XVI CONGRESSO
REGIONALE
AMD MOLISE

14 OTTOBRE 2023
HOTEL CENTRUM PALACE
CAMPOBASSO

Farmaci innovativi in diabetologia : uno sguardo al futuro prossimo venturo

Mariarosaria Cristofaro

S.C. Malattie Endocrine-Diabetologia
P.O. « A.Cardarelli» Campobasso

From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023**

Diabetes Care. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009

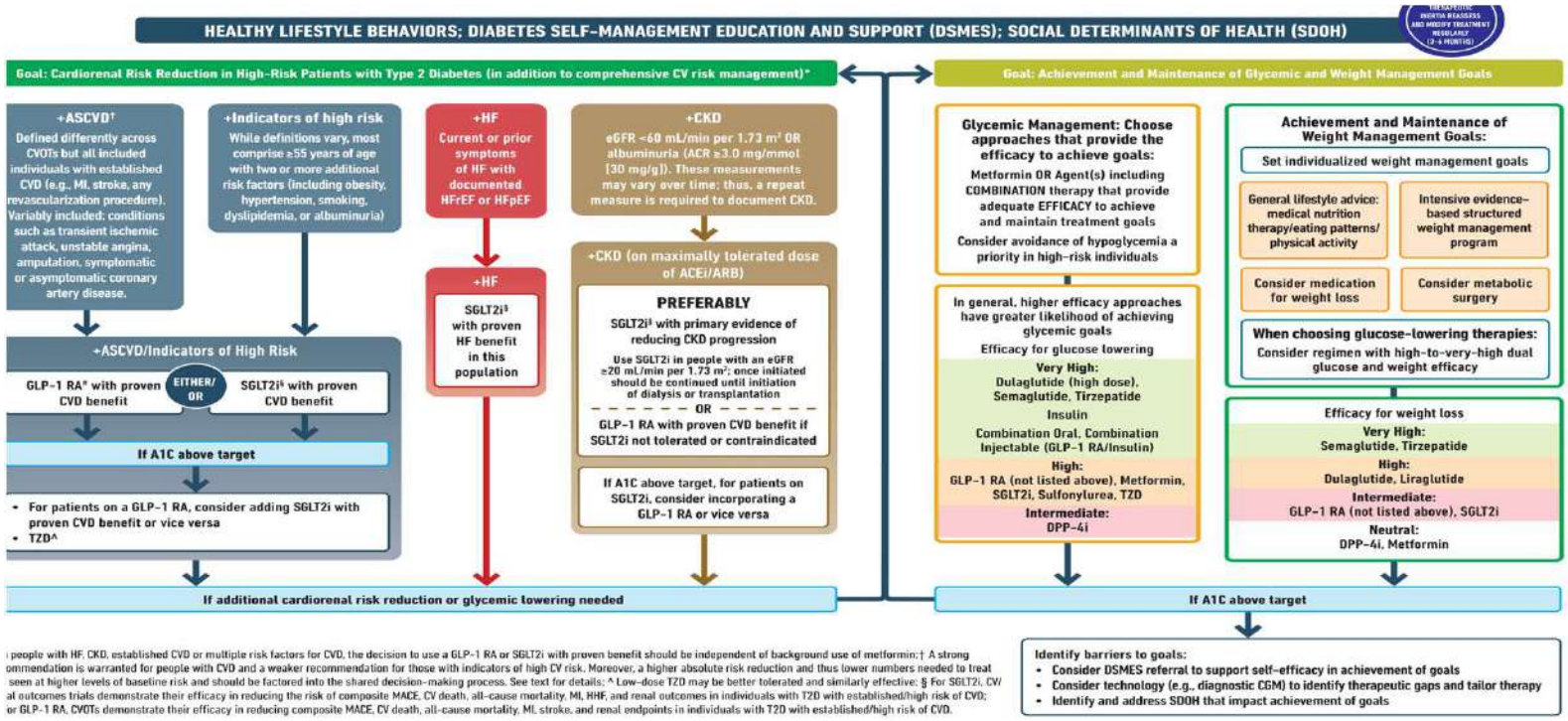


Figure Legend:

Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (45).

From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023**

Diabetes Care. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009

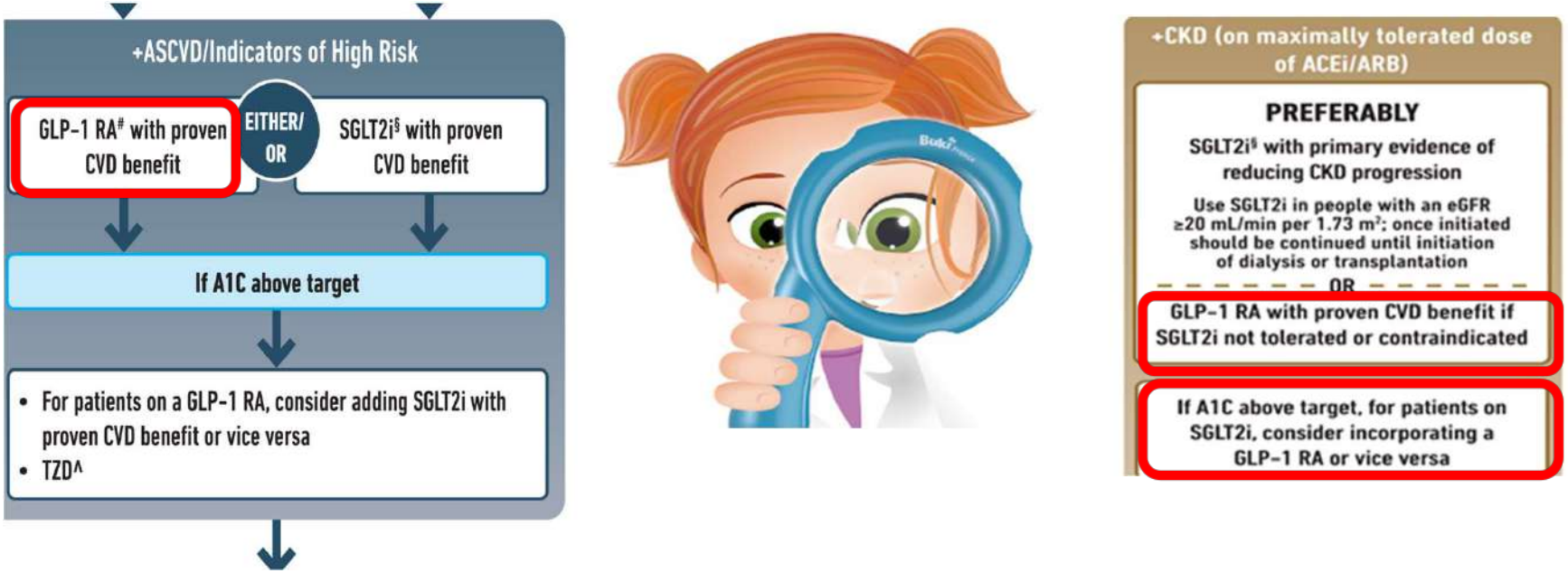
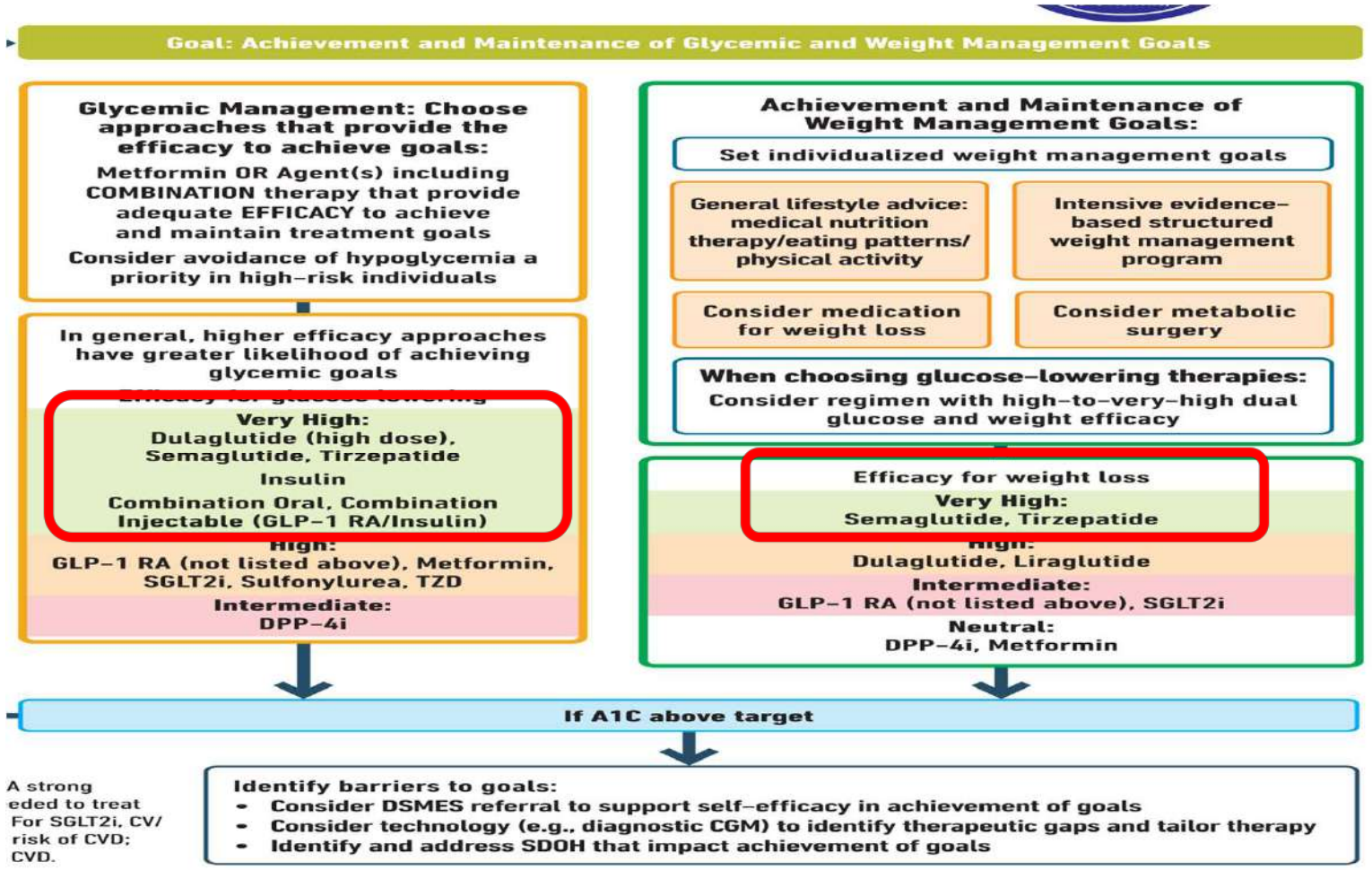


Figure Legend:

Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (45).

