Dual-agonist: un nuovo alleato

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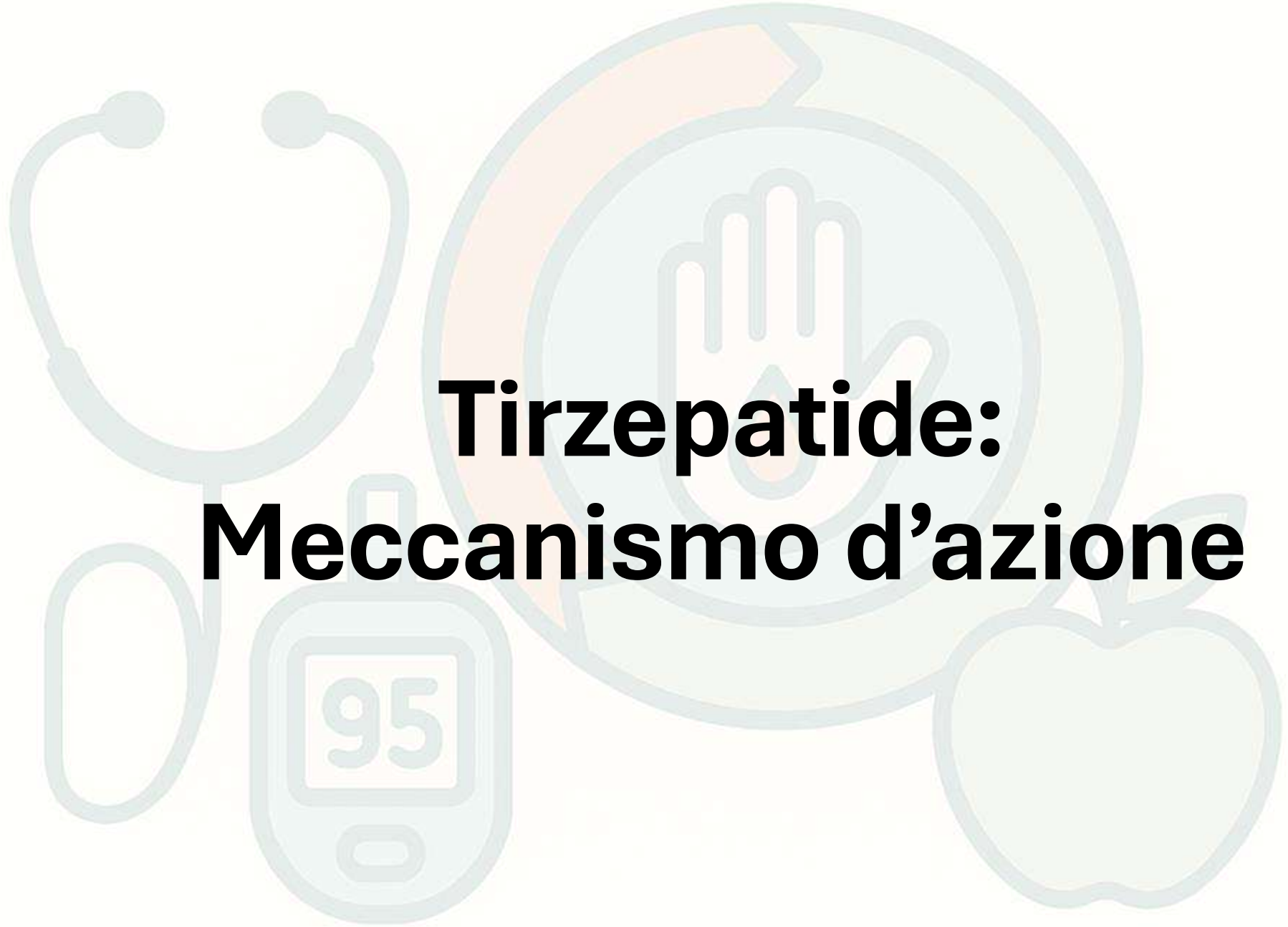
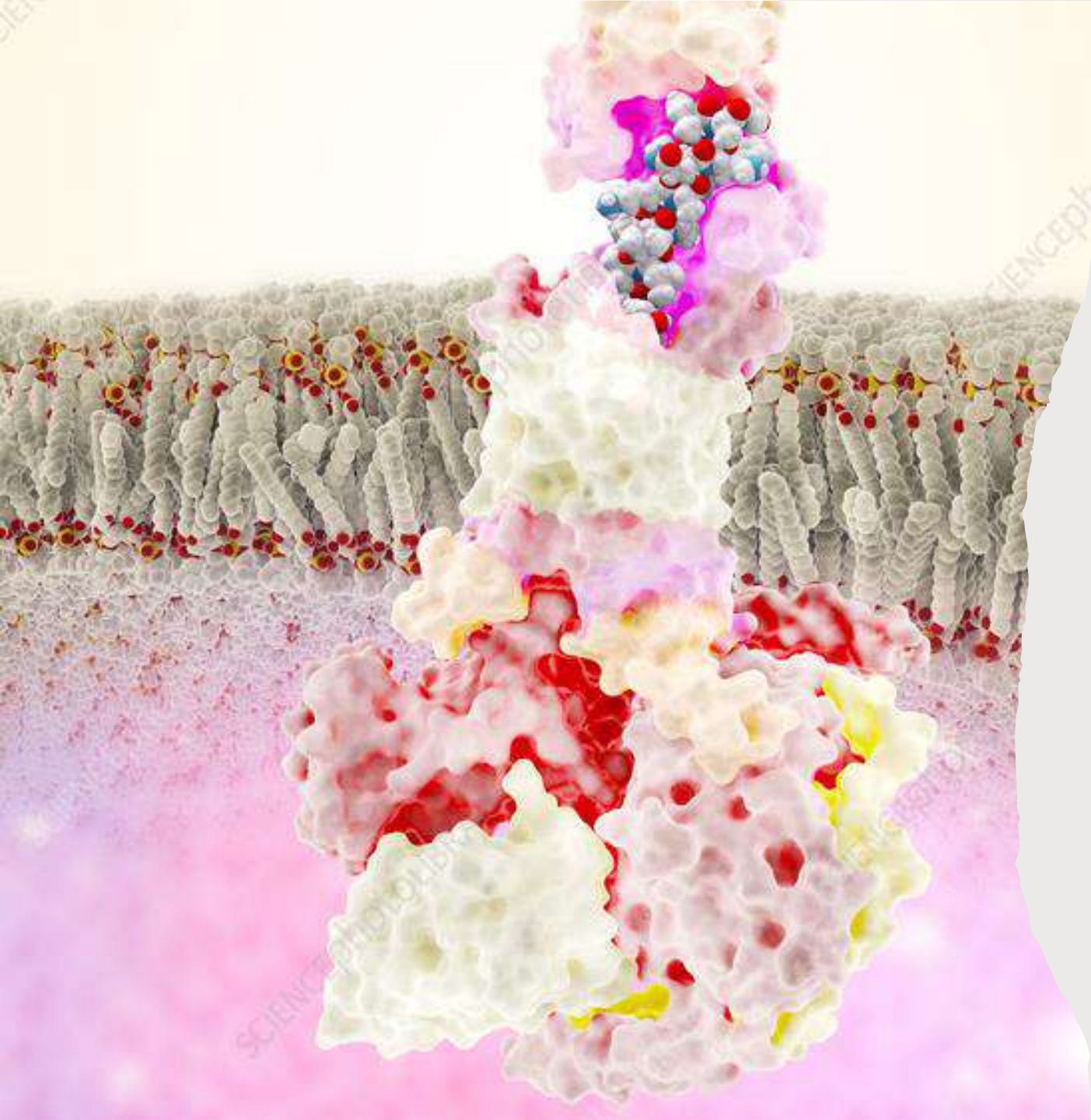


Tirzepatide: Meccanismo d’azione



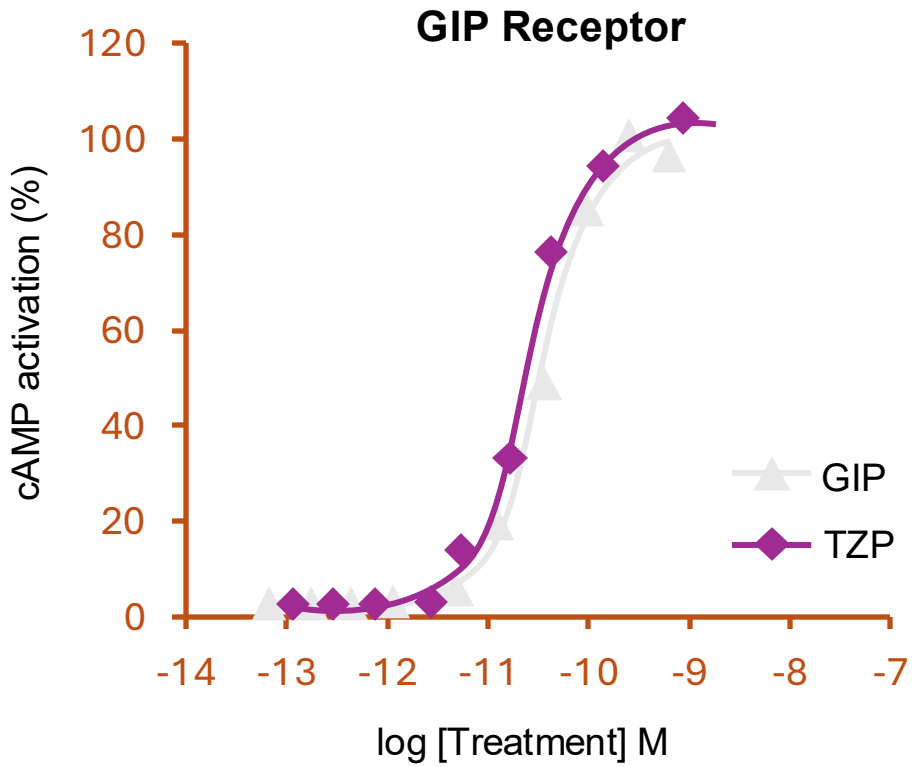
Tirzepatide

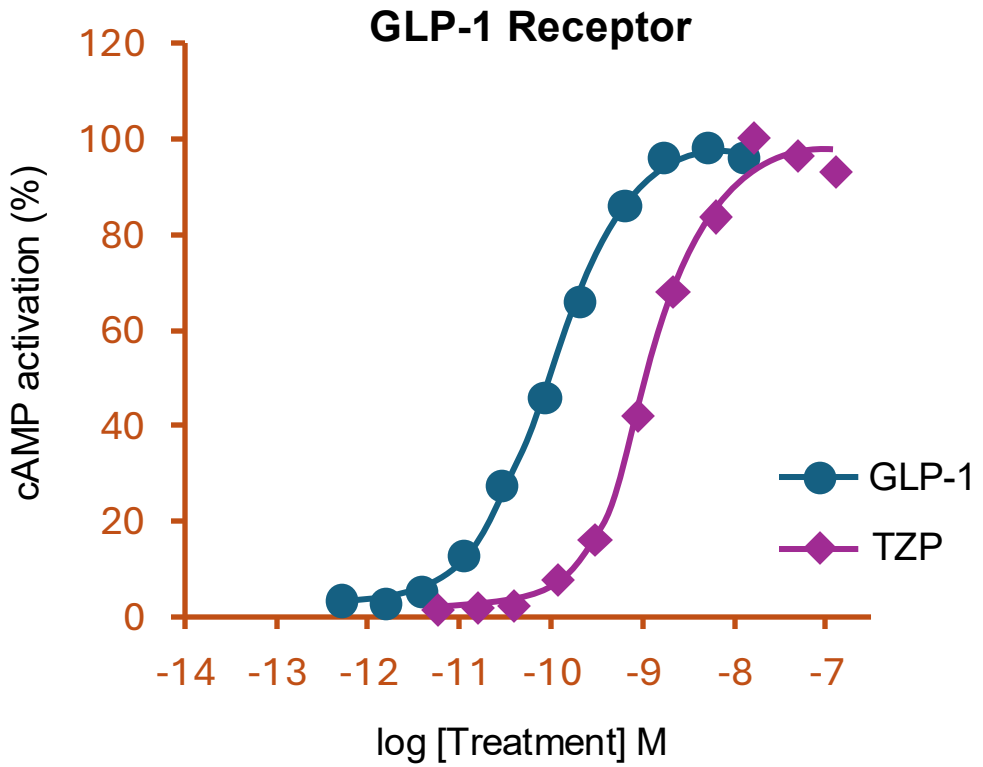
Singola molecola, attività su due target farmacologici

