

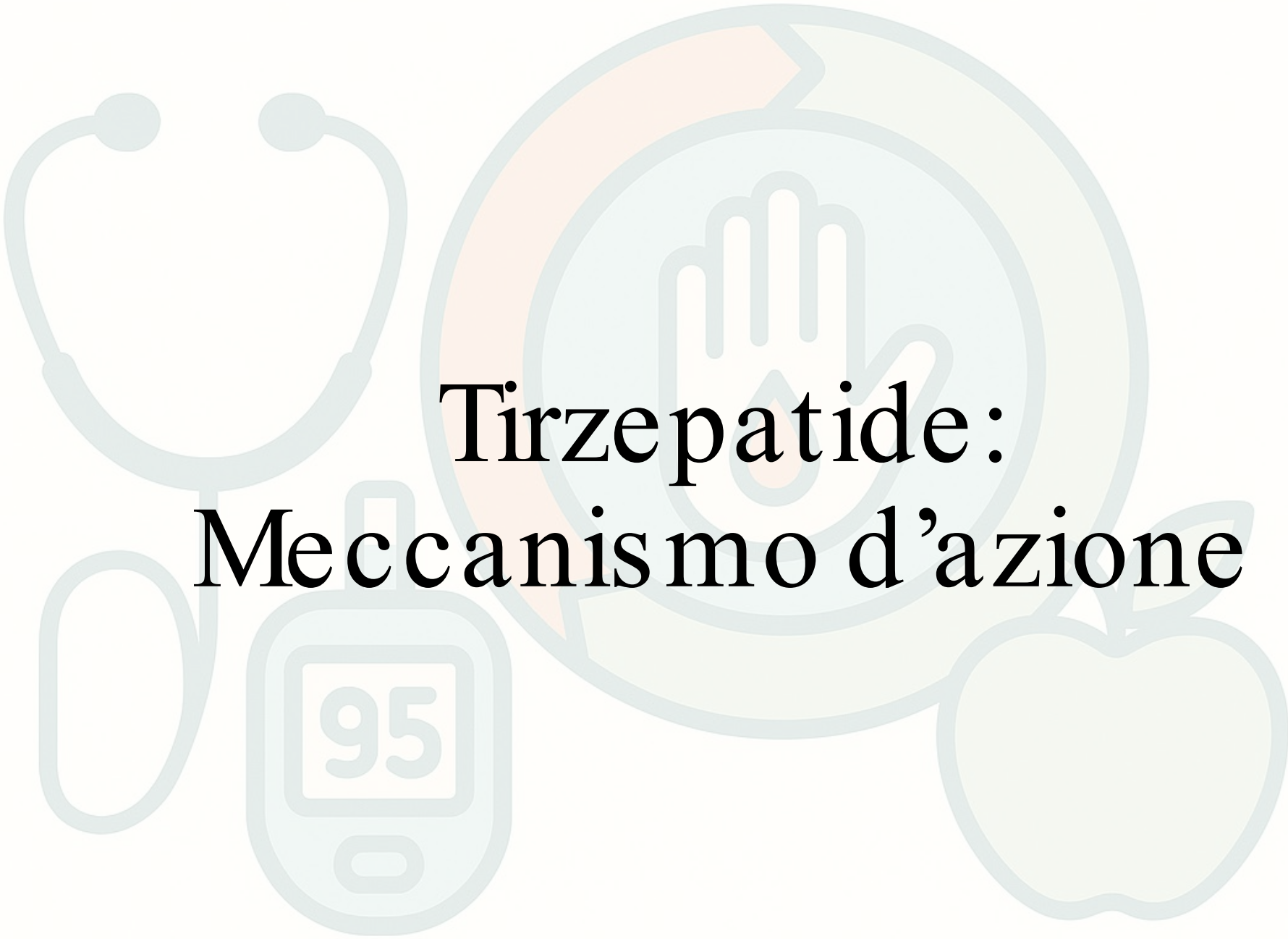


Dual-agonist: un nuovo alleato

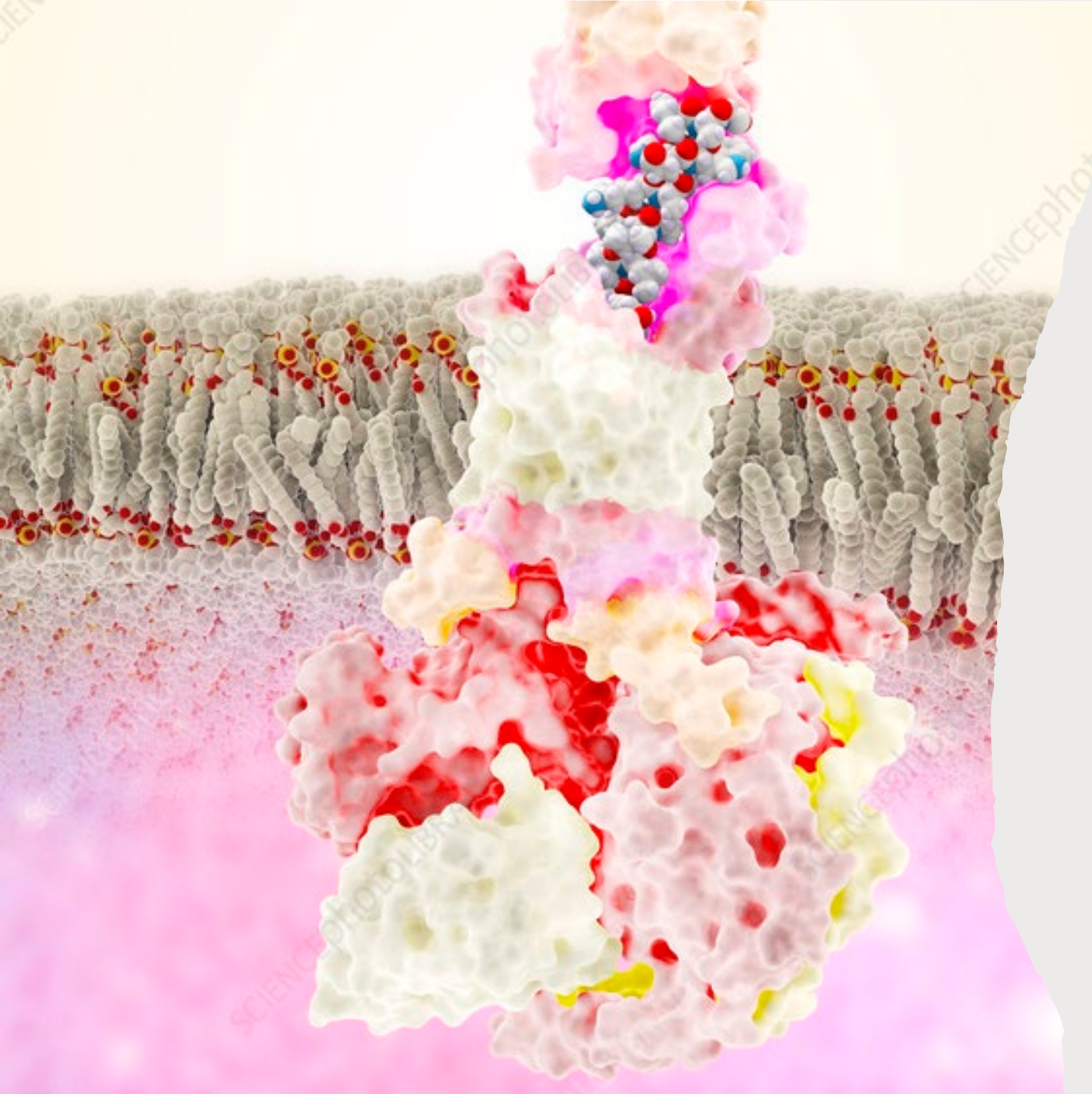
Caterina Conte

Università Telematica San Raffaele Roma

IRCCS MultiMedica, Milano

A light blue background featuring faint medical illustrations: a stethoscope on the left, a circular diagram with a hand in the center and an orange arrow pointing clockwise, a blood glucose meter at the bottom left showing the number 95, and an apple at the bottom right.

Tirzepatide: Meccanismo d'azione



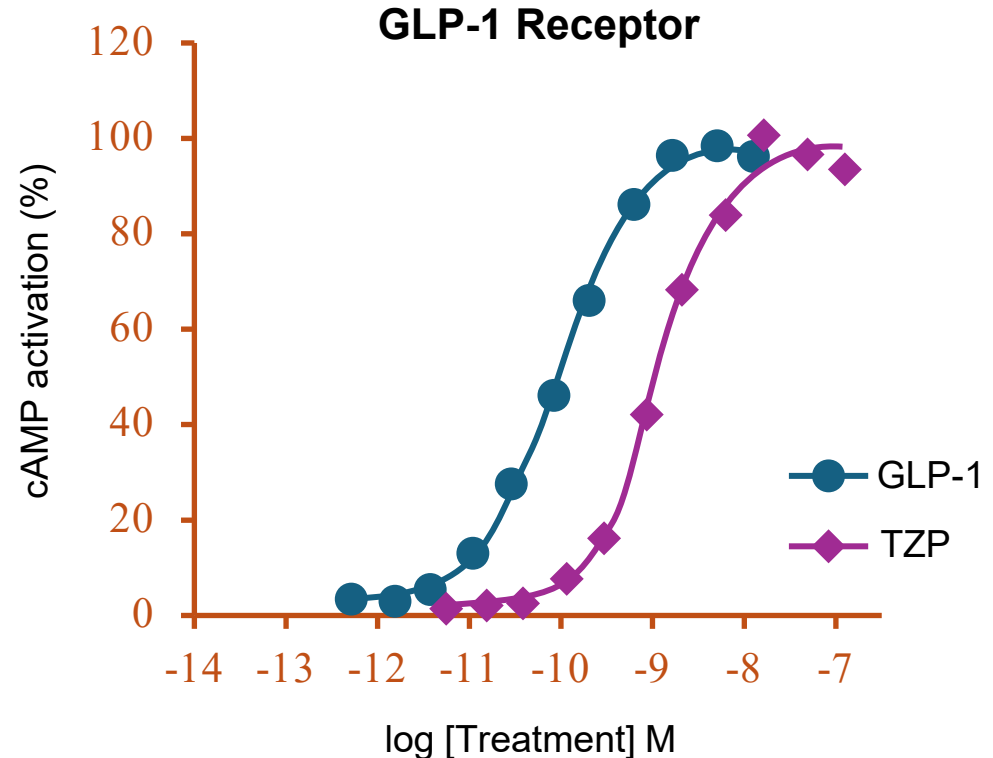
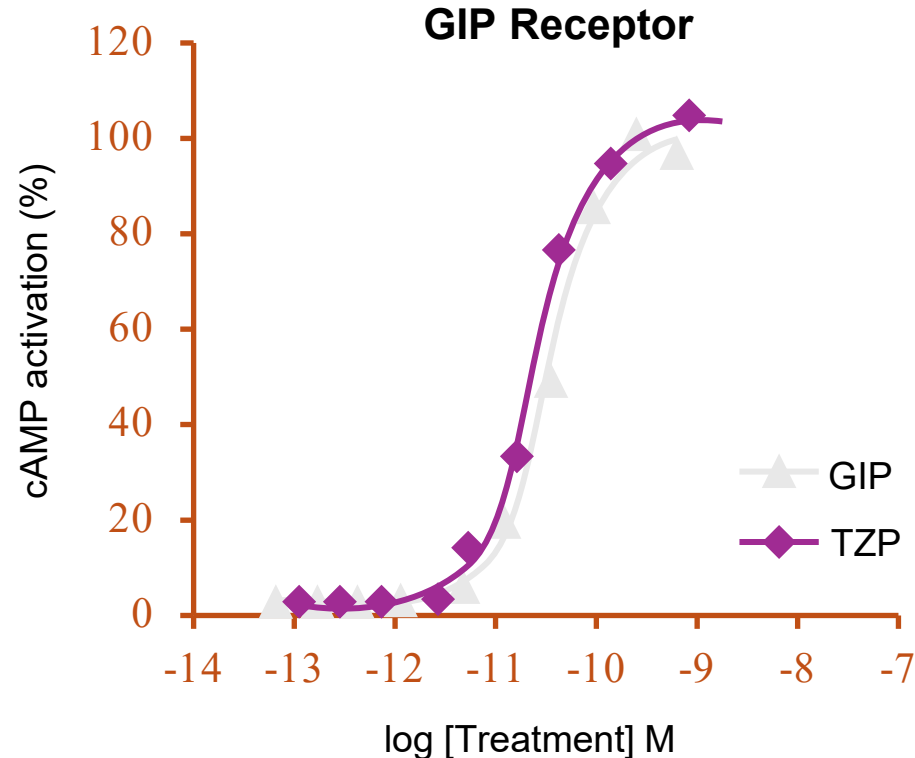
Tirzepatide

Singola molecola, attività su due target farmacologici

- Peptide multifunzionale ingegnerizzato a partire dalla sequenza nativa del peptide GIP, modificato per legarsi sia ai recettori del GIP sia a quelli del GLP-1.
- Peptide lineare di 39 amminoacidi che include un gruppo C20 acido grasso (fatty diacid) e due residui amminoacidici non codificati in posizione 2 e 13 (Aib, acido α -amino isobutirrico) per prolungarne l'emivita.
- Emivita media di circa 5 giorni (116,7 ore), che consente la somministrazione una volta a settimana.
- Le concentrazioni plasmatiche nelle persone con insufficienza renale o epatica non differiscono da quelle nei sani.
- Peso molecolare: 4,8 kDa (dula 63 kDa, sema 4,11 kDa).

