazioni di e-GFR nella popolazione con malattia renale cronica ed e-GFR basale medio di 53,4 ml/min/1.73 m^2 a 36 mesi	-4,97 ml/min/1.73 m^2	-8.51 ml/min/1.73 m^2 Differenza stimata per trattamento 3,54ml/min/1.73 m^2 (95.0% CI: 2.57-4,5) p<0,001
Riduzione di HbA1c dal basale medio di 8,39% a 36 mesi	- 1.73%	- 0.9% Differenza stimata per trattamento -083% (95.0% CI: 0,88-0,78) p<0,001
Riduzione di peso corporeo dal basale medio di 92,6 Kg a 36 mesi	-12,06% (-11,43 kg)	-4,95% (-4,65 kg) Differenza stimata per trattamento -7,1% (95.0% CI: -7,4—6,8) p<0,001

SURPASS-CVOT: RISULTATI (EASD)

- ✓ **Altri endpoint secondari**:
  - ✓ Riduzione del rischio di endpoint esteso (morteCV/IMA/ictus/rivascolarizzazione) con TZP vs dulaglutide (HR = 0.81-0.96)
  - ✓ Singole componenti MACE 3: tendenza alla riduzione di IMA (HR = 0.86; 95% CI, 0.74-1), ictus (HR = 0.91; 95% CI, 0.76-1.09), morte CV (HR = 0.89; 95% CI, 0.77-1.02)
  - ✓ Tendenza alla riduzione dell'endpoint morte CV e ospedalizzazione/visite per scompenso cardiaco (HR = 0.91; 95% CI, 0.81-1.03).

- ✓ **Eventi avversi:**
  I più frequenti sono stati nausea (25.1% TZP e 22.4% dulaglutide) e diarrea (24.8% TZP e 19.1% dulaglutide).

SURPASS-CVOT: INTERPRETAZIONE

- ✓ Lo studio SURPASS-CVOT dimostra che tirzepatide è altrettanto efficace rispetto a dulaglutide nel prevenire morte CV, IMA ed ictus in un periodo di 4 anni, con dati più favorevoli sulla mortalità totale.

- ✓ Tirzepatide, rispetto a dulaglutide 1,5 mg, offre vantaggi su peso, HbA1c e filtrato renale.

- ✓ L'analisi statistica di confronto vs placebo stimata in modo indiretto (confrontando pazienti del SURPASS-CVOT con i pazienti del REWIND) mostra una riduzione dei MACE 3 del 28% (HR = 0.72; 95% CI, 0.55-0.94; *P* = 0.02) e una riduzione della mortalità per tutte le cause del 39% (HR= 0.61; 95.0% CI: 0.45 to 0.82).

American Diabetes Association. | 85TH SCIENTIFIC SESSIONS | CHICAGO, IL JUNE 20–23, 2025

SURPASS-CVOT: analisi comparativa basata sui dati *real-world* dello studio su tirzepatide rispetto a dulaglutide sugli eventi CV maggiori in persone con DT2

Presentato da: **John Ostrominski***, MD

*Cardiovascular Medicine and Obesity Medicine,
Brigham and Women's Hospital and Harvard Medical School, Boston, MA; USA

TIRZEPATIDE E CVD: DATI REAL WORLD

- ✓ L'obiettivo di questo lavoro è stato di simulare lo studio SURPASS-CVOT utilizzando dati amministrativi da database assicurativi.
- ✓ Sono stati utilizzati dati di una compagnia assicurativa privata (per il periodo giugno 2022 – agosto 2024) ed identificati 15.775 coppie di adulti che avevano iniziato tirzepatide o dulaglutide, abbinati 1:1 tramite *propensity score* e stratificati in base all'uso al basale di SGLT2i.
- ✓ L'endpoint primario era rappresentato dagli eventi cardiovascolari maggiori (MACE: infarto miocardico, ictus o mortalità).
- ✓ Sono stati stimati gli hazard ratio (HR) e i relativi IC al 95%, con correzione per 125 covariate.
- ✓ Sono state inoltre condotte analisi aggiustate per HbA_{1c} nei soggetti con valori disponibili (54% della popolazione).
- ✓ Nel corso di un follow-up mediano di circa 6 mesi, tirzepatide è risultata associata a una **riduzione del 37% dei MACE** rispetto a dulaglutide.
- ✓ I risultati sono stati coerenti anche nell'analisi aggiustata per HbA_{1c} (HR 0,77; IC 95%: 0,62-0,95) e, in entrambe le analisi, indipendentemente dall'uso di SGLT2i.

TIRZEPATIDE E CVD: DATI REAL WORLD

	Coorte complessiva			Coorte aggiustata per HbA_{1c}[a]		
Caratteristiche dei pazienti, n (%)	**Tirzepatide (N = 115.775)**	**Dulaglutide (N = 15.775)**	**Abs Std diff[b]**	**Tirzepatide (N = 8578)**	**Dulaglutide (N = 8578**	**Abs Std diff[b]**
eGFR medio, ml/min/1,73 m_2 (DS)	74,01 (21,67)	73,74 (22,15)	0,012	73,91 (21,51)	73,55 (21,82)	0,017
Analisi primaria	**N di eventi (IR/1000 anni-persona)**	**N di eventi (IR/1000 anni-persona)**	**HR (IC 95%)**	**N di eventi (IR/1000 anni-persona)**	**N di eventi (IR/1000 anni-persona)**	**HR (IC 95%)**
Eventi cardiovascolari maggiori	275 (28,36)	384 (45,87)	0,63 (0,54, 0,73)	163 (30,73)	183 (40,05)	0,77 (0,62, 0,95)

Le caratteristiche dei pazienti sono state misurate nei 12 mesi precedenti la data di inizio del trattamento (inclusa). L'HbA_{1c} era disponibile per il 54% dei soggetti e l'eGFR per il 56%.
[a]Limitato ai soggetti con risultati di laboratorio disponibili e aggiustato in base al livello basale dell'HbA_{1c} tramite *propensity score matching*. [b]Valori >0,1 indicano uno squilibrio significativo. [c]Infarto miocardico, ictus o mortalità.
Abs Std diff = *absolute standard differences*, differenze standard assolute; BMI = *body mass index*, indice di massa corporea; CED = *cohort entry date*, data di ingresso nella coorte; IC = intervallo di confidenza; eGFR = *glomerular filtration rate*, velocità di filtrazione glomerulare stimata; HbA_{1c} = emoglobina glicata; HR = hazard ratio; IR = *incidence rate*, tasso di incidenza; DS: deviazione standard.

«In un'analisi osservazionale che simula il SURPASS-CVOT, tirzepatide ha ridotto significativamente gli eventi cardiovascolari maggiori rispetto a dulaglutide in persone con DM2 e ASCVD.
I risultati, coerenti anche dopo aggiustamento per HbA_{1c}, supportano il potenziale beneficio cardiovascolare di tirzepatide».