- **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

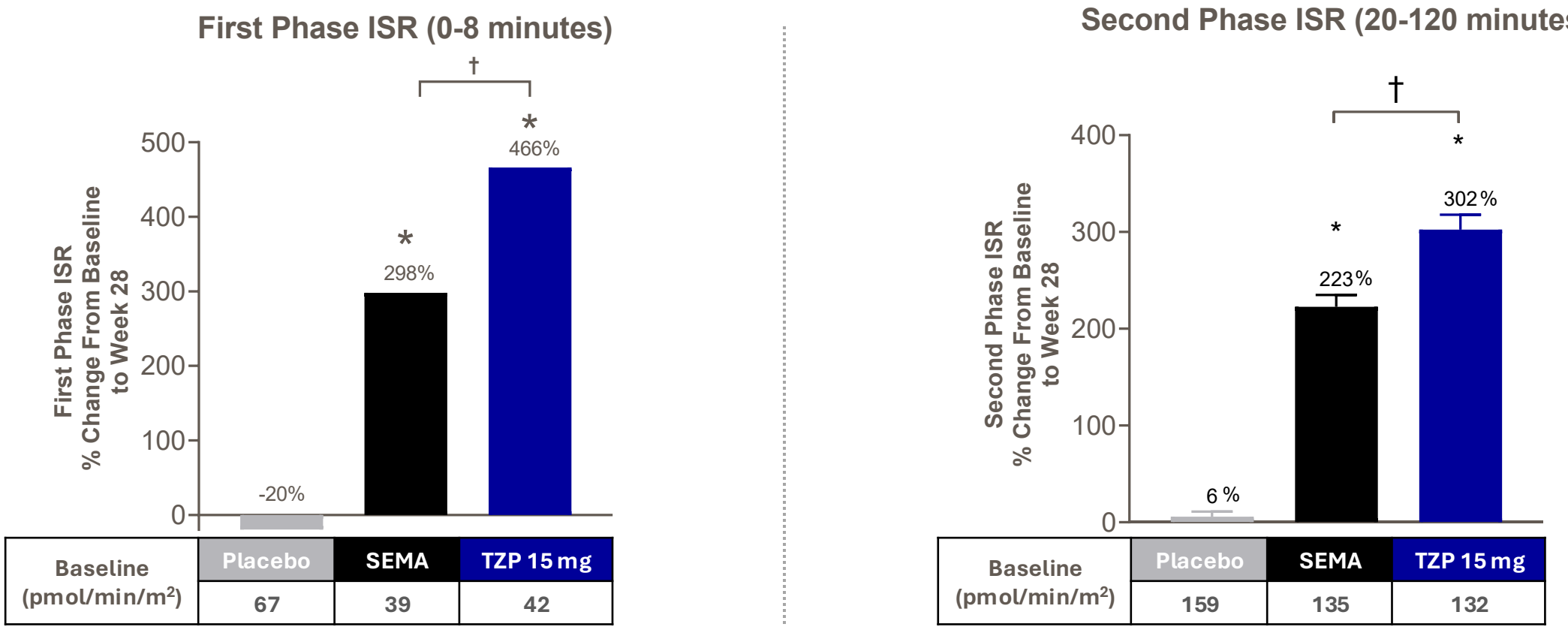
- **In vitro**, tirzepatide presenta una potenza e un'affinità per il recettore GIP simili a quelle del GIP nativo.
- La potenza e l'affinità per il recettore GLP-1 sono leggermente inferiori rispetto a quelle del GLP-1 nativo.





Coskun T, et al. Mol Metab. 2018;18:3-14

Tirzepatide: miglioramento secrezione insulinica



Baseline (pmol/min/m²)	Placebo	SEMA	TZP 15 mg
	67	39	42

Baseline (pmol/min/m²)	Placebo	SEMA	TZP 15 mg
	159	135	132

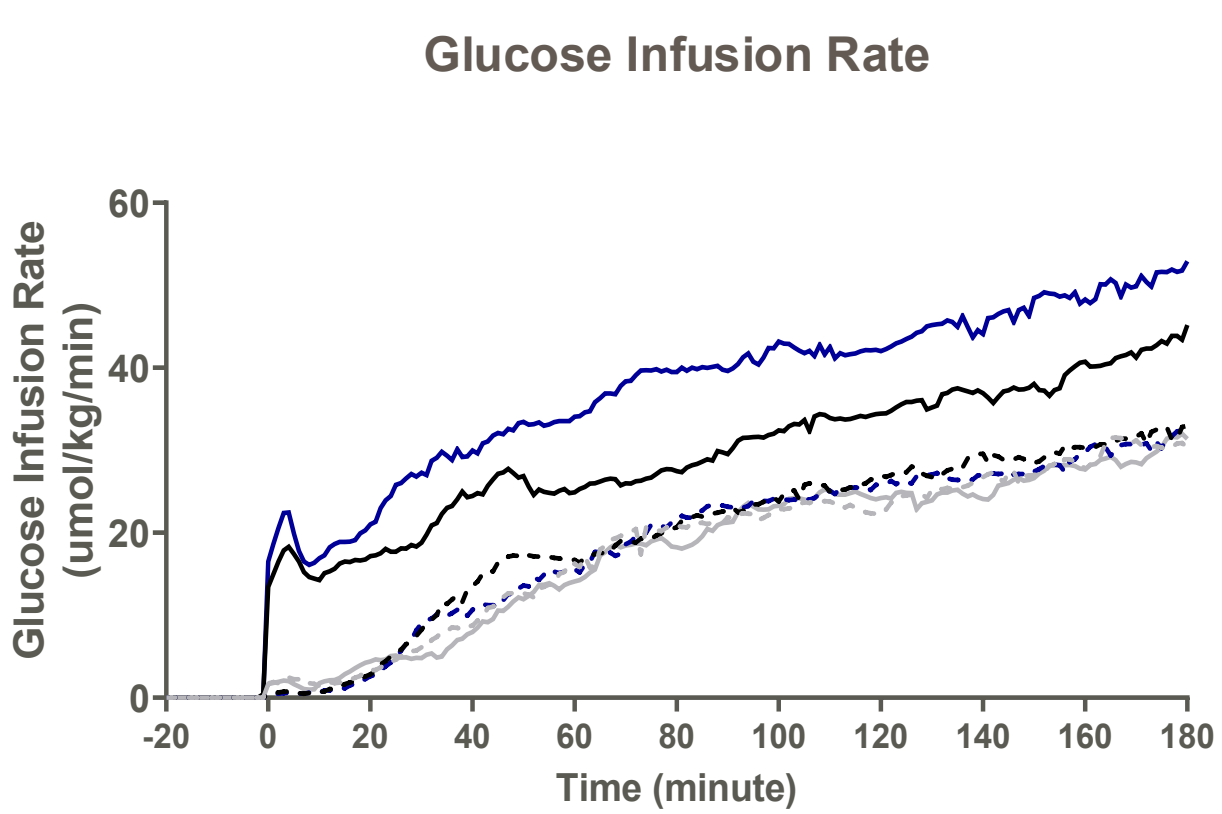
Persone con diabete di tipo 2. Effetto di tirzepatide vs placebo e semaglutide su secrezione insulinica durante clamp iperglicemico.

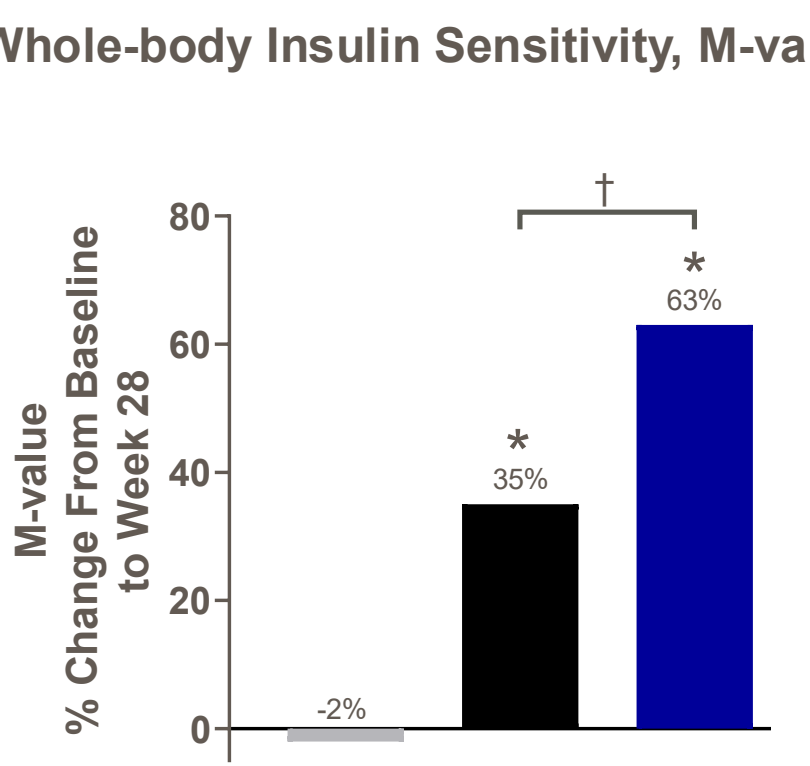
Heise T, et al. Lancet Diabetes Endocrinol. 2022;10:418-429

Tirzepatide: miglioramento sensibilità insulinica

Placebo SEMA 1 mg TZP 15 mg

Dashed: baseline Solid: Week 28

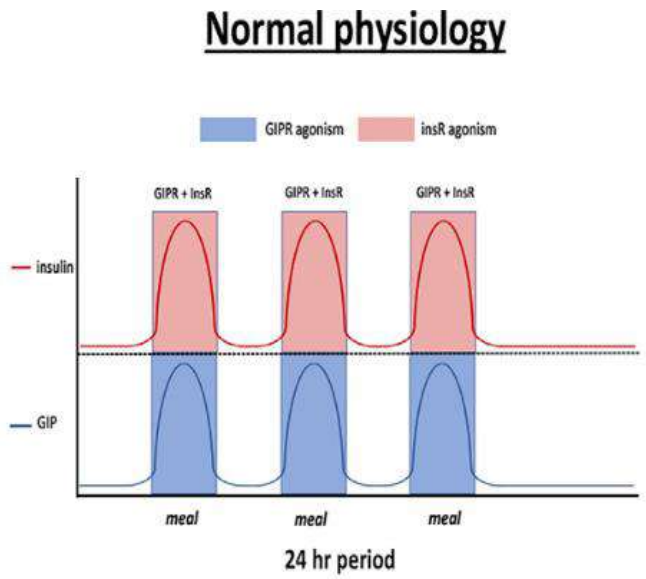


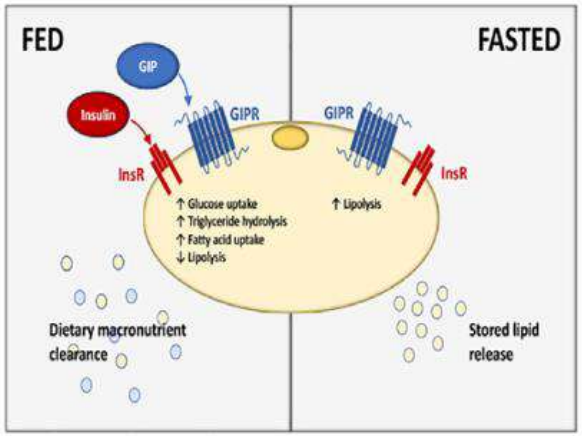


Persone con diabete di tipo 2. Effetto di tirzepatide vs placebo e semaglutide su secrezione insulinica durante clamp euglicemico iperinsulinemico.

