News 2. Tirzepatide: novità nel diabete e nell'obesità.

Dario Tuccinardi M.D. Ph.D.

Disclosure

Dr. Dario Tuccinardi has received funding from the following companies:

For providing educational sessions

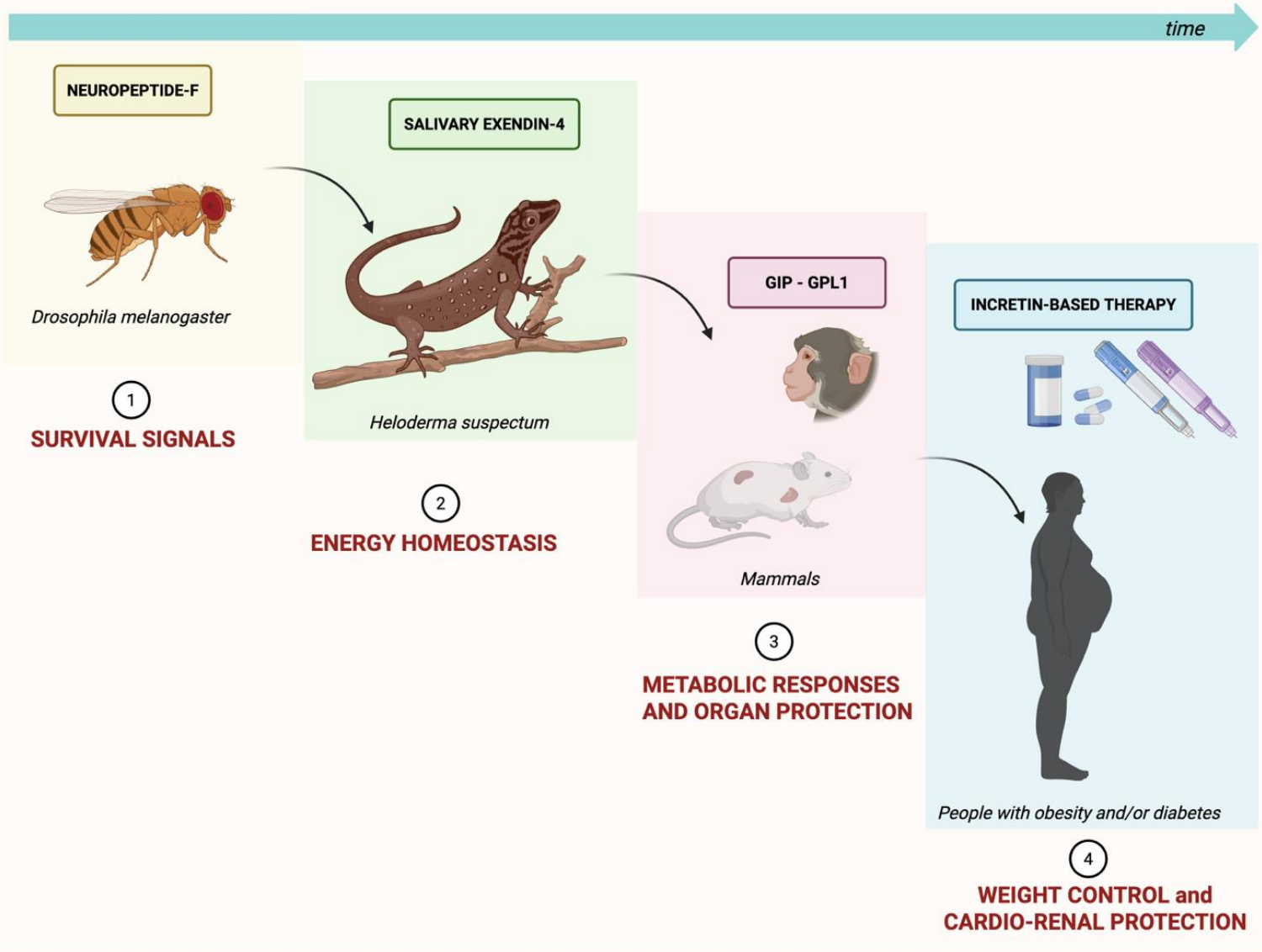
-Novo Nordisk, AstraZeneca, Eli Lilly, Mundipharma, boehringer Ingelheim

Institutional research grant support or funding for clinical trials

-Novo Nordisk, Abbott, LJ Pharma, Eisai, Eli Lilly and Boehringer Ingelheim

Institutional Scientific Board and/or consulting

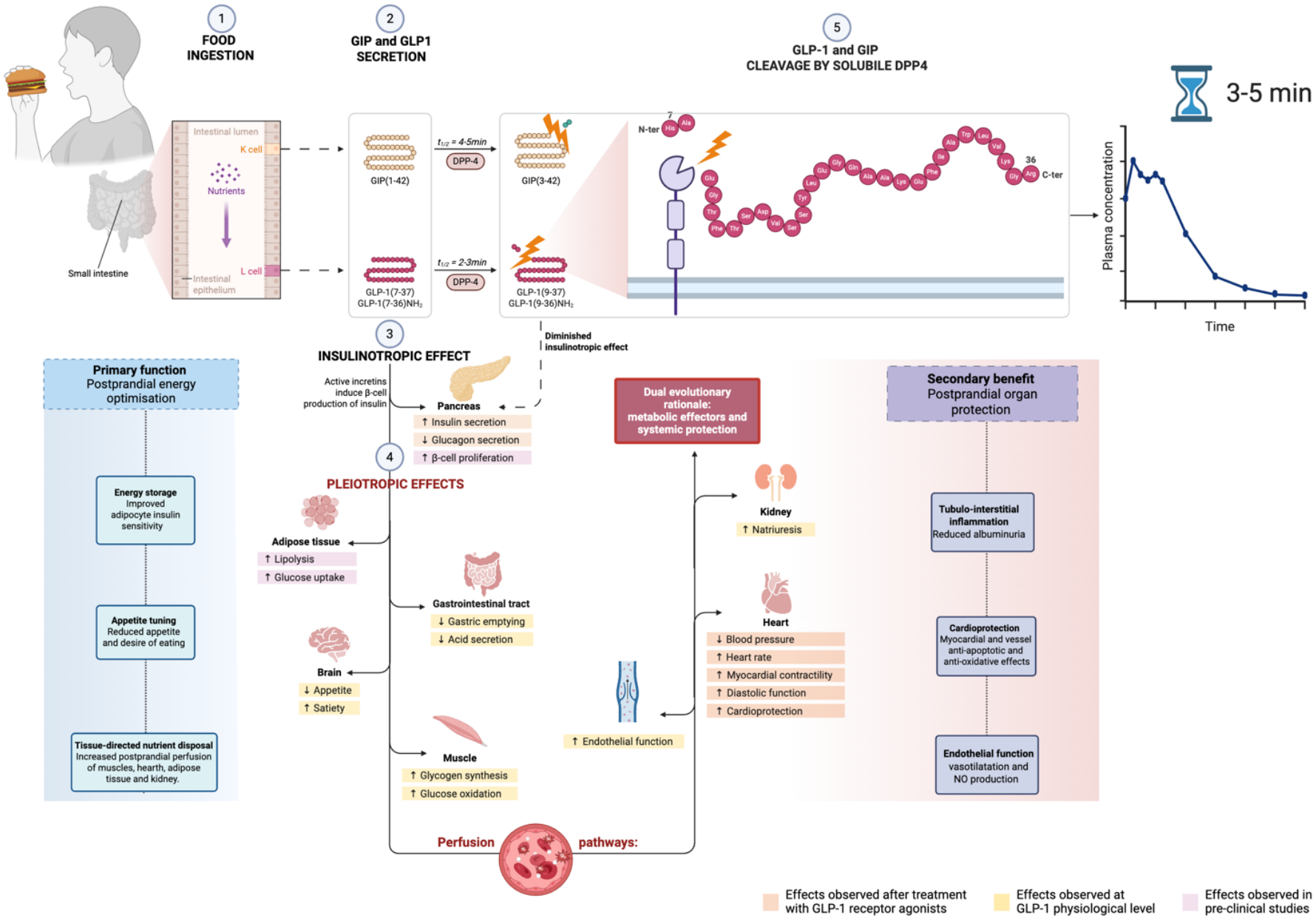
- Novo Nordisk



L'origine evolutiva degli agonisti incretinici

Dai segnali di fame ancestrali alla protezione cardio-renale

GLP-1 and GIP Beyond Glycaemia: Evolutionary Roles in Energy Optimisation and Organ Protection.
Tuccinardi D, Watanabe M, Masi D, Gianfrilli D, Manfrini S, Le Roux CW. Diabetes Metab Res Rev. 2025; in press. doi:10.1002/dmrr.70108.