TIRZEPATIDE NEL DM1

Studi retrospettivi di coorte:

✓ Akturk, HK et al.
Efficacy and Safety of Tirzepatide in Adults with Type 1 Diabetes: A Proof of Concept Observational Study.
J. Diabetes Sci. Technol. 2024, 19322968231223991.
26 pz

✓ Garg SK et al.
Cardiovascular and renal biomarkers in overweight and obese adults with type 1 diabetes treated with tirzepatide for 21 months.
Diabetes Technol Ther 2025;27:152–60.
84 pz

✓ Karakus, KE et al
Changes in Basal and Bolus Insulin Requirements with Tirzepatide as an Adjunctive Therapy in Adults with Type 1 Diabetes Using Tandem Control-IQ.
Diabetes Ther. 2024, 15, 1647–1655.
11 pz

✓ Rivera Gutierrez R et al
Effect of Tirzepatide on Body Weight and Diabetes Control in Adults With Type 1 Diabetes and Overweight or Obesity.
Mayo Clin. Proc. 2024, 100, 265–275.
51 pz

TIRZEPATIDE NEL DM1 (EASD)

Tirzepatide reduces weight and insulin dose and improves body composition in type 1 diabetes: a 12-week, randomised, double-blind, placebo-controlled trial (TIRTLE1)

J.R. Snaith [1,2], R. Frampton[1,2], D. Samocha-Bonet[1], J.R. Greenfield[1,2];

[1]Diabetes and Metabolism, Garvan Institute of Medical Research, Darlinghurst, Australia, [2]St Vincent's Clinical Campus, University of New South Wales, Sydney, Australia.

- ✓ E' il primo studio RCT doppio cieco, placebo controllato, su **24 adulti con DM1** con obesità (BMI >30), e durata di malattia > 2 anni.
  - ➢ **Endpoint primario:** variazioni del peso corporeo.
  - ➢ **Endopoint secondari:** posologia dell'insulina, HbA1c, apporto calorico e composizione corporea

- ✓ **Risultati**: TZP ha determinato un significativo calo ponderale di 8,7kg **(8,8%;** 95% IC, -12.0 -5,5Kg, p p<0.0001), con perdita di peso attribuibile per l'82% alla perdita di massa grassa (differenza media -7.2 kg; 95% CI, -10.5 -3.9 kg; p=0.0002).
- ✓ Riduzione della posologia di insulina del **35.1%** vs placebo (95% CI, -46.5 to -21.3%; p=0.0002).
- ✓ Riduzione modesta di HbA1c (differenza media di **-0.35%;** 95% CI, -0.7 0.0%; p=0.05).
- ✓ Riduzione globale dell'intake calorico (differenza media -**429 kcal/d** [95% CI -852 -5 kcal/d]
- ✓ **Nessuna ipoglicemia severa nè DKA riportate.**

TIRZEPATIDE NEL DM1

Open access Protocol

BMJ Open

Tirzepatide for the treatment of adults living with concurrent type 1 diabetes and overweight or obesity (TZP-T1D): a double-blind, placebo-matched randomised controlled trial protocol

Amanda R Purcell [1], Natassia Rodrigo,[1,2,3,4] Matilda S G Longfield [1,3] Sarah J Glastras [1,2,3]

Trial registration number: NCT06180616.

- ✓ Studio RCT doppio cieco, placebo controllato che ha valutato l'efficacia di TZP in adulti con DM1 e sovrappeso/obesità in 32 settimane
- ✓ 60 partecipanti (età 18–70 anni) con BMI ≥27 kg/m2 e HbA1c≤10% sono stati randomizzati 1:1 a ricevere tirzepatide o placebo, accanto alla terapia insulinica.

- ✓ **Endpoint primario**: variazione del peso corporeo (%).
- ✓ **Endpoint secondari**: variazioni della HbA1c (%), proporzione di calo ponderale(>5%, >10%, >15% and >20%), variazioni nelle dosi di insulina, TIR valutato tramite CGM severità delle comorbidità.
- ✓ Dati non pubblicati.

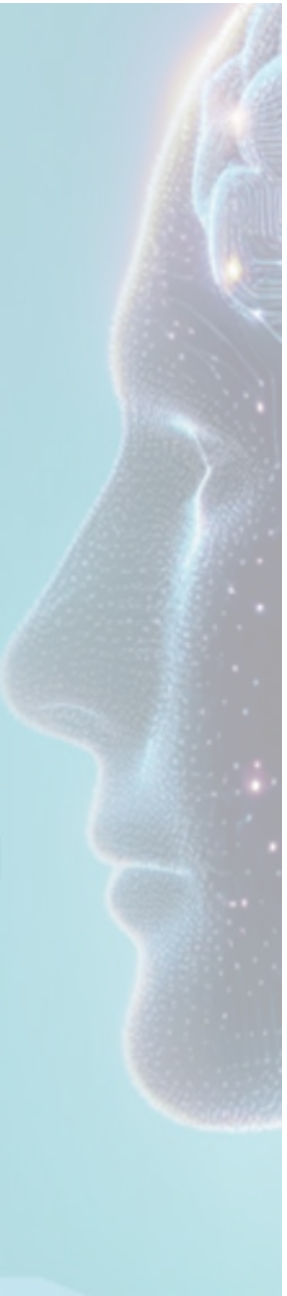
Altro grande studio RCT in fase di arruolamento (iniziato a maggio 2025 e che si prevede terminerà a dicembre 2027-trial registration number **NCT06962280)** su DM1 in 80,centri USA, Sud America, Europa.

Purcell AR, *et al. BMJ Open* 2025;**15**:e093775.

THE LANCET

www.thelancet.com Published online September 17, 2025 https://doi.org/10.1016/S0140-6736(25)01774-X

Volume 406, Issue 10511, P1484-1496,



Efficacy and safety of tirzepatide in children and adolescents with type 2 diabetes (SURPASS-PEDS): a randomised, double-blind, placebo-controlled, phase 3 trial

Tamara S Hannon, Lily C Chao, Margarita Barrientos-Pérez, Karthik Chandrasekhar Pamidipati, Laura Fernández Landó, Clare J Lee, Hiren Patel, Brandon K Bergman

- ✓ Studio multicentrico (39 centri), 8 Paesi, della durata di 30 settimane, seguite da altre 22 Settimana in aperto in cui tutti i pazienti sono stati trattati con TZP.
- ✓ Arruolati **99 bambini ed adolescenti** (età 10-17 anni) con DM2 con peso > 50 kg e BMI oltre l'85°pc per sesso ed età, in trattamento con metofomina e/o insulina basale.
- ✓ I partecipanti sono stati randomizzati (1:1:1) a ricevere TZP 5 m g (n=32), TZP 10 mg (n=33) o placebo (n=34) per 30 settimane.
- ✓ Dopo la 30° Settimana il gruppo TZP ha continuato a ricevere la stessa terapia, mentre il gruppo placebo è stato assegnato a TZP 5 mg, fino alla settimana 52.

Endpoint primario: variazioni di HbA1c dal basale alla 30° settimana.

Endpoint secondari: variazioni della glicemia a digiuno e variazioni di BMI (DS e %).