Heise T, et al. Lancet Diabetes Endocrinol. 2022;10:418-429

Tirzepatide rende gli acidi grassi del tessuto adiposo più facilmente mobilizzabili





Regmi A, et al. Cell Metab. 2024;36:1534-1549.e7

Tirzepatide rende gli acidi grassi del tessuto adiposo più facilmente mobilizzabili

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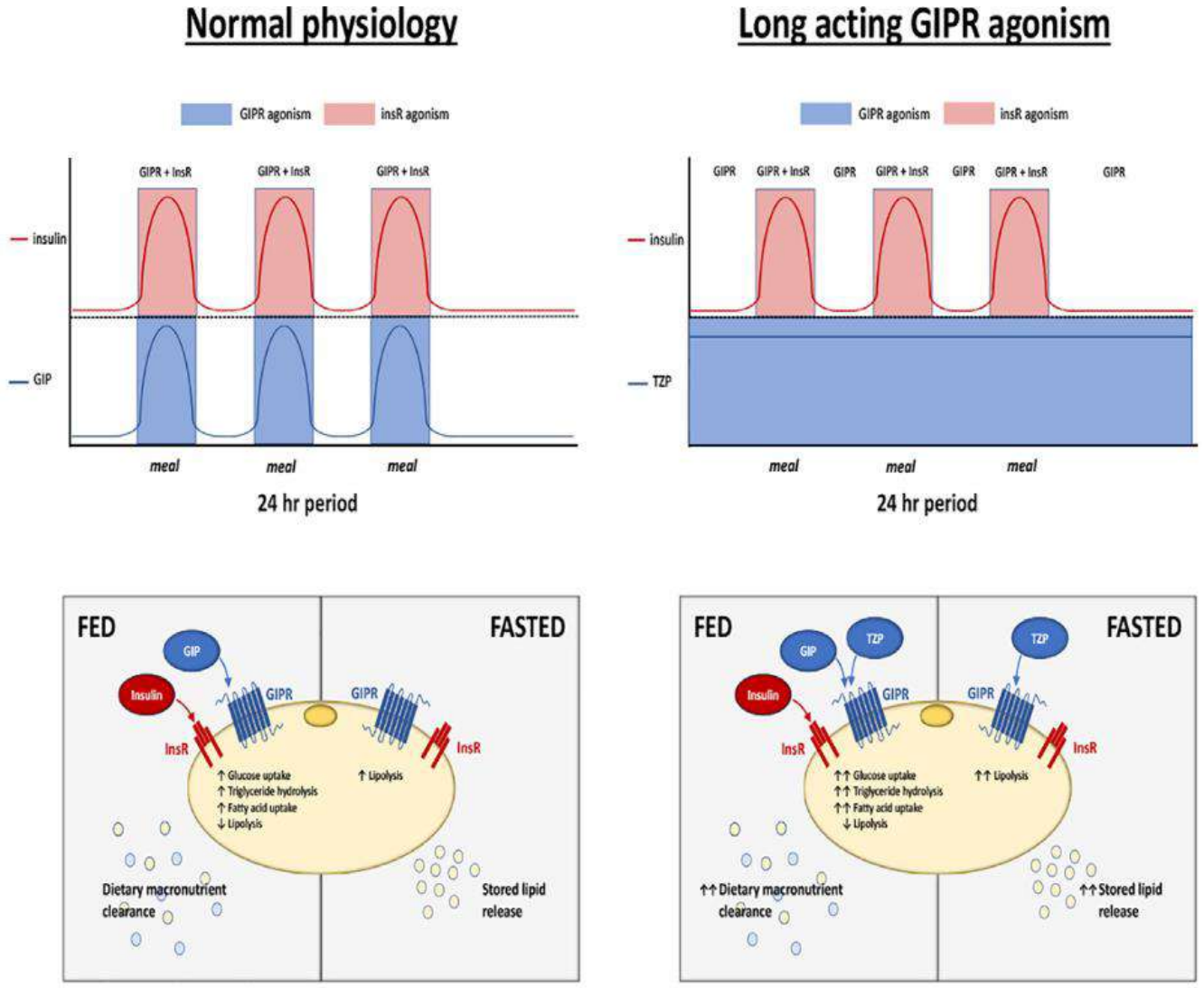
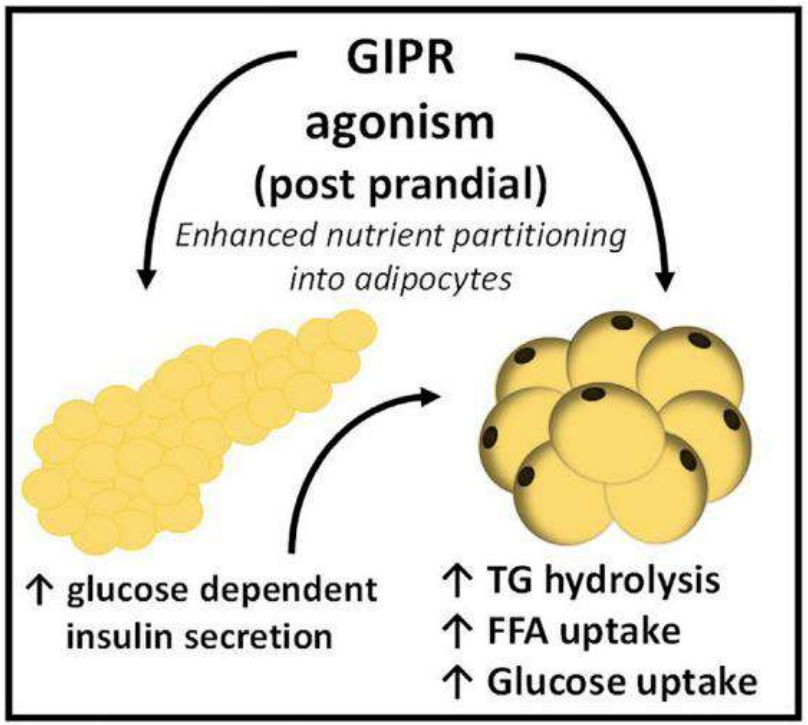
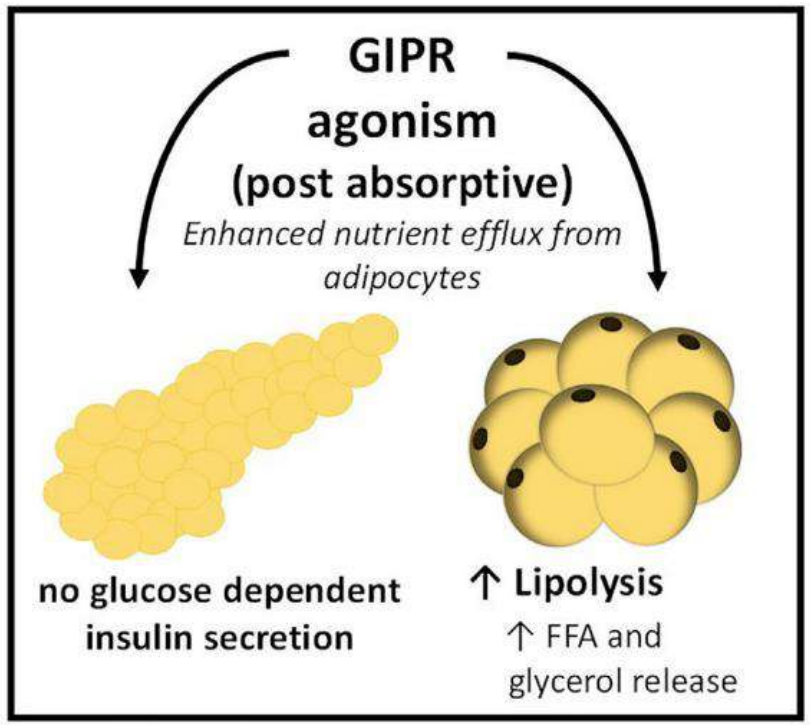


Regmi A, et al. Cell Metab. 2024;36:1534-1549.e7

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



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

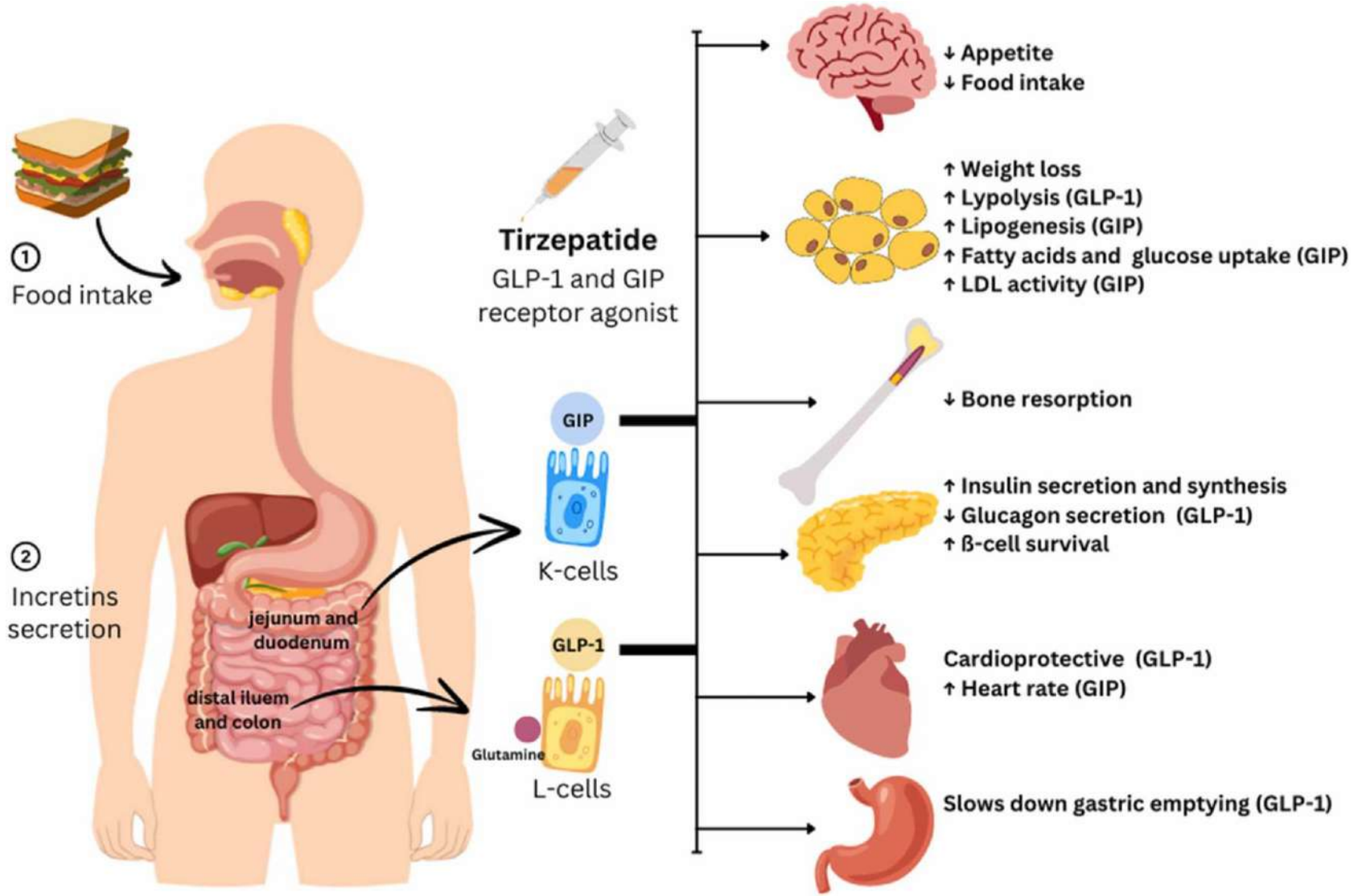


Long-acting GIPR agonism regulation of plasma lipid metabolism under postabsorptive/fasted conditions

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

Regmi A, et al. Cell Metab. 2024;36:1534-1549.e7

Tirzepatide: meccanismo d’azione



Sokary S, Bawadi H. Prim Care Diabetes. 2025;19(3):229-237.