Il doppio volto dell'incretina: energia e protezione

Come GIP e GLP-1 orchestrano la risposta postprandiale

GLP-1 and GIP Beyond Glycaemia: Evolutionary Roles in Energy Optimisation and Organ Protection.
Tuccinardi D, Watanabe M, Masi D, Gianfrilli D, Manfrini S, Le Roux CW.
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Ruoli proposti di GIP e GLP-1 nella regolazione del metabolismo[1,2,*]

Attività del GIP

Sistema nervosa centrale

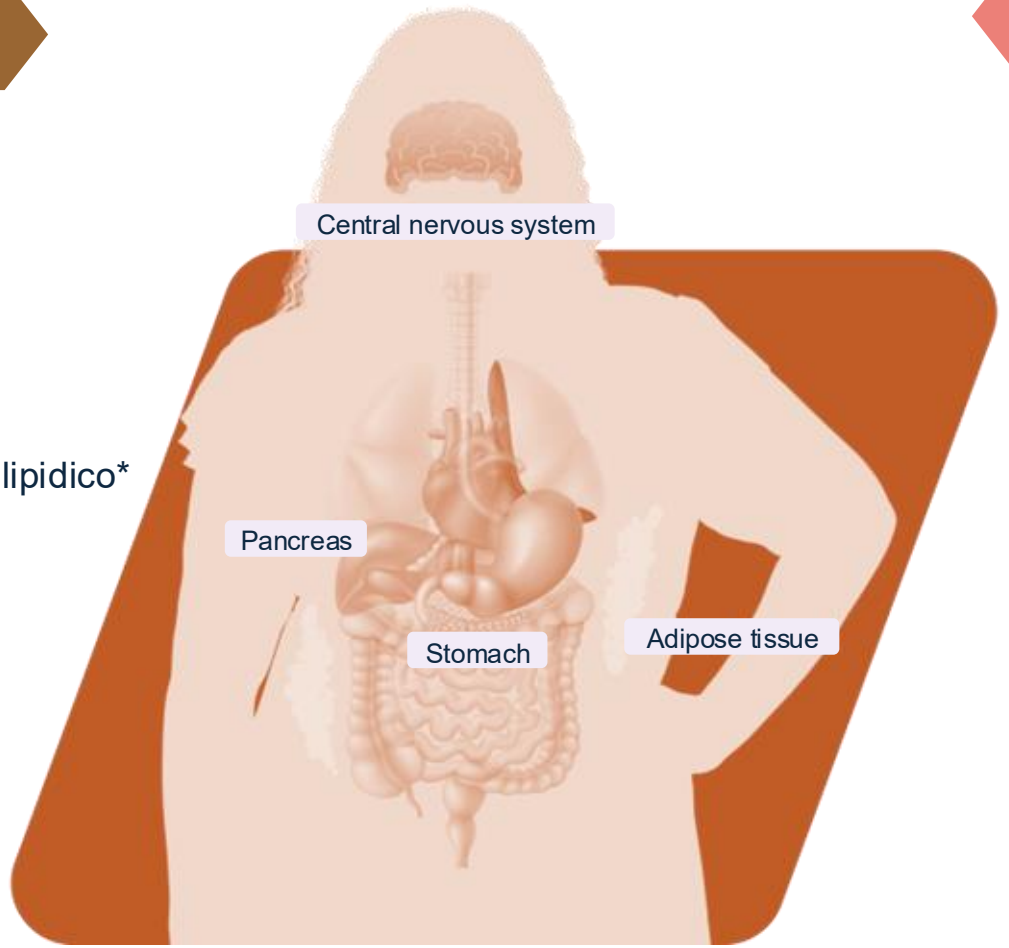
- ▼ Riduzione dell'assunzione di cibo*
- ▼ Diminuzione della nausea

Tessuto adiposo

- ▲ Aumento della sensibilità insulinica*
- ▲ Aumento capacità di tamponamento lipidico*
- ▲ Aumento del flusso sanguigno
- ▲ Aumento capacità di storage*
- ▼ Ridotta inflitrazione di cellule immunitarie pro-infiammatorie

Pancreas

- ▲ Aumento della secrezione di insulina
- ▲ Aumento del glucagone in modo glucosio-dipendente



Attività del GLP-1

Sistema nervosa centrale

- ▼ Riduzione dell'assuzione di cibo
- ▲ Aumento della sazietà
- ▲ Aumento della nausea

Pancreas

- ▲ Aumento della secrezione di insulina
- ▼ Riduzione del glucagone

Stomaco

- ▼ Ritardo svuotamento gastrico

*Demonstrated in preclinical research.
GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1.
1. Samms RJ, et al. Trends Endocrinol Metab. 2020;31(6):410–421. 2. Roh E, Choi KM. Int J Mol Sci. 2023;24(4):3384.

OBESITY TREATMENT BASED ON PATIENT PHENOTYPING

FIRST-LINE THERAPY IS LIFESTYLE MODIFICATION (MEDICAL NUTRITIONAL APPROACH AND IMPLEMENTATION OF PHYSICAL ACTIVITY and BEHAVIOURAL THERAPY)*

EXCLUDE ENDOCRINE FORMS OF OBESITY, if suspected, investigate MONOGENIC FORMS

ASSESSMENT OF THE PRESENCE OF COMPLICATIONS AND PATIENT PHENOTYPING

OBESITY TREATMENT BASED ON PATIENT COMPLICATIONS AND PHENOTYPING

METABOLIC CARDIO RENAL COMPLICATIONS

+ASCVD

Cardiovascular disease was defined as a previous myocardial infarction, previous stroke, or symptomatic peripheral arterial disease in people who are≥ 45 years of age, with a BMI ≥ 27 kg/m².

- Semaglutide 2.4 mg [4]

Naltrexone/ Bupropion (not recommended)[15]

Indicators of High CV Risk:

Definitions vary; most comprise ≥ 40 years of age, BMI ≥ 27 kg/m², male gender, high blood pressure, atherogenic dyslipidemia, smoking, prediabetes, ASCVD risks (ACC/AHA).

- Tirzepatide 15 mg [2,10]
- Semaglutide 2.4 mg [3,4]
- Liraglutide 3 mg [12]

Naltrexone/ Bupropion (not recommended)[15]

HF

Clinical heart failure (NYHA II–IV) with LVEF ≥50% (**tirzepatide**) or ≥45% (**semaglutide**), BMI ≥30 kg/m²), reduced functional capacity (KCCQ-CSS <80 or <90), 6-minute walk ≥100 m, and elevated filling pressures (NT-proBNP, echocardiographic criteria, or recent HF hospitalization). T2D was allied in the tirzepatide trial.

- Tirzepatide 15 mg [11]
- Semaglutide 2.4 mg [5]

Naltrexone/ Bupropion (not recommended) [15]

CKD

eGFR < 60 ml/ min per 1.73 m² OR albuminuria (ACR ≥ 3.0 mg/mmol (30mg/g)

- Semaglutide 2.4 mg [5]
- Tirzepatide 15 mg [11,19]

(use if eGFR>30 ml/min; If eGFR <30 use with caution due to limited data)

Orlistat (caution in obesity due to risks of nephrolithiasis or AKI)[18]

Naltrexone/ Bupropion (not recommended) [15]

GLYCEMIC CONTROL

PREDIABETES

(**HbA1c** ≥ 5.7% and < 6.5%, FPG > 100 ng/dl < 126 mg/dl, OGTT 120 min glucose ≥ 140 mg/dl < 200

- Tirzepatide 15 mg
- Liraglutide 3 mg [12,74]
- Orlistat 120 mg [14]

Metformin: off-label; may reduce diabetes incidence [24].

TYPE 2 DIABETES

(**HbA1c** ≥ 6.5% and < 6.5, FPG > 100 ng/dl < 126 mg/dl, OGTT 120 min

- Tirzepatide 15 mg
- Liraglutide 3 mg [33]

SGLT2is support weight loss [37,38,39,40,41], if glycemic control allows, insulin[44,45], thiazolidinediones, and sulfonylureas should be avoided [203]

TYPE 1 DIABETES

(OFF-LABEL only for weight loss purposes)

- Tirzepatide 15 mg [52]
- [51]

MASH/MASLD

Adults with biopsy-confirmed MASH, fibrosis stage (F2–F3) for **semaglutide** 2.4 and **tirzepatide** 15 mg, F0-F3 for **liraglutide** 3 mg , BMI ≥25 kg/m² for **semaglutide** 2.4 mg and **liraglutide** 3 mg . BMI ≥27 kg/m² for **tirzepatide** 15 mg; with or without type 2 diabetes but not for semaglutide 2.4.

- Semaglutide 2.4 mg [54]
- Tirzepatide 15 mg
- Liraglutide 3 mg OD [57]

MECHANICAL COMPLICATIONS

OSTEOARTRITIS

Adults ≥18 years with BMI ≥30 kg/m², clinically and radiographically confirmed knee osteoarthritis (ACR criteria; Kellgren–Lawrence grade 2–3), and baseline knee pain ≥40/100 on the WOMAC pain scale.

- Semaglutide 2.4 mg [63]
- Tirzepatide 15 mg (NCT01985165)
- Orlistat 120 mg [14]
- Naltrexone/bupropione [64]
- Phentiramine/Topiramate [26]

OSAS

Adults ≥18 years, BMI ≥30 kg/m², with moderate-to-severe obstructive sleep apnea (AHI ≥15 events/hour); CPAP use allowed (tirzepatide) or excluded (liraglutide); no diagnosis of T2D.

- Tirzepatide 15 mg [68]
- Liraglutide 3 mg [69]
- Phentiramine/ Topiramate [70]

WEIGHT LOSS TARGETS /OWCMC**

Set individualized weight management goals

5-10% WL

- Orlistat [14]
- Liraglutide 3 mg [74]
- Naltrexone/ Bupropion [27]
- Phentermine/Topiramate (low-mid doses) [60]

10-20% WL

- Tirzepatide 5 mg [2]
- Semaglutide 2.4 mg [3]
- Phentermine/Topiramate

>20% WL

- Tirzepatide 15mg
- Semaglutide 7.2 mg [77] (not available yet)
- Cagrisema [78] (not available yet)

AGE

≥ 2 y.o. [104]
Setmelanotide (rare genetic obesity)
Metreleptin (rare genetic obesity)

6-12 y.o.
Liraglutide 3mg [109] (EMA only)

12-18 y.o.
Liraglutide 3mg [112]
Semaglutide 2.4mg [113]
Phentermine/Topiramate [115] (FDA only)
Orlistat 120 mg [114] (FDA only)

18-65 y.o.
Tirzepatide 15 mg
Semaglutide 2.4 m
Naltrexone/Bupropion [27,28]
Phentermine/Topiramate [26]
Orlistat [14]

>65 y.o.
adjustment nec
Tirzepatide 15 mg [2] (Us e; monitor sensitivity in el ly)
>75 yrs)
Naltrexone/Bupropion [27] (Caution; limited data ≥65 yrs)
Phentermine/Topiramate [26] (Caution; monitor CNS/renal)
Orlistat [14] (Usable; limited efficacy data)

Sarcopenic o esity
pervised Resistance Tra g + Protein ay [118]
Liraglutide 3 mg is preferred for gradual weight loss with lean mass preservation and proven cardiovascular safety [33]

EATING BEHAVIOUR

EMOTIONAL EATING

- Bupropion /
- Tirzepatide 15 mg [136]
- mg [125]

BINGE EATING

Not AOMs approved explicitly for binge eating disorder.