Tutti i dati sono stati rivalutati a 52 settimane. Raccolti dati di sicurezza.

PREVENIRE E’ MEGLIO CHE CURARE…

…MA QUANDO NECESSARIA, LA CURA DELLA PERSONA CON DIABETE NELL’ERA DELL’INTELLIGENZA ARTIFICIALE, NON PUO’ PRESCINDERE DALL’USO DI FARMACI «INTELLIGENTI»

GRAZIE PER L'ATTENZIONE

End point primario nei singoli studi CVOT con i GLP-1 Ras: chi ha raggiunto il MACE?

	LEADER (liraglutide)[20]	SUSTAIN 6 (subcutaneous semaglutide)[21]	Harmony Outcomes (albiglutide)[22]	REWIND (dulaglutide)[23]	EXSCEL (exenatide)[24]	PIONEER 6 (oral semaglutide)[25]	ELIXA (lixisenatide)[26]
Three-point MACE*	0·87 (0·78–0·97; p=0·01) ✓	0·74 (0·58–0·95; p=0·02) ✓	0·78 (0·68–0·90; p=0·0006) ✓	0·88 (0·79–0·99; p=0·026) ✓	0·91 (0·83–1·00; p=0·06) ✗	0·79 (0·57–1·11; p=0·17) ✗	1·02 (0·89–1·17; p=0·81) ✗
Stroke	0·89† (0·72–1·11; p=0·3‡)	0·61† (0·38–0·99; p=0·04‡)	0·86 (0·66–1·14; p=0·3‡)	0·76† (0·61–0·95; p=0·017‡)	0·85 (0·70–1·03)	0·74† (0·35–1·57)	1·12 (0·72–1·58; p=0·54‡)
Myocardial infarction	0·88§ (0·75–1·03; p=0·11‡)	0·74§ (0·51–1·08; p=0·12‡)	0·75 (0·61–0·90; p=0·003‡)	0·96§ (0·79–1·16; p=0·65‡)	0·97 (0·85–1·10)	1·18§ (0·73–1·90)	1·03 (0·87–1·22; p=0·71‡)
Cardiovascular death	0·78 (0·66–0·93; p=0·007‡)	0·98 (0·65–1·48; p=0·92‡)	0·93 (0·73–1·19; p=0·21‡)	0·91 (0·78–1·06; p=0·21‡)	0·88 (0·76–1·02)	0·49 (0·27–0·92)	0·98 (0·78–1·22; p=0·85‡)

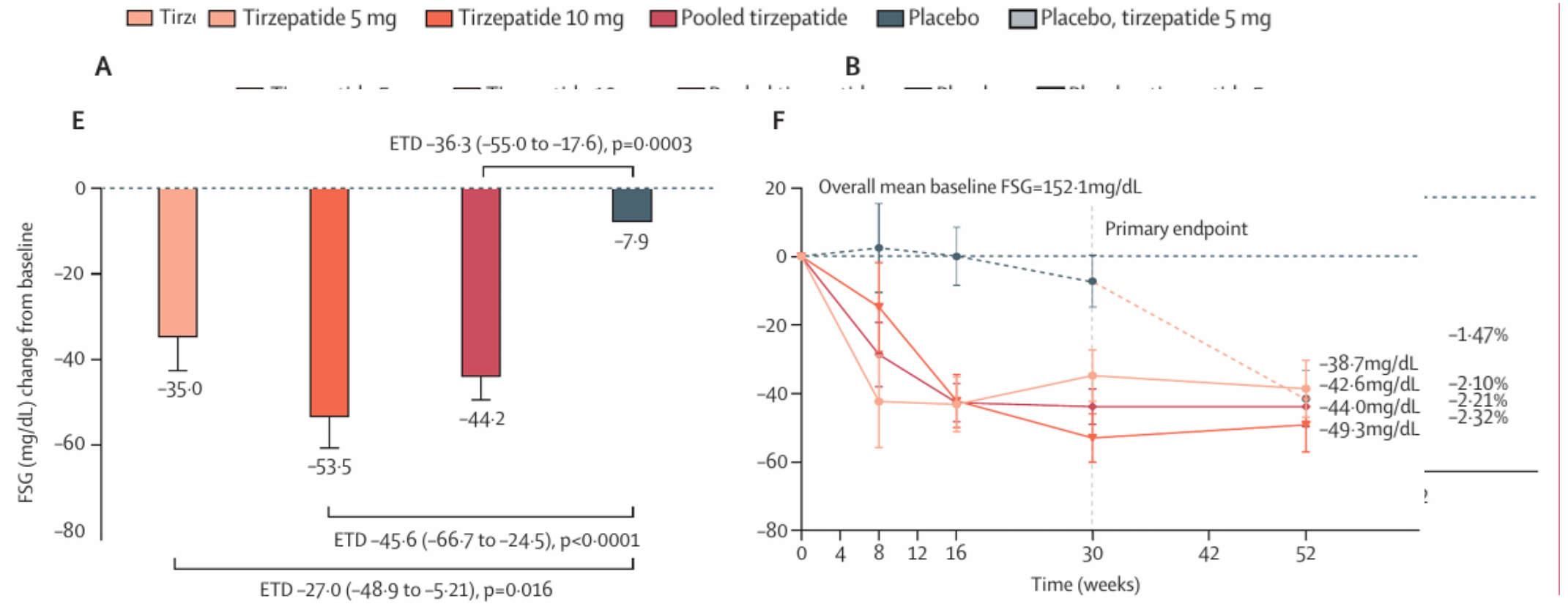
Data are hazard ratio (95% CI; p value [if available]). MACE=major adverse cardiovascular events. *Three-point major adverse cardiovascular events consists of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. †Non-fatal stroke only. ‡Nominal p value. §Non-fatal myocardial infarction only.

Bentley-Lewis R, et al. *Am Heart J* 2015;169(5):631-8; Pfeffer MA, et al. *N Engl J Med* 2015;373:2247-57; Marso SP, et al. *N Engl J Med* 2016;375:311-22; Mann JFE, et al. *N Engl J Med* 2017;377(22):2197-8; Marso SP, et al. *N Engl J Med* 2016;375:1834-44; Mentz RJ, et al. *Am Heart J* 2017;187:1-9; Holman RR, et al. *N Engl J Med* 2017 ;377:1228-39; Hernandez AF, et al. *Lancet* 2018;392:1519-29; Gerstein HC, et al. *Lancet*. 2019;394(10193):121-130.