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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. placebo[1]** Drug-naïve o washout da qualsiasi OAM	**SURPASS-2** **vs. semaglutide[2]** Add-on a metformin	**SURPASS-3** **vs. insulin degludec[3]** Add-on a metformina +/- SGLT-2i	**SURPASS-4** **vs. insulina glargine[4]** Add-on a ≥1 e ≤3 OAMs (metformina, SGLT-2i, o SU)	**SURPASS-5** **vs. placebo[5]** Con insulina glargine +/- metformina **SURPASS-6** **vs. insulin lispro[6] (TID)** Con insulina glargine +/- metformina

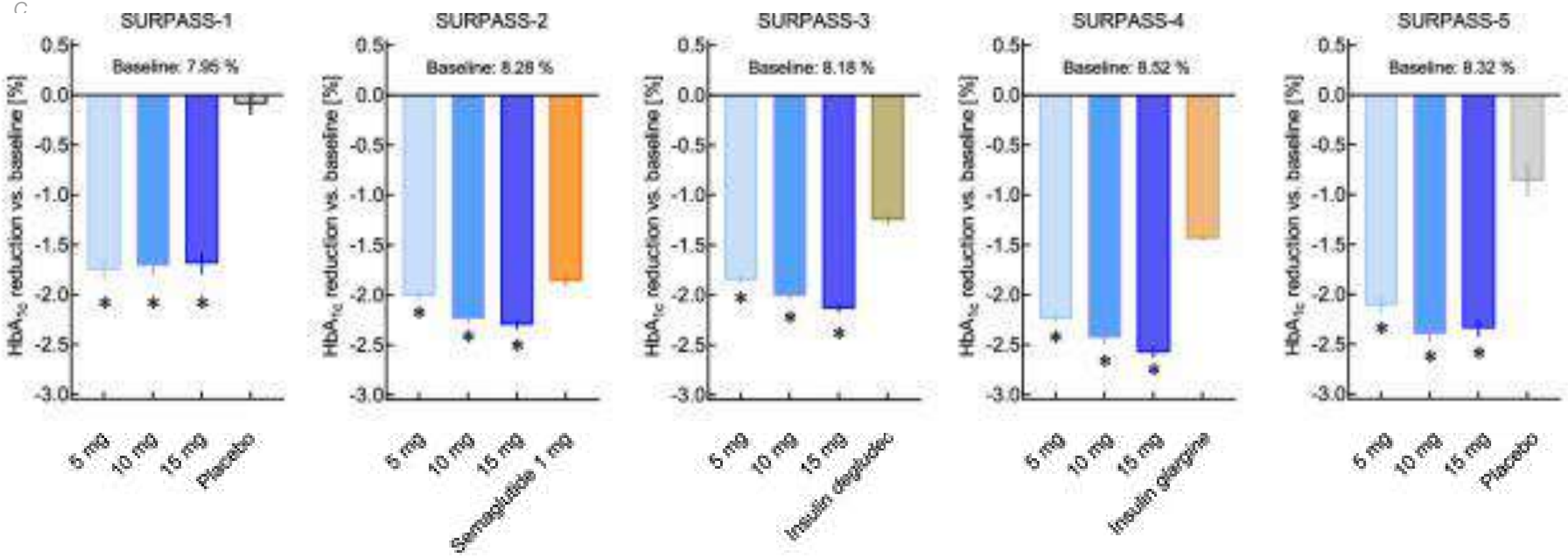
SURPASS-CVOT[7]
H2H: TZP vs. dulaglutide
>12,000 participanti (in corso)

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).

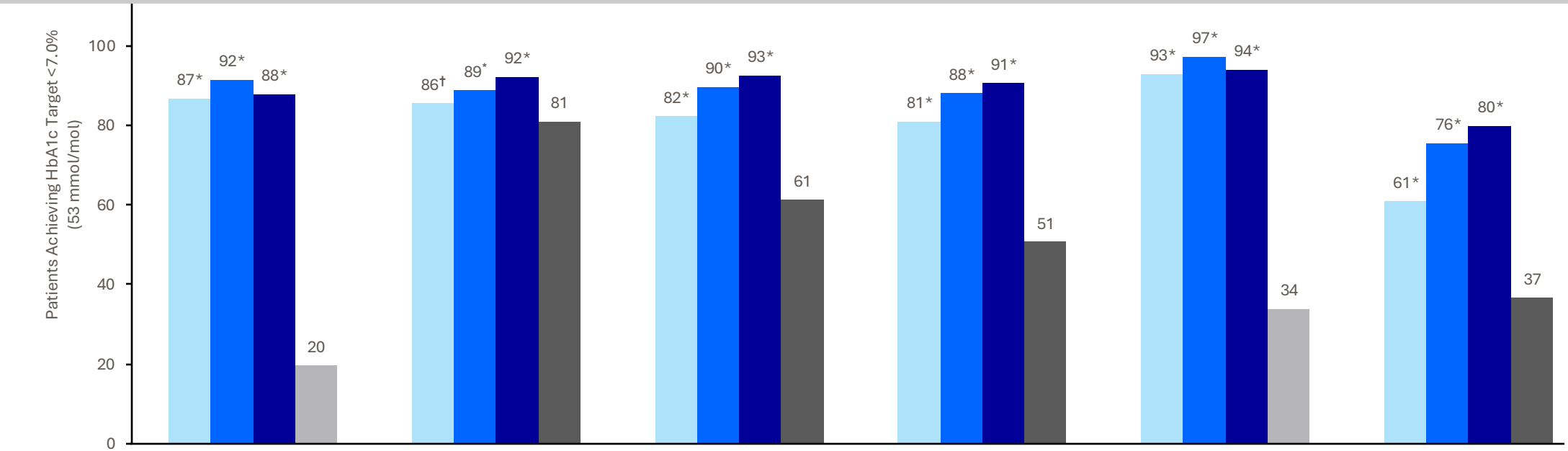
SURPASS 1-5 (HbA1C)



Nauck MA, D'Alessio DA. Cardiovasc Diabetol. 2022;21:169

SURPASS 1-6 (HbA1C < 7%)

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

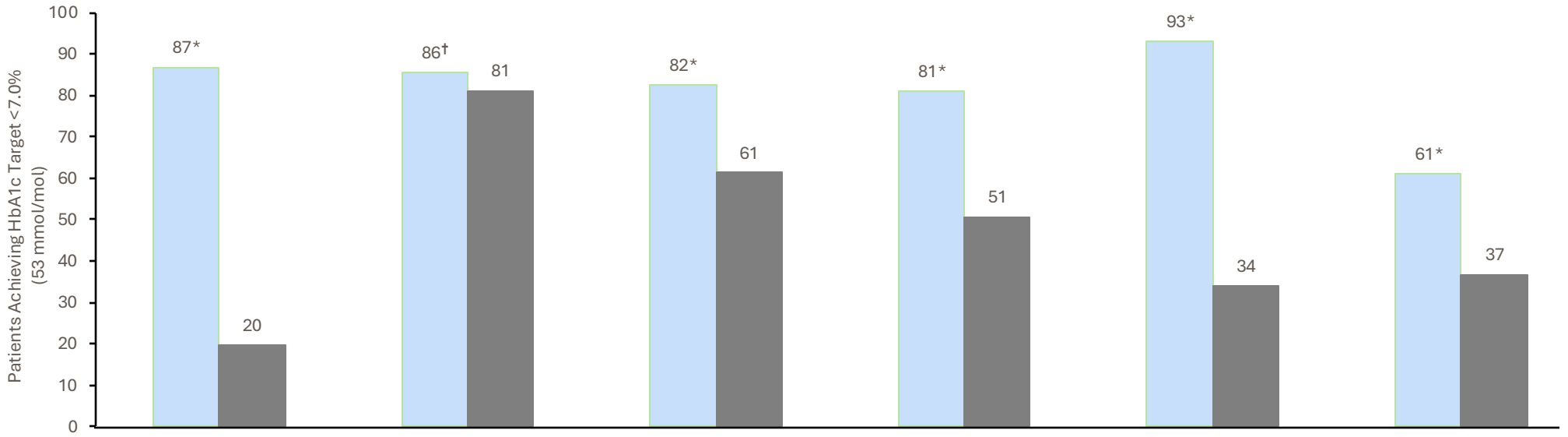


*p<0.001, †p<0.05 vs. placebo or active comparator.

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. 6. Rosenstock J, et al. JAMA. 2023;330(17):1631–1640

SURPASS 1-6 (HbA1C < 7%) – TZP 5mg

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



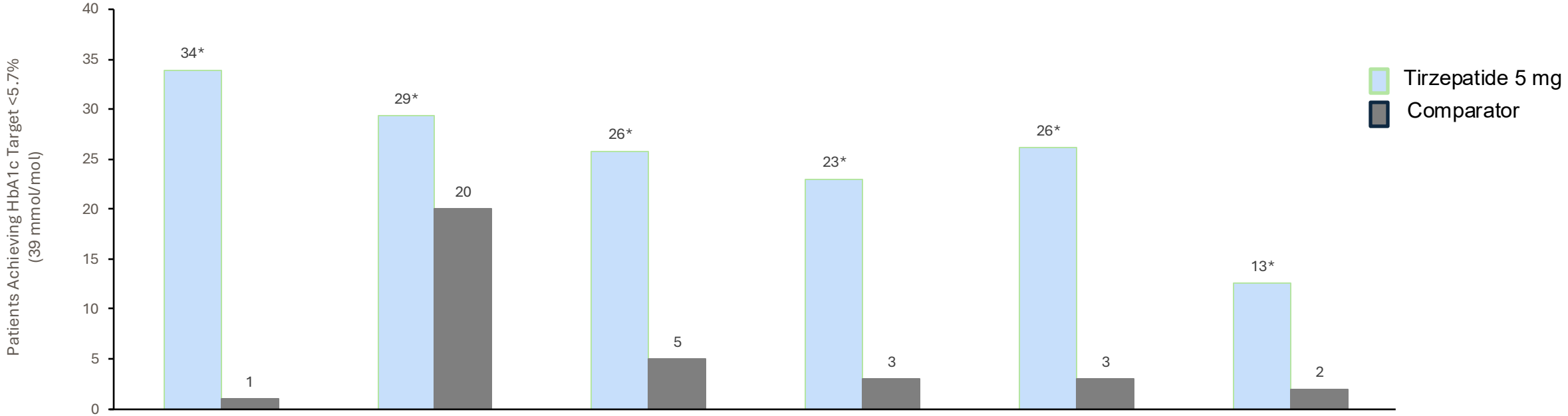
Superiority vs.	Placebo	SEMA 1 mg	Insulin degludec	Insulin glargine	Placebo	Insulin lispro
Background therapy	Monotherapy	Add-on to MET	Add-on to MET or MET + SGLT2i	Add-on to MET, SGLT2i, or SU	Add-on to insulin glargine ± MET	Add-on to insulin glargine ± MET

*p<0.001, †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. 6. Rosenstock J, et al. JAMA. 2023;330(17):1631–1640