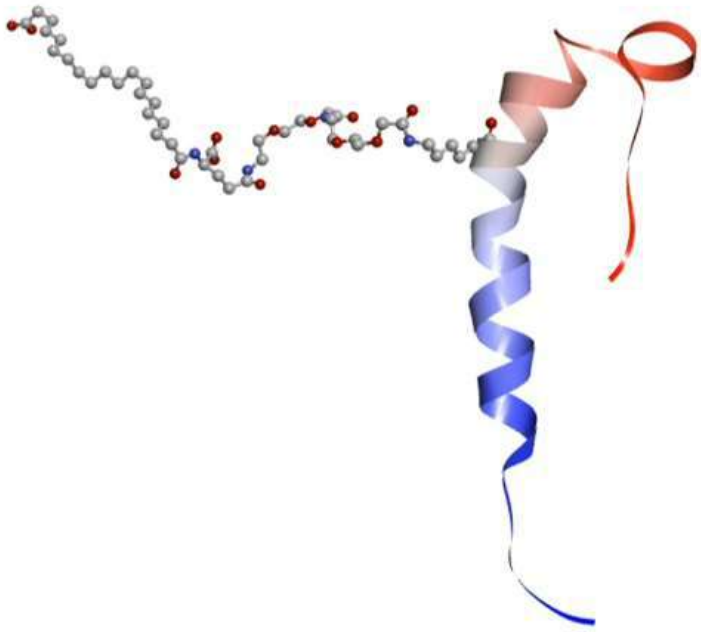
From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023**

Diabetes Care. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009



Tirzepatide *Mounjaro*

- **Structure: linear peptide, 39 amino acids based on the GIP sequence[1]**
  - **Binds to both GIPR and GLP-1R**
  - **Includes a C20 fatty diacid moiety**
- **Mean half-life: approximately 5 days[1]**
- **Plasma concentrations in people with renal impairment do not differ vs healthy people[2]**



This 3-dimensional rendering of tirzepatide is not an exact reproduction of the molecule and should be used for representative purposes only.
GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1R = glucagon-like peptide-1 receptor.

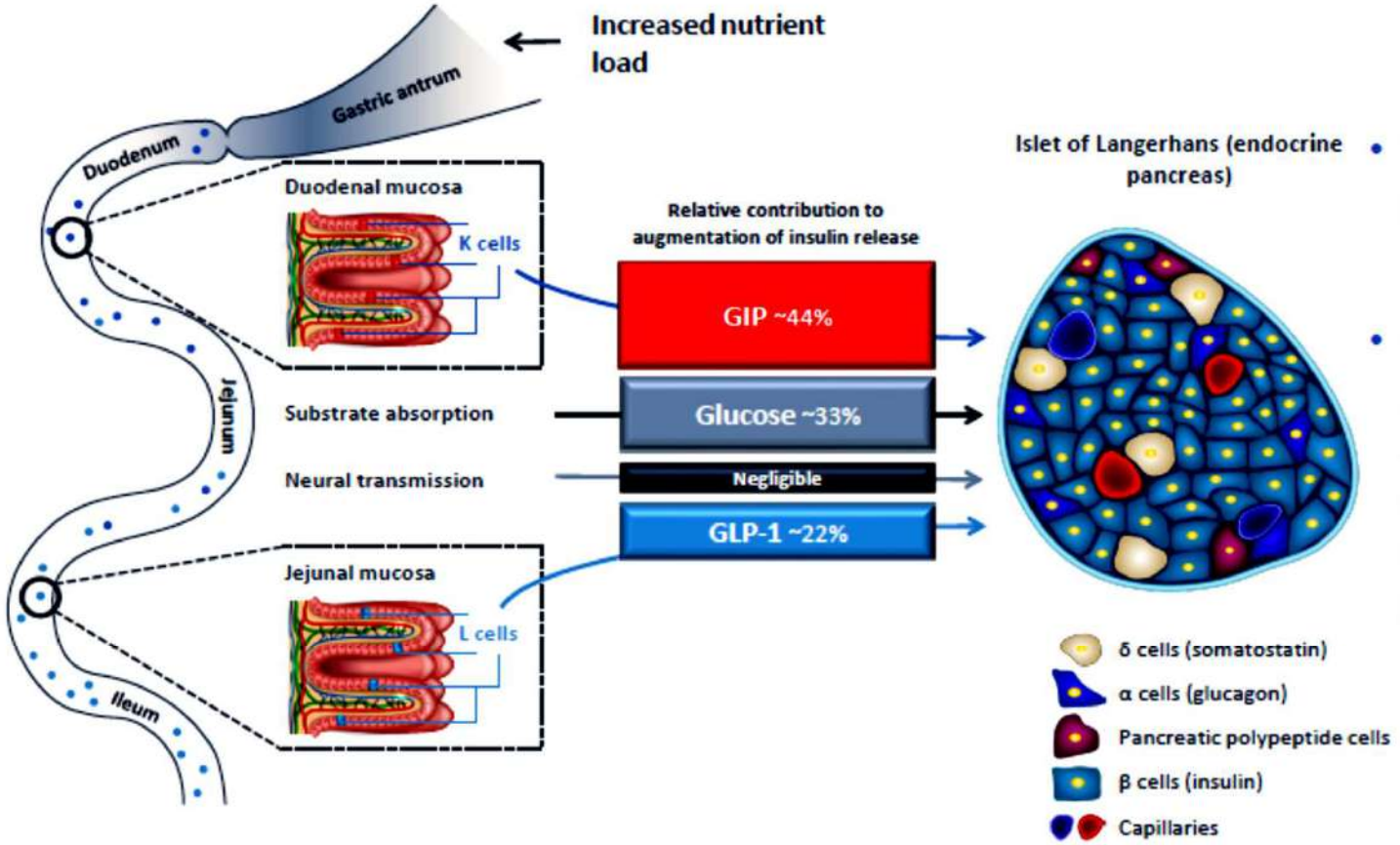
1. Coskun T, et al. *Mol Metab*. 2018;18:3-14. 2. Urva S, et al. *Diabetes*. 2020;69(suppl 1):Abstract 971-P.

GLP-1 and GIP are the two major incretins

GLP-1	GIP
▪ Released from L cells in ileum and colon, -NH2 term inaction by DPP-IV	▪ 42 aa peptide, from K cells in duodenum, -NH_2 term inactivation by DPP-IV
▪ Stimulates insulin secretion from β-cell in response to meal	▪ Stimulates insulin secretion from β-cell in response to meal
▪ Inhibition of gastric emptying	▪ Minimal effects on gastric emptying
▪ Inhibits glucagon secretion	▪ Stimulates glucagon secretion at euglycemia during fasting
▪ Reduction of food intake and body weight	▪ No significant effects on satiety or body weight
▪ Promotes expansion of β-cell mass – differentiation, ↓apoptosis	▪ Promotes expansion of β-cell mass in vitro

After Drucker DJ. Diabetes Care. 2003;26:2929–2940 and
Meier JJ, et al. Best Pract Res Clin End Met. 2004;18:587–606