- Liraglutide 3.0 mg [123]
- Phentermine/ Topiramate [128]
- Naltrexone/B upropion [28]
- Orlistat 120 mg [129]
- Semaglutide 2.4 mg [125]
- Tirzepatide 15 mg [128,134]

SPECIAL POPULATIONS

CANCER safety

No significant increase in thyroid cancer risk from
- Semaglutide 2.4 mg [1]
- Tirzepatide 15 mg [141]

Ev ng-term GLP-1 RA use may increase thyroid cancer risk in mixed T2D populations.[145]

No evidence of increased cancer risk (for other AOMs: **Orlistat, Phentermine/Topiramate, Bupropion/Naltrexone**

Familial Partial Lipodystrophy 1-3 (FPLD1-3)
Acquired Partial Lipodystrophy (Barraquer-Simons)
HIV-Associated Lipodystrophy
- Semaglutide 2.4 mg [152]

MONOGENIC OR SYNDROMIC OBESITY
Congenital leptin deficiency
- Metreleptin [153]

(biallelic POMC, PCSK1, or LEPR deficiency and for BBS)
- Setmelanotide 3 mg [154]

ACQUIRED HYPOTALAMIC OBESITY
- Setmelanotide 3 mg [154]
- Semaglutide 2.4 mg [155]

PREGNANCY/WILLINGNESS TO CONCEIVE

AOMs are either contraindicated or advised against during pregnancy due to insufficient safety data and potential risks to the fetus

Stop **Liraglutide 3 mg/Semaglutide 2.4 mg** at least 2 months before

Stop **Tirzepatide 15 mg** at least 1 month before

COSTS /QALY

BS
176, 177

If additional weight loss and reduction of weight-related complications are needed

Bariatric Surgery [177]

If insufficient weight loss or weight regain after BS consider: Tirzepatide [197], Semaglutide [194], Liraglutide [195,196]

*This framework promotes a phenotype-based, individualized approach to obesity care, prioritizing complications and patient preferences over rigid treatment hierarchies, with patient-HCP shared decision-making considering goals, tolerability, contraindications, and cost. **OWCMC, obesity without clinically manifest complications

Tuccinardi D, et AL. 29 August 2025 Journal of Endocrinological Investigation https://doi.org/10.1007/s40618-025-02700-7 (in press)

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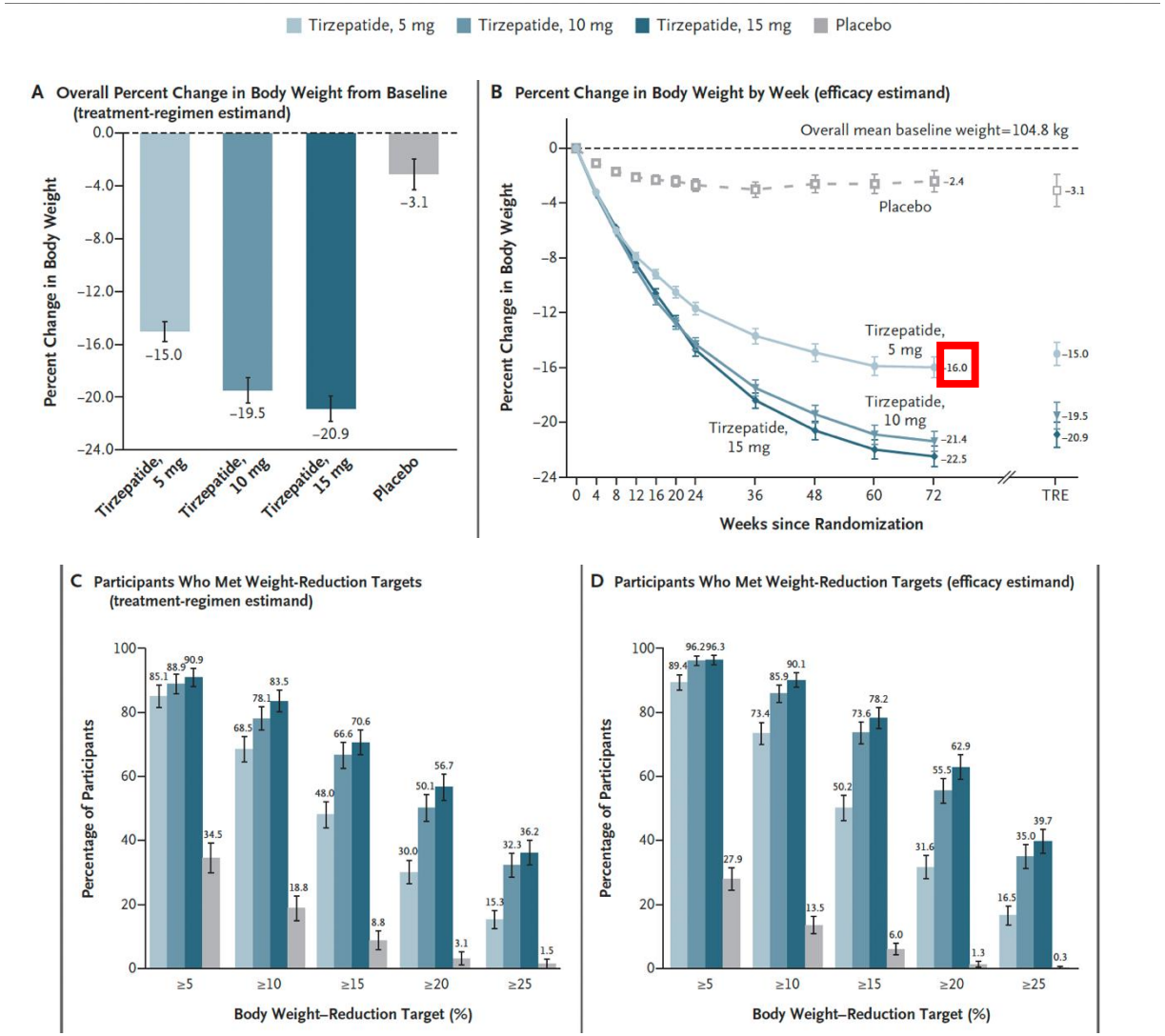
Efficacia e durabilità: la base del paradigma tirzepatide

Studio cardine in adulti con obesità senza diabete



Nel SURMOUNT-1, i pazienti in trattamento con **tirzepatide** hanno ottenuto una perdita di peso media del 15–21% rispetto al 3% con placebo, oltre l'80% dei pazienti ha raggiunto ≥10% e **oltre il 50% ha raggiunto il ≥20%** di calo ponderale.
L'effetto è progressivo, stabile fino alla settimana 72 e mostra durabilità.

Già alla dose di 5mg ha dimostrato una perdita di peso maggiore rispetto al placebo **fino al 16% dopo 72 settimane**

Jastreboff AM et al. N Engl J Med. 2022;387:205–216.
Tuccinardi D, et AL. 29 August. Journal of Endocrinological Investigation

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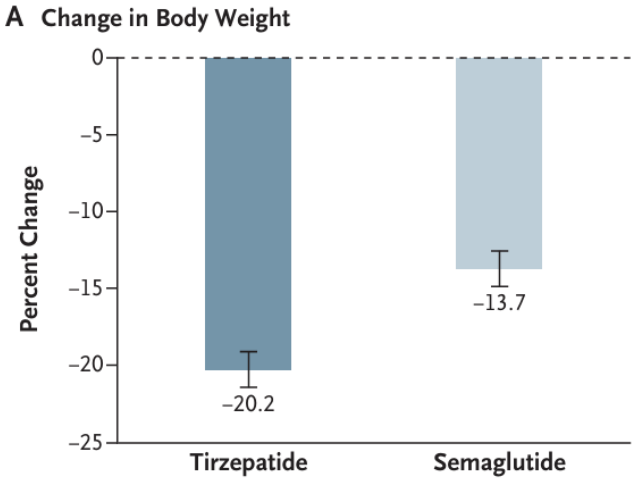
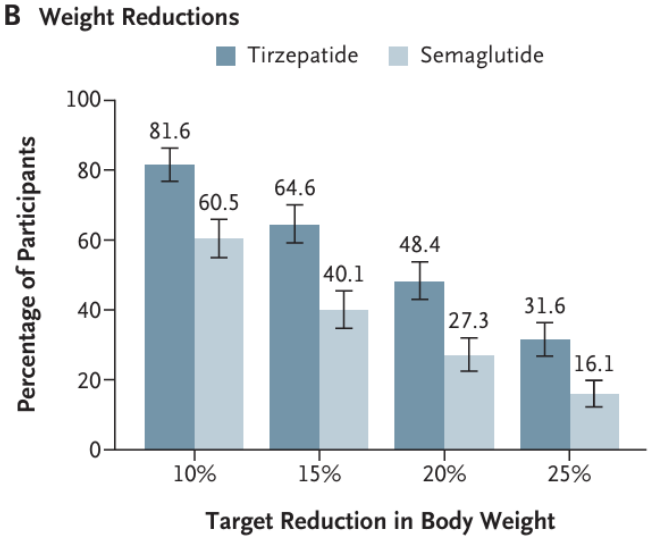
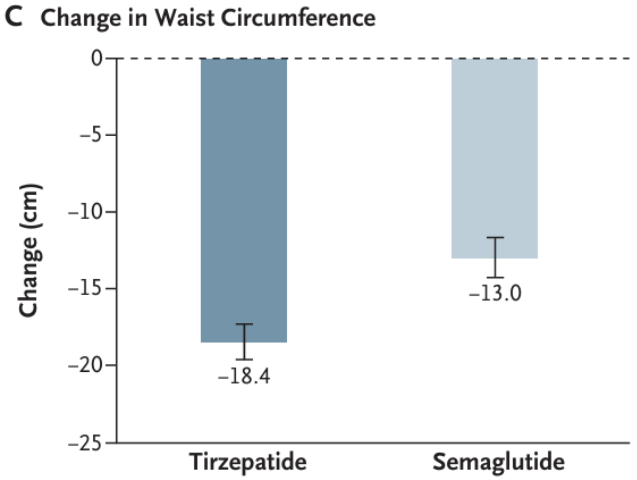
Tirzepatide vs semaglutide: confronto diretto nell'obesità senza diabete (SURMOUNT-5)