SURPASS 1-6 (HbA1C < 5.7%) – TZP 5mg

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



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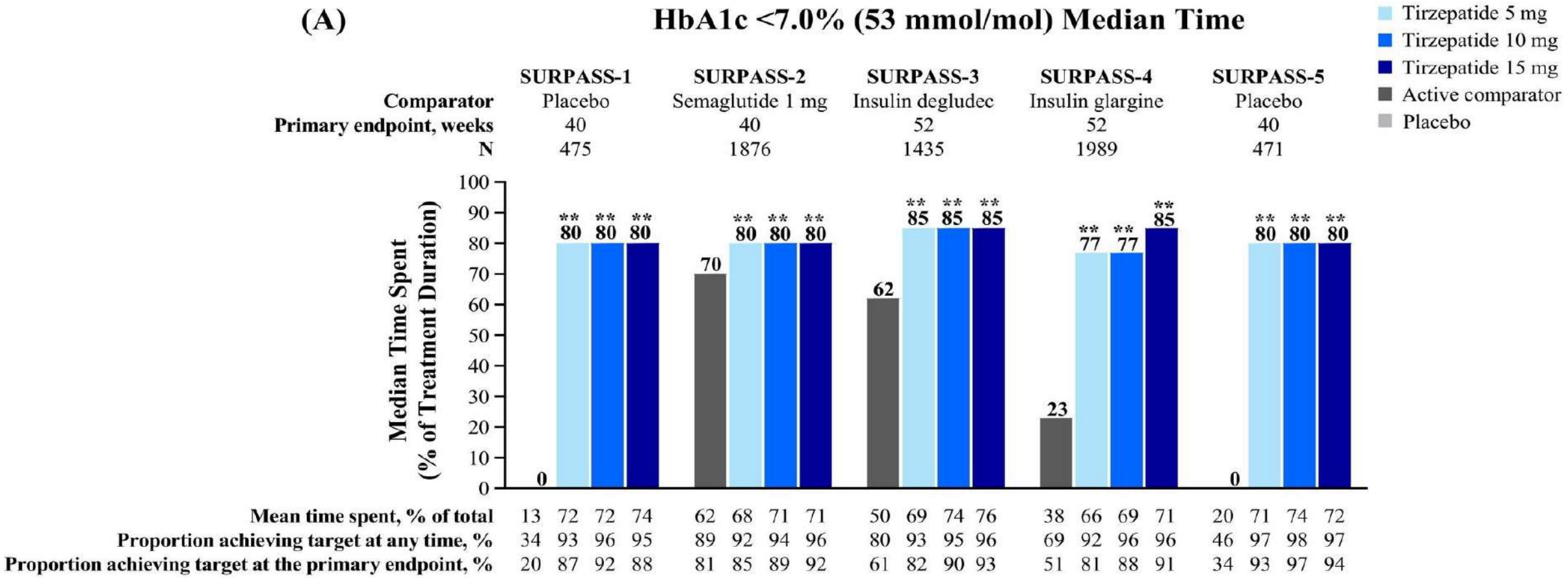
*p<0.001

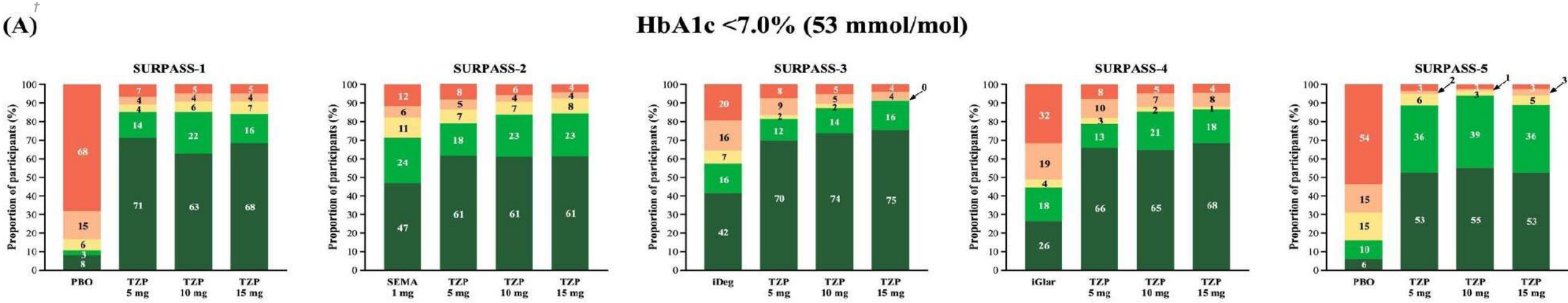
1. Rosenstock J, et al. Lancet. 2021;398(10295):143-155. 2. Frias JP, et al. N Eng J Med. 2021;385(6):503-515. 3. Ludvik B, et al. Lancet. 2021;398(10300):583-598. 4. Del Prato S, et al. Lancet. 2021;398(10313):1811-1824. 5. Dahl D, et al. JAMA. 2022;327(6):534-545. 6. 6. Rosenstock J, et al. JAMA. 2023;330(17):1631–1640

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



Bergman BK, et al. Diabetes Obes Metab. 2025;27(6):3223-3232

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



Bergman BK, et al. Diabetes Obes Metab. 2025;27(6):3223-3232

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

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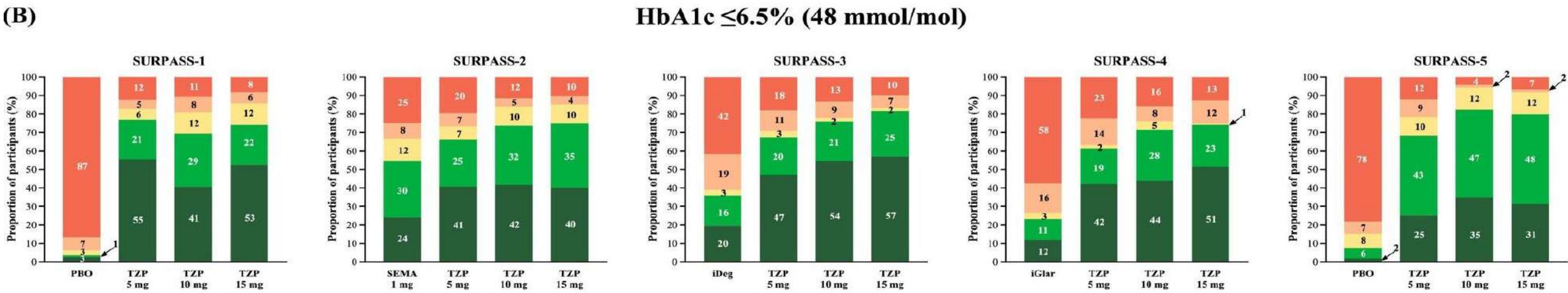
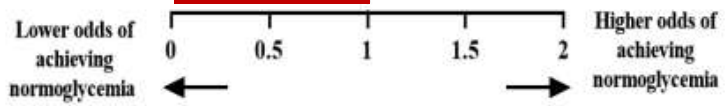


Bergman BK, et al. Diabetes Obes Metab. 2025;27(6):3223-3232

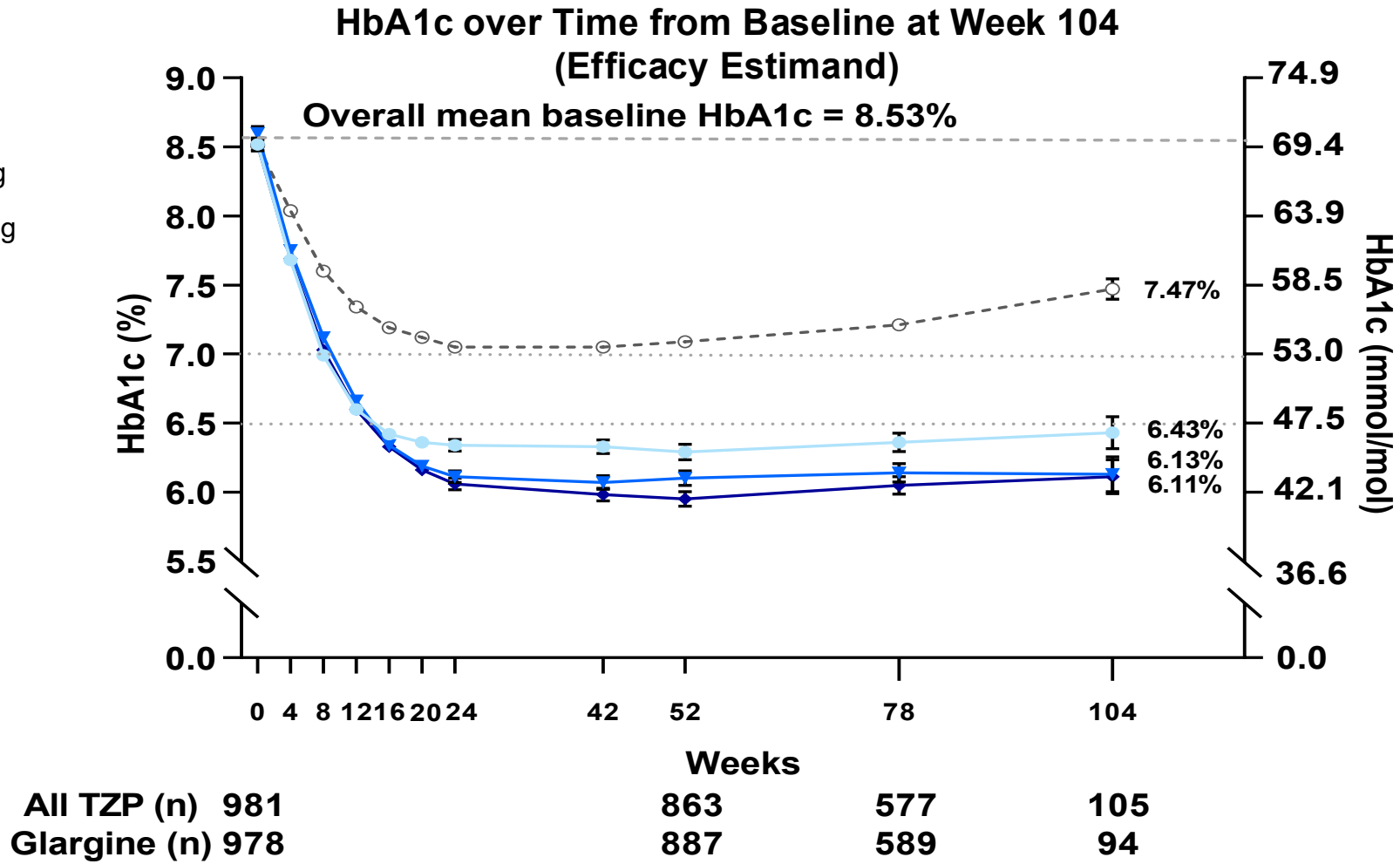
Età inferiore, durata più breve di malattia, HbA1c più bassa e monoterapia con metformina sono predittori di maggiore probabilità di ottenere HbA1c < 5,7%

Baseline Parameter	Mean (SD)	OR with 95% CI	OR (95% CI)	P-value	OR Reference
Age (y)	58 (10.3)		0.87 (0.84,0.90)	<0.001	By 5-year increase
Duration of Diabetes (y)	9.0 (6.9)		0.76 (0.71, 0.80)	<0.001	By 5-year increase
HbA_{1c} (mmol/mol)	67.4 (10.7)		0.58 (0.53, 0.63)	<0.001	By 10.93 mmol/mol
HbA_{1c} (%)	8.3 (1.0)				By (1%) increase
Fasting Serum Glucose (mmol/L)	9.5 (2.8)		0.76 (0.71, 0.82)	<0.001	By 1 SD increase
Fasting Serum Glucose (mg/dL)	172 (49.8)				By 1 SD increase
eGFR (ml/min/1.73m²)	92.1 (19.3)		1.22 (1.13, 1.31)	<0.001	By 1 SD increase
Baseline OAM					
Metformin only	-		-	-	-
More than One OAM	-		0.57 (0.48, 0.68)	<0.001	Metformin Only
No Oral Medication	-		0.84 (0.65, 1.08)	0.175	Metformin Only
Other	-		0.33 (0.15, 0.71)	0.005	Metformin Only