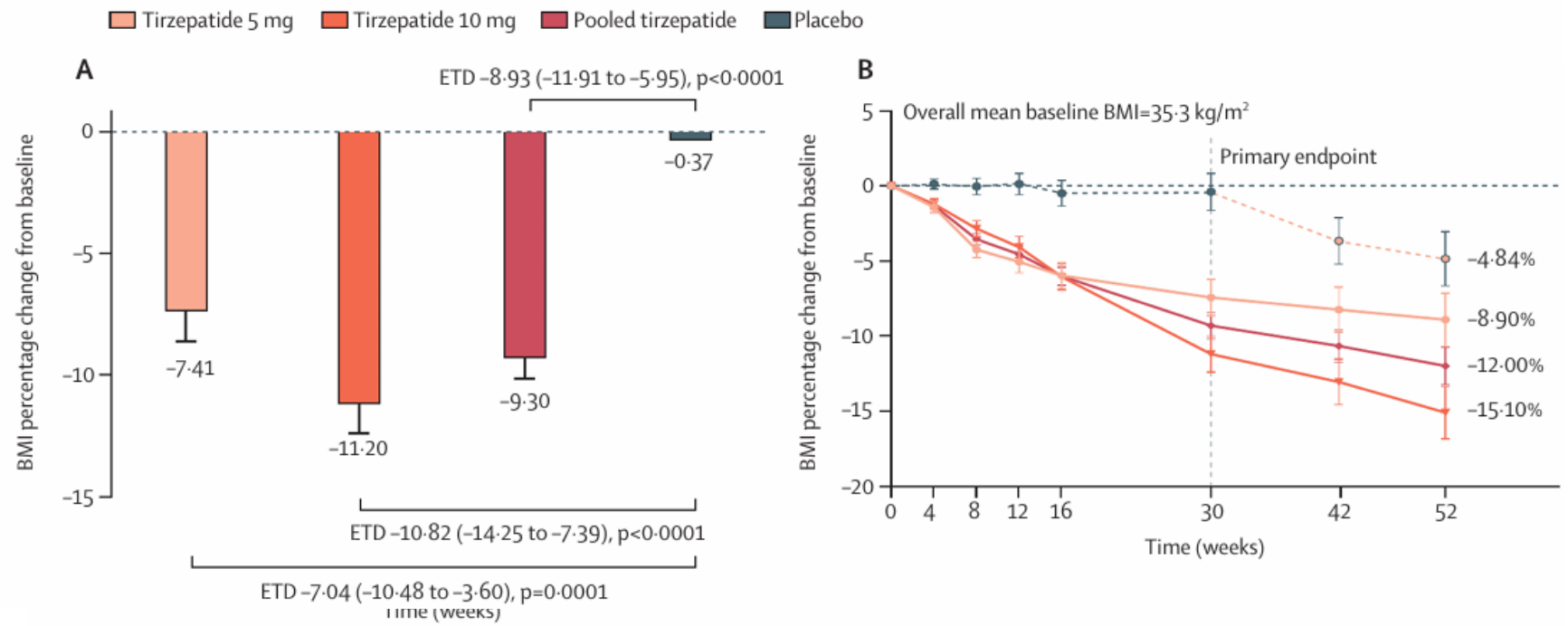
✓ Comprovata Protezione cardiovascolare

✗ Protezione cardiovascolare non dimostrata

SURPASS-PEDS: RISULTATI su parametri GLICEMICI



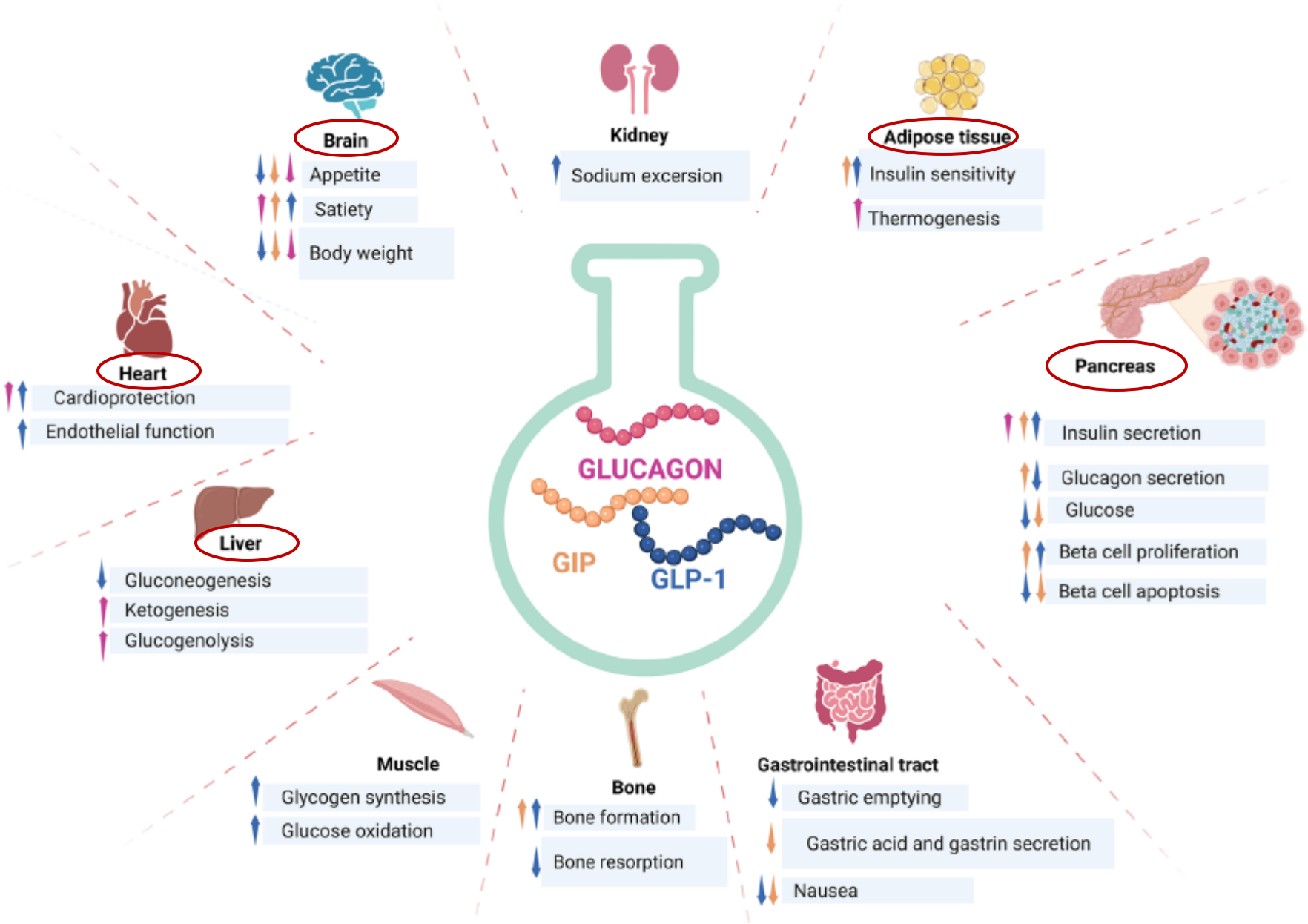
SURPASS-PEDS: RISULTATI su parametri ANTROPOMETRICI e LIPIDICI



Calo ponderale a 30 settimane: **6,8%** per il gruppo TZP 5 mg e **10,5 %** per il gruppo TZP 10 mg
A 52 settimane il calo di peso è stato dell **'8%** per il gruppo TZP 5 mg e del **13,8%** per il gruppo TZP 10 mg.
Nel gruppo switch (placebo-TZP 5 mg) il calo di peso è stato del **3,7%**.