Trial di fase 3b, 72 settimane, 751 adulti con obesità senza diabete, randomizzati 1:1 a tirzepatide o semaglutide massimo dosaggio tollerato







Nel SURMOUNT-5, tirzepatide ha ottenuto un calo ponderale medio del **−20,2 % rispetto al −13,7%** con semaglutide, −6,5 pp (P < 0,001), con quasi il 50% dei partecipanti che ha superato il 20 % di perdita di peso e **una maggiore riduzione della circonferenza della vita −5,4 cm (P < 0,001).** Risultati coerenti in entrambi i sessi e nei sottogruppi di BMI e prediabete.

Aronne LJ et al. *N Engl J Med*. 2025;393(1):26-36. doi:10.1056/NEJMoa2416394.
Tuccinardi D, et AL. 29 August. Journal of Endocrinological Investigation

GLYCEMIC CONTROL

PREDIABETES

HbA1c 5.7–6.4%, fasting plasma glucose 100–125 mg/dL, or 2-hours OGTT glucose 140–199 mg/dL

- Tirzepatide 15 mg [2]
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- Orlistat 120 mg [14]

Metformin: off-label use; may reduce the incidence of type 2 diabetes[24].

TYPE 2 DIABETES

HbA1c ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL, or 2-hours OGTT plasma glucose ≥ 200 mg/dL

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- Semaglutide 2.4 mg [29]
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SGLT2 inhibitors support weight loss [37,38,39,40,41], If glycemic control allows, insulin[44,45], thiazolidinediones, and sulfonylureas should be avoided due to their propensity to induce weight gain.[203]

TYPE 1 DIABETES

(OFF-LABEL only for weight loss purposes)

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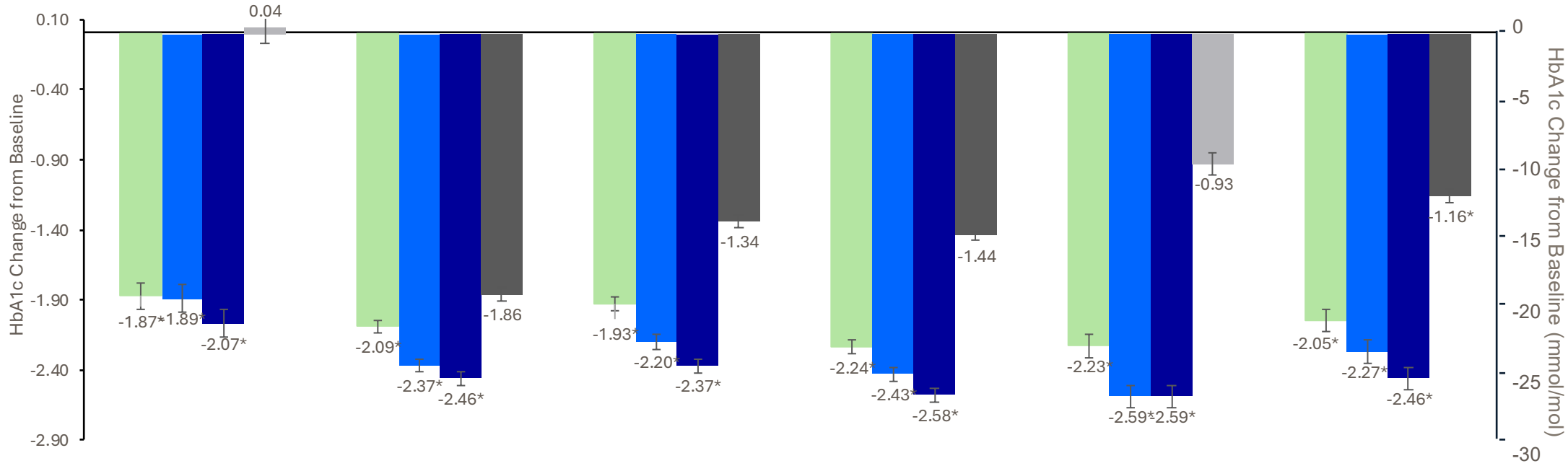
- Semaglutide 2.4 mg [51]

SURPASS PROGRAM: tirzepatide provides superior reduction in HbA1c from baseline to primary endpoint vs all comparators

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

*p<0.001 vs. placebo or active comparator.

Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c. Number of participants (N) mentioned is randomized participants.

DPP4i= dipeptidyl peptidase-4 inhibitor; HbA1c = glycated hemoglobin; LSM = least squares mean; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SE = standard error; SEMA = semaglutide; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545. 6. Rosenstock J, et al. Poster from *ADA 2023* 750P.

Prevenzione del diabete

GLYCEMIC CONTROL

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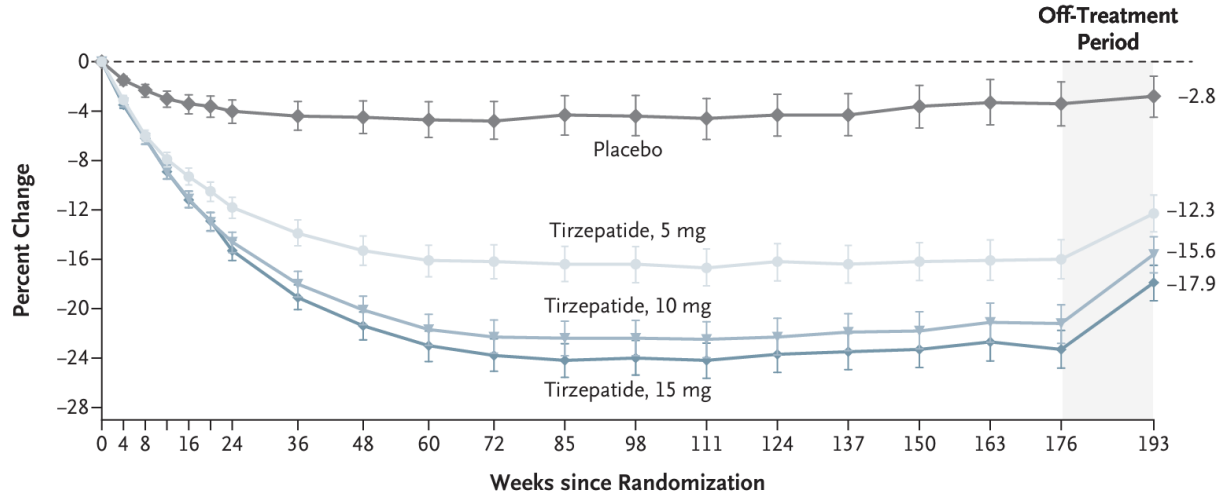
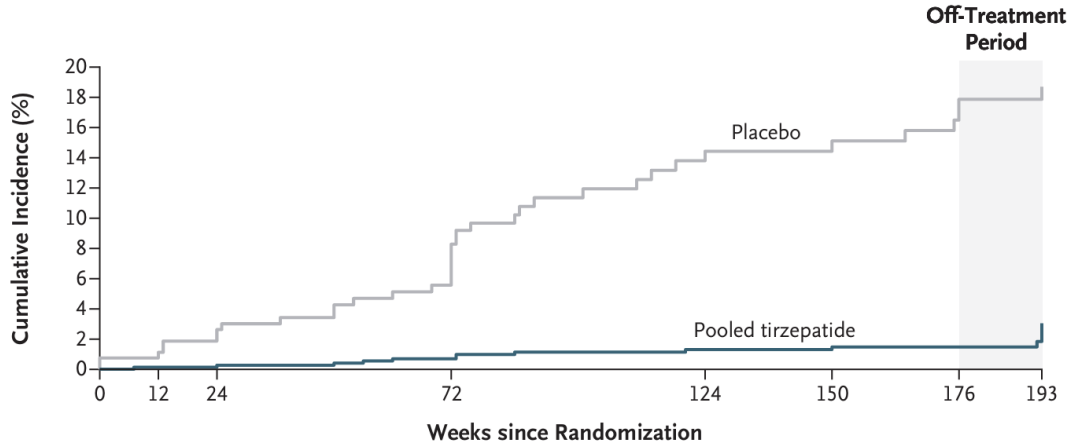
B Change in Body Weight



C Incidence of Type 2 Diabetes



No. at Risk								
Placebo	270	266	257	209	137	126	121	99
Pooled tirzepatide	762	751	742	700	581	570	557	494
No. of Participants with Diagnosis								
Placebo	2	3	7	20	31	32	36	37
Pooled tirzepatide	0	1	2	5	9	10	10	18

Tirzepatide ha ridotto del **90–93% il rischio relativo** e di circa **12 punti percentuali il rischio assoluto** di sviluppare il diabete tipo 2 nei soggetti con obesità e prediabete, con un **NNT di 9** per prevenire un caso di diabete in 3 anni.