Potenza e affinità per i recettori GIP e GLP-1

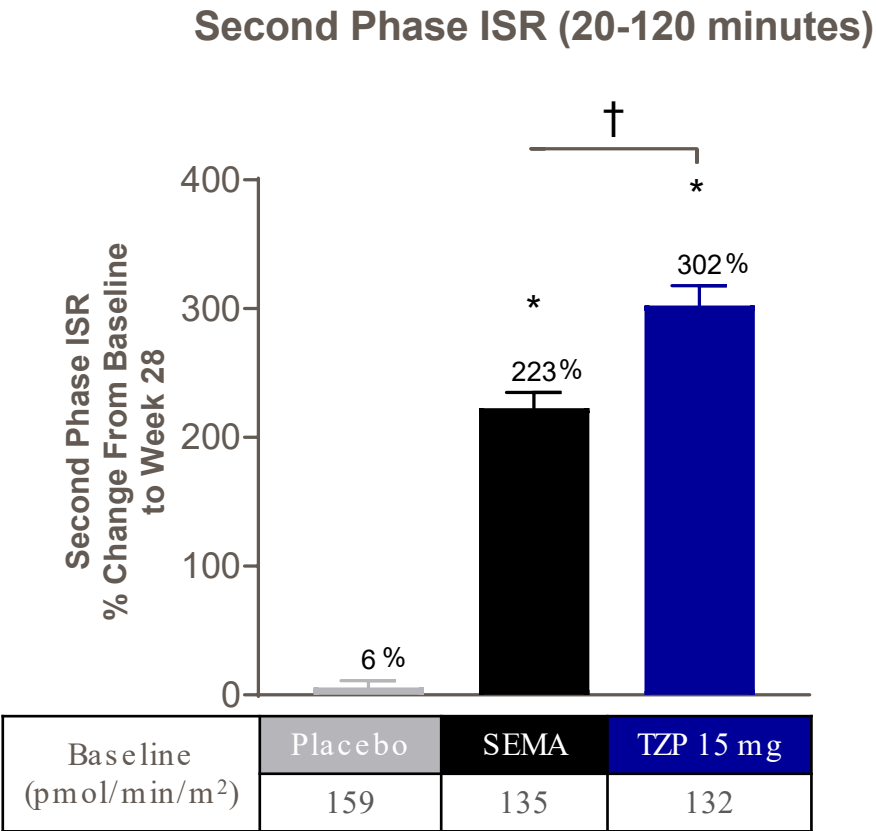
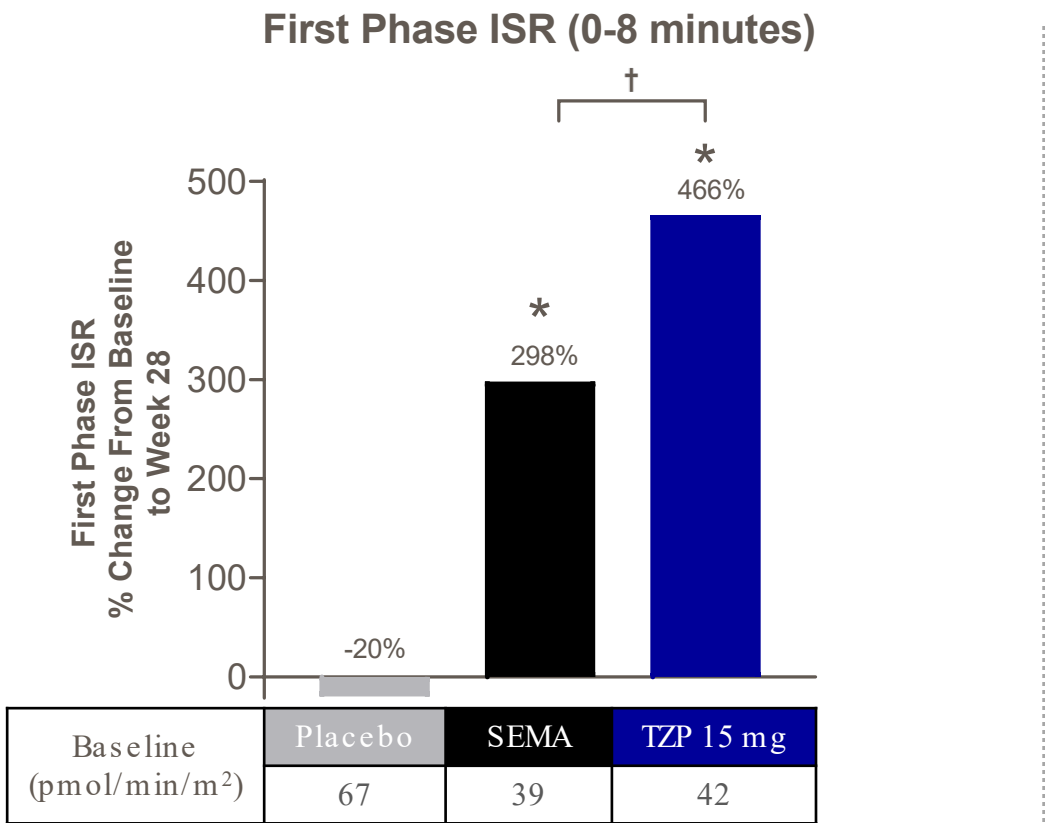
- In vitro, tirzepatide presenta una potenza e un'affinità per il recettore GIP simili a quelle del GIP nativo.
- La potenza e l'affinità per il recettore GLP-1 sono leggermente inferiori rispetto a quelle del GLP-1 nativo.



Tirzepatide: miglioramento secrezione insulinica

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Personen mit Diabetes Typ 2. Effekt von Tirzepatid vs Placebo und Semaglutid auf die Insulinsekretion während des hyperglykämischen Clamps.

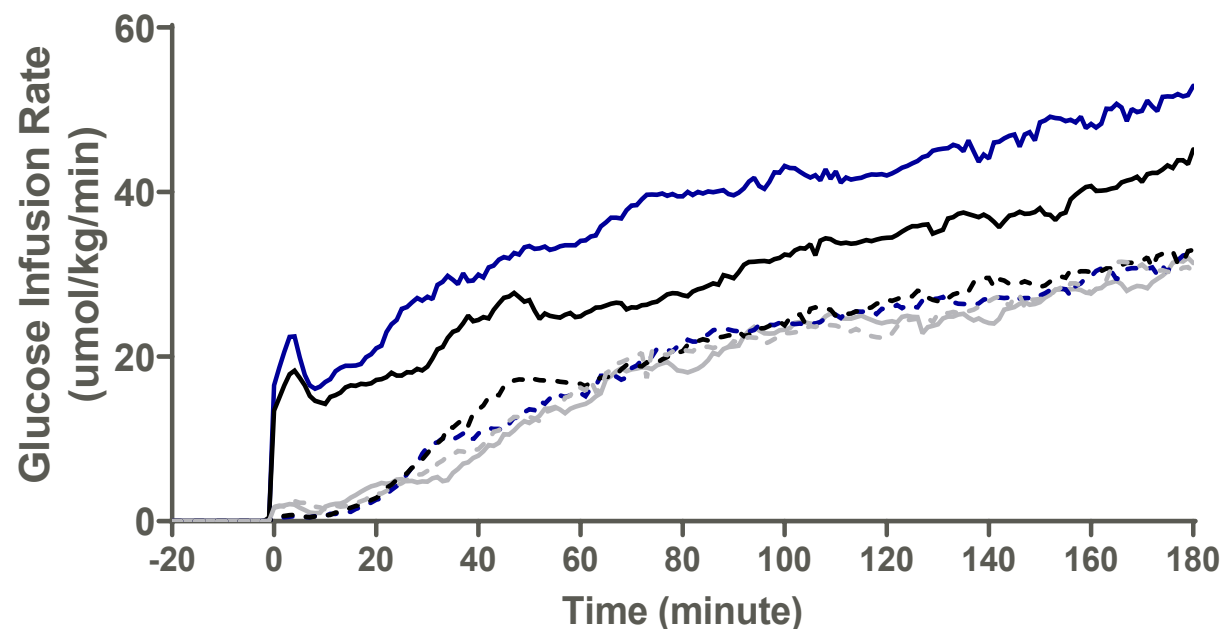
Tirzepatide: miglioramento sensibilità insulinica

■ Placebo ■ SEMA 1 mg ■ TZP 15 mg

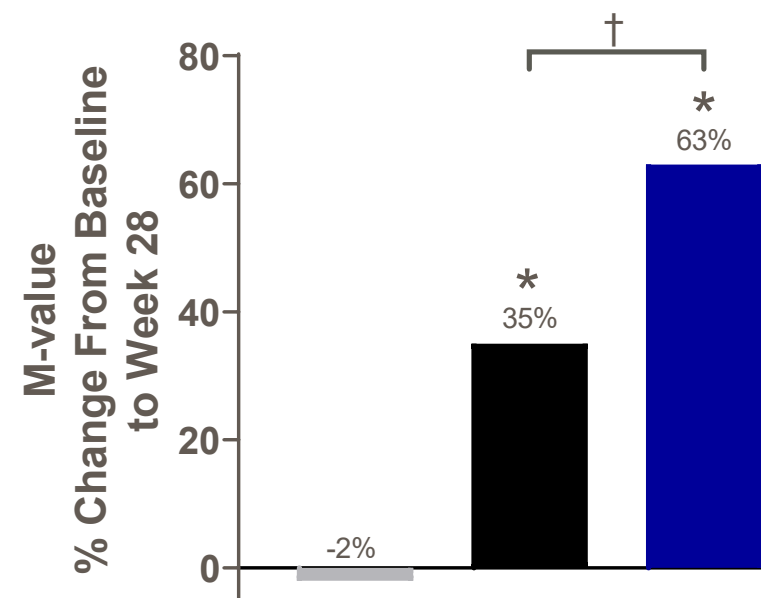
Dashed: baseline

Solid: Week 28

Glucose Infusion Rate

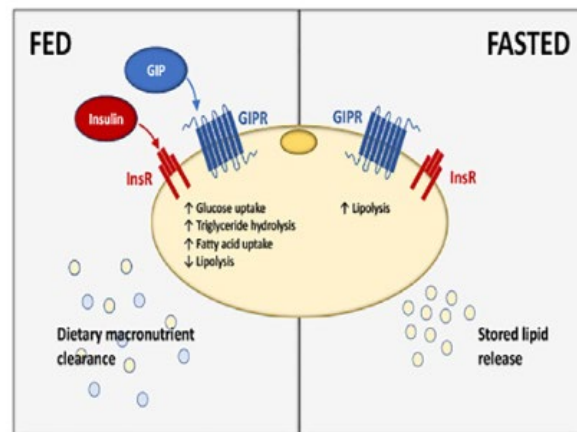
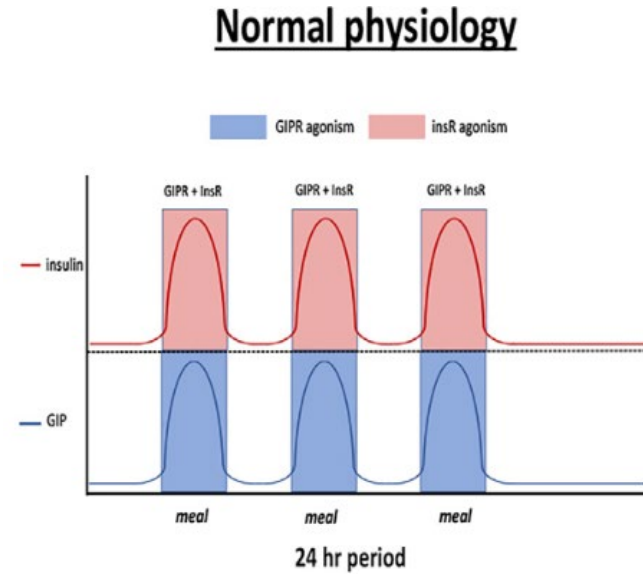


Whole-body Insulin Sensitivity, M-value



Persone con diabete di tipo 2. Effetto di tirzepatide vs placebo e semaglutide su secrezione insulinica durante clamp euglicemico iperinsulinemico.

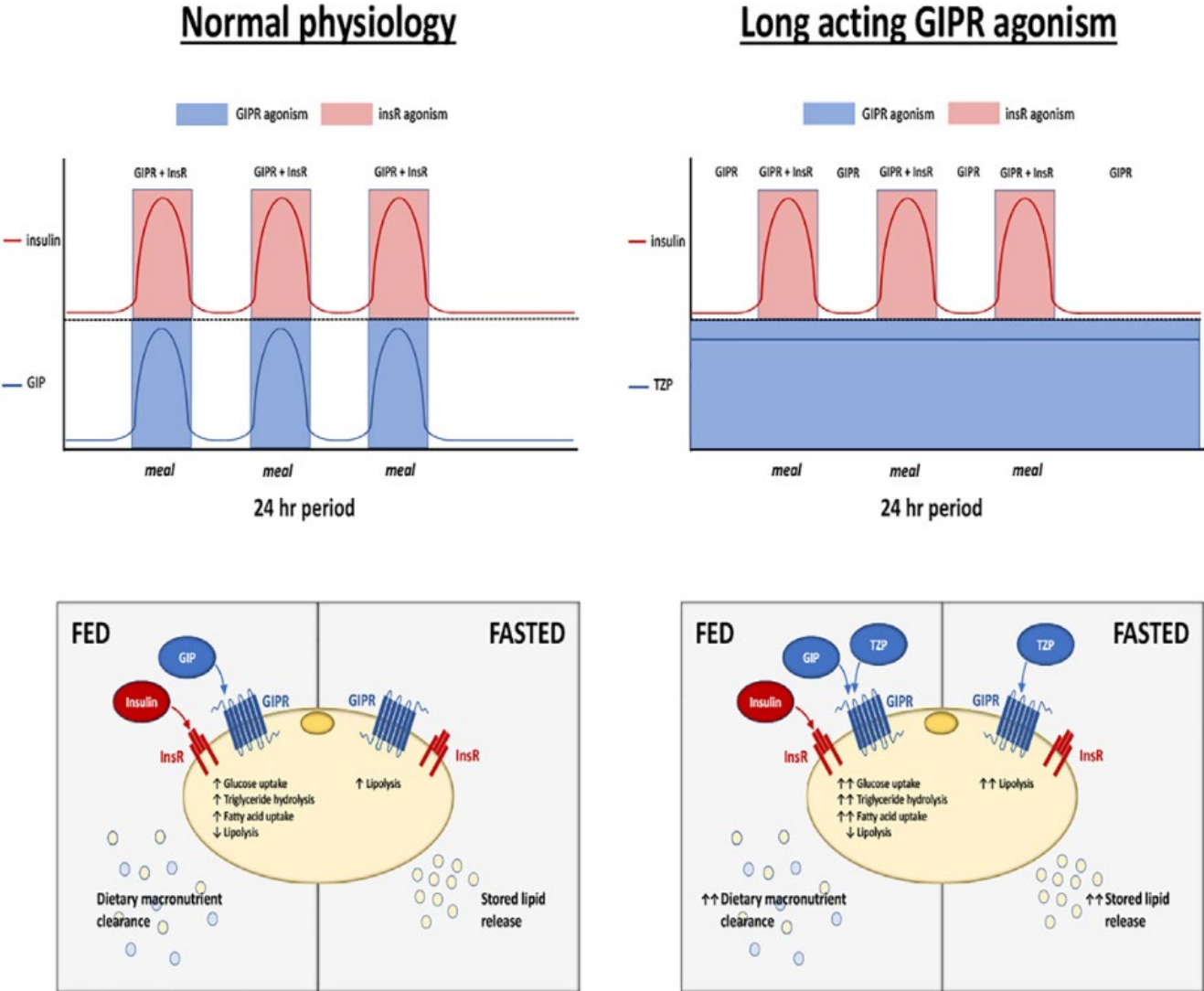
Tirzepatide rende gli acidi grassi del tessuto adiposo più facilmente mobilizzabili