The Incretin Hormones GIP and GLP-1 Signal to the Pancreas

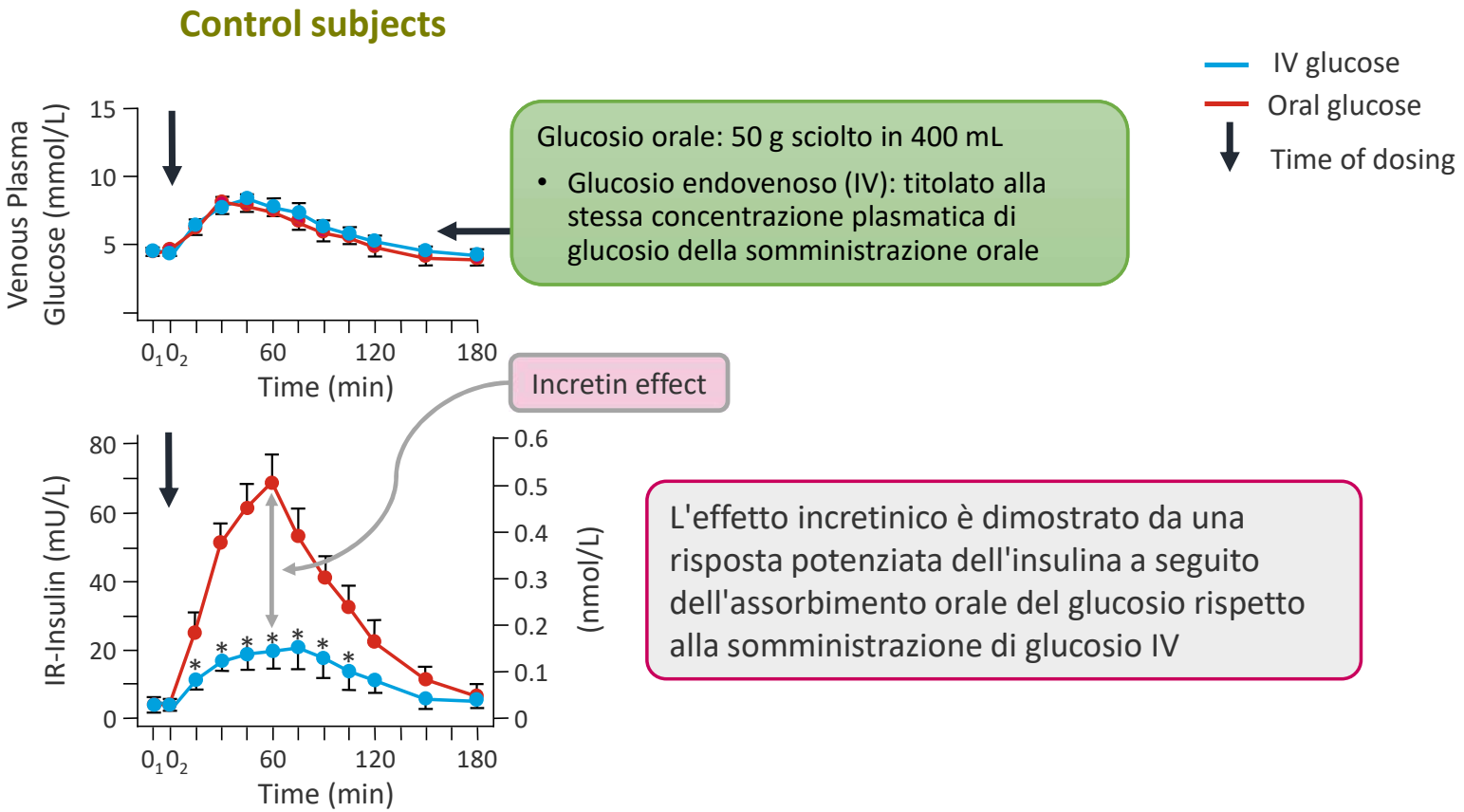


- Nutrient load in the gut stimulates release of the incretin hormones GIP and GLP-1
- GIP and GLP-1 signal to pancreatic islets to enhance glucose-dependent insulin secretion and subsequent PPG clearance in healthy people

GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1; PPG = postprandial glucose.

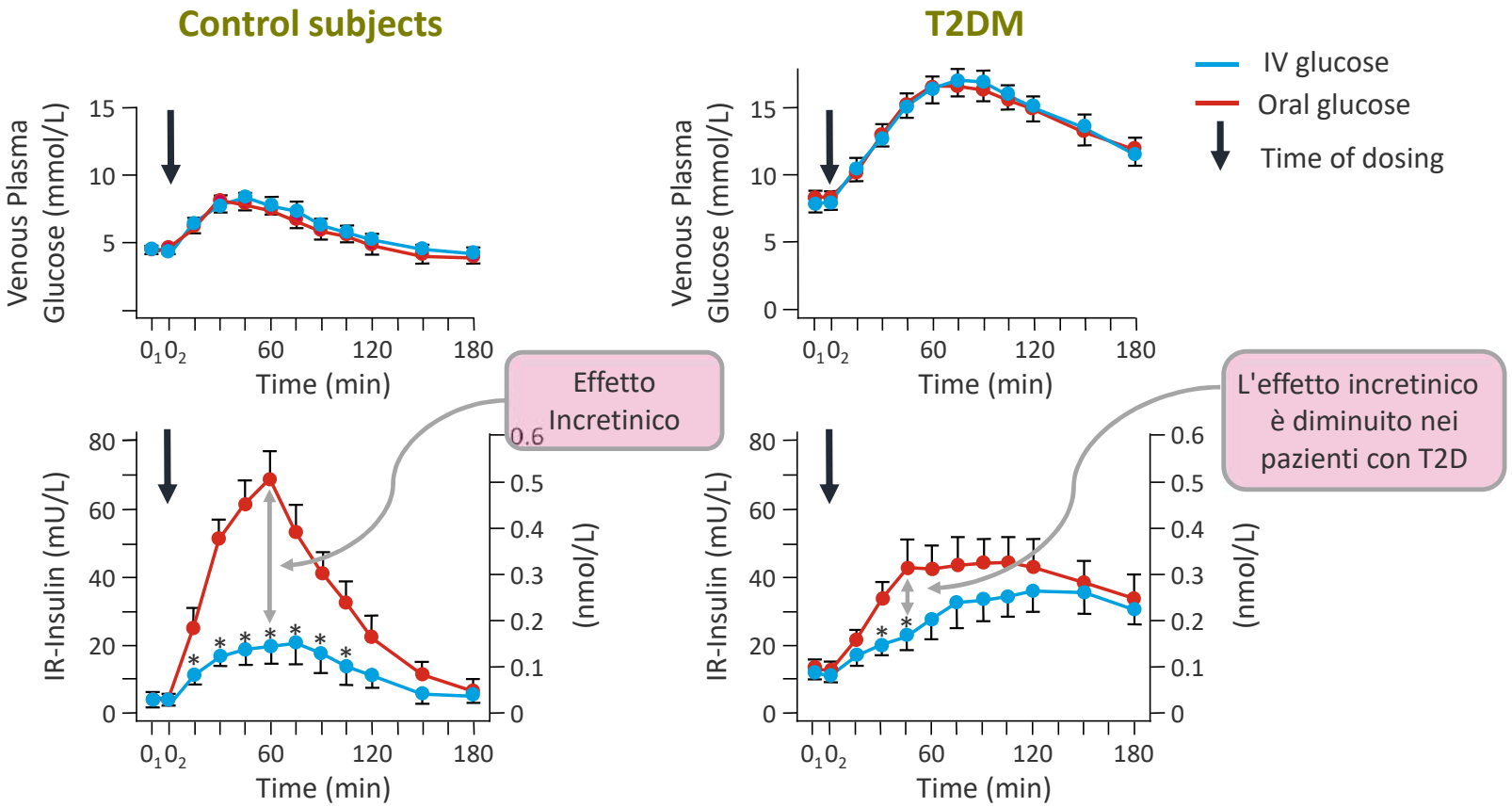
Nauck MA, Meier JJ. *Diabetes*. 2019;68(5):897-900.

L'effetto Incretinico



Mean ± SE; *p≤.05. IR=immunoreactive
Nauck et al. *Diabetologia* 1986;29:46-52

L'effetto Incretinico è ridotto nei pazienti con T2DM



Mean ± SE; *p≤.05. IR=immunoreactive; IV=intravenous; T2D=type 2 diabetes
Nauck et al. *Diabetologia* 1986;29:46-52

Analoghi GLP1 e protezione CV

trial	Farmaco	MACE	Morte CV	MI	stroke	Morte da tutte le cause
ELIXA	Lixixenatide	Ns	Ns	ns	ns	ns
LEADER	Liraglutide	**0.87 P=0.01**	**0,78 P=0.007**	ns	ns	**0,85 P=0.02**
SUSTAIN	Semaglutide	**0.74 P=0.02**	ns	ns	**0.61 P=0.04**	ns
EXSCEL	exenatide LAR	Ns	ns	ns	ns	**0,864 P=0.016**
REWIND	Dulaglutide	**0.88 P=0.02**	ns	ns	**0.76 P=0.017**	**0.90 P=0.067**

Lo studio REWIND ha incluso una percentuale maggiore di individui con diabete di tipo 2 ad alto rischio cardiovascolare ma senza malattie cardiovascolari pregresse (68,5%) rispetto ai precedenti CVOT

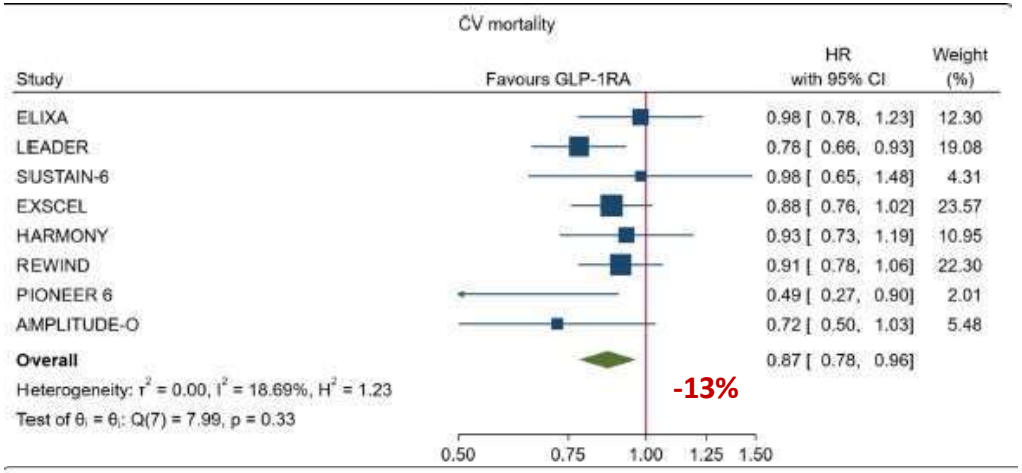
Giugliano et al. Cardiovasc Diabetol (2021) 20:189
https://doi.org/10.1186/s12933-021-01366-8