Tirzepatide ha ridotto di oltre il 2 % la HbA1c rispetto al placebo e ha determinato una significativa riduzione del BMI (7% -11%), mantenendo i risultati dopo 1 anno.

AGONISTI GIP E GLP-1....MA NON SOLO



Anastasiou IA et al, Current Obesity Reports (2025) 14:34

Acta Diabetologica (2025) 62:1359–1370
https://doi.org/10.1007/s00592-025-02534-y

REVIEW ARTICLE

Beyond GLP-1: efficacy and safety of dual and triple incretin agonists in personalized type 2 diabetes care—a systematic review and network meta-analysis

Kangling Yan[1] · Haichuan Yu[2] · Benoît Blaise[3]

Received: 4 December 2024 / Accepted: 7 May 2025 / Published online: 5 June 2025

Peso

Intervention	Trials	Sample Size	Mean Difference (95% CrI)	SUCRA
Ref: PLB	21	1050	0	28.22%
Cotadutide	6	701	−3.067 (−4.653, −1.502)	61.86%
Tirzepatide	11	5798	−7.481 (−8.897, −6.039)	93.41%
insLispro	1	708	4.723 (0.672, 8.783)	7.84%
Semaglutide	3	546	−4.152 (−6.514, −1.840)	72.82%
insGlargine	1	978	4.290 (−0.371, 8.90)	11.39%
Survodutide	1	237	−4.615 (−8.094, −1.142)	75.50%
Mazutide	2	171	−3.039 (−5.708, -0.3878)	61.59%
Dulaglutide	5	154	−0.776 (−2.644, 1.079)	37.44%
Retatrutide	2	227	−8.601 (−11.20, −5.950)	97.89%
insDegludec	1	359	5.185 (1.131, 9.167)	6.01%
SAR425899	2	223	−2.581 (−5.338, 0.192)	56.32%
Liraglutide	1	67	−2.643 (−6.325, 1.057)	56.91%
RG7697	1	35	0.0774 (−3.627, 3.806)	31.81%

Forest plot: −20, 0, 20

HbA1c

Intervention	Trials	Sample Size	Mean Difference (95% CrI)	SUCRA
Ref: PLB	20	1043	0	2.92%
Cotadutide	5	694	−0.660 (−0.988, −0.343)	28.45%
Tirzepatide	11	5335	−1.883 (−2.151, −1.635)	98.40%
insLispro	1	629	−0.781 (−1.524, −0.066)	36.78%
Semaglutide	3	549	−1.471 (−1.868, −1.077)	79.10%
insGlargine	1	978	−0.905 (−1.618, −0.211)	43.77%
Survodutide	1	236	−1.386 (−2.012, −0.762)	72.73%
Mazutide	2	171	−1.369 (−1.904, −0.801)	72.25%
Dulaglutide	5	156	−1.249 (−1.606, −0.877)	64.50%
Retatrutide	2	227	−1.461 (−1.994, −0.925)	77.73%
insDegludec	1	359	−1.056 (−1.772, −0.364)	52.76%
SAR425899	2	223	−0.762 (−1.282, −0.244)	35.47%
Liraglutide	1	67	−0.563 (−1.268, 0.127)	25.27%
RG7697	1	40	−0.169 (−0.838, 0.506)	9.89%

Forest plot: −3, 0, 0.6

FPG

Intervention	Trials	Sample Size	Mean Difference (95% CrI)	SUCRA
Ref: PLB	18	886	0	0.55%
Cotadutide	4	79	−28.14 (−41.28, −14.93)	34.83%
Tirzepatide	12	5873	−57.30 (−65.41, −48.92)	90.60%
insLispro	1	694	−27.06 (−51.48, −4.21)	35.93%
Semaglutide	2	502	−44.34 (−60.03, −28.40)	68.63%
insGlargine	1	978	−53.77 (−76.89, −30.39)	82.77%
Mazutide	2	171	−30.46 (−47.18, −13.51)	40.34%
Dulaglutide	5	161	−29.28 (−42.32, −15.64)	36.94%
Retatrutide	2	227	−39.22 (−58.57, −19.40)	59.12%
insDegludec	1	359	−58.98 (−82.30, −35.43)	89.68%
SAR425899	2	223	−27.51 (−47.47, −7.44)	35.16%
Liraglutide	1	67	−21.90 (−47.11, 3.24)	25.48%

Forest plot: −90, 04

REWIND -Researching cardiovascular Events with a Weekly INcretin in Diabetes

Studio multicentrico randomizzato doppio cieco placebo controllato.
Popolazione: **9.901 pazienti** di 24 Paesi/ durata media di DM2 10 anni/ e valore basale di glicata 7,3%
Il 31% dei pazienti aveva malattia CV nota (IMA, ictus,angina instabile, rivascolarizzazione, ospedalizzazioen per eventi ischemici). **Follow up maggiore di 5 anni.**
Outcome primario: comparsa di MACE 3.
Outcome secondari: singole componenti del MACE 3, ospedalizzazione per angina o scompenso, mortalità per tutte le cause
Risultati: Dulaglutide 1,5 mg si è dimostarta superiore la placebe per MACE 3
Effect on major adverse cardiovascular events (HR = 0.88; 95% CI, 0.79-0.99**) -12%**

Safety outcomes

Adverse events occurred among 68% of all participants receiving tirzepatide vs. 44% of the placebo group. Two participants receiving 5 mg tirzepatide discontinued treatment due to an adverse event. A serious adverse event occurred in one person in each of the three study groups.

The most common adverse events for those receiving tirzepatide were gastrointestinal-related and mild or moderate in severity. Most of the gastrointestinal adverse events occurred during dose escalation and became less frequent later in the trial. There were no cases of severe hypoglycemia or glycemic rescue. Level two hypoglycemia with a glucose of less than 54 mg/dL occurred in 15% of tirzepatide recipients vs. 6% of the placebo group.

Hannon said no differences in growth-related measures were seen between the tirzepatide and placebo groups.

“Overall, [tirzepatide] was well tolerated with a safety profile very consistent with adults with type 2 diabetes and other studies of GLP-1 receptor agonists in children and adolescents with type 2 diabetes,” Hannon said during the press conference.

SURPASS CVOT punti critici

Eldad Einav, MD, FACC

The SURPASS-CVOT trial's design marks the first head-to-head CV outcomes trial within the cardiometabolic space. Historically, CV outcomes trials for antidiabetic medications relied on placebo-controlled studies to secure an FDA label for CV risk reduction. However, as GLP-1 therapies became the standard of care for patients with type 2 diabetes and high CV risk, there was a need for alternative methods to avoid significant challenges, such as ethical concerns, and to effectively demonstrate CV benefits.