Jastreboff AM et al. N Engl J Med. 2025;392:958–971

Tuccinardi D, et AL. 29 August. Journal of Endocrinological Investigation

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PREDIABETES

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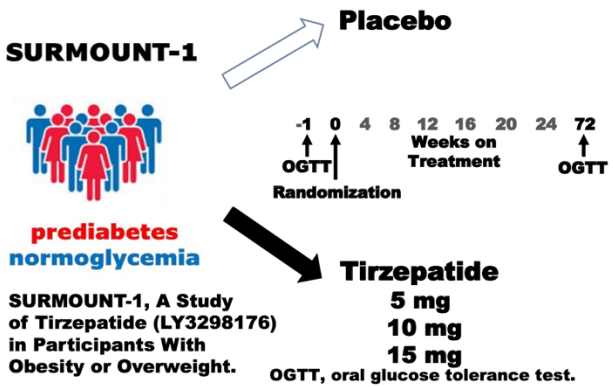
Tirzepatide Enhances β-Cell Function and Insulin Sensitivity in People with Obesity without Diabetes

SURMOUNT-1 post hoc analysis: insulin sensitivity improves with weight loss and direct GIP-mediated effects, while β-cell function enhancement is primarily driven by tirzepatide itself, independent of weight reduction

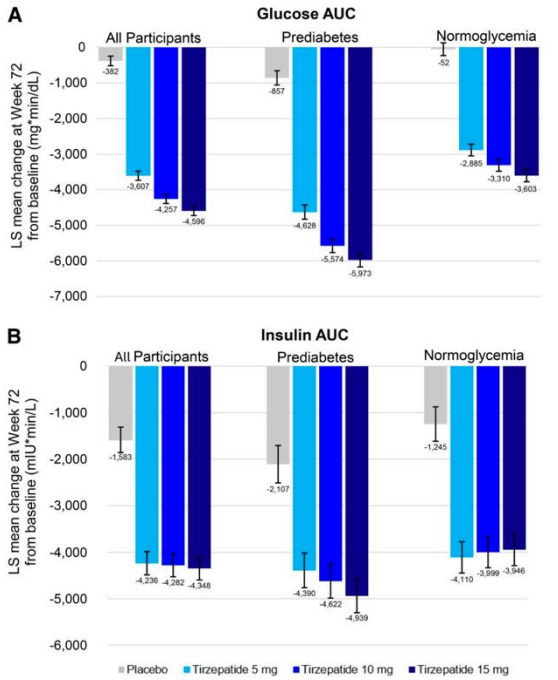
Objective: to assess insulin sensitivity and β-cell function in adults with obesity or overweight (BMI ≥ 27 kg/m²) and with either prediabetes or normoglycemia at baseline treated with tirzepatide for 72 weeks (post hoc analysis from SURMOUNT-1 trial)

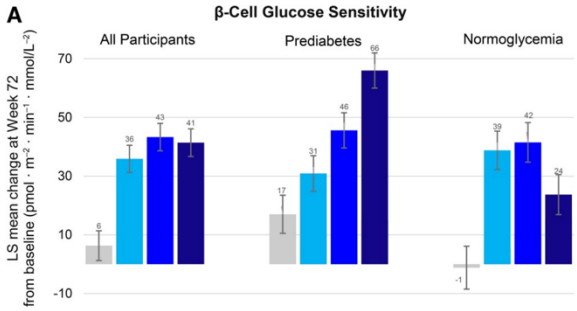


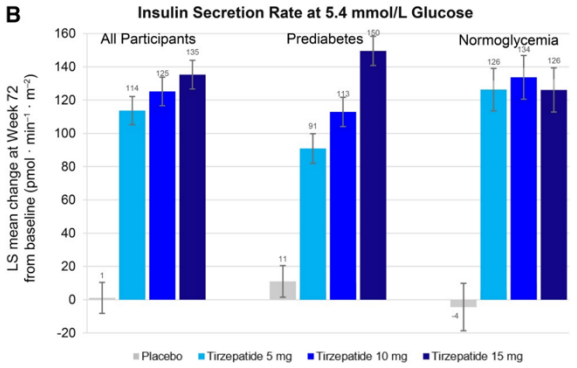
Responses with tirzepatide (vs. placebo)

- **Body weight** ↓
- **Blood glucose** ↓
- **Insulin sensitivity** ↑ — mostly related with weight reduction and partly with tirzepatide
- **β-cell function** ↑ — mostly related with tirzepatide

All responses were observed in participants with prediabetes and with normoglycemia.







Diabetes Care 2025;48(9):1622–1627 | https://doi.org/10.2337/dc25-0763

Tuccinardi D, et AL. 29 August. Journal of Endocrinological Investigation

GLYCEMIC CONTROL

PREDIABETES

HbA1c 5.7–6.4%, fasting plasma glucose 100–125 mg/dL, or 2-hours OGTT glucose 140–199 mg/dL

- **Tirzepatide 15 mg** [2]
- **Semaglutide 2.4 mg** [22]
- **Liraglutide 3 mg** [12,74]
- **Orlistat 120 mg** [14]

Metformin: off-label use; may reduce the incidence of type 2 diabetes[24].

TYPE 2 DIABETES

HbA1c ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL, or 2-hours OGTT plasma glucose ≥ 200 mg/dL

- **Tirzepatide 15 mg** [31]
- **Semaglutide 2.4 mg** [29]
- **Liraglutide 3 mg** [33]

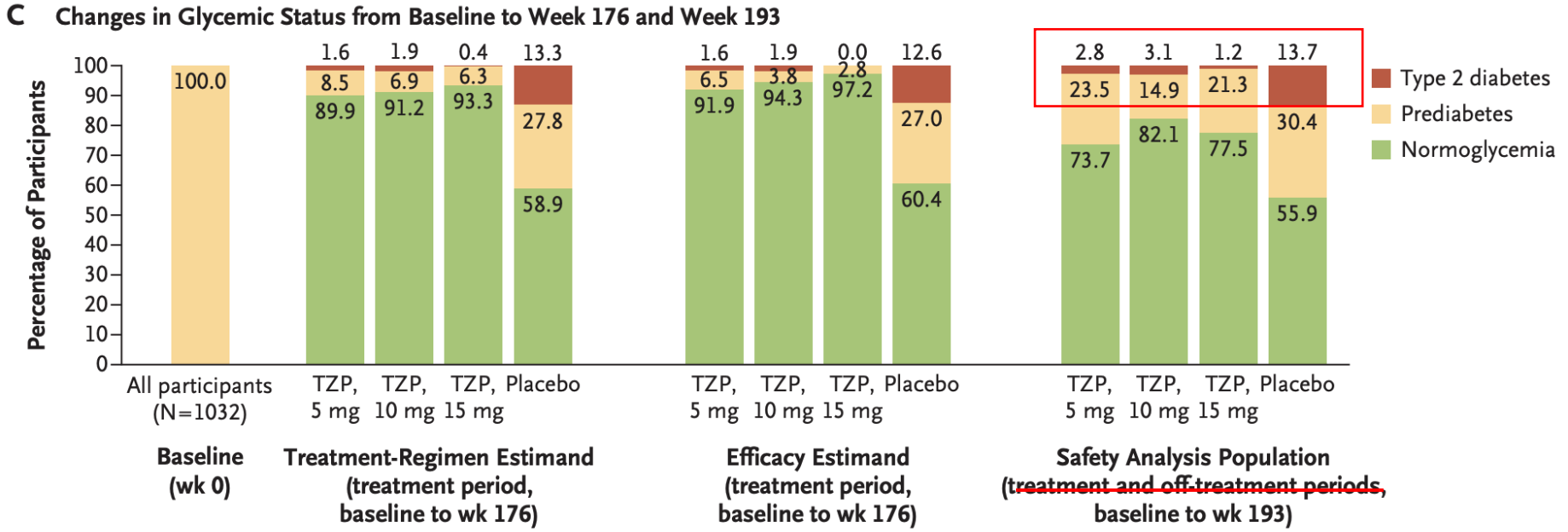
SGLT2 inhibitors support weight loss [37,38,39,40,41], If glycemic control allows, insulin[44,45], thiazolidinediones, and sulfonylureas should be avoided due to their propensity to induce weight gain.[203]

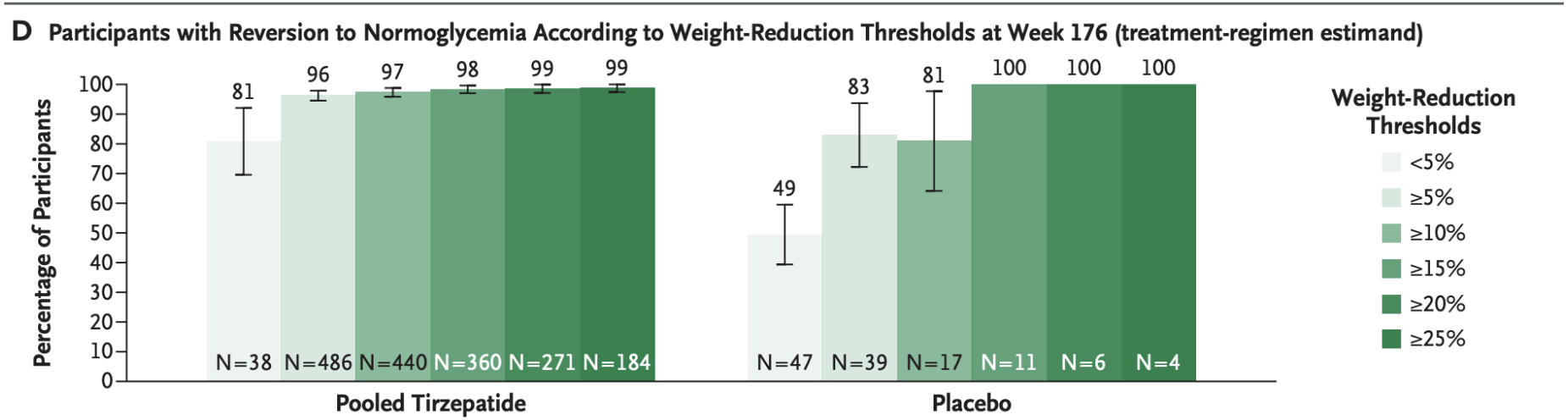
TYPE 1 DIABETES

(OFF-LABEL only for weight loss purposes)

- **Tirzepatide 15 mg** [52]
- **Semaglutide 2.4 mg** [51]

Tirzepatide drives long-term reversion to normoglycemia — sustained only with continued therapy At 176 weeks, >90% achieved normoglycemia; rates declined after withdrawal, highlighting the link between weight maintenance and glycemic remission.