Rosenstock J, Del Prato S, et al. Diabetes Care. 2023 Nov 1;46(11):1986-1992

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



Del Prato S, et al. Lancet. 2021;398(10313):1811-1824

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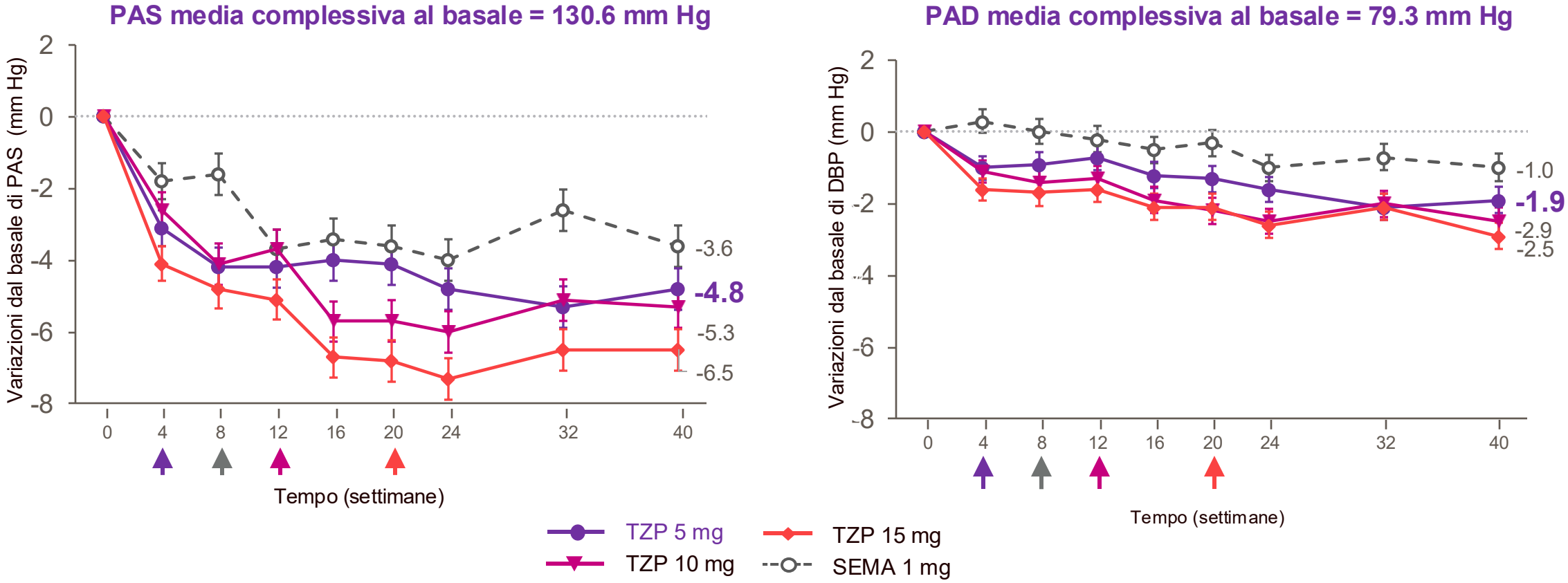
Tirzepatide: Oltre l’HbA1c

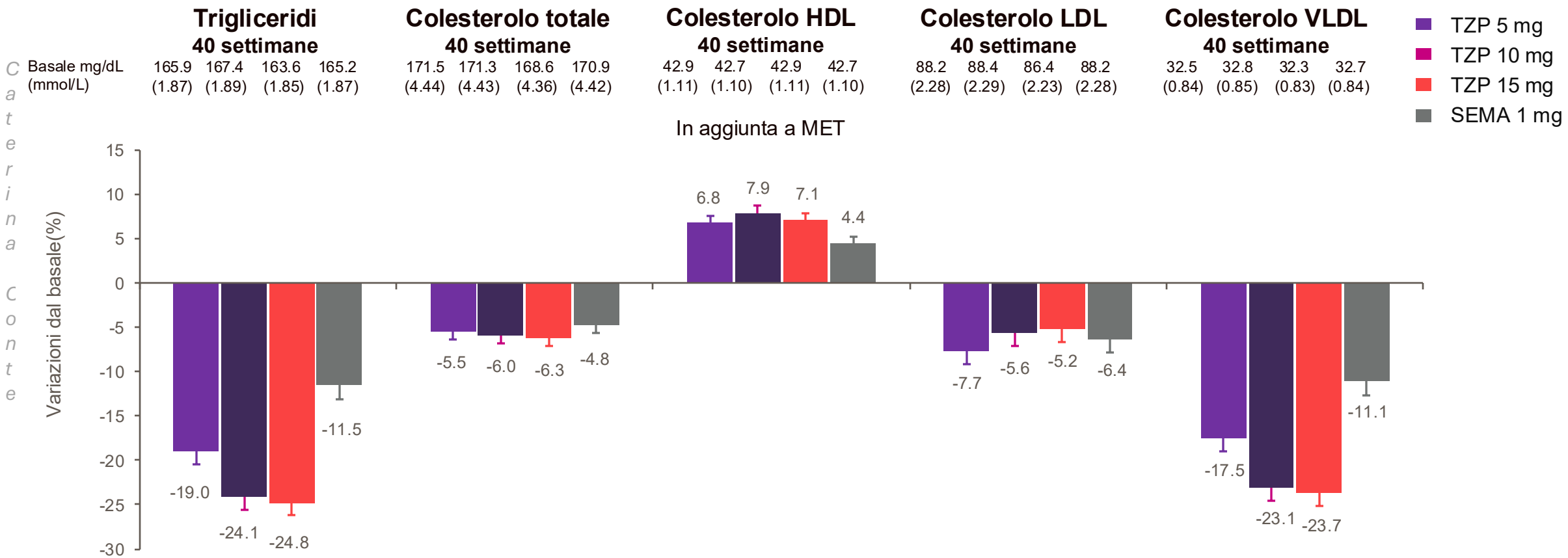
Variazione della pressione arteriosa sistolica e diastolica a 40 settimane (SURPASS-2)



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.

Frias JP, et al. N Engl J Med. 2021;385(6):503-515

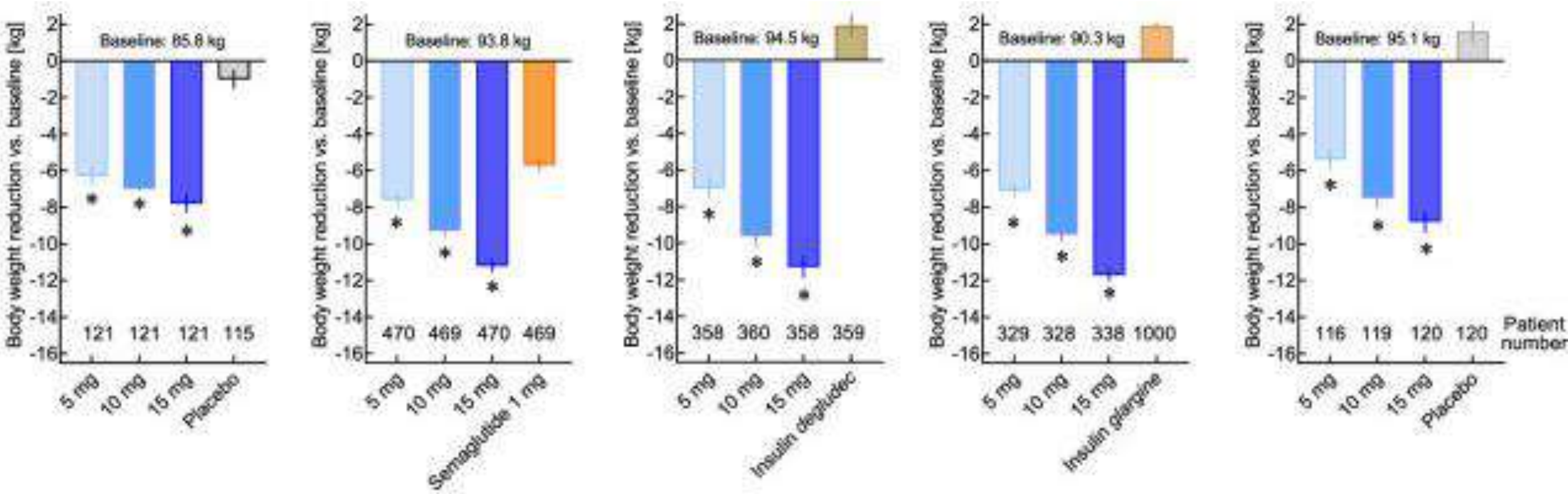
Miglioramento del profilo lipidico a 40 settimane (SURPASS-2)



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..

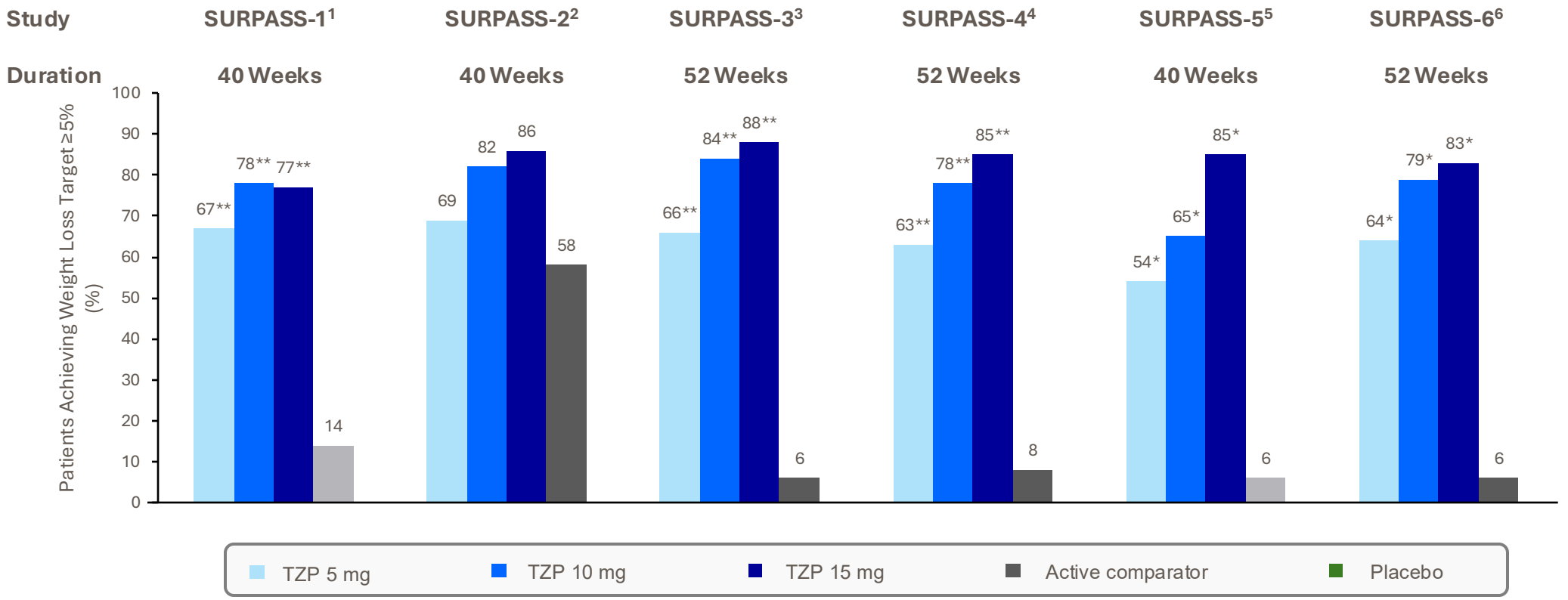
Frias JP, et al. N Engl J Med. 2021;385(6):503-515

SURPASS 1-5 (peso corporeo)