Tirzepatide rende gli acidi grassi del tessuto adiposo più facilmente mobilizzabili

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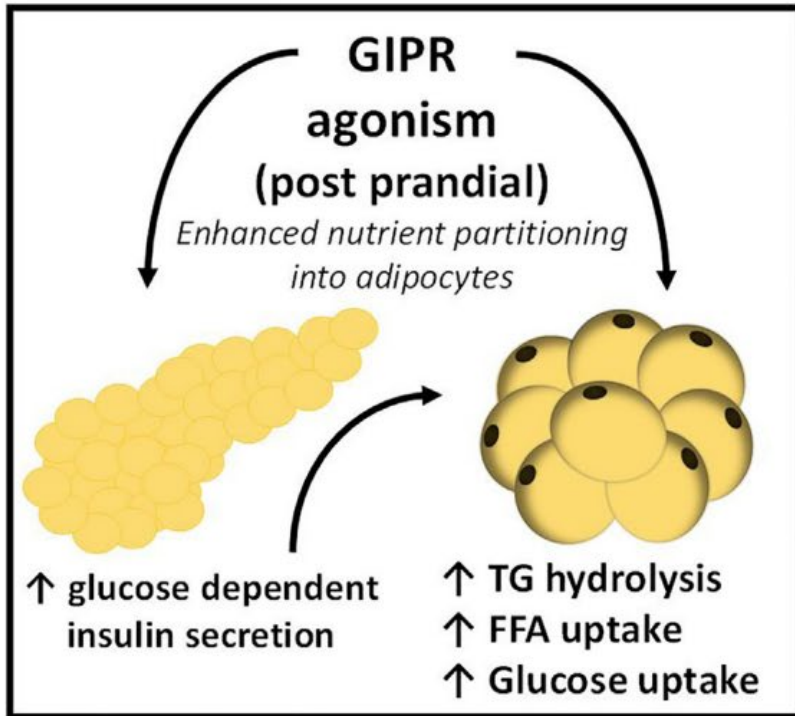
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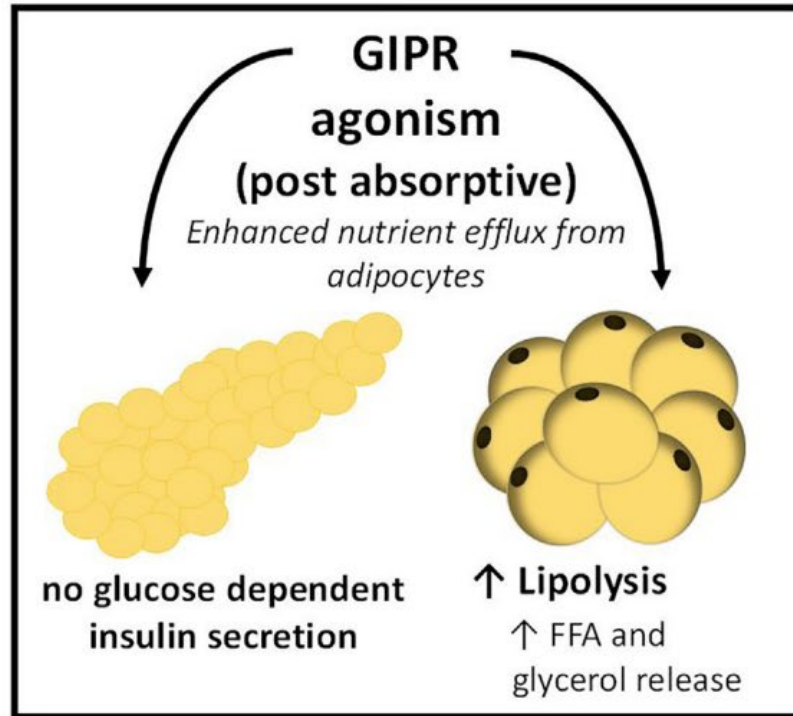
Effetti dell'agonismo GIPR a lunga durata d'azione sul tessuto adiposo

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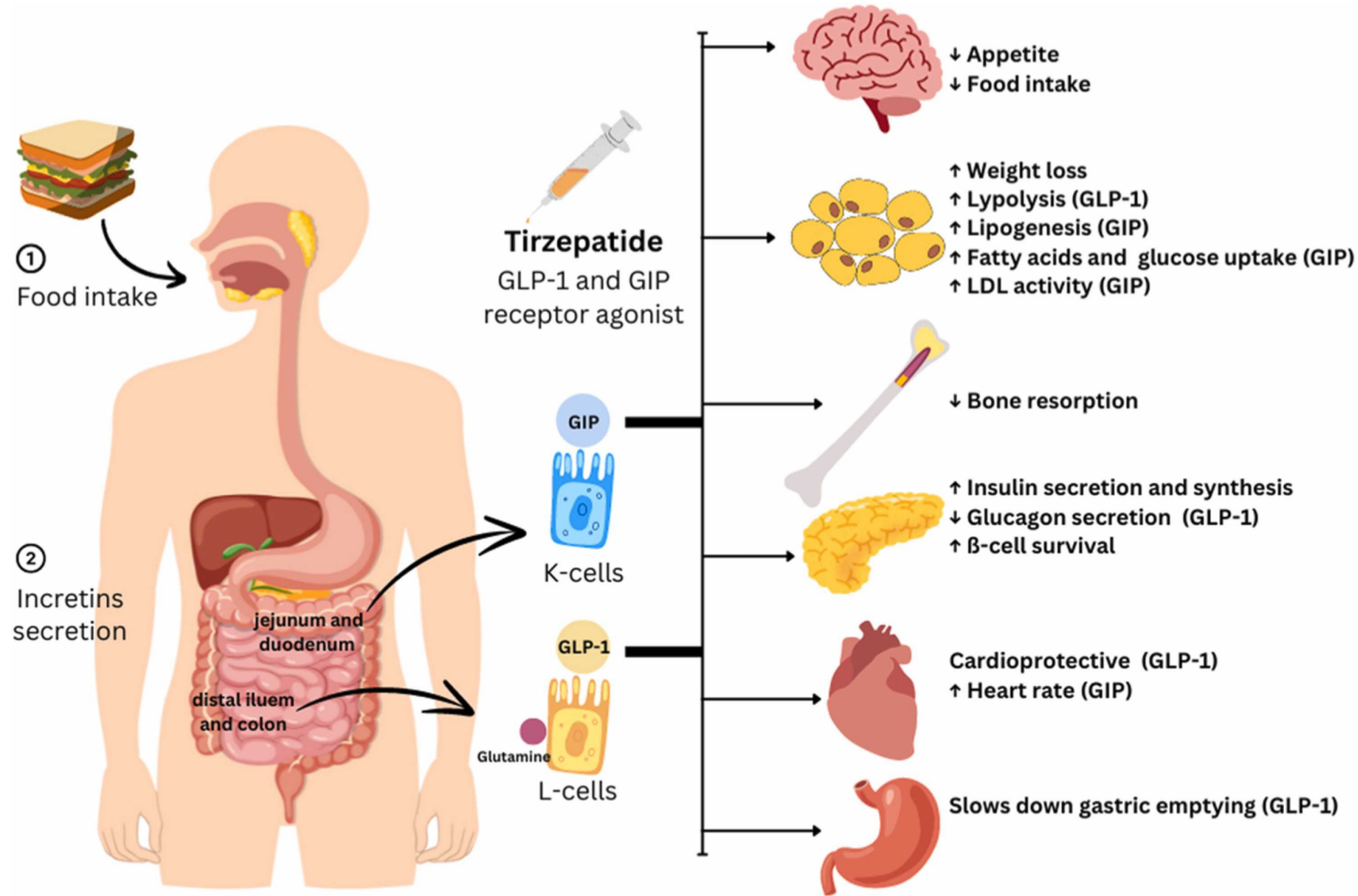
Long-acting GIPR agonism regulation of plasma lipids and glucose under post-prandial/hyperglycemic conditions



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

Tirzepatide aumenta la sensazione di sazietà e reduce la sensazione di fame, aumentando il tempo simil-post prandiale e aumentando la lipolisi

Tirzepatide: meccanismo d'azione



A light blue background featuring faint, stylized medical icons: a stethoscope on the left, a hand with a pulse line in the center, a glucose meter at the bottom left showing the number '95', and an apple at the bottom right. A large, semi-transparent circular graphic with orange and green segments is also visible behind the text.

Tirzepatide: Efficacia nel DM2

Programma SURPASS

Popolazione: 7699 partecipanti con DM2

Monoterapia	Combinazione di 2 farmaci	Combinazione di 2-3 farmaci	Combinazione di 2-4 farmaci	Combinazione con insulina
SURPASS-1 vs. placebo¹ Drug-naïve o washout da qualsiasi OAM	SURPASS-2 vs. semaglutide² Add-on a metformin	SURPASS-3 vs. insulin degludec³ Add-on a metformina +/- SGLT-2i	SURPASS-4 vs. insulina glargine⁴ Add-on a ≥ 1 e ≤ 3 OAMs (metformina, SGLT-2i, o SU)	SURPASS-5 vs. placebo⁵ Con insulina glargine +/- metformina SURPASS-6 vs. insulin lispro⁶ (TID) Con insulina glargine +/- metformina

SURPASS-CVOT⁷

H2H: TZP vs. dulaglutide
>12,000 partecipanti (in corso)

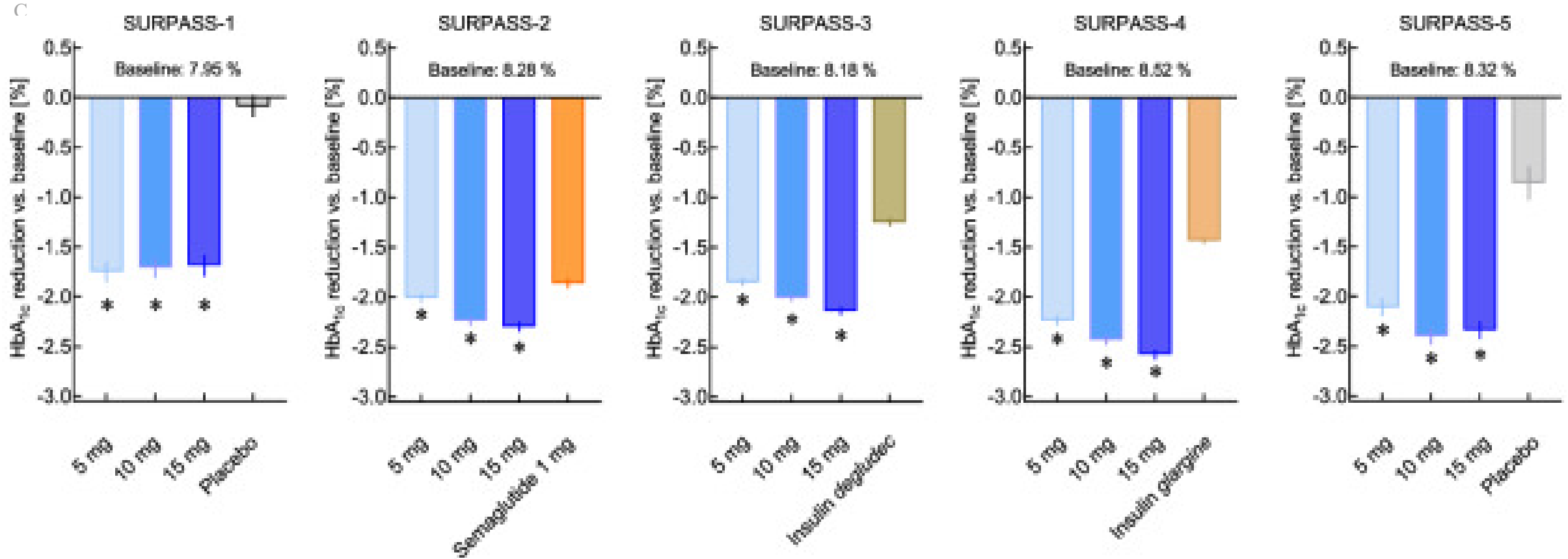
SURPASS-EARLY

Effetto di TZP se utilizzato precocemente nello schema terapeutico, rispetto alla tp convenzionale intensificata per il trattamento del DM2 (in corso)

CVOT = cardiovascular outcomes trial; H2H = head-to-head; OAM = oral antihyperglycemic medication; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TID = three times daily; T2D = type 2 diabetes; 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. <https://clinicaltrials.gov/ct2/show/NCT04537923> (Accessed May 06, 2022). 7. <https://clinicaltrials.gov/ct2/show/NCT04255433> (Accessed May 06, 2022).