The trial design relies on indirect comparisons and statistical assumptions, which may limit how firmly we can claim CV protection. Nicholls and colleagues outlined a preservation-of-effect framework. The concept was that if tirzepatide could be shown to be noninferior to dulaglutide, one could reasonably infer that tirzepatide carries the same protective effect dulaglutide showed in REWIND. Nicholls proposes a noninferiority margin of approximately 1.05, derived from a Bayesian meta-analysis of six GLP-1 CV outcomes trials. This margin suggests that if tirzepatide preserves at least 50% of dulaglutide's cardiovascular benefit, cardioprotection can be inferred.

The preservation-of-effect case hinges on how solid and transferable dulaglutide’s benefit is to the SURPASS-CVOT setting. In REWIND, the effect on major adverse cardiovascular events was modest (HR = 0.88; 95% CI, 0.79-0.99) and mostly in a primary prevention population, while SURPASS-CVOT is entirely secondary prevention with wider use of modern therapies like SGLT2 inhibitors. The noninferiority margin is derived from a Bayesian meta-analysis across heterogeneous GLP-1 CVOTs, so the inference depends on cross-trial assumptions that may not fully hold.

The pre-specified “imputed placebo” analysis helps, but it is still model-based rather than randomized. Taken together, these factors add uncertainty to the conclusion.

SURPASS CVOT punti critici

SURPASS-CVOT surprised me. Tirzepatide, a dual GIP/GLP-1 agonist, has already shown standout weight reduction and cardiometabolic measurements across trials. In this study it again delivered larger A1c reductions, greater weight reduction and a stronger renal signal than dulaglutide. Even so, it failed to achieve statistical superiority for major adverse CV events. Furthermore, the trial ran in a contemporary care setting with wider use of SGLT2 inhibitors, and the dosing clearly favored tirzepatide, which was titrated to the maximum tolerated dose up to 15 mg, while dulaglutide remained at a fixed 1.5 mg as in REWIND. Given the cardiometabolic advantages, modern background therapy and dosing setup, failure to establish superiority was disappointing.
What draws attention is the 16% lower risk for all-cause mortality. However, although intriguing, this was a secondary outcome that was not adjusted for multiplicity, and it was not accompanied by a clear reduction in CV death or major adverse CV events, so a direct CV explanation is uncertain and it's possible non-CV drivers influenced the outcome, or even chance.

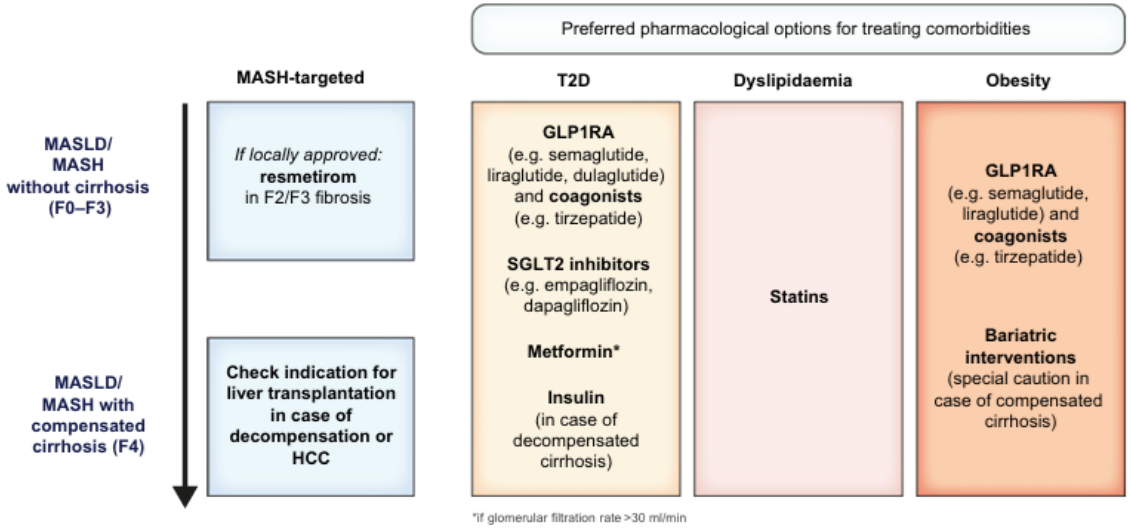
SURPASS-CVOT shows tirzepatide is safe from a CV perspective and superior to dulaglutide in weight, glycemic and kidney outcomes. The question is whether noninferiority to an active GLP-1 with cardioprotective effect is enough to infer conclusive CV protection.
The prespecified putative placebo analysis matched SURPASS-CVOT participants to a REWIND-like population to estimate how tirzepatide might perform vs. a hypothetical placebo. In that indirect model, tirzepatide was associated with lower risk for several outcomes, including CV death/MI/stroke, all-cause death and CV death/heart failure events, each reaching statistical significance.
However, this analysis is an indirect, model-based estimate that stitches together two different trials. That means extra statistical assumptions and room for bias.
Because of that, and the direct comparison being nonsuperior, the putative placebo analysis should be treated as supportive evidence rather than conclusive proof of cardiovascular protection.

Tirzepatide clearly showed metabolic and renal benefits in SURPASS-CVOT and confirmed CV safety. Whether that translates into an FDA CV indication is much less certain. The FDA typically grants a “reduces risk of CV death, MI or stroke” claim when a randomized outcomes trial shows superiority vs. placebo. No antidiabetic drug has ever received a CV indication based on noninferiority to an active comparator. SURPASS-CVOT did not achieve superiority on major adverse CV events. It used dulaglutide as the active comparator despite only a modest benefit in REWIND, and the argument leans on a preservation-of-effect framework that has not been used to approve a cardiometabolic CV indication. Taken together, a CV claim based on SURPASS-CVOT alone is not straightforward. To move beyond supportive evidence, tirzepatide would probably need superiority on a prespecified CV endpoint in additional outcomes work such as SURMOUNT-MMO, plus consistent real-world data and meta-analyses that address differences in population and background therapy.

- ✓ Nel 2024 studi RCT sulle OSAS. Riduzioen dell'indice di apnea-ipopnea di circa il 50% dopo terapia per 52 settimane.

- ✓ Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is defined as steatotic liver disease (SLD) in the presence of one or more cardiometabolic risk factor(s) and the absence of harmful alcohol intake. The spectrum of MASLD includes steatosis, metabolic dysfunction-associated steatohepatitis (MASH, previously NASH), fibrosis, cirrhosis and MASH-related hepatocellular carcinoma (HCC).