N Engl J Med 2025;392:958-71. DOI: 10.1056/NEJMoa2410819

Not All Prediabetes Is the Same: Heterogeneity Explains Why Only Some Individuals Progress to Diabetes.

Distinct pathophysiological subtypes — from β-cell failure to hyperinsulinemic insulin resistance — determine who will and who will not progress despite treatment or weight loss.

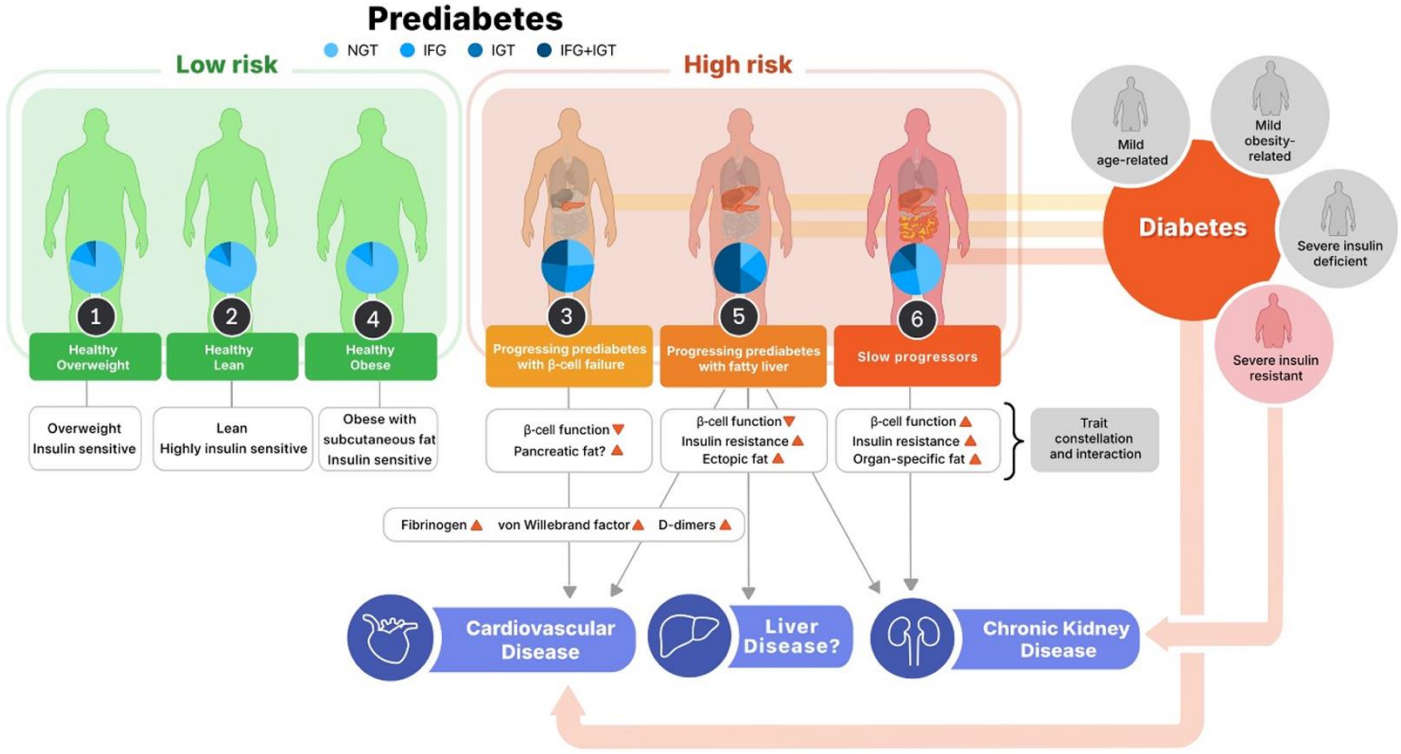
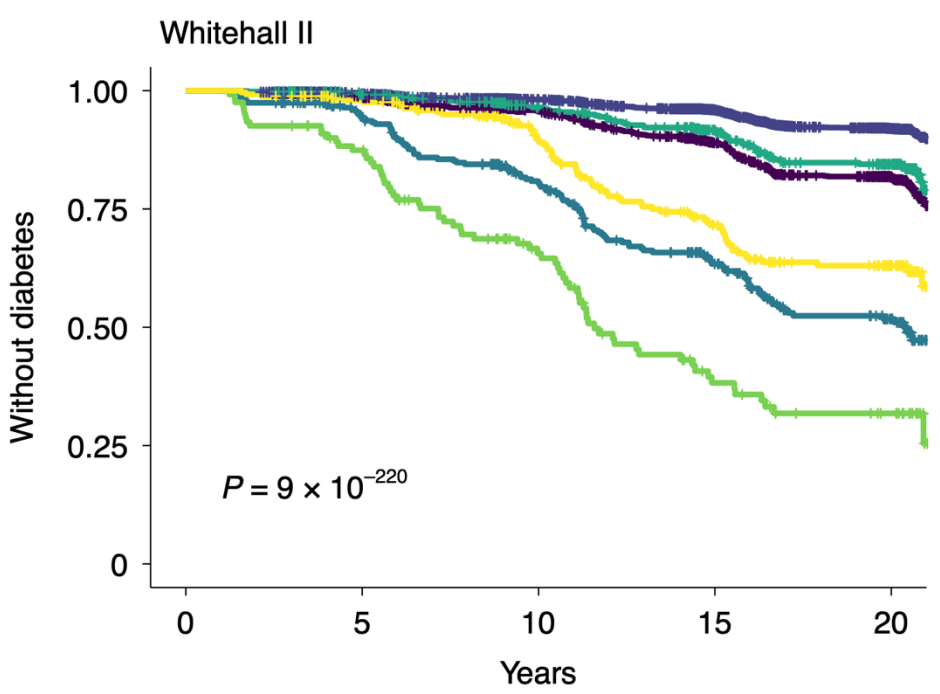


Figure 1—Distinct constellations of traits, including variations in insulin sensitivity, β-cell function, and organ-specific fat distribution, are seen among prediabetes subtypes. For these subtypes there are different trajectories toward diabetes, its subtypes, associated complications, and mortality. NGT, normal glucose tolerance.



Wagner R et al. Nat Med. 2021;27:49–57.
Wagner R et al. Diabetes Care. 2025;48:1–10.

MASLD/ MASH

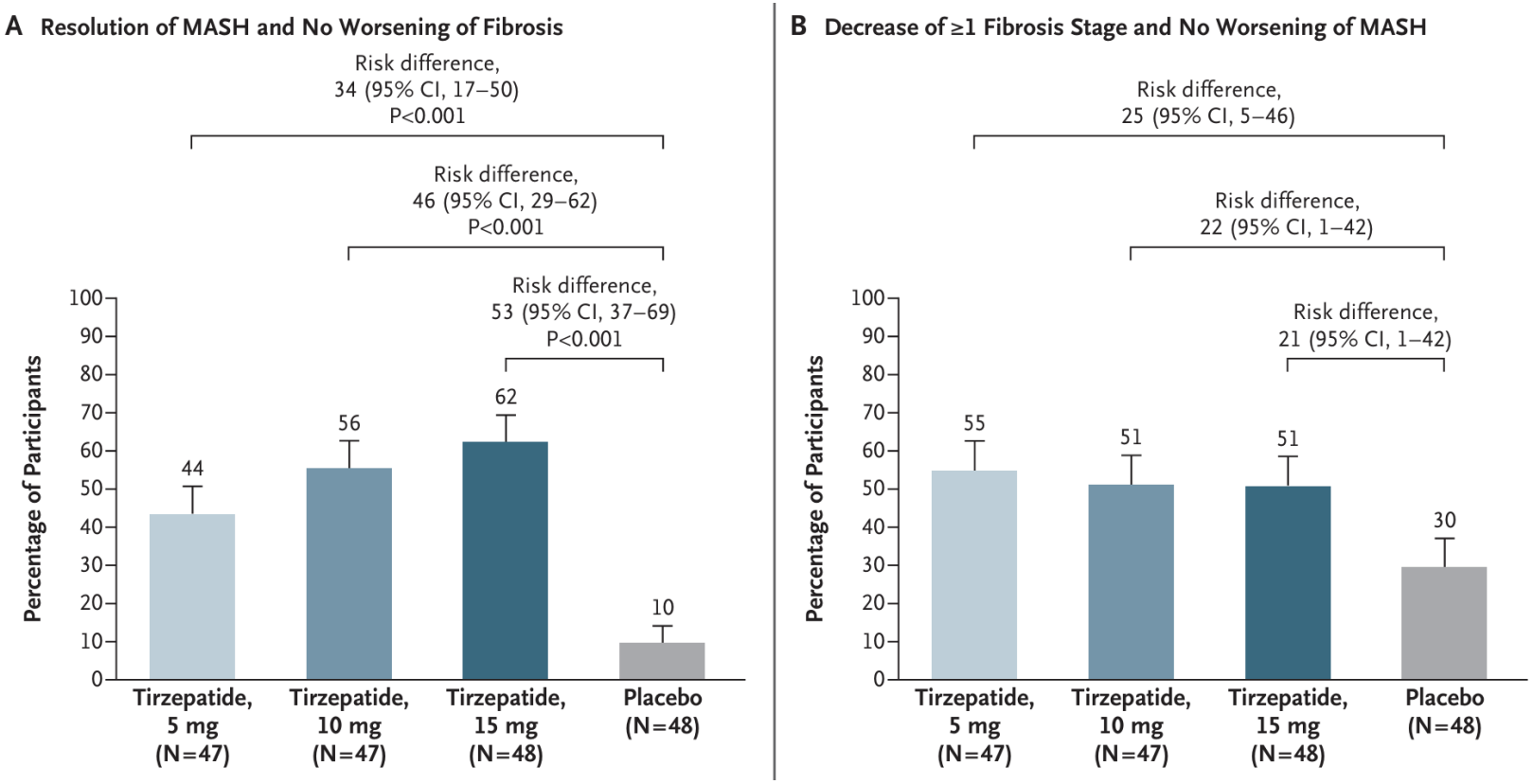
Tirzepatide e MASH: dal trattamento del metabolismo alla regressione istologica