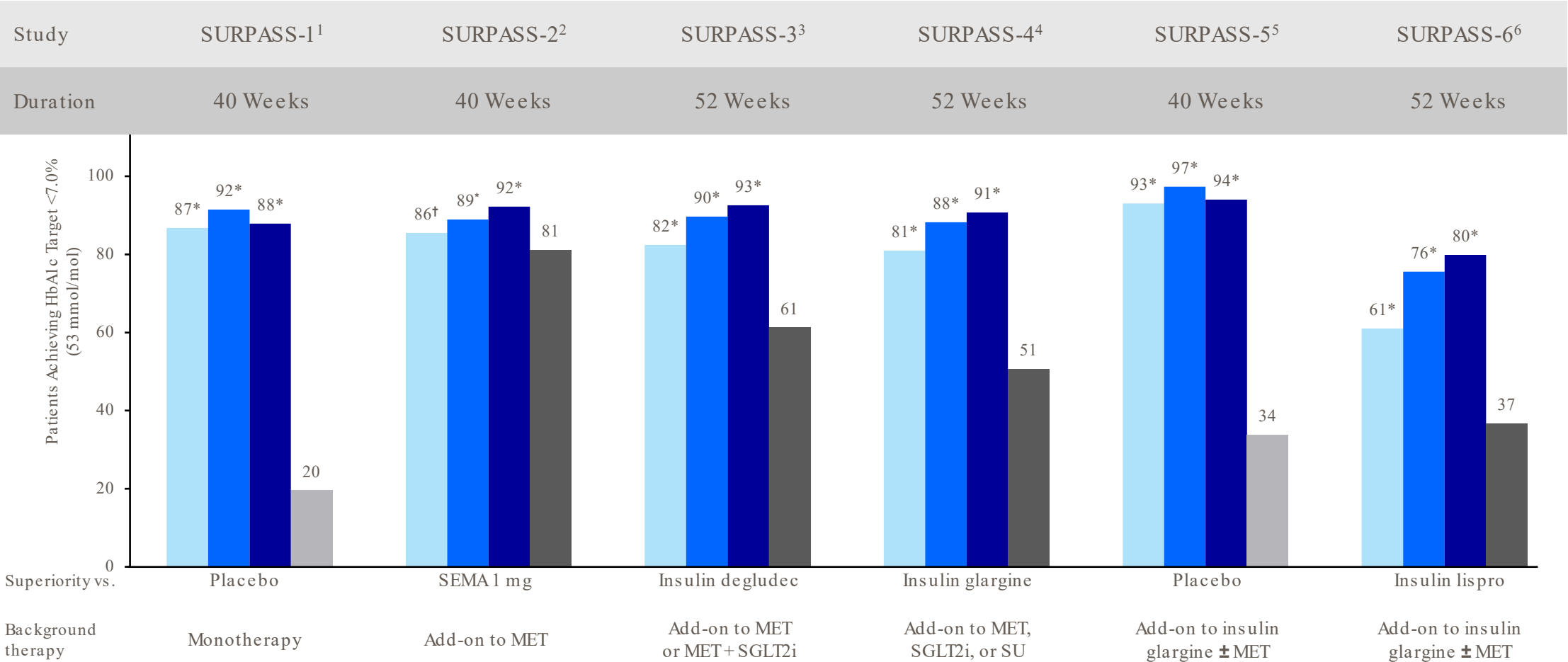
SURPASS 1-5 (HbA1C)



SURPASS 1-6 (HbA1c < 7%)

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*p<0.001, †p<0.05 vs. placebo or active comparator.

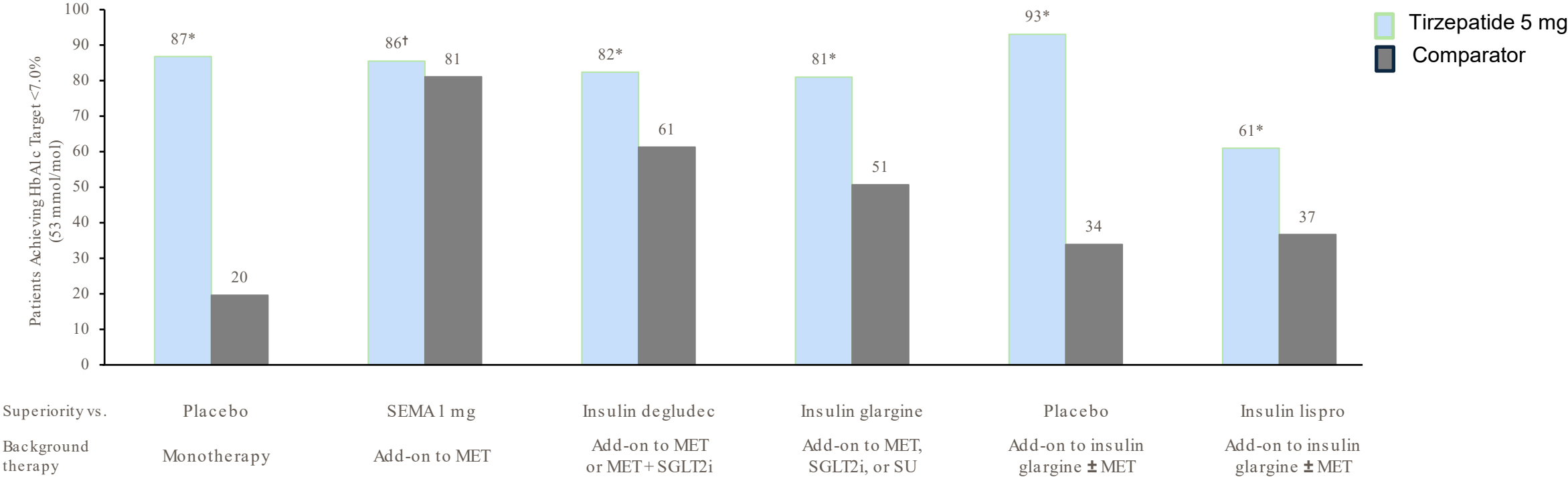
1. Rosenstock J, et al. Lancet. 2021;398(10295):143-155. 2. Frias JP, et al. N Eng J Med. 2021;385(6):503-515. 3. Ludvik B, et al. Lancet. 2021;398(10300):583-598. 4. Del Prato S, et al. Lancet. 2021;398(10313):1811-1824. 5. Dahl D, et al. JAMA. 2022;327(6):534-545. 6. Rosenstock J, et al. JAMA. 2023;330(17):1631-1640

SURPASS 1-6 (HbA1C < 7%) – TZP 5mg

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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



*p<0.001, †p<0.05 vs. placebo or active comparator.

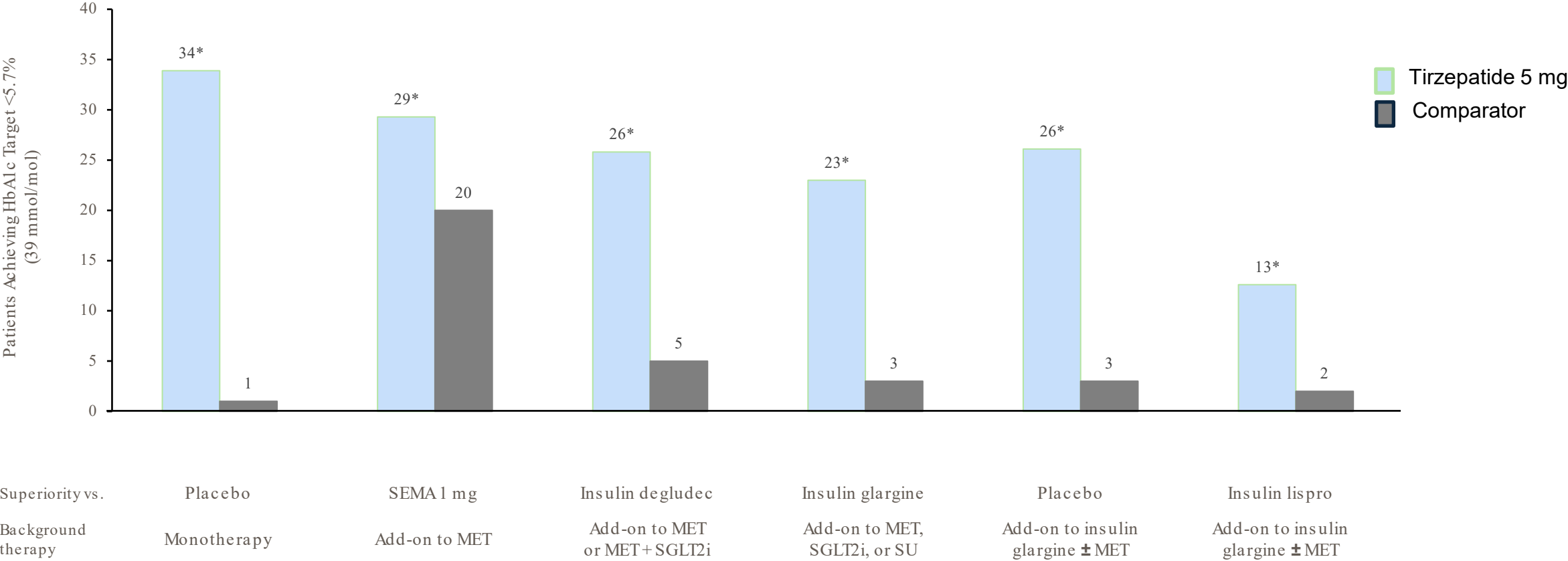
1. Rosenstock J, et al. Lancet. 2021;398(10295):143-155. 2. Frias JP, et al. N Eng J Med. 2021;385(6):503-515. 3. Ludvik B, et al. Lancet. 2021;398(10300):583-598. 4. Del Prato S, et al. Lancet. 2021;398(10313):1811-1824. 5. Dahl D, et al. JAMA. 2022;327(6):534-545. 6. Rosenstock J, et al. JAMA. 2023;330(17):1631-1640

SURPASS 1-6 (HbA1C < 5.7%) – TZP 5mg

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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

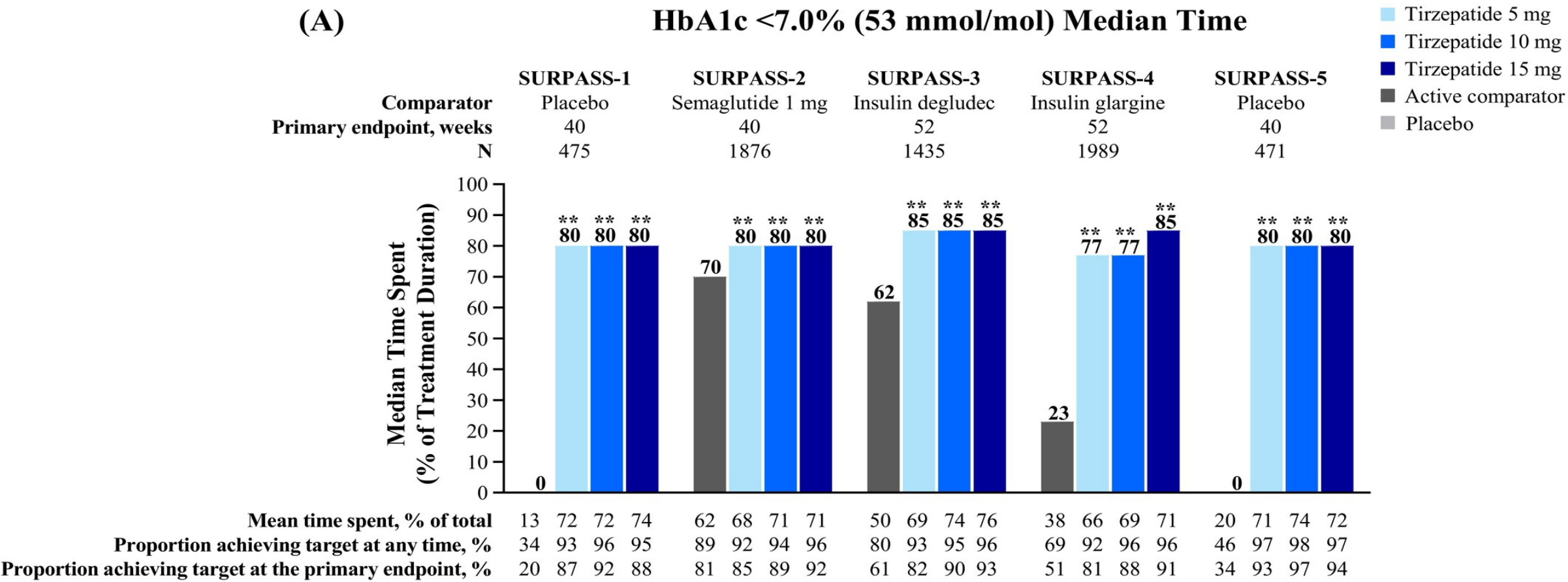


*p<0.001

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. JAMA. 2023;330(17):1631–1640

SURPASS 1-5 (% tempo con HbA1C < 7%)

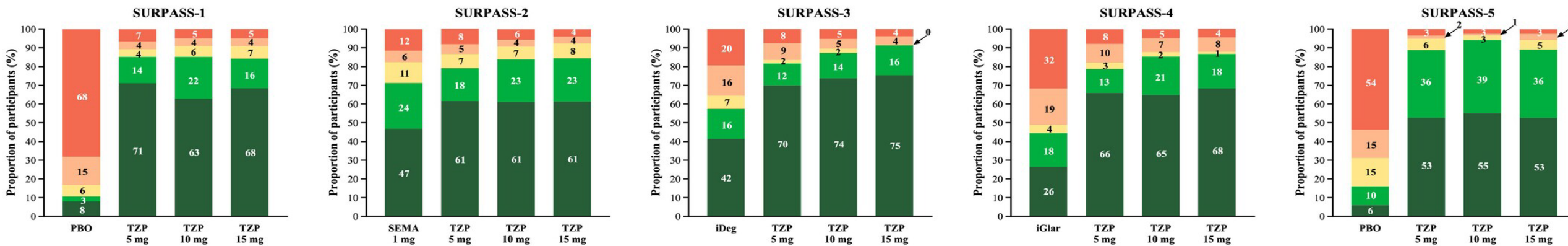
(A) HbA1c <7.0% (53 mmol/mol) Median Time



SURPASS 1-5 (% partecipanti con HbA1C < 7%)

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HbA1c <7.0% (53 mmol/mol)

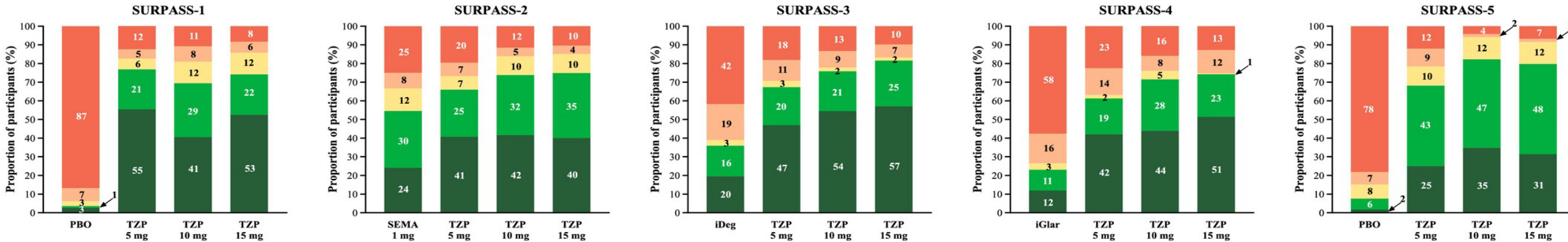


SURPASS 1-5 (% partecipanti con HbA1C < 6.5%)