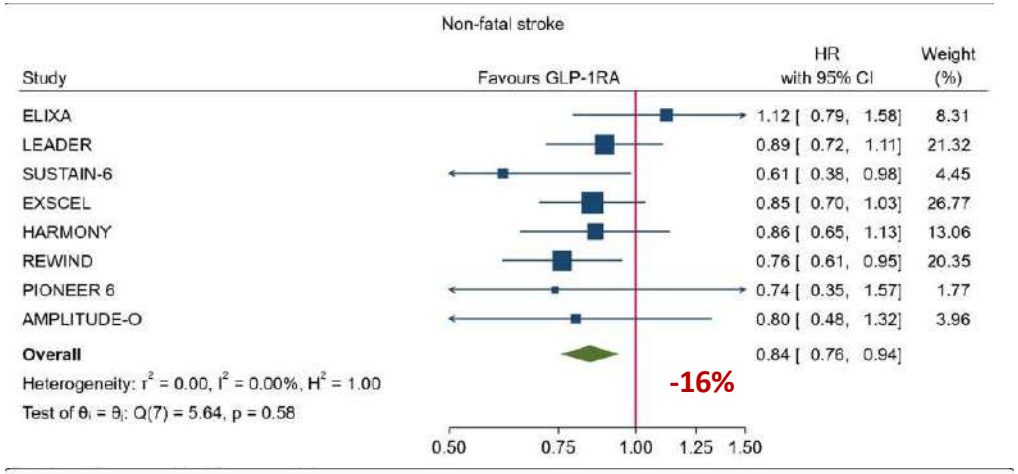
Cardiovascular Diabetology

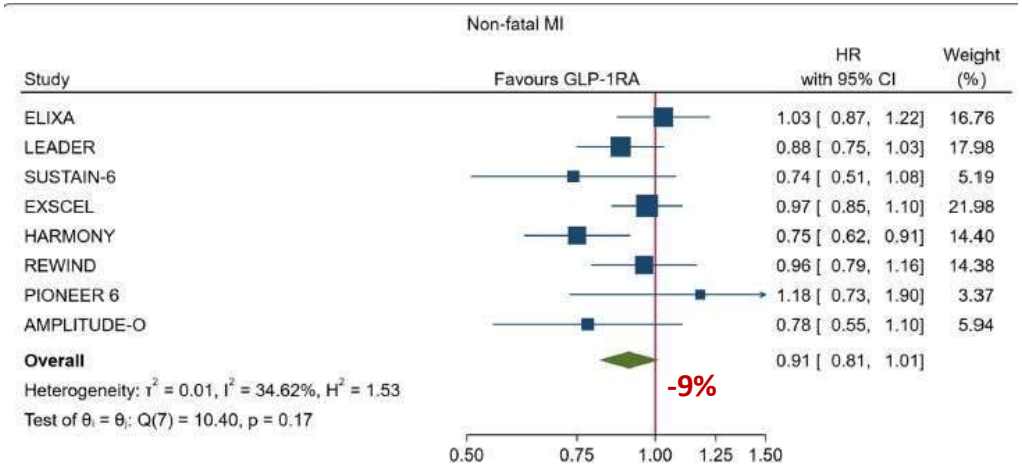
ORIGINAL INVESTIGATION Open Access

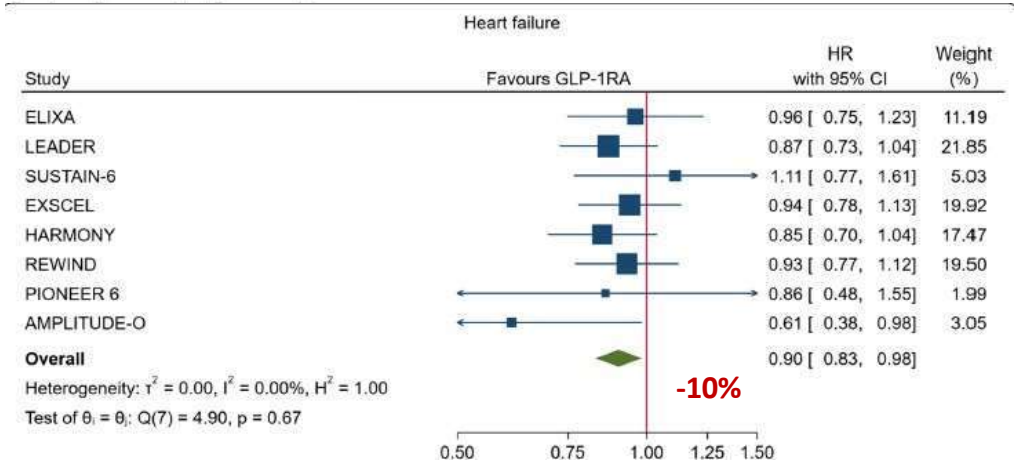
GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs

Dario Giugliano[1,2*†], Lorenzo Scappaticcio[1,2†], Miriam Longo[1,2†], Paola Caruso[1,2], Maria Ida Maiorino[3], Giuseppe Bellastella[1], Antonio Ceriello[4], Paolo Chiodini[5] and Katherine Esposito[2,3]

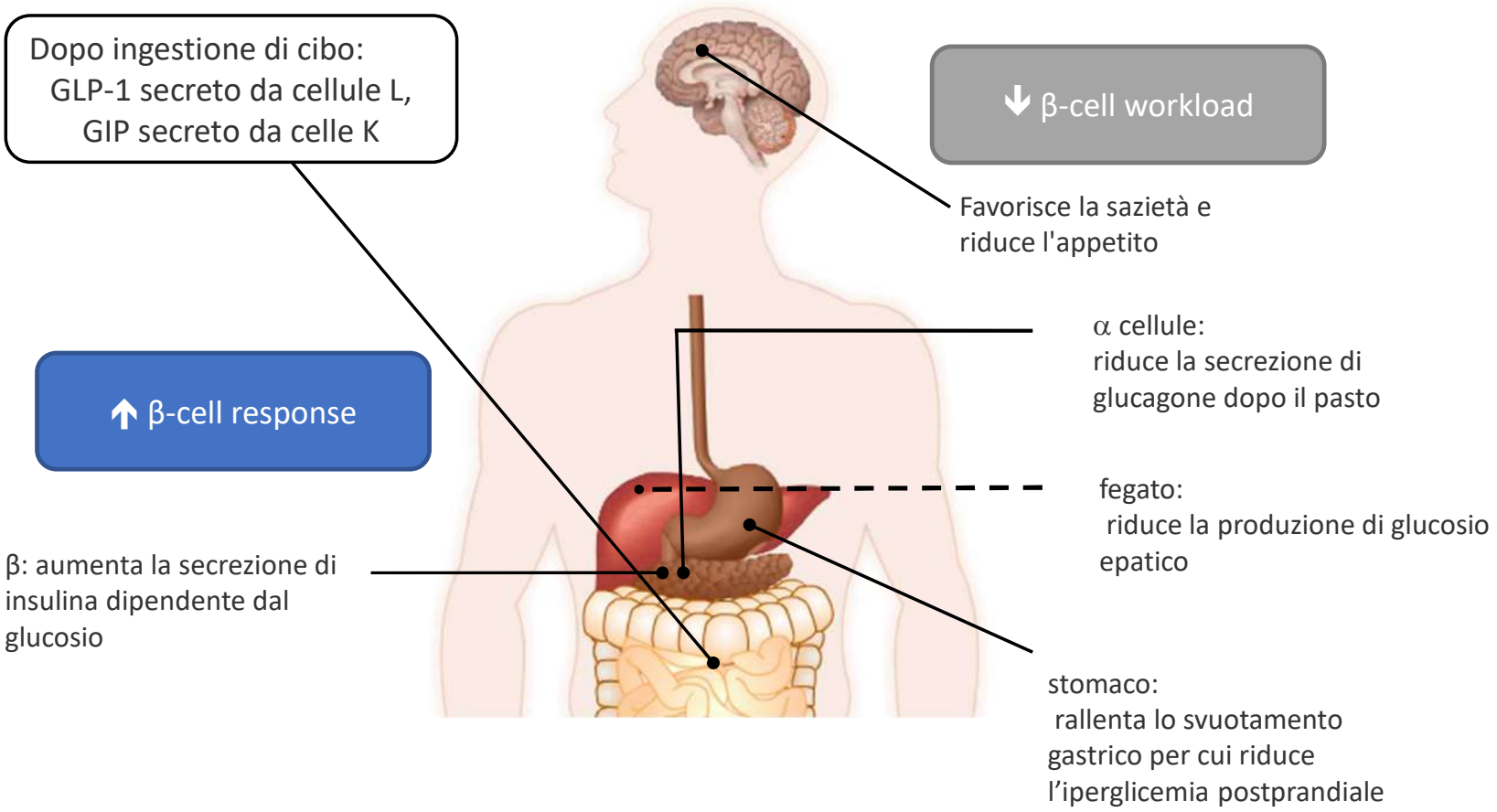








GLP-1 e GIP – Regolazione omeostasi glucidica



Can next generation incretin therapies combine GLP-1R and GIPR-mediated actions?