Nauck MA, D'Alessio DA. Cardiovasc Diabetol. 2022;21:169

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



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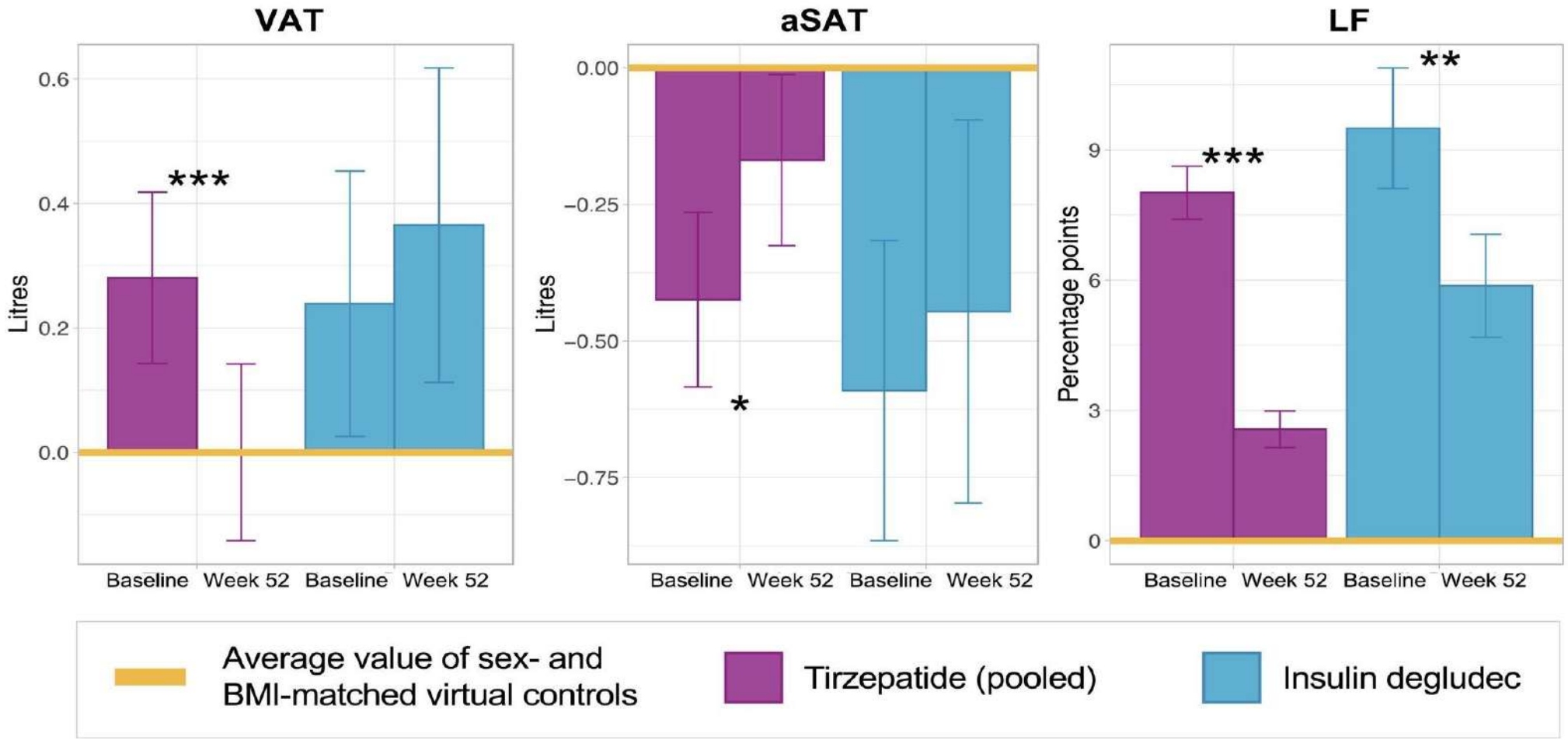
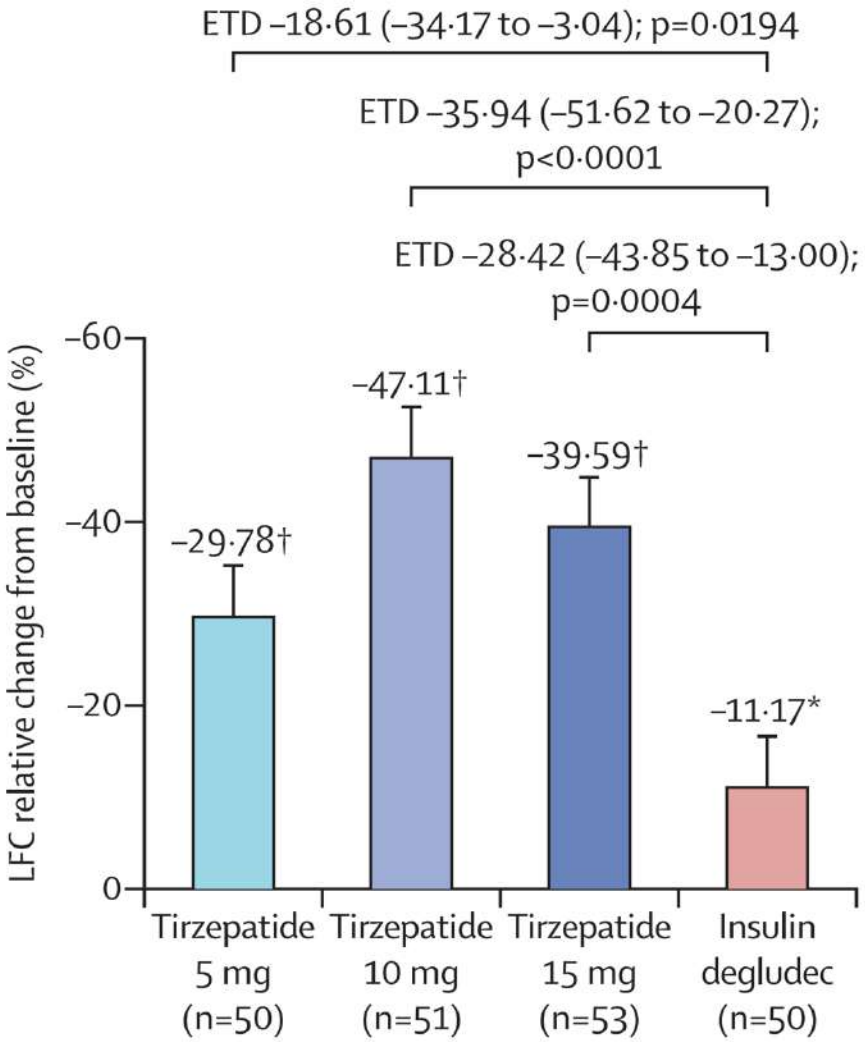
Composizione del calo ponderale (SURPASS 3 MRI)

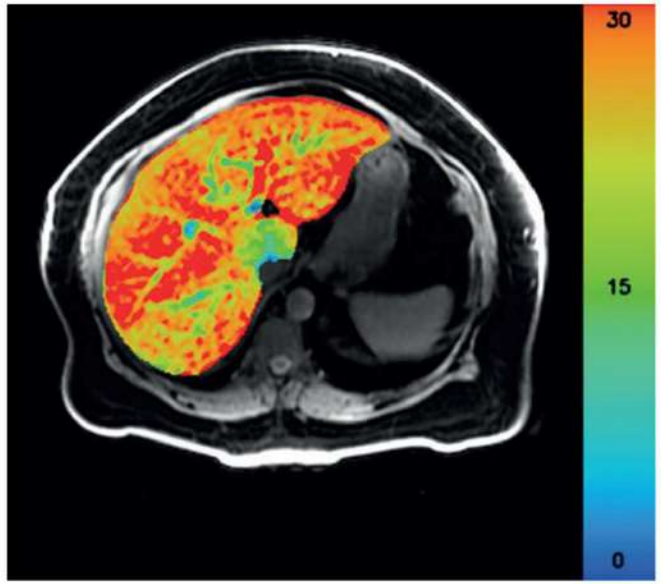


Cariou B, et al. Diabetes Obes Metab. 2024;26(6):2446-2455

Riduzione del grasso intraepatico (SURPASS-3 MRI)

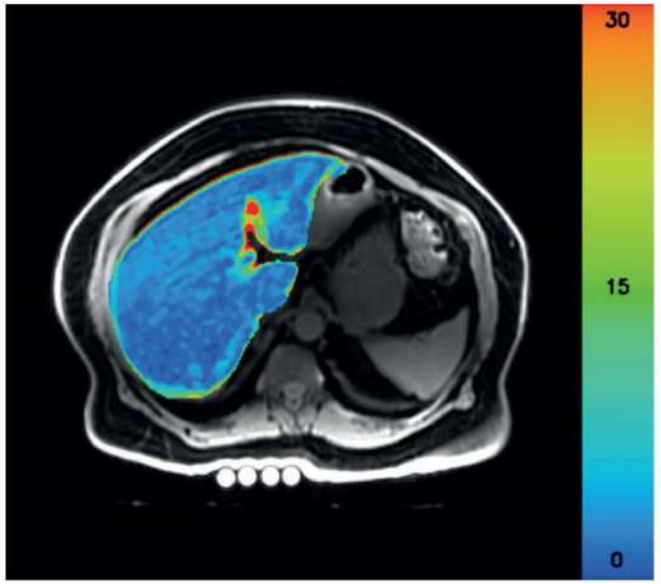


Male, 59 Years, on Metformin + SGLT-2i
randomized to **Tirzepatide 5 mg**



LFC at baseline: 27·3%

BMI: 44.8 kg/m^2; body weight: 134.2 kg; WC: 139.7 cm
HbA_{1c}: 78.1 mmol/mol (9.3%)



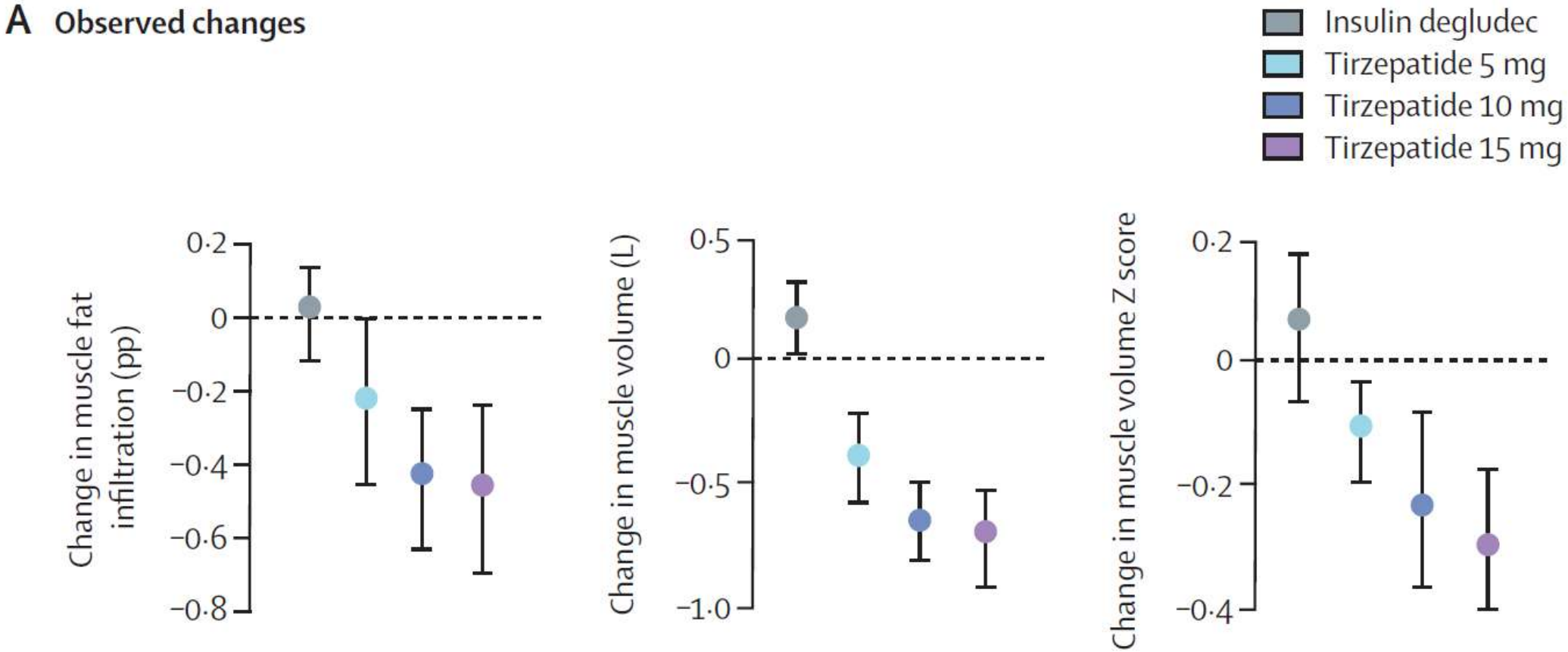
LFC at week 52: 2·6%

BMI: 36.2 kg/m^2; body weight: 108.4 kg; WC: 124.4 cm
HbA_{1c}: 43.2 mmol/mol (6.1%)

ETD, estimated treatment difference; LFC, liver fat content; * p<0·05; †p<0·0001; ‡ p<0·01, vs baseline.