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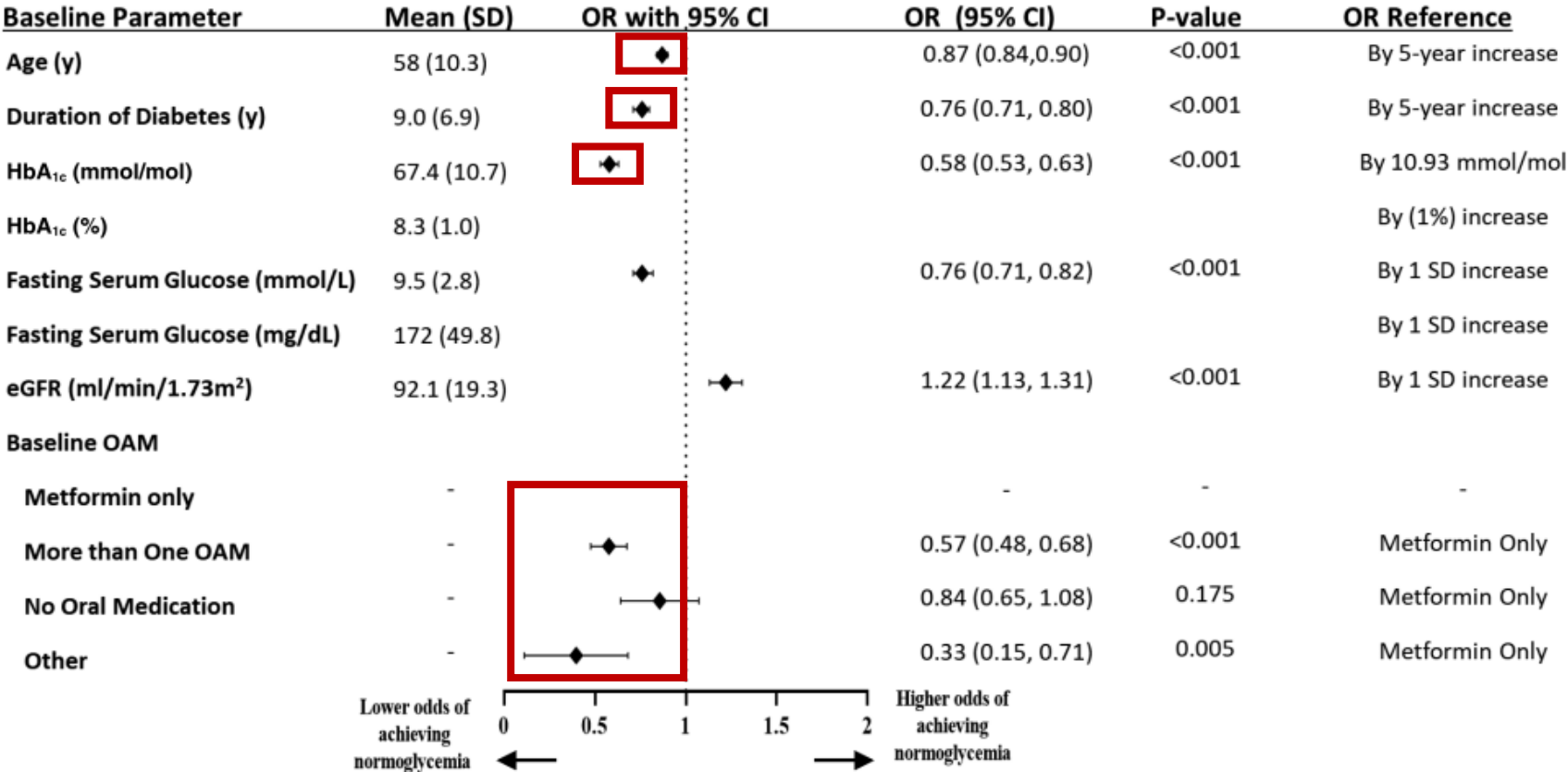
HbA1c ≤6.5% (48 mmol/mol)



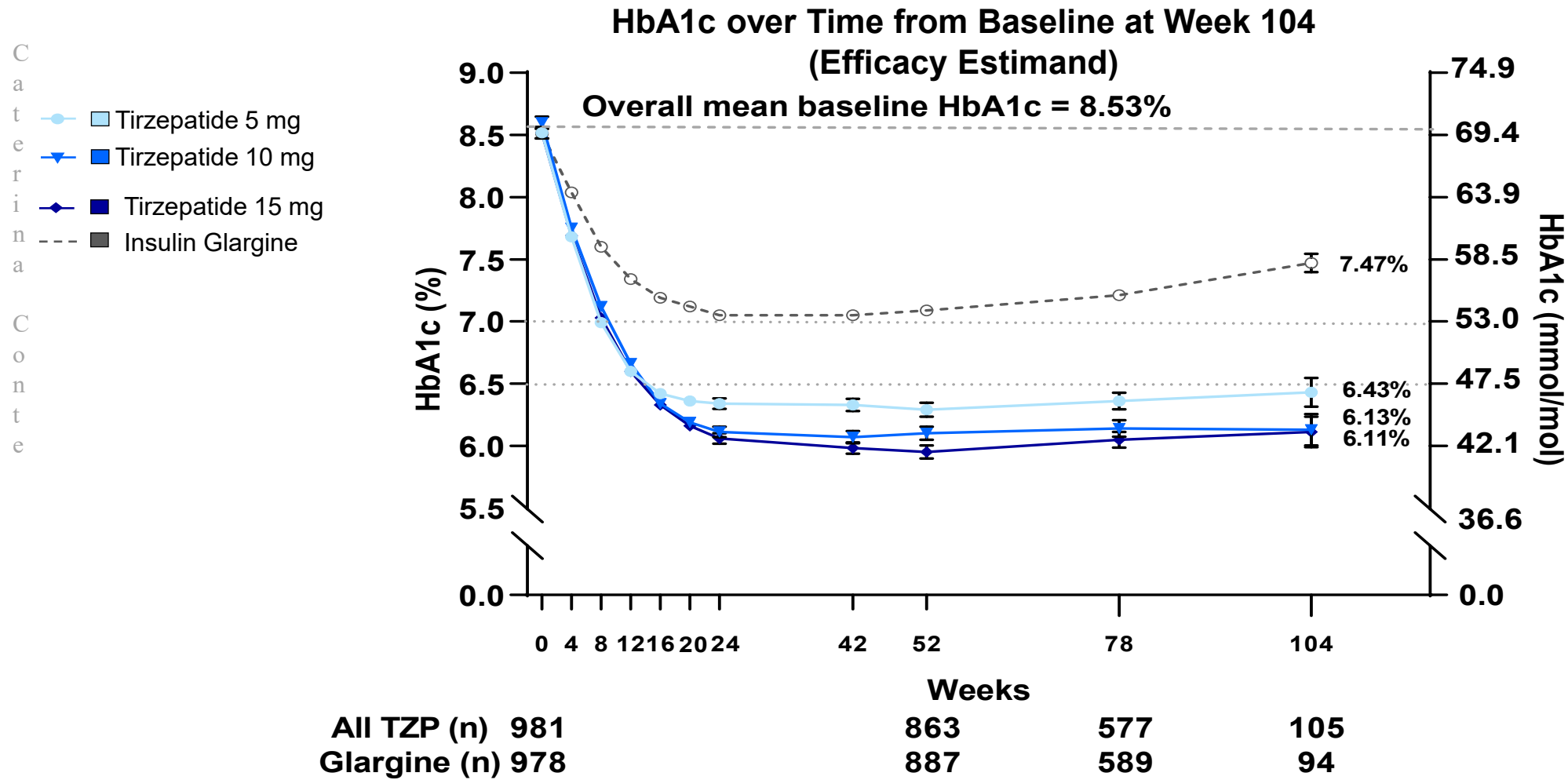
Età inferiore, durata più breve di malattia, HbA1c più bassa e monoterapia con metformina sono predittori di maggiore probabilità di ottenere HbA1c < 5,7%

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Tirzepatide consente una riduzione sostenuta dell'HbA1c fino a 104 settimane (SURPASS-4)



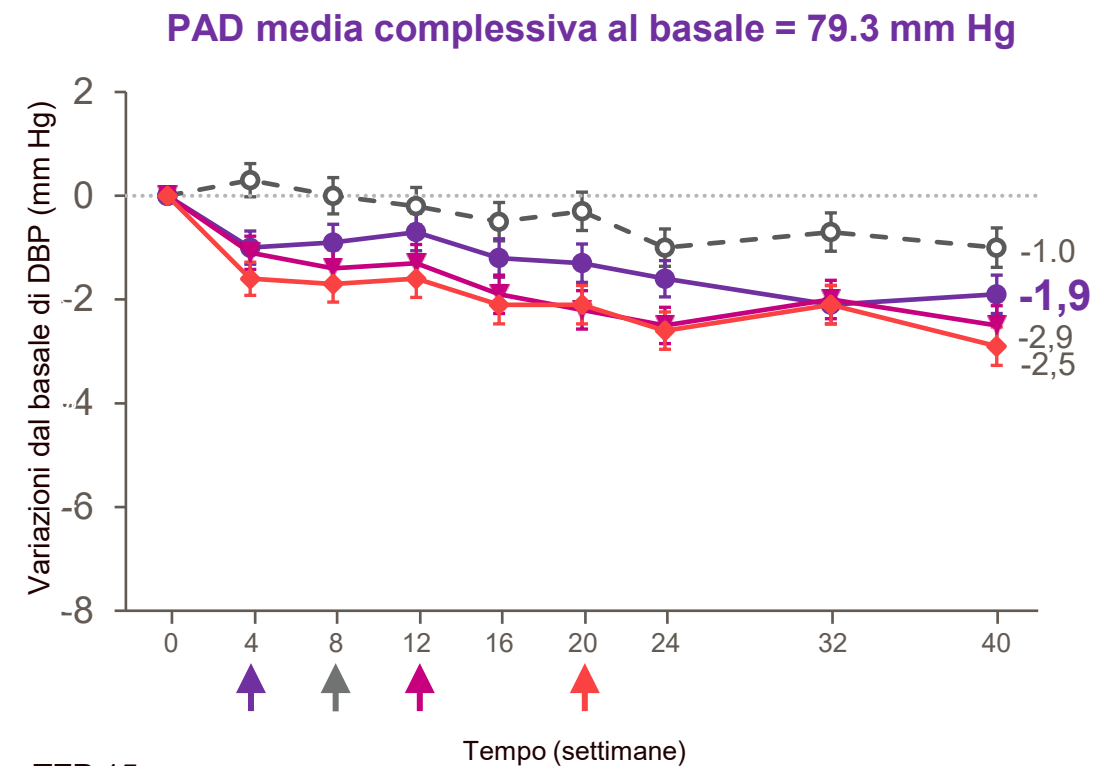
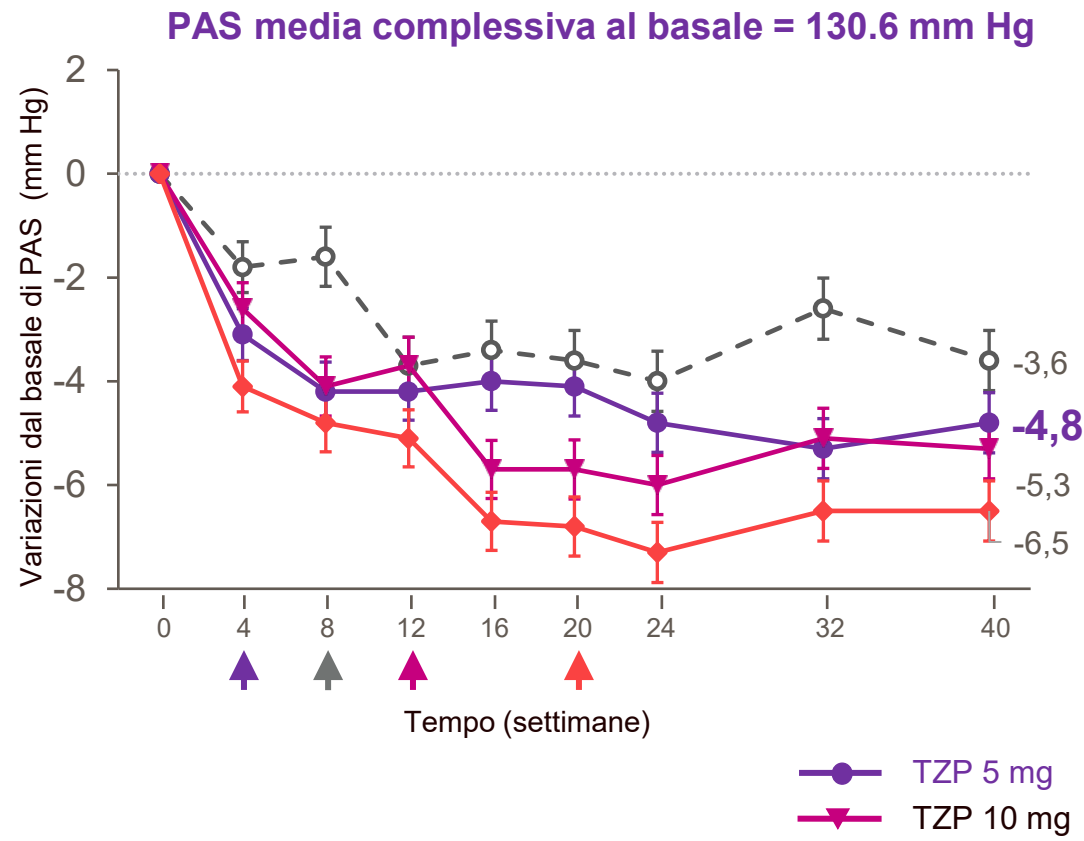


Tirzepatide: Oltre l'HbA1c

Variazione della pressione arteriosa sistolica e diastolica a 40 settimane (SURPASS-2)