GLP-1 Receptor Agonism

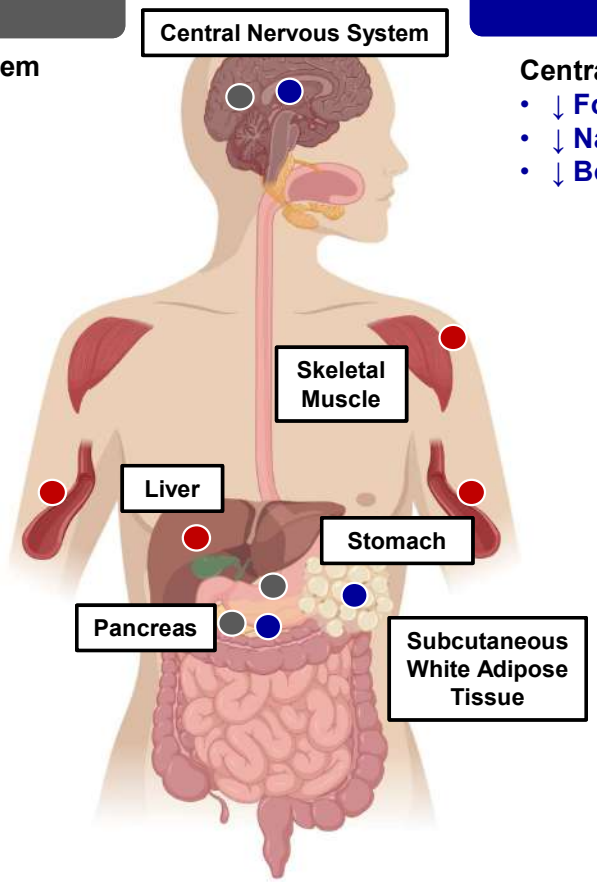
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation



- GLP-1 Receptor Agonism
- GIP Receptor Agonism
- Indirect Action

GIP Receptor Agonism

Central Nervous System
- ↓ Food intake
- ↓ Nausea
- ↓ Body weight

Pancreas
- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia, Dietary Triglyceride

Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation

Adapted from: Samms RJ, et al. *Trends Endocrinol Metab*. 2020;31(6):410-421

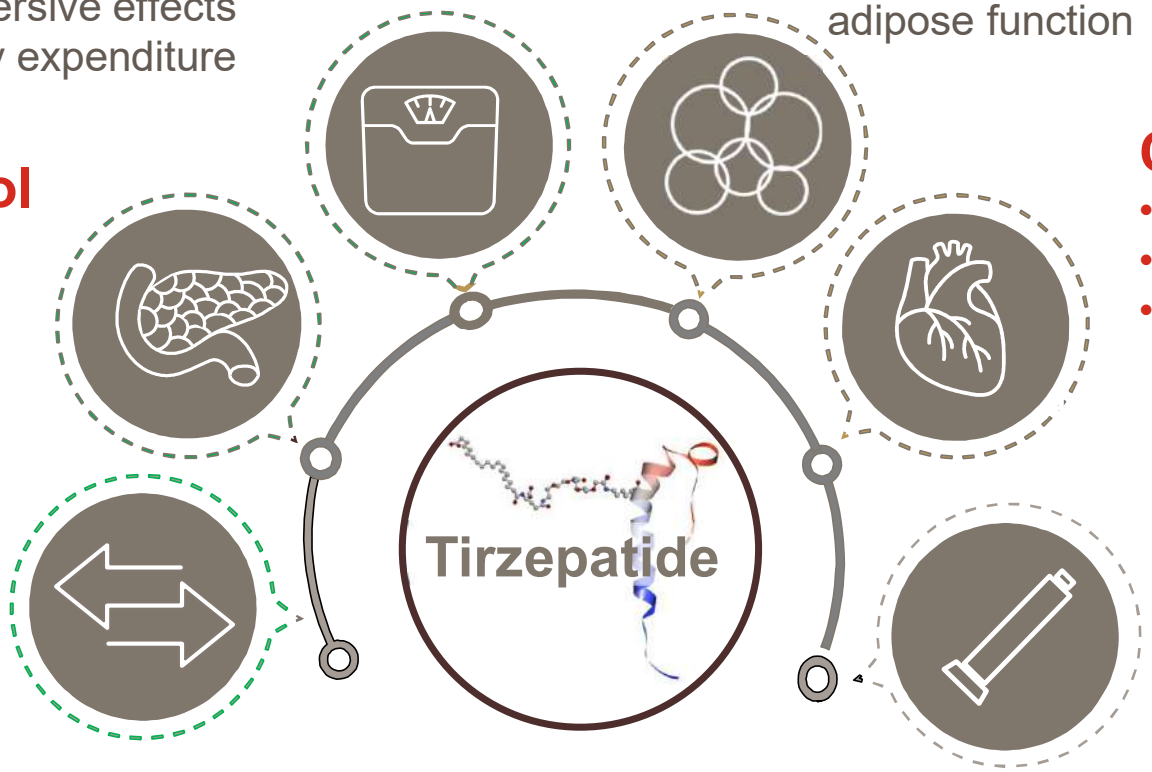
Tirzepatide

Weight loss
- Food intake
- Antiaversive effects
- Energy expenditure

Lipid metabolism
Lipid partitioning and adipose function

Glycemic control
- Insulin secretion
- Glucagon
- Insulin sensitivity

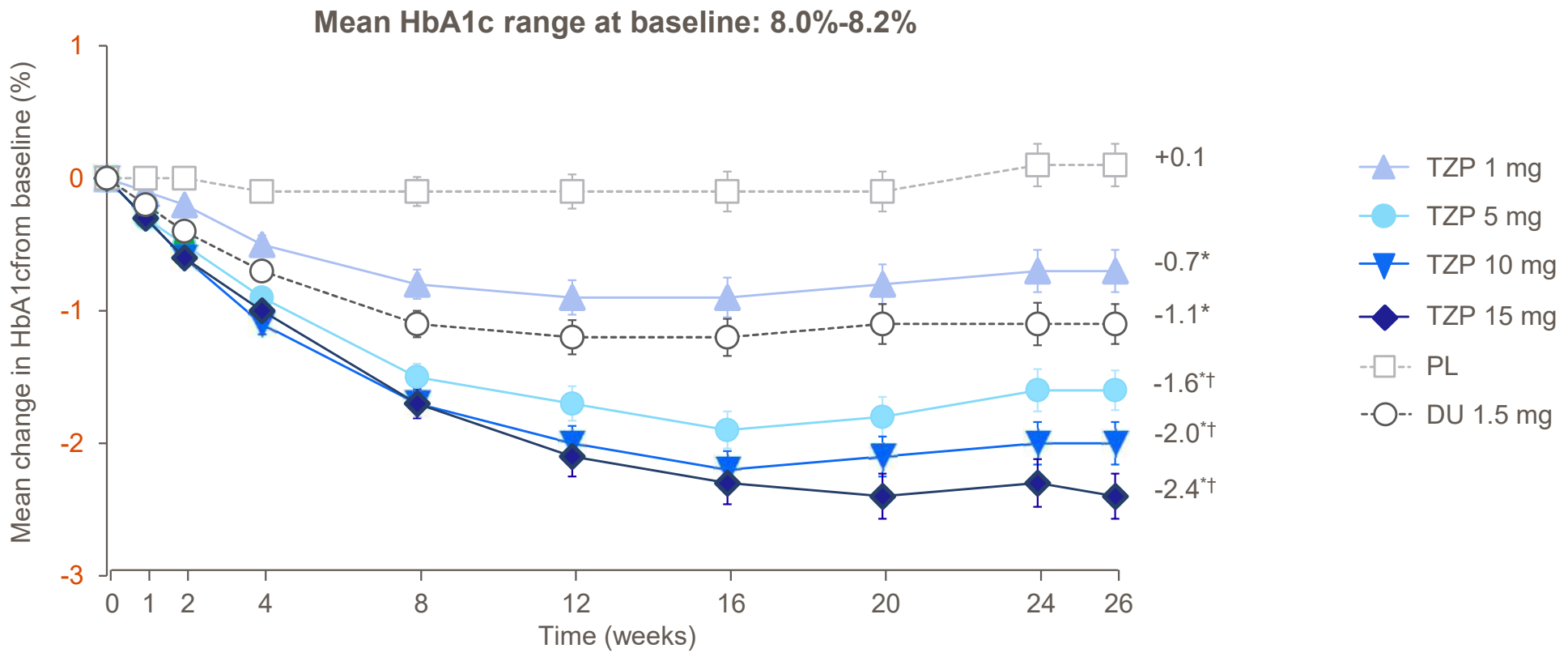
Cardiovascular
- Plasma lipid control
- Inflammation
- Endothelial function



Receptor pharmacology
Dual agonism

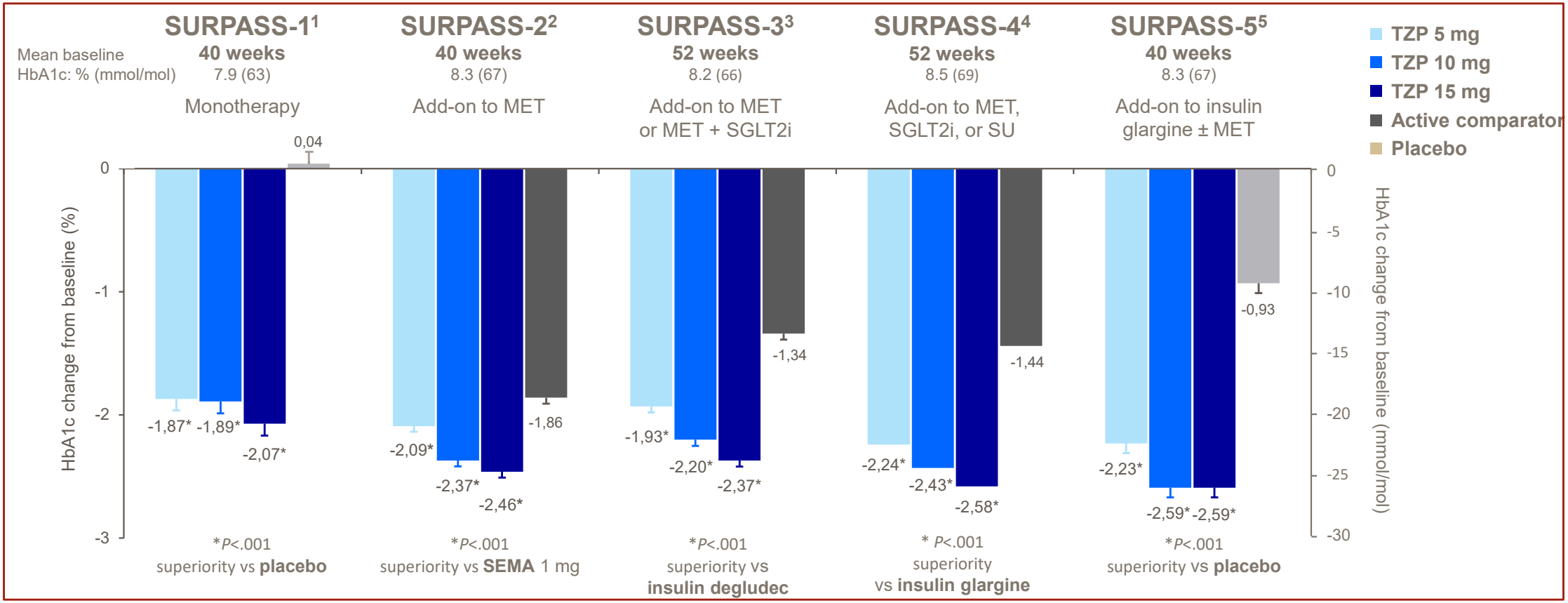
Dose escalation

Tirzepatide improves glycemic control vs selective GLP-1RA



MMRM analysis, mITT on-treatment population. Values reported are LSM (SE).
*P<.05 vs PL; †P<.05 vs DU 1.5 mg.
DU = dulaglutide; HbA1c = glycated hemoglobin; LSM = least-squares mean; mITT = modified intention-to-treat; MMRM = mixed model repeated measures; PL = placebo; TZP = tirzepatide.
Frias JP, et al. *Lancet.* 2018;392(10160):2180-2193.