Adults with biopsy-confirmed MASH, fibrosis stage F2–F3 for **semaglutide** 2.4 mg and **tirzepatide** 15 mg; F0–F3 for **liraglutide 3 mg**. BMI ≥25 kg/m² for **semaglutide** 2.4 mg and **liraglutide** 3 mg; BMI ≥27 kg/m² for **tirzepatide** 15 mg, with or without type 2 diabetes; BMI not restricted, and ,with or without type 2 diabetes, for **semaglutide** 2.4.

Semaglutide 2.4 mg [54]

Tirzepatide 15 mg [56]

Liraglutide 3 mg OD[57]



Dopo 52 settimane, tirzepatide ha determinato la **risoluzione della MASH nel 54% dei pazienti**, rispetto al 10% con placebo, con una **riduzione assoluta del rischio del 44%** e un **NNT di 3**.
Anche la regressione fibrotica è stata significativamente superiore al placebo (52% vs 30%), con **ARR del 22%** e **NNT di 5**.

Rohit Loomba, M.D. N Engl J Med 2024;391:299-310
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HF

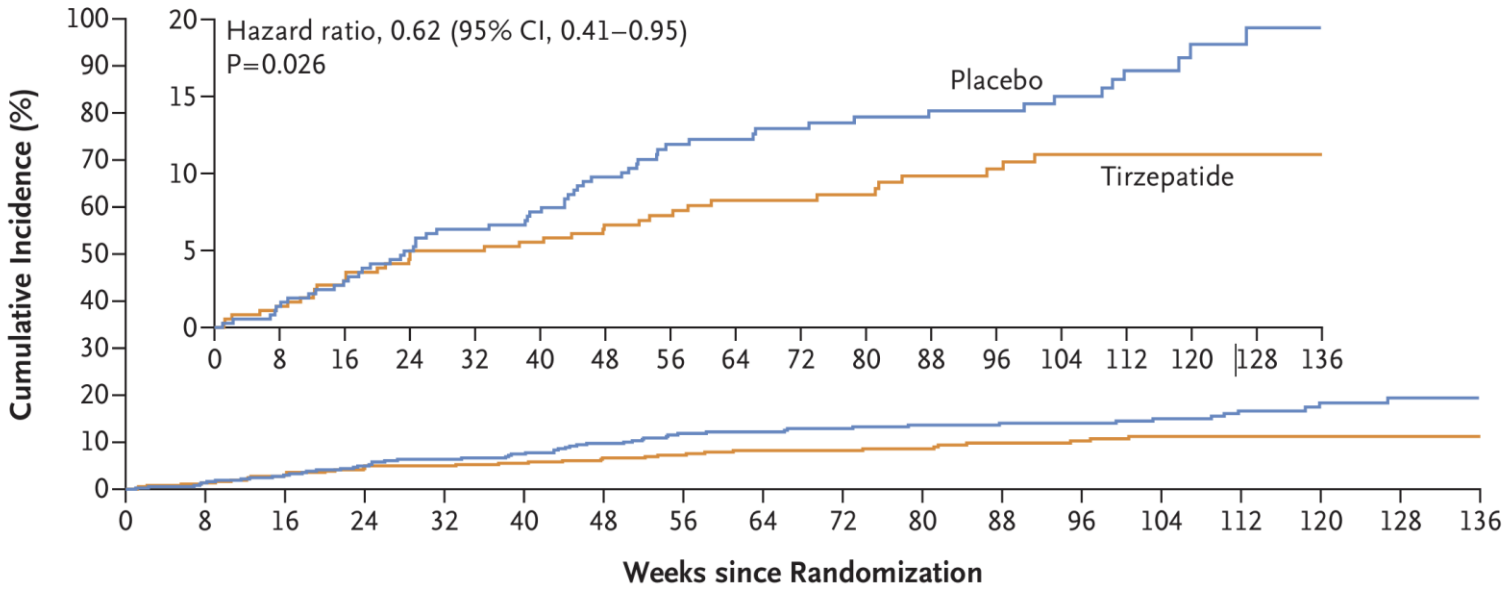
Clinical heart failure (NYHA II–IV) with preserved or mildly reduced ejection fraction (LVEF ≥50% for **tirzepatide**, ≥45% for **semaglutide**), BMI ≥30 kg/m², impaired functional capacity (KCCQ-CSS <80–90), 6MWT distance ≥100 m, and elevated filling pressures (e.g., NT-proBNP, echocardiographic abnormalities, or recent HF hospitalization). Type 2 diabetes was an inclusion criterion in the tirzepatide trial.

Tirzepatide 15 mg [11]

Semaglutide 2.4 mg [5]

Naltrexone/ Buproprion (not recommended) [15]

Tirzepatide nello scompenso con frazione di eiezione preservata e obesità



No. at Risk																		
Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45
Tirzepatide	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46

Tirzepatide è indicato per il trattamento dei pazienti affetti da diabete tipo -2 e per la gestione del peso corporeo. Non sono autorizzate da FDA/EMA indicazioni al trattamento dello scompenso cardiaco con tirzepatide

Nel trial SUMMIT, tirzepatide ha ridotto del **38% il rischio relativo HR 0.62 (IC 95% 0.41–0.95; p=0.026)**, e di circa **5 % il rischio assoluto** di morte cardiovascolare o nuovo evento di scompenso rispetto al placebo, con un **NNT di 19** in due anni. L'effetto è stato guidato in larga parte dalla riduzione delle ospedalizzazioni per scompenso (HR 0.44; **NNT ≈ 26)**

Milton Packer, M.D. N Engl J Med 2025;392:427-437
Tuccinardi D, et AL. 29 August. Journal of Endocrinological Investigation

Indicators of High CV Risk:

Definitions vary; however, most include age ≥40 years, BMI ≥27 kg/m², male sex, hypertension, atherogenic dyslipidemia, smoking, prediabetes, and elevated ASCVD risk (per ACC/AHA criteria)

Tirzepatide 15 mg [2,10]

Semaglutide 2.4 mg [3,4]

Liraglutide 3 mg [12]

Naltrexone/ Buproprion (not recommended)[15]

Oltre il peso: effetti sul rischio cardiovascolare nello studio SURMOUNT-5

Tertiary Endpoints – efficacy estimand

Endpoints	Semaglutide MTD	Tirzepatide MTD	Estimated treatment difference (95% CI)
Change in systolic blood pressure, mmHg	−7.7 (−8.9 to −6.4)	−10.2 (−11.4 to −8.9)	−2.5 (−4.2 to −0.7)
Change in diastolic blood pressure, mmHg	−3.2 (−4.0 to −2.3)	−4.6 (−5.5 to −3.8)	−1.5 (−2.7 to −0.3)
Change in HbA1c, %	−0.39 (−0.42 to −0.36)	−0.50 (−0.53 to −0.47)	−0.10 (−0.15 to −0.06)
Change in fasting serum glucose, mg/dL	−11.6 (−12.4 to −10.7)	−13.4 (−14.2 to −12.5)	−1.8 (−3.1 to −0.6)
Change in fasting insulin, pmol/L	−35.0 (−39.5 to −30.1)	−53.0 (−56.2 to −49.5)	−27.7 (−34.7 to −20.0)
Change in triglycerides, mg/dL	−27.5 (−30.9 to −24.1)	−34.9 (−38.0 to −31.8)	−7.4 (−12.0 to −2.8)
Change in VLDL cholesterol, mg/dL	−5.3 (−6.0 to −4.6)	−6.8 (−7.4 to −6.2)	−1.5 (−2.4 to −0.6)
Change in non-HDL cholesterol, mg/dL	−12.8 (−15.7 to −9.9)	−15.6 (−18.4 to −12.7)	−2.7 (−6.8 to 1.3)
Change in LDL cholesterol, mg/dL	−5.9 (−8.6 to −3.2)	−7.8 (−10.4 to −5.2)	−1.9 (−5.6 to 1.9)
Change in HDL cholesterol, mg/dL	2.9 (2.0 to 3.8)	5.7 (4.8 to 6.7)	2.8 (1.5 to 4.1)

- The CIs have not been adjusted for multiplicity and should not be used to make inferences. Data are LSM (95% CI).
- CI=Confidence Interval; HbA1c=Glycated Haemoglobin; HDL=High-Density Lipoprotein; LDL=Low-Density Lipoprotein; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose; VLDL=Very-Low-Density Lipoprotein.