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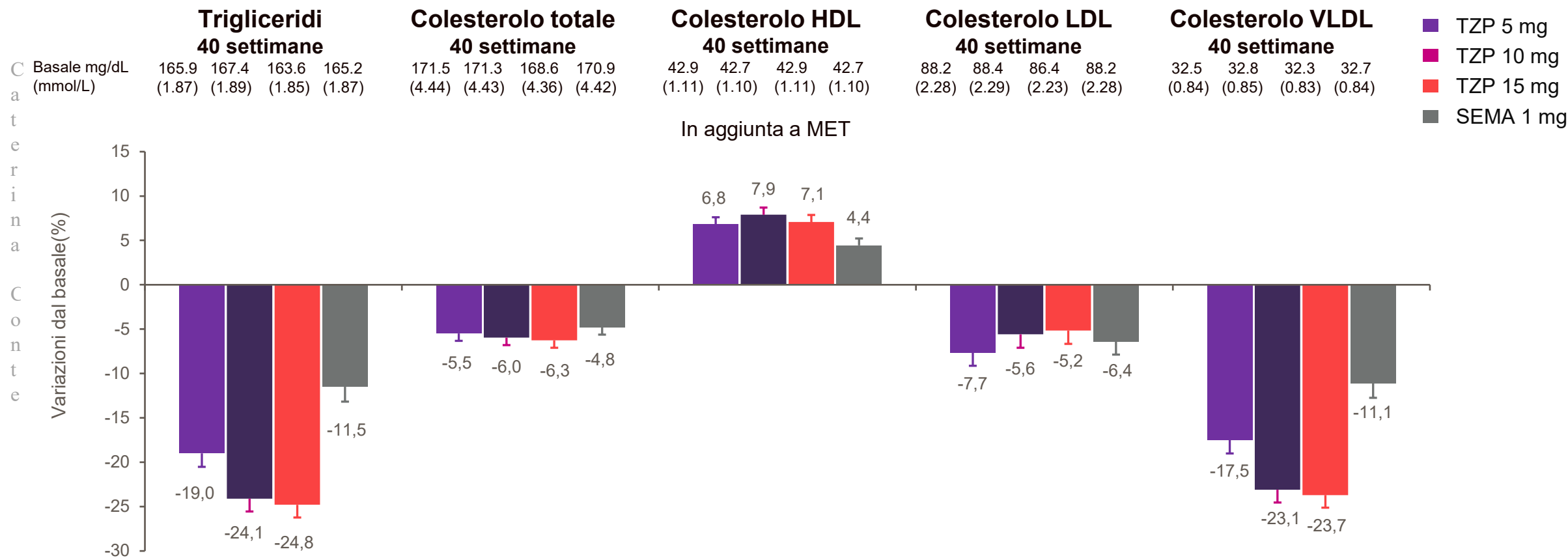
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I dati sono espressi come LSM (SE); popolazione mITT (set di analisi della sicurezza). Le frecce indicano quando sono state raggiunte le dosi di TZP 5 mg, 10 mg, 15 mg e SEMA 1 mg. La prevalenza si riferisce alla proporzione di soggetti che hanno manifestato un evento durante un intervallo di tempo.

DBP = pressione arteriosa diastolica; LSM = media dei minimi quadrati; mITT = "intent-to-treat" modificata; SBP = pressione arteriosa sistolica; SEMA = semaglutide; TZP = tirzepatide.

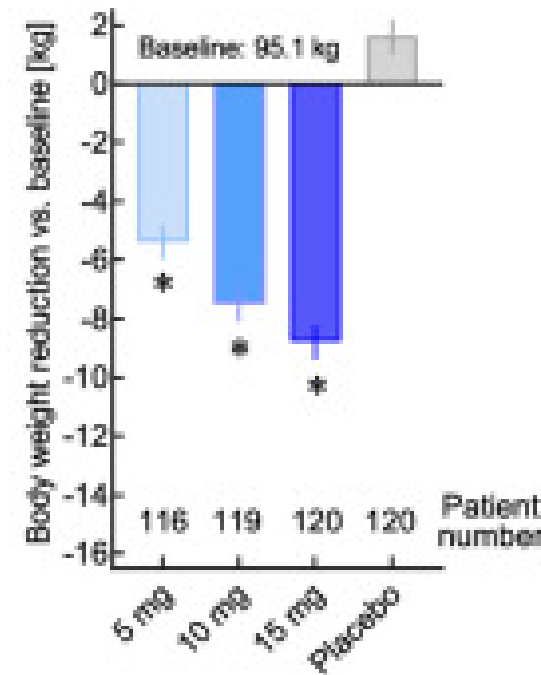
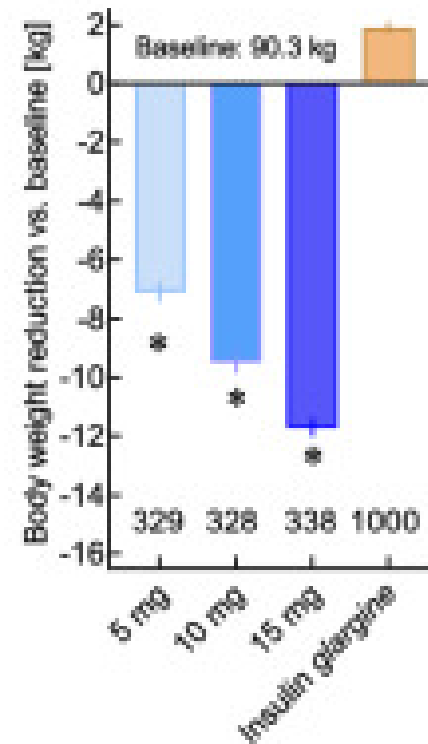
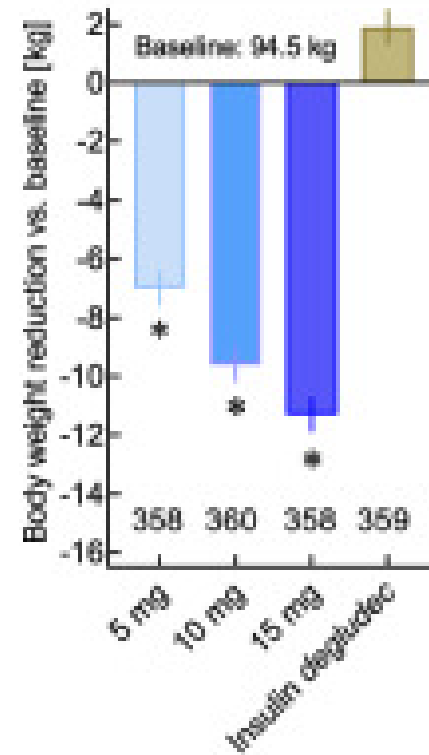
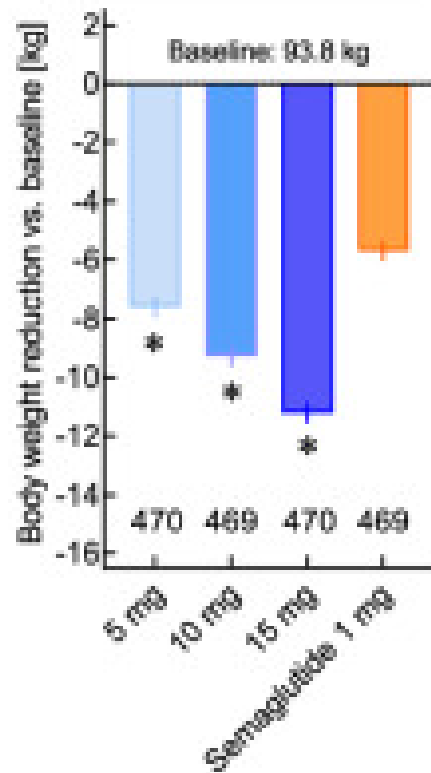
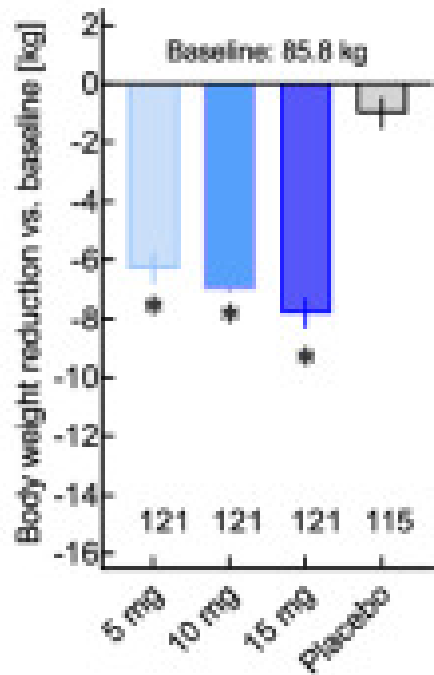
Miglioramento del profilo lipidico a 40 settimane (SURPASS-2)



I dati sono percentuali medie stimate (SE) dall'analisi MMRM utilizzando la trasformazione logaritmica; popolazione mITT (set di analisi di efficacia).
HDL = lipoproteine ad alta densità; LDL = lipoproteine a bassa densità; MET = metformina; mITT = popolazione "intent-to-treat" modificata; MMRM = modello misto a misure ripetute; SEMA = semaglutide; TZP = tirzepatide; VLDL = lipoproteine a densità molto bassa..

SURPASS 1-5 (peso corporeo)

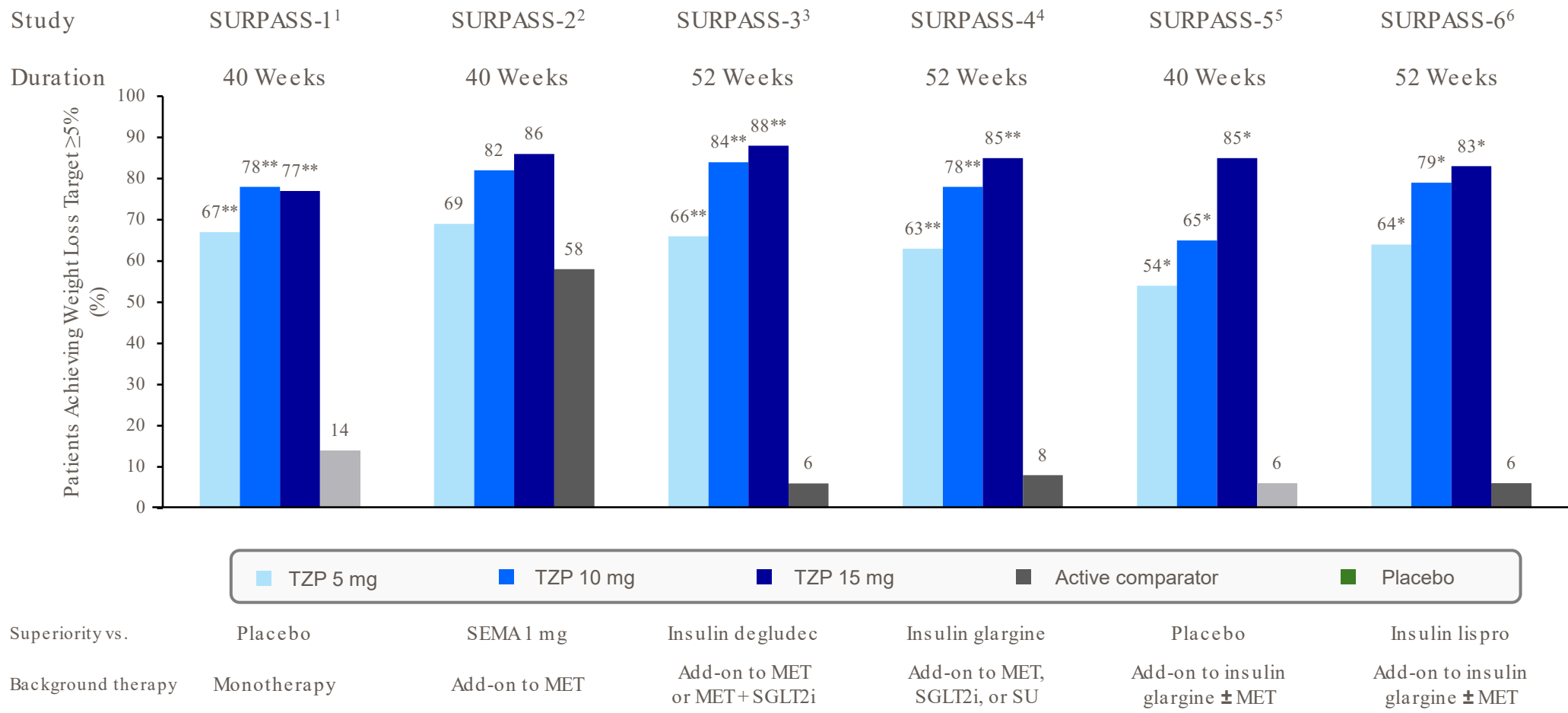
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La maggior parte dei pazienti raggiunge una riduzione di peso significativa >5% rispetto al basale

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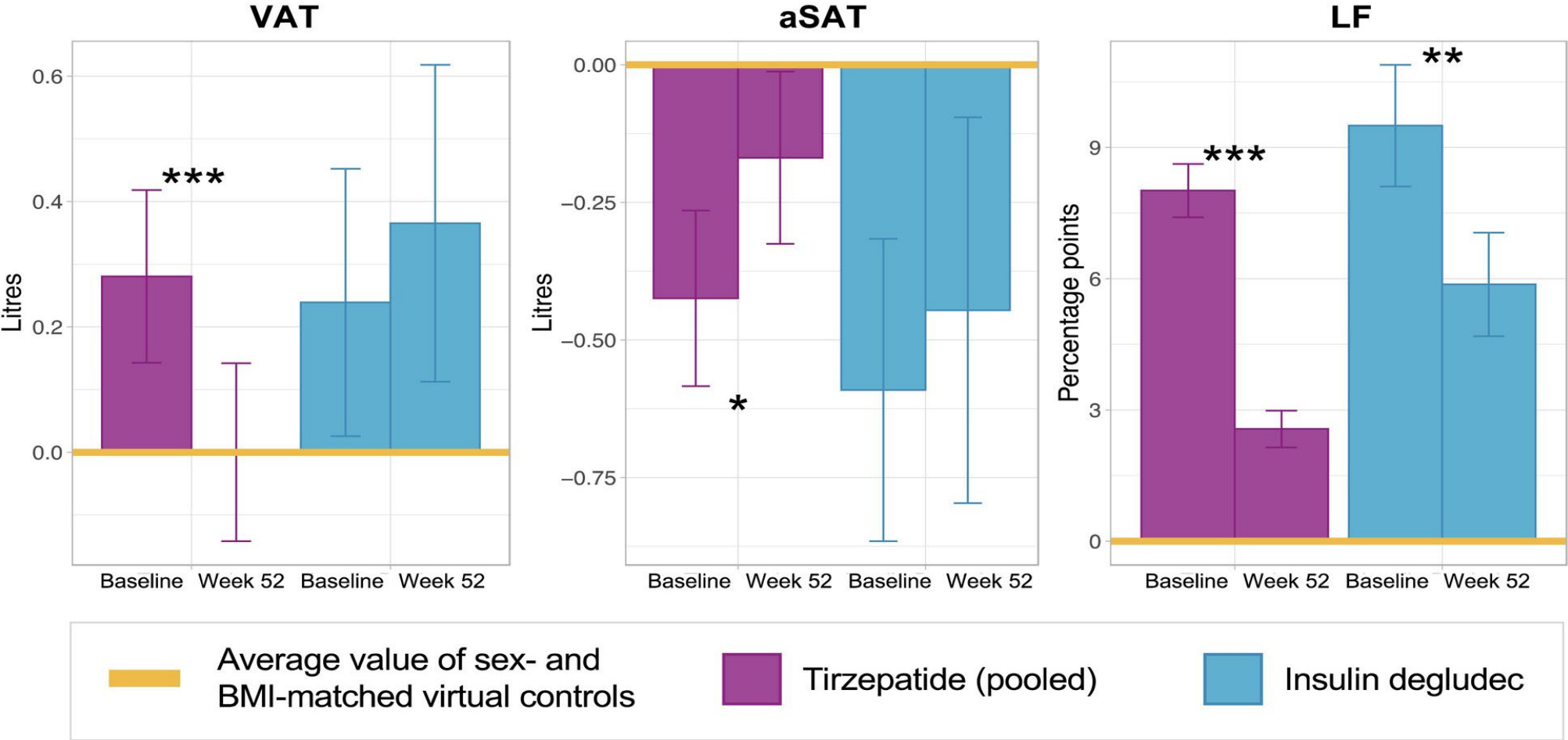
*p<0.001 vs. placebo or active comparator.