HbA1c Reduction from Baseline to Primary Endpoint

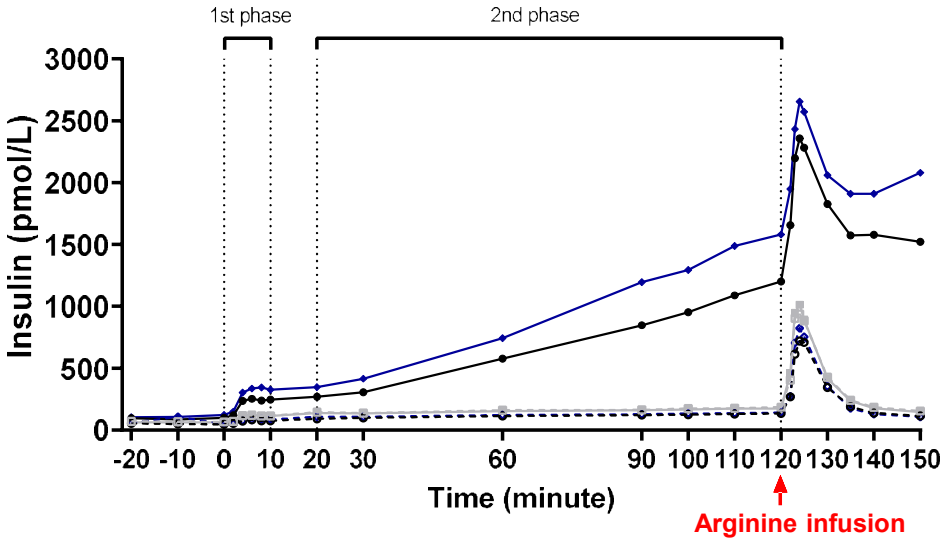


Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c.
HbA1c = glycated haemoglobin; LSM = least squares mean; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TZP = tirzepatide.

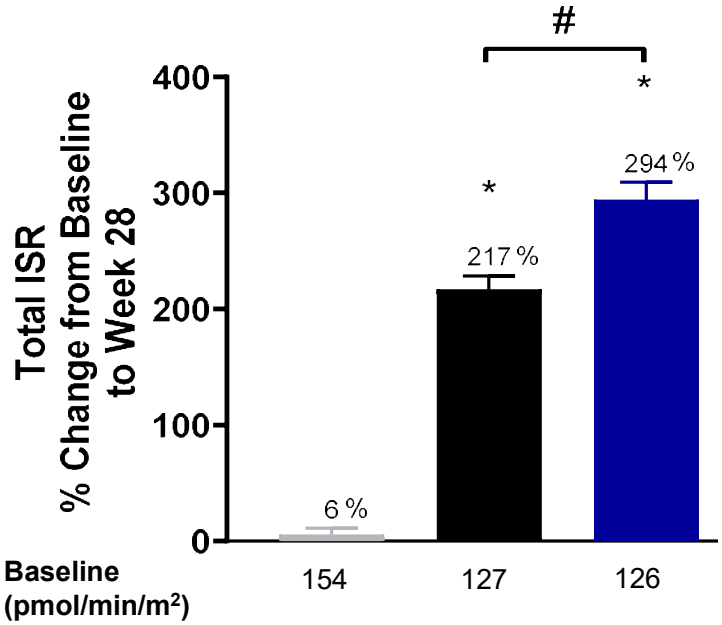
1Rosenstock J et al, *Lancet* 2021; Frias JP et al, *N Eng J Med* 2021; Ludvik B et al, *Lancet* 2021; Del Prato S et al, *Lancet* 2021; Dahl D et al, *JAMA* 2022

Insulin Secretion Rate: tirzepatide improves insulin secretion in T2D patients vs a selective GLP-1 agonist

Insulin concentrations during clamp



Total ISR (0-120 min)

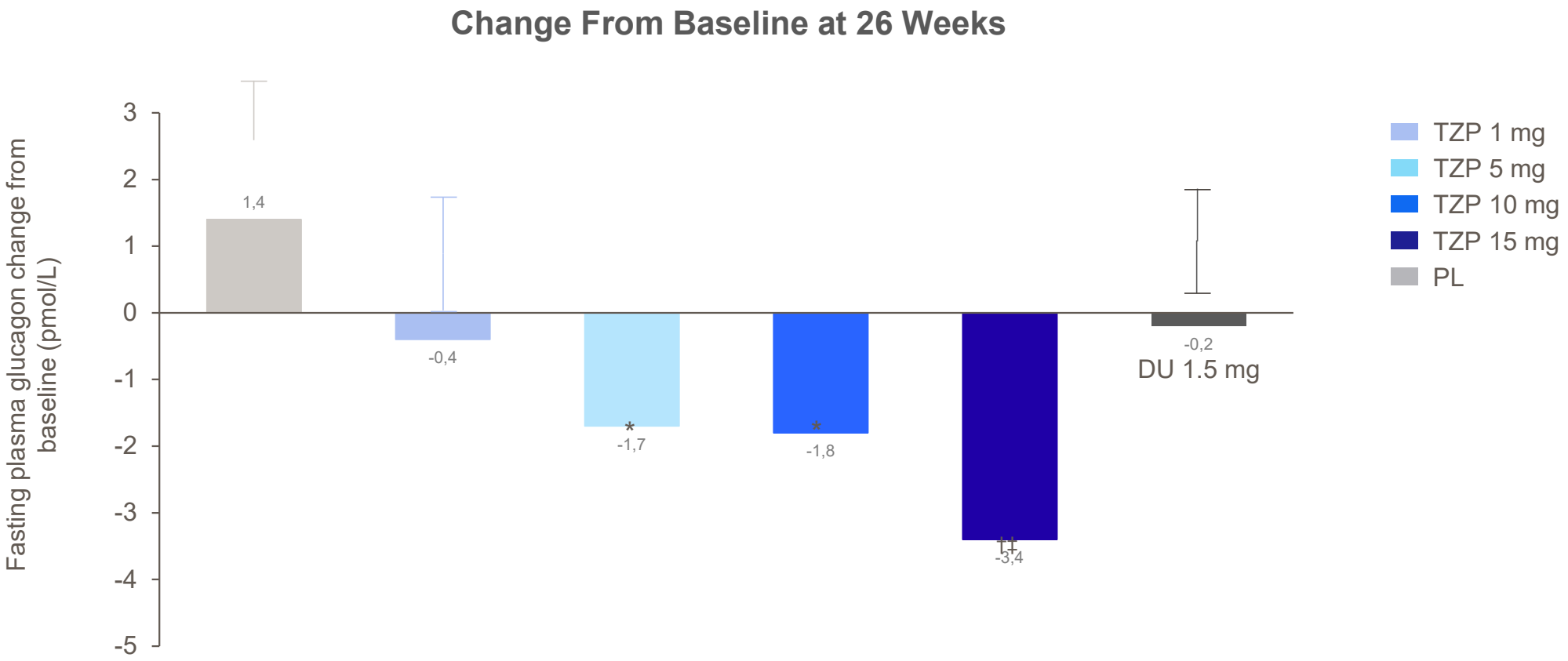


Placebo Semaglutide 1.0mg Tirzepatide 15mg

Dashed: baseline Solid: Week 28

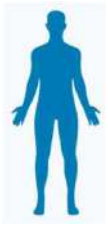
Left: Data are group averages. Dashed lines represent baseline values; solid lines represent Week 28 values. Arrow indicates a 5-gram intravenous arginine bolus was administered at 120 minutes.
Right: Data are estimates (with standard errors). *p<0.001 vs placebo, #p=0.003 tirzepatide vs semaglutide for ANCOVA on change from baseline. ANOVA (baseline). PD analysis set. *Heise T et al Lancet Diabetes Endocrine Org, 2022; 10:418/29*