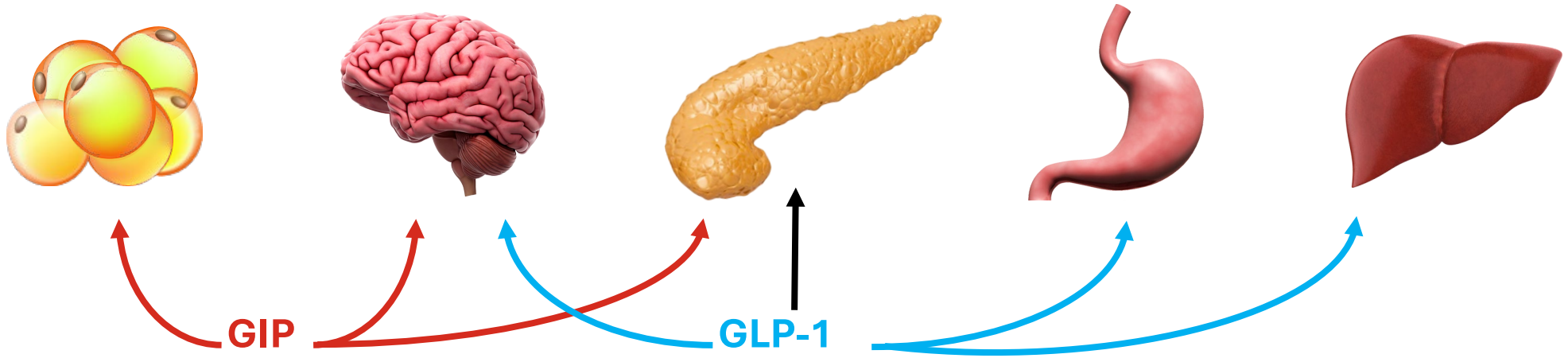
- ✓ LG EASL-EASD-EASO 2024 adults with non-cirrhotic MASH with significant liver fibrosis (stage ≥2) should be considered for treatment with resmetirom.
- ✓ GLP1RAs are safe to use in MASH (including compen sated cirrhosis) and should be used for their respective indications, namely type 2 diabetes and obesity, as their use improves cardiometabolic outcomes



- ✓ STUDIO RCT SUMMIT (pubblicato su JAC maggio 2025): he triad of obesity, HFpEF, and CKD identifies patients with considerable functional impairment and an unfavorable prognosis, who nevertheless respond favorably to tirzepatide. Long-term tirzepatide improves renal function (both by cystatin C and creatinine), but the measurement of eGFR in patients with obesity receiving incretin-based drugs is likely to be skewed (distort) by the effects of fat and muscle mass (and by changes in body composition) on the synthesis of both cystatin C and creatinine.

- ✓ Review e metanalaisi su effetti renali di TZP (febbario 2025; World J Diabetes) In 15 studi RCT su pazienti cone senza DM2. Conslusioni: short-term data from RCTs with low RoB suggests that tirzepatide positively impacts UACR without detrimental effects on eGFR in subjects with T2D and obesity without T2D, with a reassuring renal safety profile. Larger RCTs are warranted to prove the longer-term renal benefits of tirzepatide, which might also prevent eGFR decline and worsening of CKD.

EFFETTI FISIOLOGICI DEGLI AGONISTI GIP E GLP-1



Tessuto adiposo:
- ↑ Sensibilità insulinica
- Miglioramento del metabolismo lipidico

SNC:
- ↓ Appetito
- ↑ Sazietà
- ↓ Nausea

Insula pancreatica:
- ↑ Secrezione insulinica
- ↑ Secrezione di glucagone

SNC:
- ↓ Appetito
- ↑ Sazietà

Insula pancreatica:
- ↑ Secrezione insulinica
- ↓ Secrezione di glucagone

Stomaco:
- Rallentamento svuotamento gastrico

Fegato:
- ↓ Gluconeogenesi

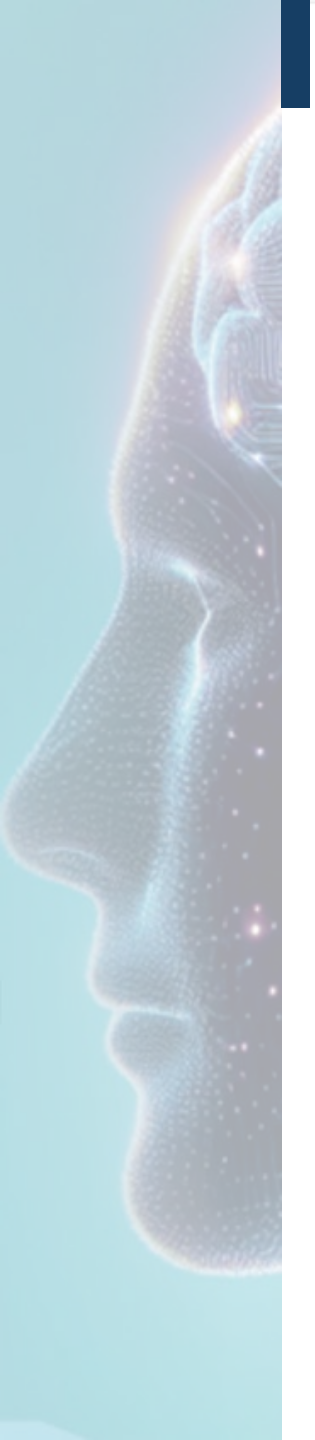
SNC:
- ↑ Dispendio energetico
- Appetite regulation

Insula pancreatica:
- ↑ Insulin secretion

Stomaco:
- Delayed gastric emptying

Fegato:
- ↑ Glycogenolysis
- ↑ Gluconeogenesis
- Improvements in lipid metabolism

Modificato da :1 Hædersdal S, et al. *Nat Rev Endocrinol.* 2023;19(6):321-335. 2. Hammoud R, Drucker DJ. *Nat Rev Endocrinol.* 2023;19(4):201-216



Tissue Barriers. 2024 Oct;12(4):2292461. doi: 10.1080/21688370.2023.2292461. Epub

Brain uptake pharmacokinetics of albiglutide dulaglutide, tirzepatide, and DA5-CH in the s for new treatments of Alzheimer's and Parki diseases

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Affiliations + expand

PMID: 38095516 PMCID: PMC11583597 DOI: 10.1080/21688370.2023.2292461

Abstract

Background: A number of peptide incretin receptor agonists (IRAs) show promise as Alzheimer's disease (AD) and Parkinson's disease (PD). Transport across the blood-bra is one way for IRAs to act directly within the brain. To determine which IRAs are high p candidates for treating these disorders, we have studied their brain uptake pharmacol

Methods: We quantitatively measure the ability of four IRAs to cross the BBB. We inje CD-1 mice intravenously with ^{125}I- or ^{14}C-labeled albiglutide, dulaglutide, DA5-CH, or used multiple-time regression analyses to measure brain kinetics up to 1 hour. For tho to enter the brain 1 h after intravenous injection, we also investigated their ability to e longer time frame (i.e., 6 h).

Results: Albiglutide and dulaglutide had the fastest brain uptake rates within 1 hour. to enter the brain rapidly, reaching equilibrium quickly. Tirzepatide does not appear t within 1 h after iv injection but like albumin, did so slowly over 6 h, presumably via the pathways.

Conclusions: We find that IRAs can cross the BBB by two separate processes; one tha that is slow. Three of the four IRAs investigated here have fast rates of transport and s into consideration for testing as AD and PD therapeutics as they would have the abilit and directly on the brain as a whole.