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. JAMA. 2023;330(17):1631-1640.

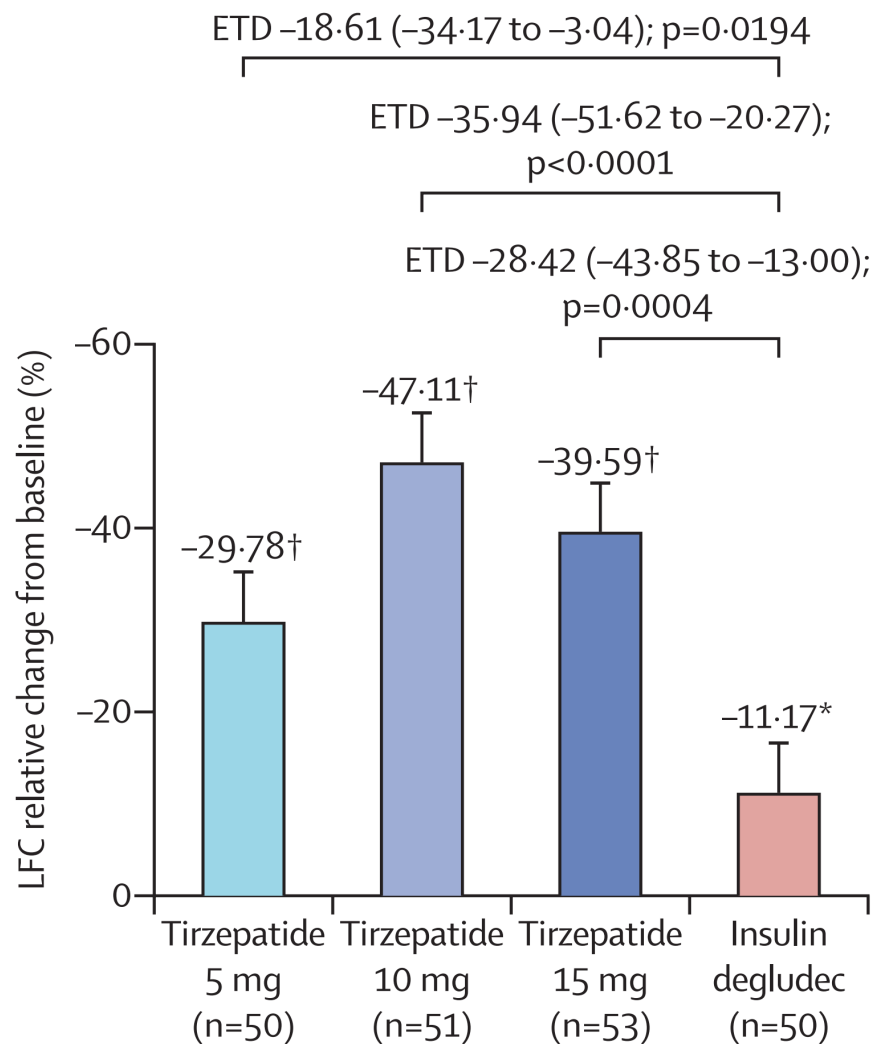
Composizione del calo ponderale (SURPASS 3 MRI)

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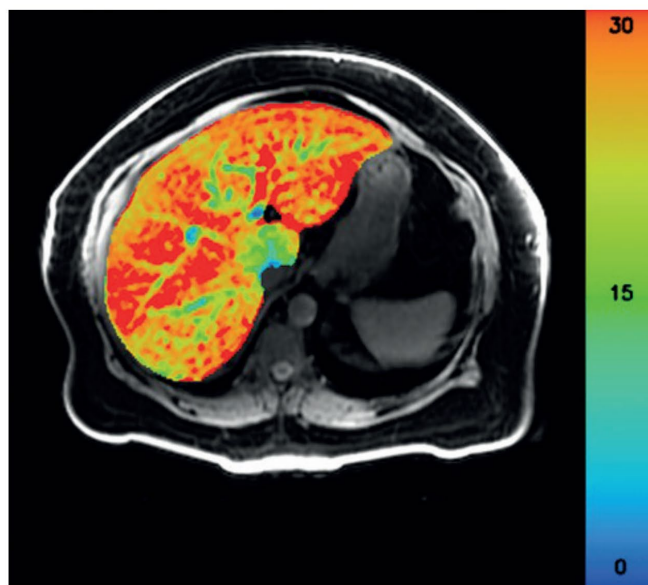
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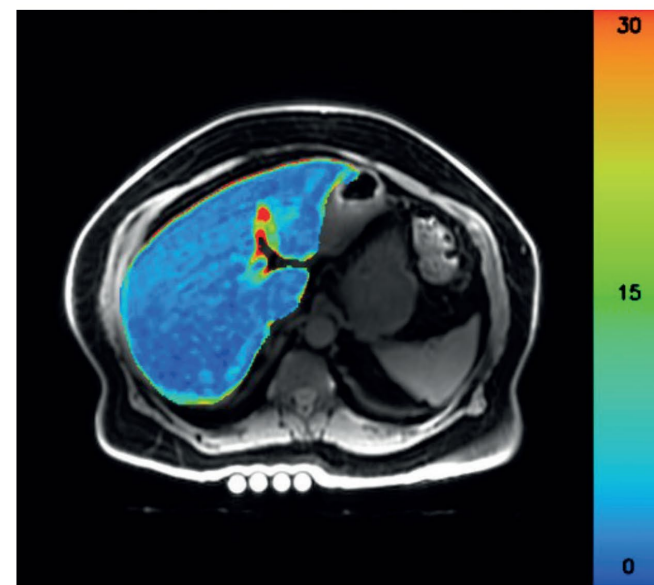
Riduzione del grasso intraepatico (SURPASS-3 MRI)



Male, 59 Years, on Metformin + SGLT-2i
 randomized to **Tirzepatide 5 mg**



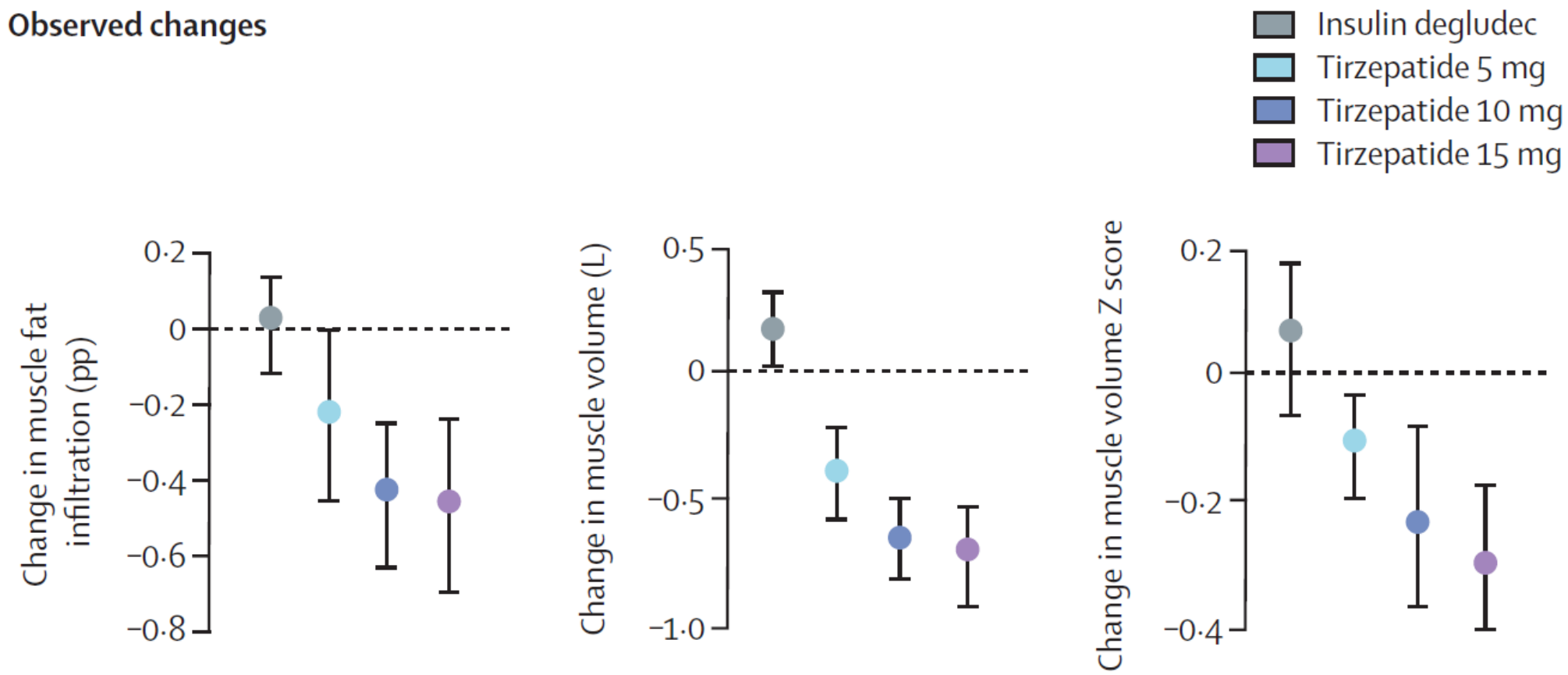
LFC at baseline: 27.3%
 BMI: 44.8 kg/m²; body weight: 134.2 kg; WC: 139.7 cm
 HbA_{1c}: 78.1 mmol/mol (9.3%)



LFC at week 52: 2.6%
 BMI: 36.2 kg/m²; body weight: 108.4 kg; WC: 124.4 cm
 HbA_{1c}: 43.2 mmol/mol (6.1%)

Riduzione del grasso intramuscolare (miosteatosi)

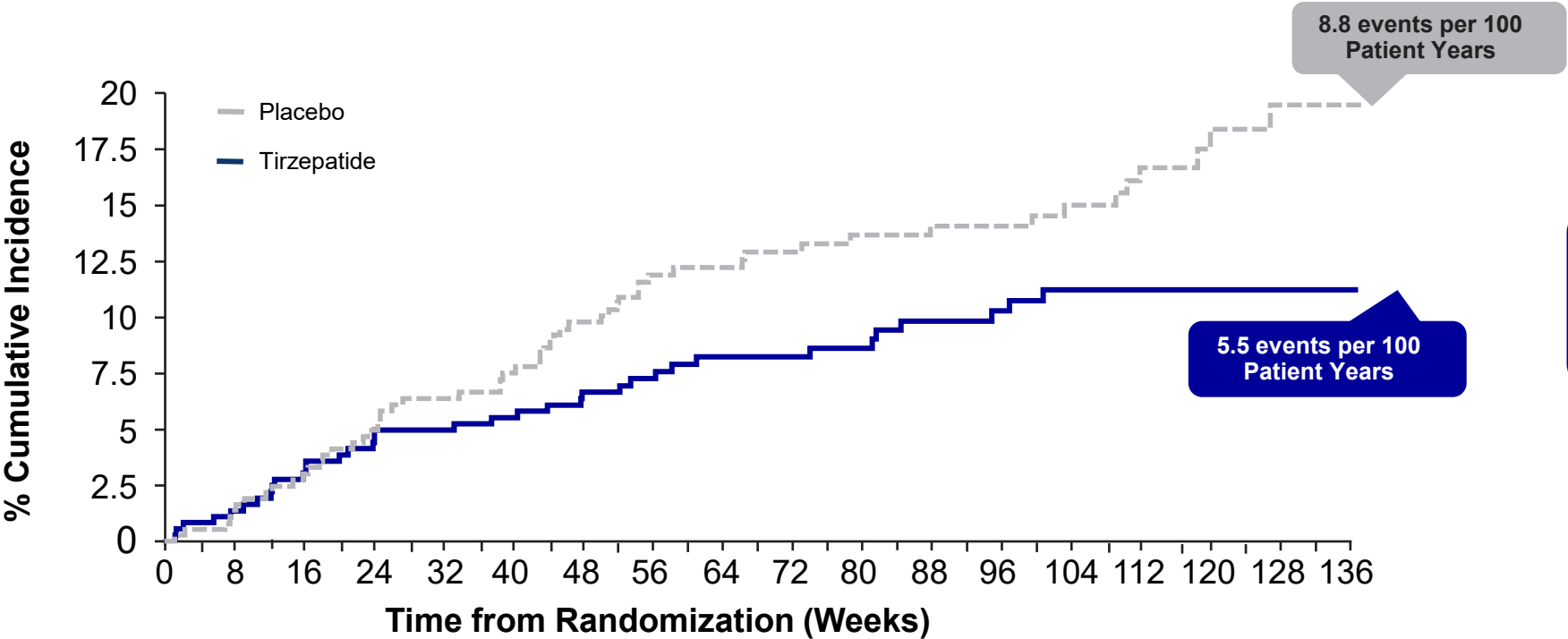
A Observed changes



SUMMIT Primary Endpoint: tempo al primo evento (morte CV o peggioramento SC)