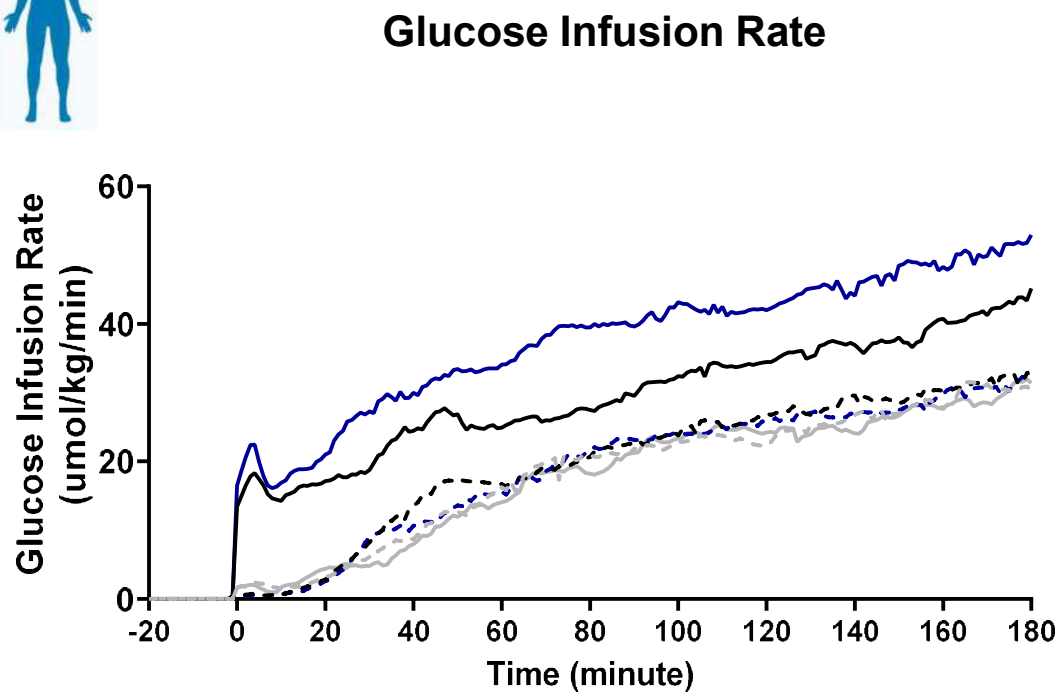
Tirzepatide Lowers Glucagon Levels in a Phase 2b Study

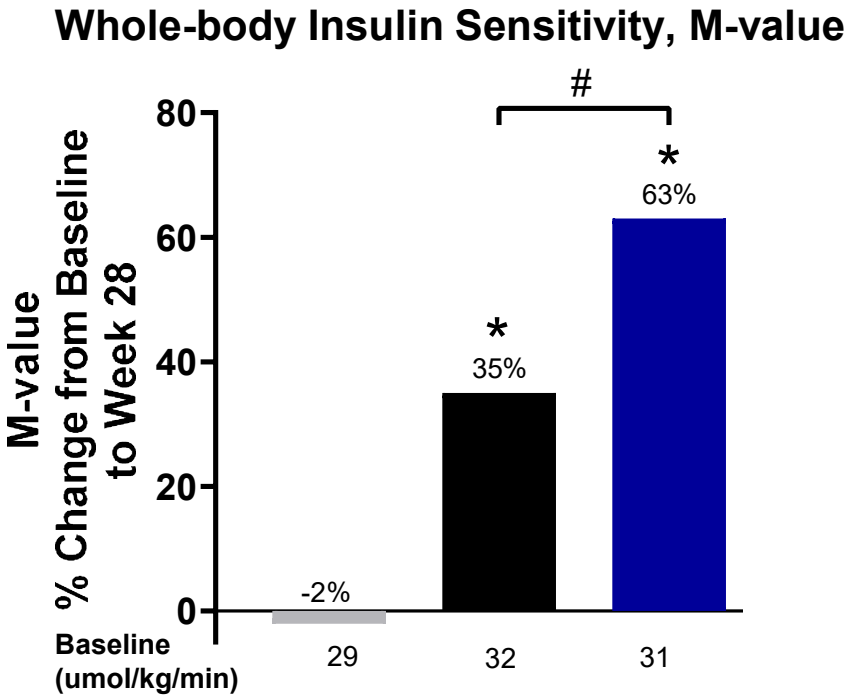


Data are LS mean (SE) from MMRM on treatment data analyses.
*P<.05 vs placebo; †P<.001 vs placebo; ‡P<.05 vs 1.5 mg dulaglutide.
DU = dulaglutide; MMRM = mixed model repeated measures; PL = placebo; TZP = tirzepatide.
Frias JP, et al. *Lancet.* 2018;392(10160):2180-2193.

Insulin sensitivity: tirzepatide improves insulin sensitivity in T2D patients vs a selective GLP-1 agonist (semaglutide)







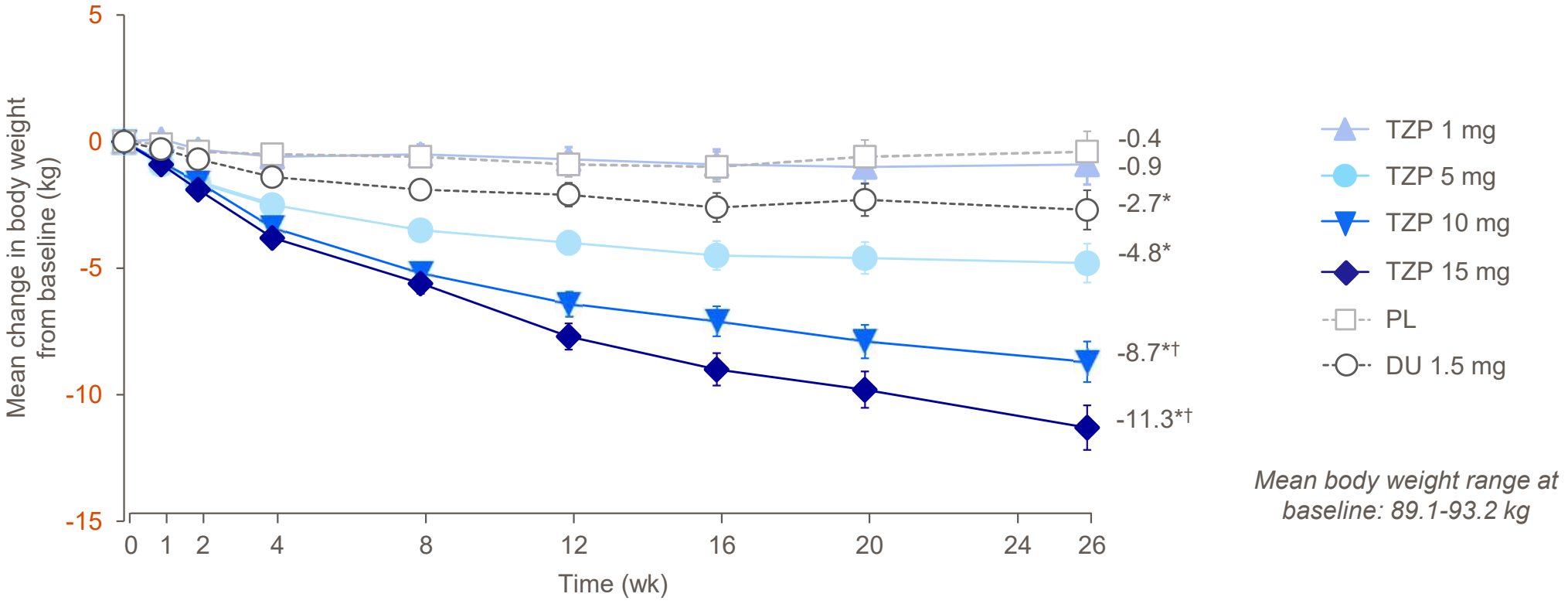
Placebo Semaglutide 1.0mg Tirzepatide 15mg

Dashed: baseline Solid: Week 28

Left: Data are group averages. Dashed lines represent baseline values; solid lines represent Week 28 values. Right: estimates. *p<0.001 vs placebo, #p=0.003 tirzepatide vs semaglutide for ANCOVA on change from baseline. ANOVA (baseline). PD analysis set.

Heise T et al Lancet Diabetes Endocrine Org, 2022; 10:418/29

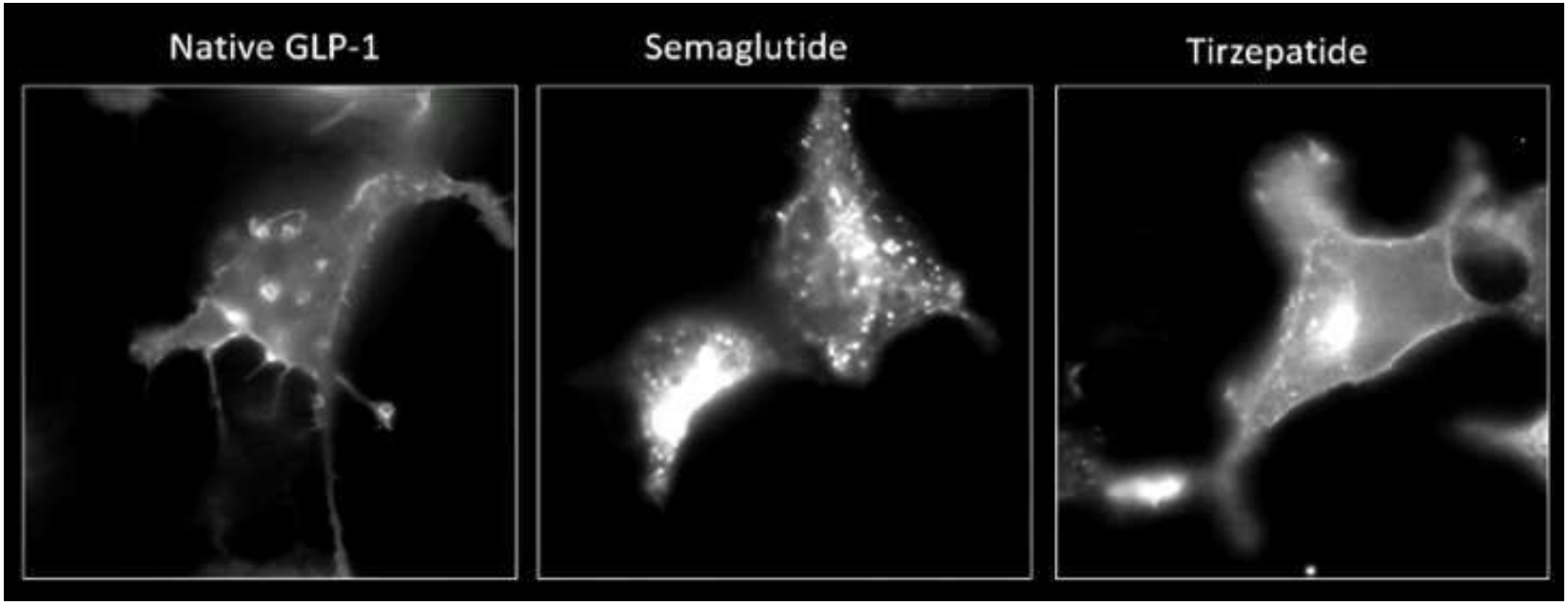
Tirzepatide reduces body weight vs selective GLP1-RA



Mean body weight range at baseline: 89.1-93.2 kg

MMRM analysis, mITT on-treatment population. Values reported are LSM (SE).
*P<.05 vs PL; †P<.05 vs DU 1.5 mg.
DU = dulaglutide; HbA1c = glycated hemoglobin; LSM = least-squares mean; mITT = modified intention-to-treat; MMRM = mixed model repeated measures; PL = placebo; TZP = tirzepatide.
Frias JP, et al. *Lancet.* 2018;392(10160):2180-2193.