Mol Metab. 2024 Nov:89:102019. doi: 10.1016/j.molmet.2024.102019. Epub 2024 Aug 30.

The GLP-1 medicines semaglutide and tirzepatide do not alter disease-related pathology, behaviour or cognitive function in 5XFAD and APP/PS1 mice

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PMID: 39216535 PMCID: PMC11408156 DOI: 10.1016/j.molmet.2024.102019

Abstract

Objective: The development of glucagon-like peptide-1 receptor (GLP-1R) agonists for the treatment of type 2 diabetes and obesity has been accompanied by evidence for anti-inflammatory and cytoprotective actions in the heart, blood vessels, kidney, and brain. Whether GLP-1R agonists might be useful clinically for attenuating deterioration of cognitive dysfunction and reducing the progression of Alzheimer's disease remains uncertain.

Methods: Here we evaluated the actions of semaglutide and tirzepatide, clinically distinct GLP-1 medicines, in two mouse models of neurodegeneration.

Results: Semaglutide reduced body weight and improved glucose tolerance in 12-month-old male and female 5XFAD and APP/PS1 mice, consistent with pharmacological engagement of the GLP-1R. Nevertheless, amyloid plaque density was not different in the cerebral cortex, hippocampus, or subiculum of semaglutide-treated 12-month-old 5XFAD and APP/PS1 mice. IBA1 and GFAP expression were increased in the hippocampus of 5XFAD and APP/PS1 mice but were not reduced by semaglutide. Moreover, parameters of neurobehavioral and cognitive function evaluated using Open Field testing or the Morris water maze were not improved following treatment with semaglutide. To explore whether incretin therapies might be more effective in younger mice, we studied semaglutide and tirzepatide action in 6-month-old male and female 5XFAD mice. Neither semaglutide nor tirzepatide modified the extent of plaque accumulation, hippocampal IBA1+ or GFAP+ cells, or parameters of neurobehavioral testing, despite improving glucose tolerance and reducing body weight. mRNA biomarkers of inflammation and neurodegeneration were increased in the hippocampus of male and female 5XFAD mice but were not reduced after treatment with semaglutide or tirzepatide.

Conclusions: Collectively, these findings reveal preservation of the metabolic actions of two GLP-1 medicines, semaglutide and tirzepatide, yet inability to detect improvement in structural and functional parameters of neurodegeneration in two mouse models of Alzheimer's disease.

› Endocrine. 2025 Feb;87(2):486-497. doi: 10.1007/s12020-024-04013-w. Epub 2024 Sep 2.

Tirzepatide administration improves cognitive impairment in HFD mice by regulating the SIRT3–NLRP3 axis

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PMID: 39222203 DOI: 10.1007/s12020-024-04013-w

Abstract

Purpose: High-fat diet (HFD) currently is reported that in connection with cognitive impairment. Tirzepatide is a novel dual receptor agonist for glycemic control. But whether Tirzepatide exerts a protective effect in HFD-related cognitive impairment remains to be explore.

Methods: During the study, the cognitive dysfunction mice model induced by HFD were established. The expressions synapse-associated protein and other target proteins were detected. The oxidative stress parameters, levels of inflammatory cytokine were also detected.

Results: Our findings proved that Tirzepatide administration attenuates high fat diet-related cognitive impairment. Tirzepatide administration suppresses microglia activation, alleviates oxidative stress as well as suppressed the expression of NLRP3 in HFD mice by up-regulating SIRT3 expression. In conclusion, Tirzepatide attenuates HFD-induced cognitive impairment through reducing oxidative stress and neuroinflammation via SIRT3-NLRP3 signaling.

Conclusion: This study suggest that Tirzepatide has neuroprotective effects in HFD-related cognitive dysfunction mice model, which provides a promising treatment of HFD-related cognitive impairment.

› JAMA Netw Open. 2025 Jul 1;8(7):e2521016. doi: 10.1001/jamanetworkopen.2025.21016.

Neurodegeneration and Stroke After Semaglutide and Tirzepatide in Patients With Diabetes and Obesity

Huan-Tang Lin [1 2 3], Yung-Fong Tsai [1 2], Pei-Lun Liao [4 5], James Cheng-Chung Wei [6 7 8]

Affiliations + expand

PMID: 40663350 DOI: 10.1001/jamanetworkopen.2025.21016

Free article

Abstract

Importance: Glucagon-like peptide 1 receptor agonists (GLP-1RAs), such as semaglutide and tirzepatide, provide cardiometabolic benefits to patients with type 2 diabetes and obesity, but their potential benefits in mitigating neurodegenerative and cerebrovascular diseases remain unclear.

Objective: To evaluate the association of semaglutide and tirzepatide with the incidence of dementia, Parkinson disease, ischemic stroke, intracerebral hemorrhage, and all-cause mortality compared with other antidiabetic drugs in adults with type 2 diabetes and obesity.

Design, setting, and participants: This retrospective cohort study analyzed electronic health record-based data from the TriNetX US network (December 1, 2017, to June 30, 2024) in adults aged 40 years or older with type 2 diabetes and obesity initiating semaglutide, tirzepatide, or other antidiabetic drugs, excluding those with prior neurodegenerative or cerebrovascular diseases. Propensity score matching was used to balance the baseline characteristics.

Exposures: Patients treated with antidiabetic drugs were categorized as GLP-1RA (semaglutide or tirzepatide) or other antidiabetic drug (biguanides, sulfonylureas, dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter 2 inhibitors, thiazolidinediones, and α-glucosidase inhibitors) users.

Main outcomes and measures: The primary outcomes were the incidence of neurodegenerative diseases (dementia, Parkinson disease, and mild cognitive impairment) and cerebrovascular (stroke and intracerebral hemorrhage) diseases, while the secondary outcome was all-cause mortality. Cox proportional hazard models were used to estimate hazard ratios (HRs) with 95% CIs.

Results: A total of 60 860 adults with type 2 diabetes and obesity were included, with 30 430 each in the GLP-1RA group (mean [SD] age, 57.9 [9.9] years; 50.2% female) and the other antidiabetic drug group (mean [SD] age, 58.0 [10.8] years; 51.4% female) after propensity score matching. During a 7-year follow-up, GLP-1RA users had a lower risk of dementia (HR, 0.63; 95% CI, 0.50-0.81), stroke (HR, 0.81; 95% CI, 0.70-0.93), and all-cause mortality (HR, 0.70; 95% CI, 0.63-0.78), with no significant differences in the risk of Parkinson disease or intracerebral hemorrhage. Subgroup analyses revealed greater benefits in patients aged 60 years or older, women, and patients with a body mass index of 30 to 40.

Conclusions and relevance: In this cohort study, the use of GLP-1RAs semaglutide and tirzepatide was associated with a lower risk of dementia, stroke, and all-cause mortality in adults with type 2 diabetes and obesity. These findings suggest potential neuroprotective and cerebrovascular benefits of GLP-1RAs beyond glycemic control, warranting further trials to confirm these outcomes.