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HR 0.62
(95% CI 0.41-0.95)
P=.026

RRR 38%

Participants at Risk

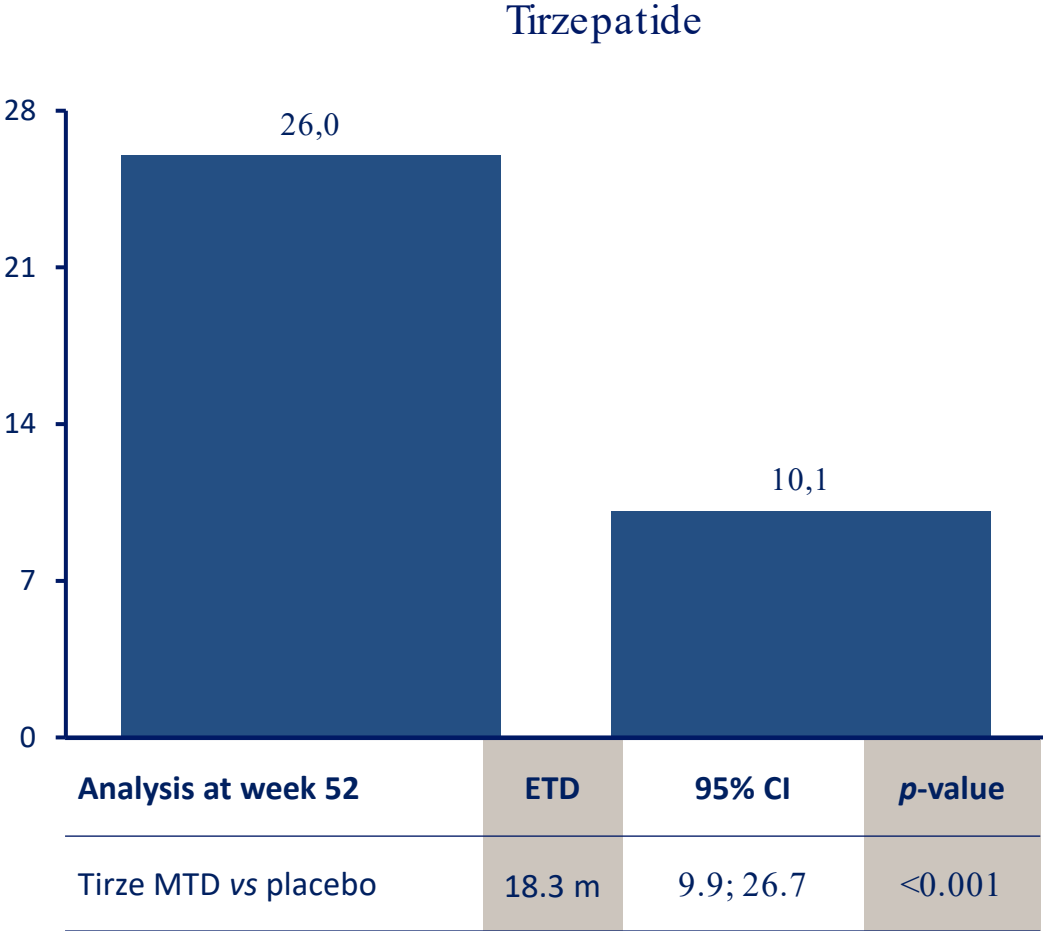
Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45
Tirzepatide	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46

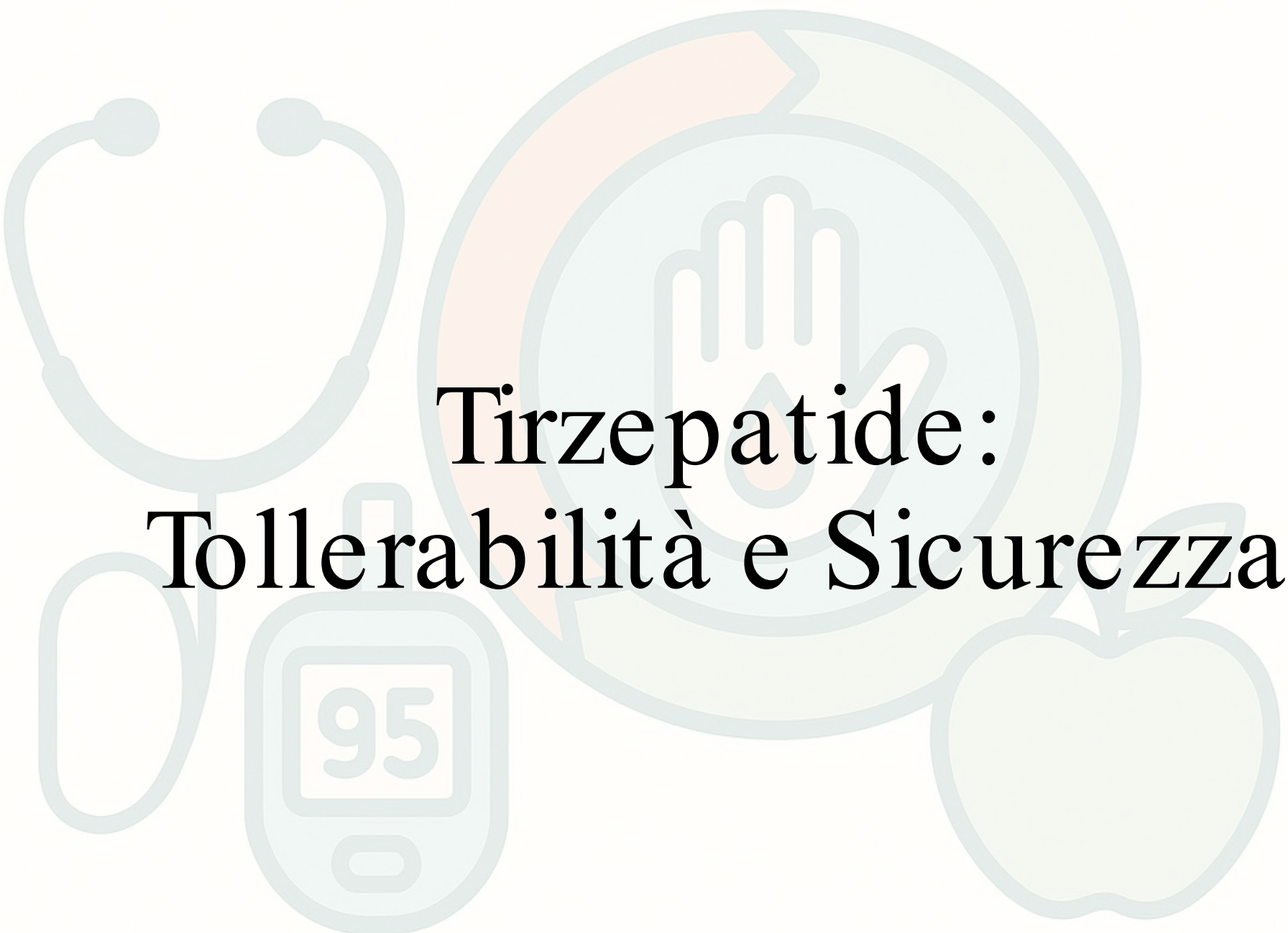
- ^aWorsening HF event was defined as heart failure symptoms requiring hospitalization, intravenous drugs for HF in an urgent care setting or intensification of oral diuretics. Changes in oral diuretics without worsening HF was not designated as an event.
- CI=Confidence Interval; CV=Cardiovascular; HF=Heart Failure; HR=Hazard Ratio; RRR=Relative Risk Reduction.

Funzione fisica (6MWT) in partecipanti con HFpEF (SUMMIT)

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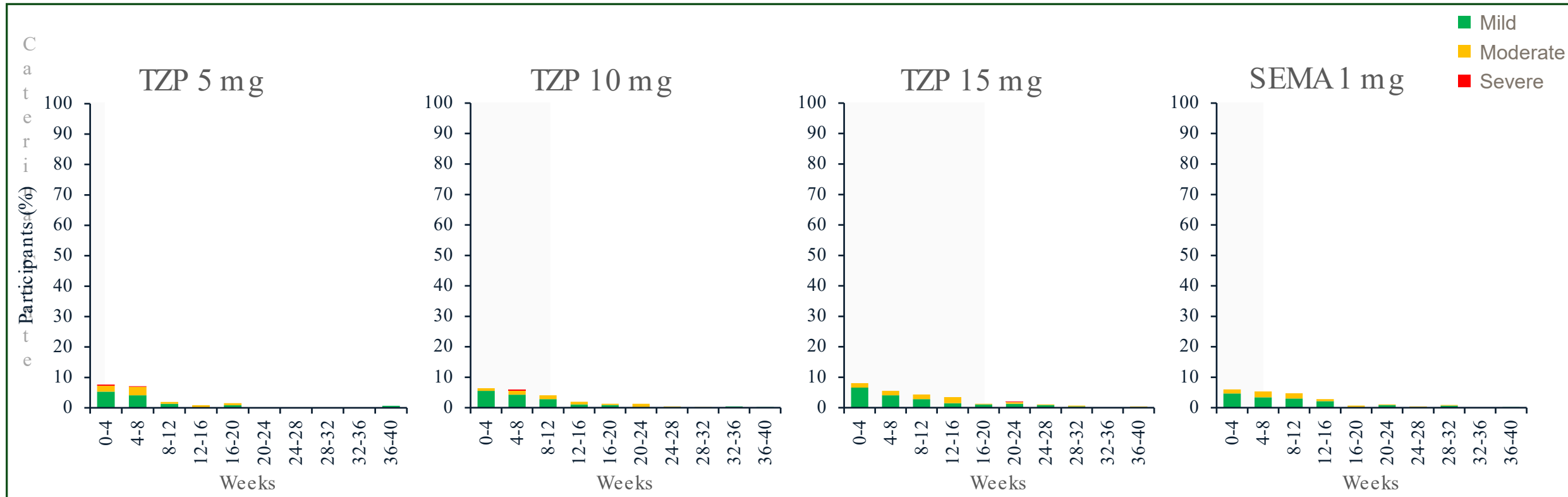


The background features several faint, light blue icons. At the top left is a stethoscope. In the center is a hand with an orange heart shape on the palm. At the bottom left is a blood pressure monitor displaying the number '95'. At the bottom right is an apple. A large, faint circular graphic with orange and green segments is also visible behind the text.

Tirzepatide: Tollerabilità e Sicurezza

Incidenza di Nausea Nel Corso di 40 settimane

SURPASS-2 (Tirzepatide versus Semaglutide)



La maggior parte dei casi di nausea è stata di intensità lieve o moderata, transitoria e si è verificata durante il periodo di aumento graduale della dose in tutti i gruppi.

Incidenza di Ipoglicemia

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SURPASS-1 ¹	TZP 5 mg N=121	TZP 10 mg N=121	TZP 15 mg N=121	Placebo N=115
Hypoglycemia (blood glucose <54 mg/dL[3.0 mmol/L])	0	0	0	1 (1)
Severe hypoglycemia ^a	0	0	0	0
SURPASS-2 ²	TZP 5 mg N=470	TZP 10 mg N=469	TZP 15 mg N=470	SEMA 1 mg N=469
Hypoglycemia (blood glucose <54 mg/dL[3.0 mmol/L])	3 (0.6)	1 (0.2)	8 (1.7)	2 (0.4)
Severe hypoglycemia ^a	1 (0.2)	0	1 (0.2) ^b	0
SURPASS-3 ³	TZP 5 mg N=358	TZP 10 mg N=360	TZP 15 mg N=359	Insulin degludec N=360
Hypoglycemia (blood glucose <54 mg/dL[3.0 mmol/L])	5 (1.4)	4 (1.1)	7 (1.9)	26 (7.3)
Severe hypoglycemia ^a	0	0	1 (0.3) ^c	0

Data are n (%); mITT population (safety analysis set). Note: Patients may be counted in more than 1 level. Data after initiation of new glucose-lowering therapy are not included.

^aSevere event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia; ^b1 patient randomized to TZP 15 mg had an event of hypoglycemia that was not considered severe by the investigator but was reported as an SAE; ^c1 episode of severe hypoglycemia was reported during the study for a patient assigned to the TZP 15-mg group during the escalation period (day 28). Semaglutide 1 mg, insulin degludec, and insulin glargine are active comparators in the SURPASS-2, SURPASS-3, and SURPASS-4 trials, respectively.

mITT= modified intent-to-treat; SAE= severe adverse event; SEMA= semaglutide; TZP = tirzepatide.

Incidenza di Ipoglicemia

C a t e r i n a	SURPASS-4 ¹	TZP 5 mg N=329	TZP 10 mg N=328	TZP 15 mg N=338	Insulin glargine N=1000
	Hypoglycemia (blood glucose <54 mg/dL[3.0 mmol/L])	29 (8.81)	20 (6.10)	27 (7.99)	191 (19.10)
	Severe hypoglycemia ^a	1 (0.30)	0	3 (0.89)	11 (1.10)
C o n t e	SURPASS-5 ²	TZP 5 mg N=116	TZP 10 mg N=119	TZP 15 mg N=120	Placebo N=120
	Hypoglycemia (blood glucose <54 mg/dL[3.0 mmol/L])	18 (15.5)	23 (19.3)	17 (14.2)	15 (12.5)
	Severe hypoglycemia ^a	0	2 (1.6)	1 (0.8)	0
	SURPASS-6 ³	TZP 5 mg N=243	TZP 10 mg N=238	TZP 15 mg N=236	Insulin Lispro N=708
	Hypoglycemia (blood glucose <54 mg/dL[3.0 mmol/L])	29 (11.9)	22 (9.2)	25 (10.6)	340 (48)
	Severe hypoglycemia ^a	0	3 (1.3)	0 (0)	30 (4.2)

Data are n (%); mITT population (safety analysis set). Note: Patients may be counted in more than 1 level. Data after initiation of new glucose-lowering therapy are not included.

^aSevere event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia; ^b1 patient randomized to TZP 15 mg had an event of hypoglycemia that was not considered severe by the investigator but was reported as an SAE; ^c1 episode of severe hypoglycemia was reported during the study for a patient assigned to the TZP 15-mg group during the escalation period (day 28). Semaglutide 1 mg, insulin degludec, and insulin glargine are active comparators in the SURPASS-2, SURPASS-3, and SURPASS-4 trials, respectively.

mITT=modified intent-to-treat; SAE=severe adverse event; SEMA=semaglutide; TZP=tirzepatide.

GRAZIE!

Dual-agonist: un nuovo alleato

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