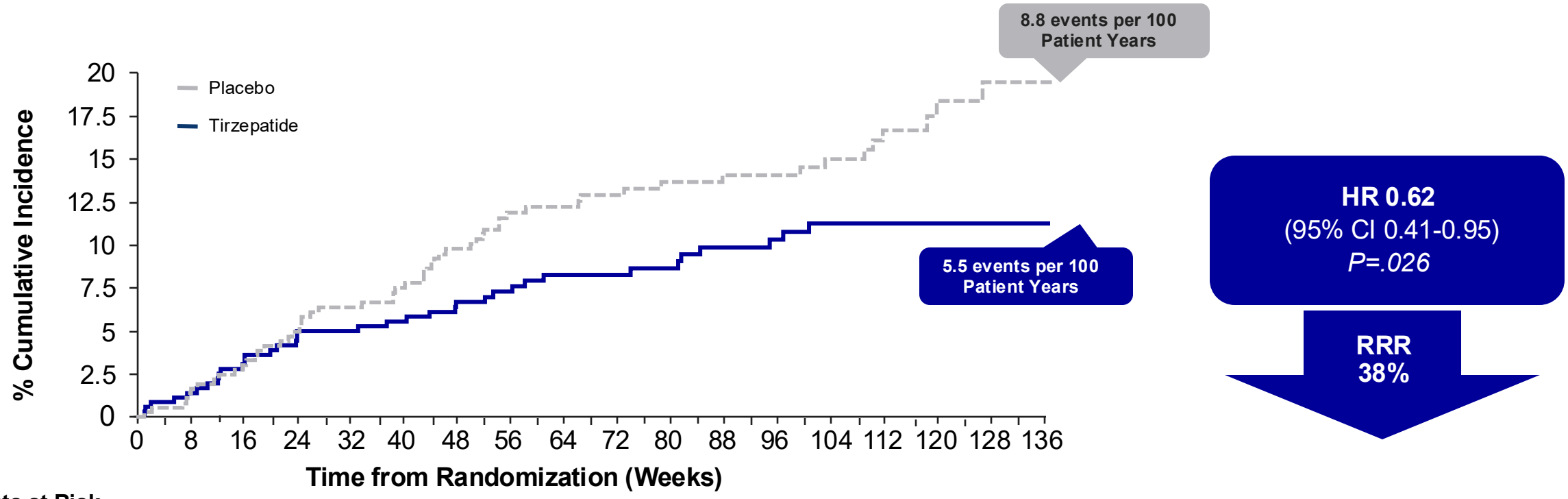
Gastaldelli A, et al, Lancet Diabetes Endocrinol 2022;10(6):393-406

Riduzione del grasso intramuscolare (miosteatosi)



Sattar N, et al. Lancet Diabetes Endocrinol. 2025;13(6):482-493

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



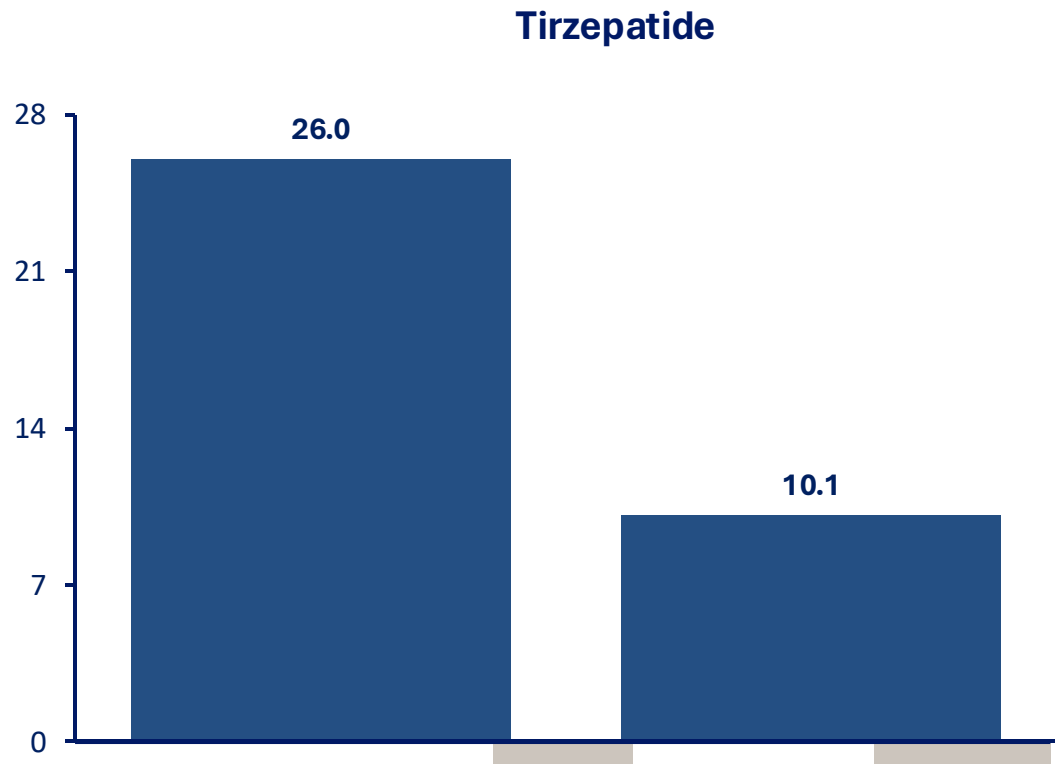
Participants at Risk

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

- [a]Worsening 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.

Packer M, et al. N Engl J Med. 2025;392(5):427-437

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



Analysis at week 52	ETD	95% CI	*p*-value
Tirze MTD *vs* placebo	18.3 m	9.9; 26.7	<0.001

Packer M, et al. N Engl J Med. 2025;392(5):427-437

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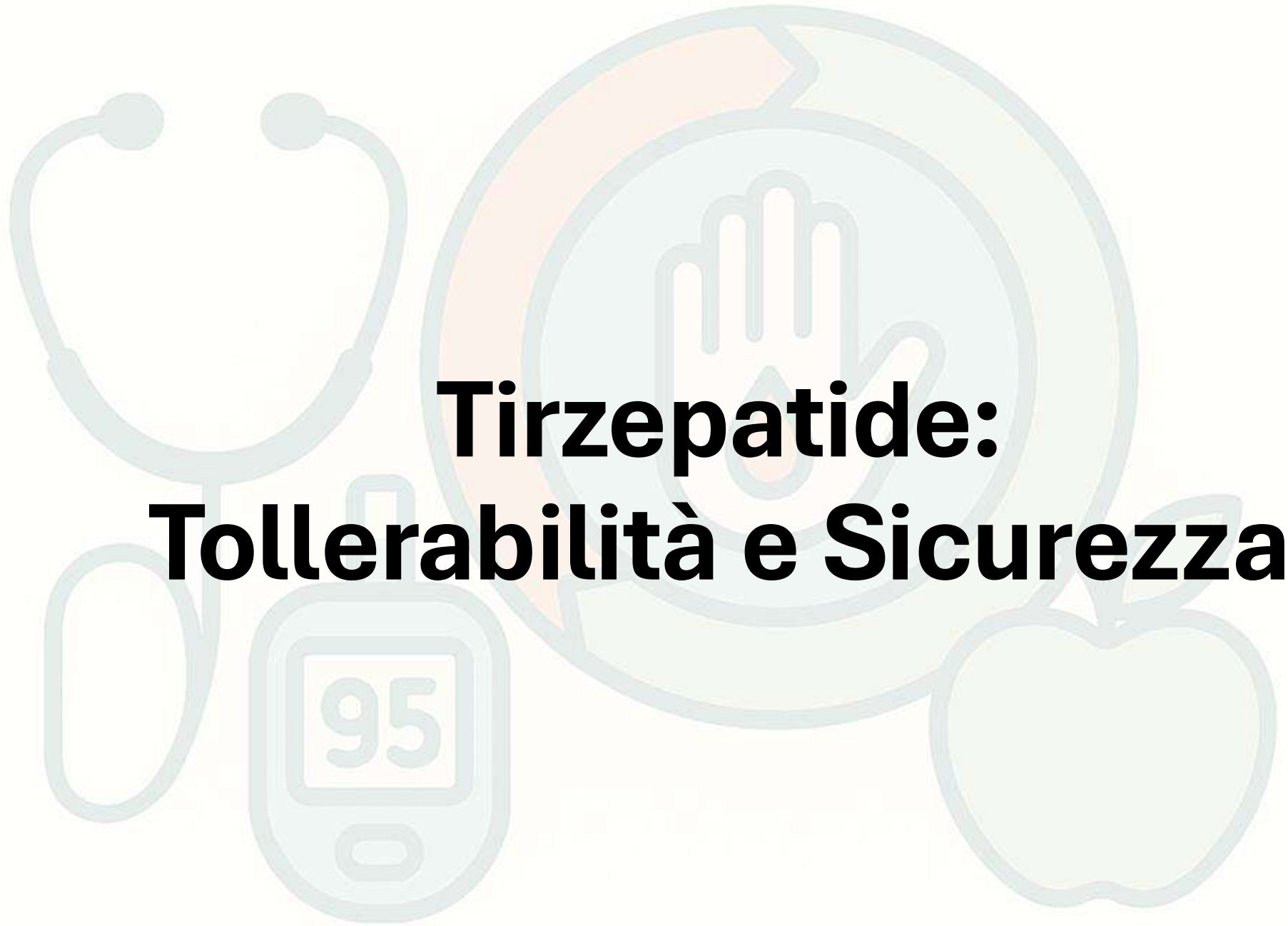
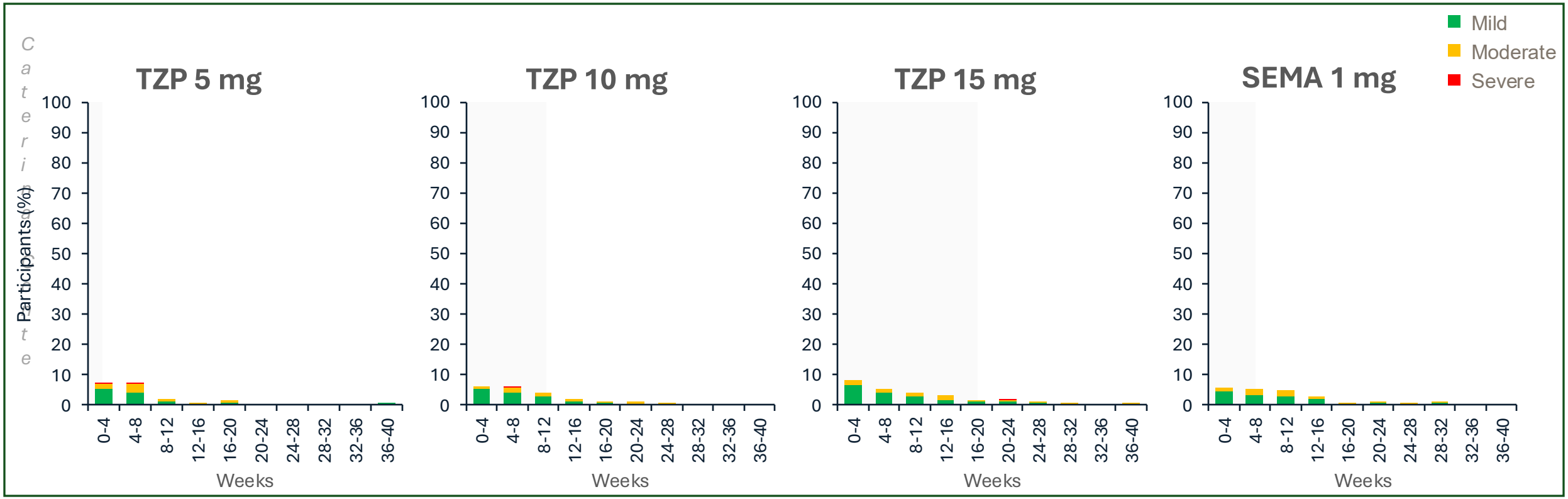


Tirzepatide: Tollerabilità e Sicurezza

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.

Frias JP, et al. N Engl J Med. 2021;385(6):503-515

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.
[a]Severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia;[b]1 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; [c]1 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.

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.

Incidenza di Ipoglicemia

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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)
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.
[a]Severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia; [b]1 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; [c]1 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.

1. Del Prato S, et al. Lancet. 2021;398(10313):1811-1824. 2. Dahl D, et al. JAMA. 2022;327(6):534-545. 3. Rosenstock J, et al. JAMA. 2023;330(17):1631–1640.

GRAZIE!

Dual-agonist: un nuovo alleato

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