Aronne LJ et al. *N Engl J Med.* 2025;393(1):26-36. doi:10.1056/NEJMoa2416394.
Tuccinardi D, et AL. 29 August. Journal of Endocrinological Investigation

OSA

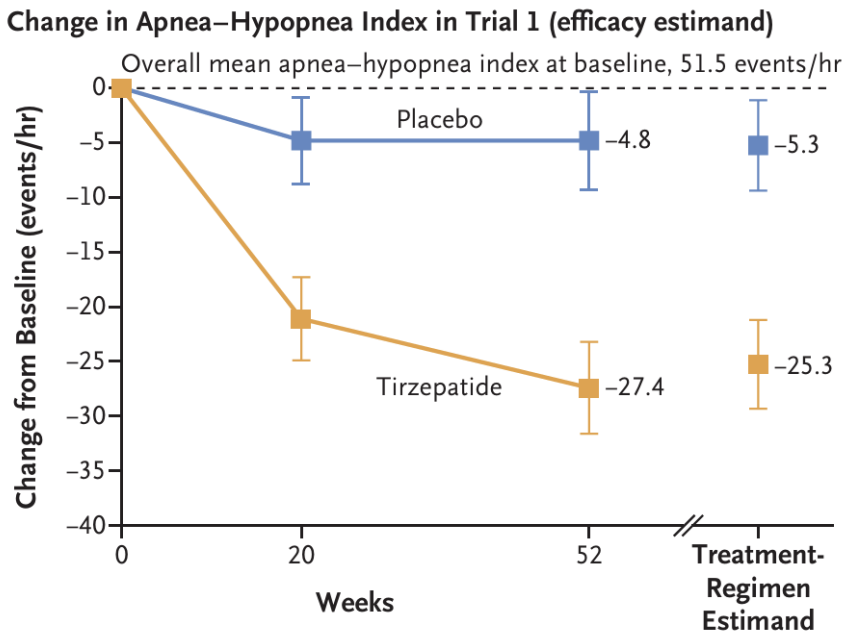
Adults ≥18 years, BMI ≥30 kg/m², with moderate-to-severe obstructive sleep apnea (AHI ≥15 events/h); CPAP use allowed (tirzepatide) or excluded (liraglutide); no diagnosis of T2D.

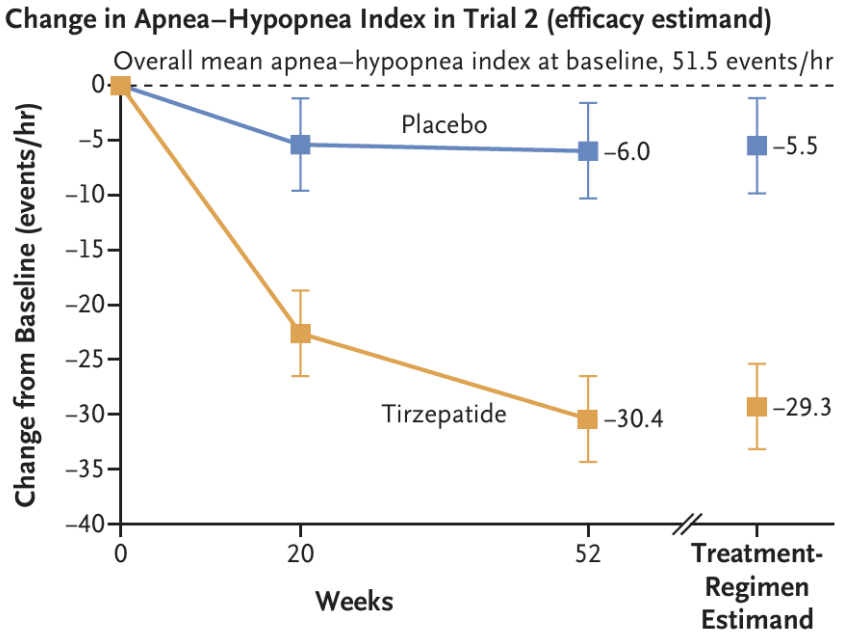
Tirzepatide 15 mg [68]

Liraglutide 3 mg [69]

Phentiramine/ Topiramate[70]

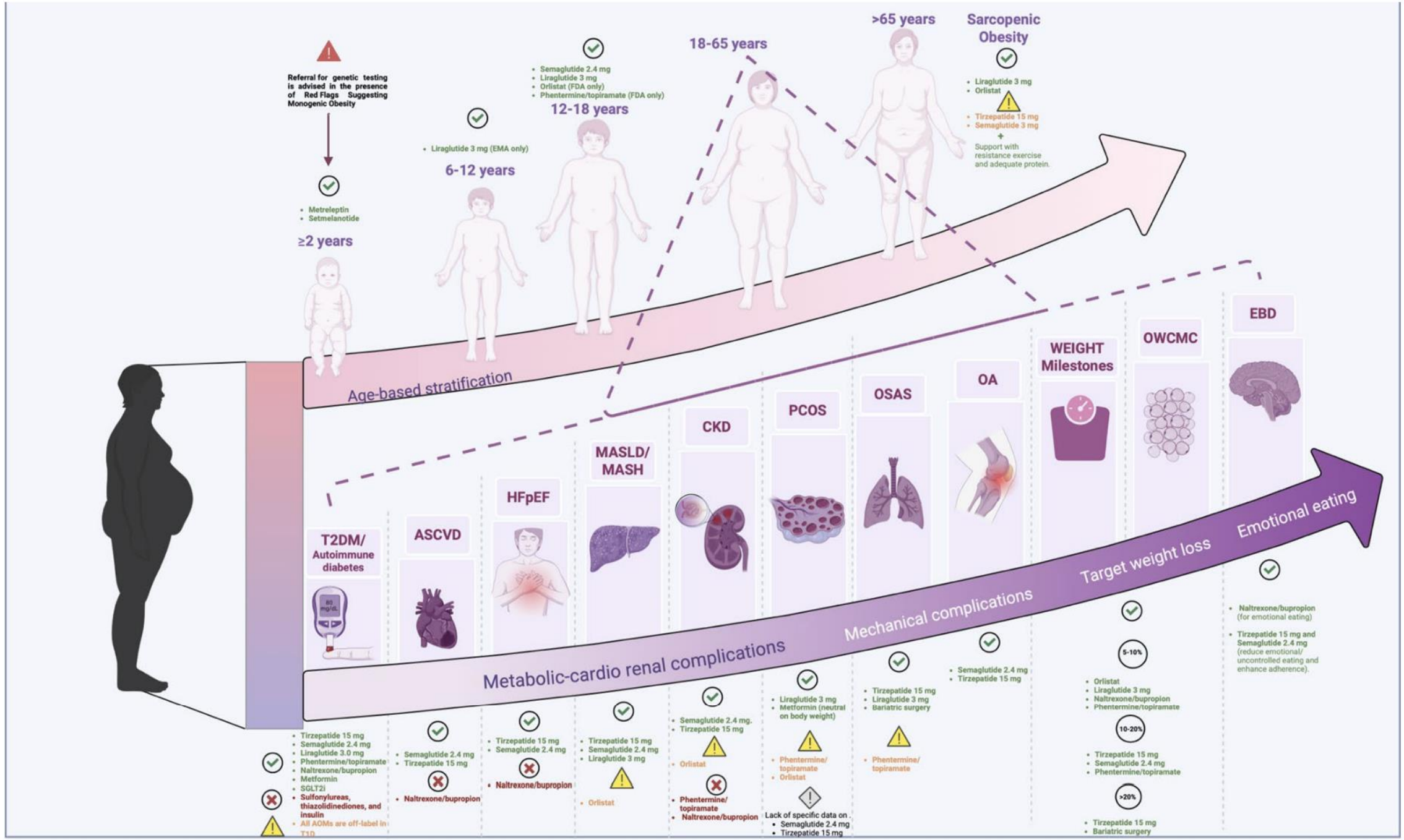
Tirzepatide migliora l'apnea ostruttiva del sonno nei soggetti con obesità, con o senza CPAP





In entrambi i trial SURMOUNT-OSA, **tirzepatide ha ridotto l'indice apnea-ipopnea di circa 25–30 eventi/ora** (−50%) e il peso di ~20%, con miglioramento di sonnolenza, pressione arteriosa e infiammazione. Efficacia comparabile nei soggetti con e senza CPAP, con circa la metà dei pazienti che raggiunge la remissione clinica dell'OSA.

Malhotra A, et al.*N Engl J Med*. 2024;391(13):1193-1205. doi:10.1056/NEJMoa2404881.
Tuccinardi D, et AL. 29 August. Journal of Endocrinological Investigation



Tuccinardi D, et AL. 29 August 2025 Journal of Endocrinological Investigation https://doi.org/10.1007/s40618-025-02700-7 (in press)

MESSAGGI CHIAVE

Dalle radici biologiche alla terapia moderna: l'evoluzione di GIP e GLP-1, da ormoni ancestrali del metabolismo a target chiave della medicina di precisione per l'obesità.

Dai trial alla rivoluzione terapeutica: tirzepatide riduce peso, rischio di diabete, danno cardio-renale, fegato grasso e apnea del sonno.

Dal singolo al doppio agonista: nello studio SURMOUNT-5 **tirzepatide è risultato superiore a semaglutide nella riduzione del peso corporeo** a 72 settimane e ha presentato un tasso di discontinuazione per EA gastrointestinali inferiore rispetto a semaglutide