Tirzepatide causes faster recycling of internalizaed GLP-1R



GLP-1 and semaglutide cause internalization of GLP-1 receptor → limits the effect

TZP increases membrane GLP-1 receptor → potentiates the effect

Mol Metab. 2021 Jul;49:101181

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

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

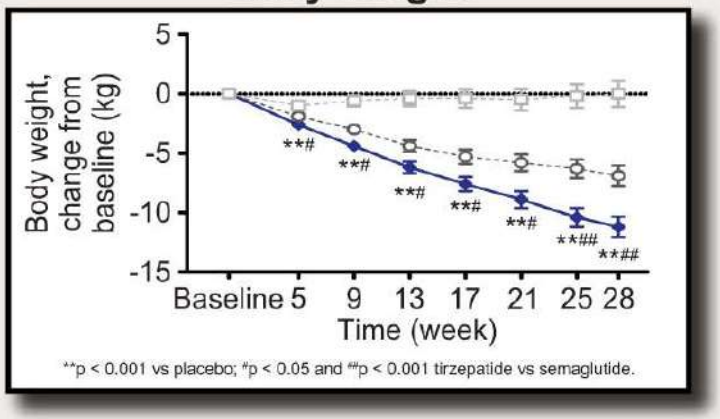
Placebo
(n = 28)

Semaglutide 1 mg
(n = 45)

Tirzepatide 15 mg
(n = 48)

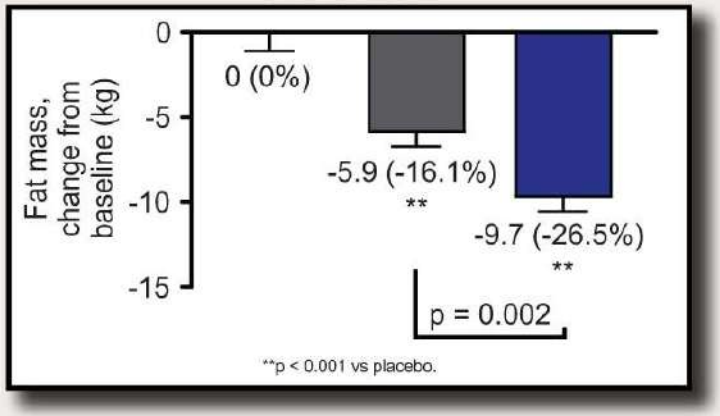
Tirzepatide led to significant improvements over semaglutide and placebo on body weight and fat mass.

Body weight



**p < 0.001 vs placebo; #p < 0.05 and ##p < 0.001 tirzepatide vs semaglutide.

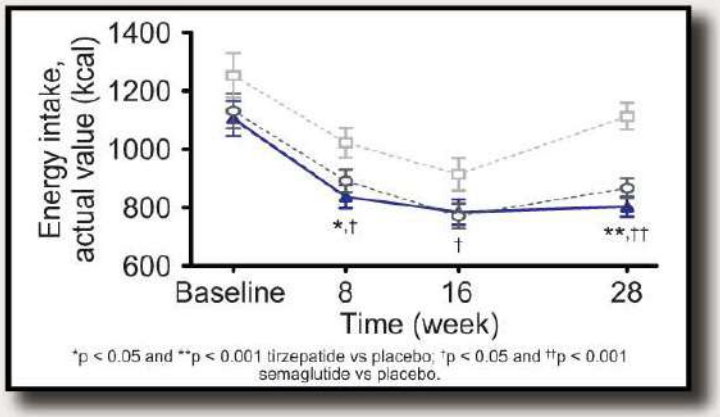
Fat mass



**p < 0.001 vs placebo.

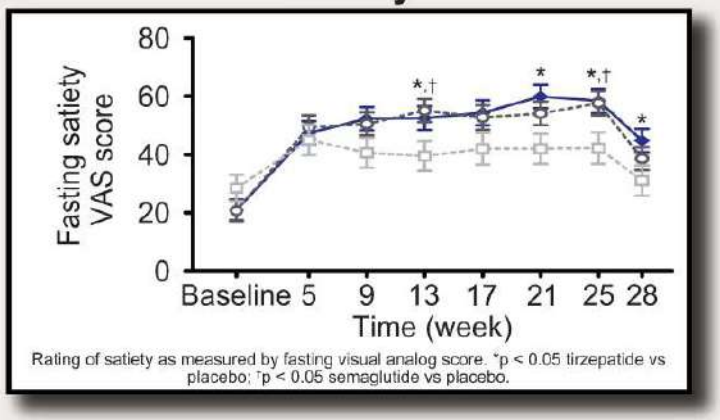
Tirzepatide and semaglutide similarly reduced fasting appetite and energy intake during *ad libitum* lunch.

Calorie intake



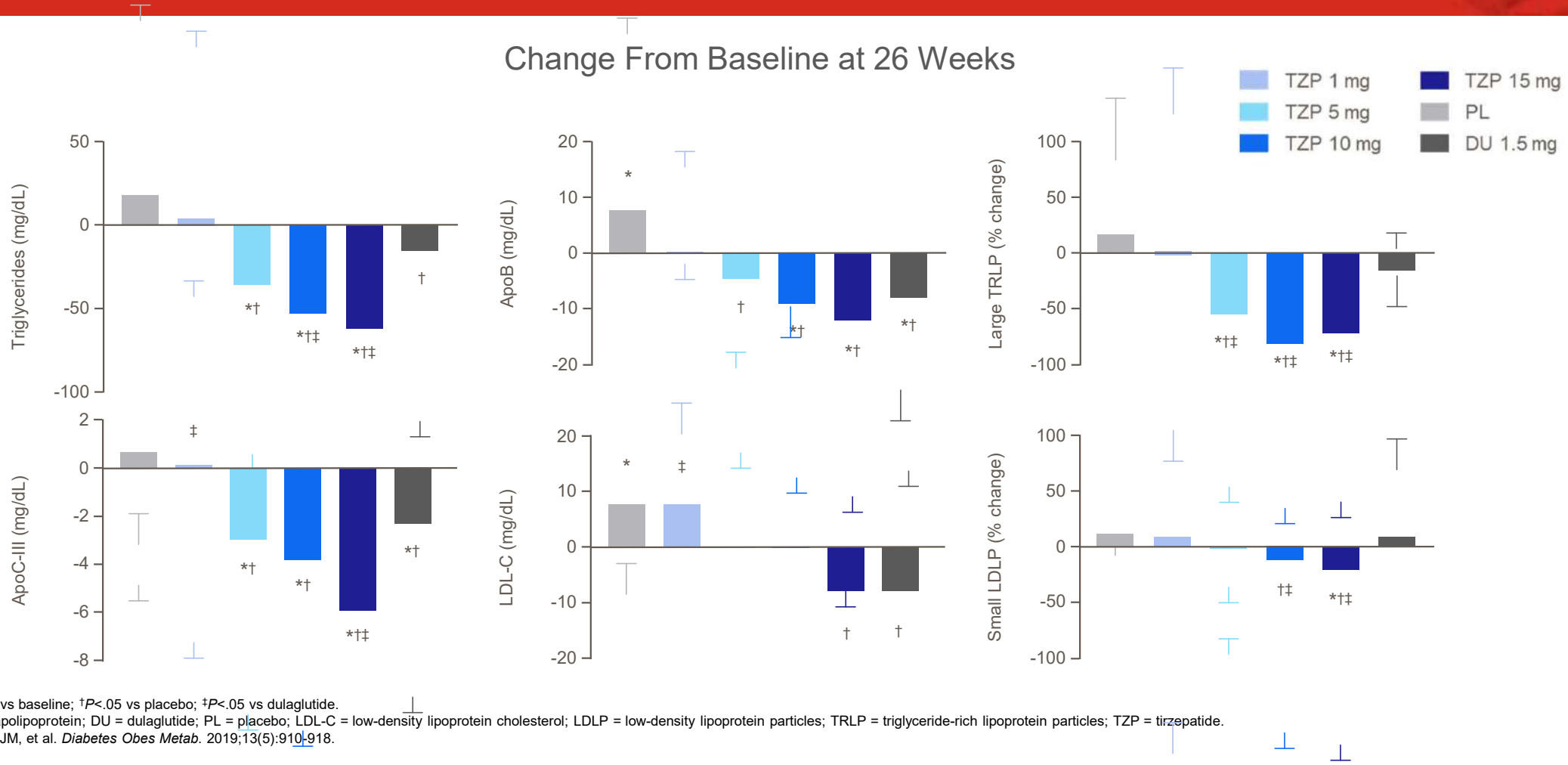
*p < 0.05 and **p < 0.001 tirzepatide vs placebo; †p < 0.05 and ††p < 0.001 semaglutide vs placebo.

Satiety



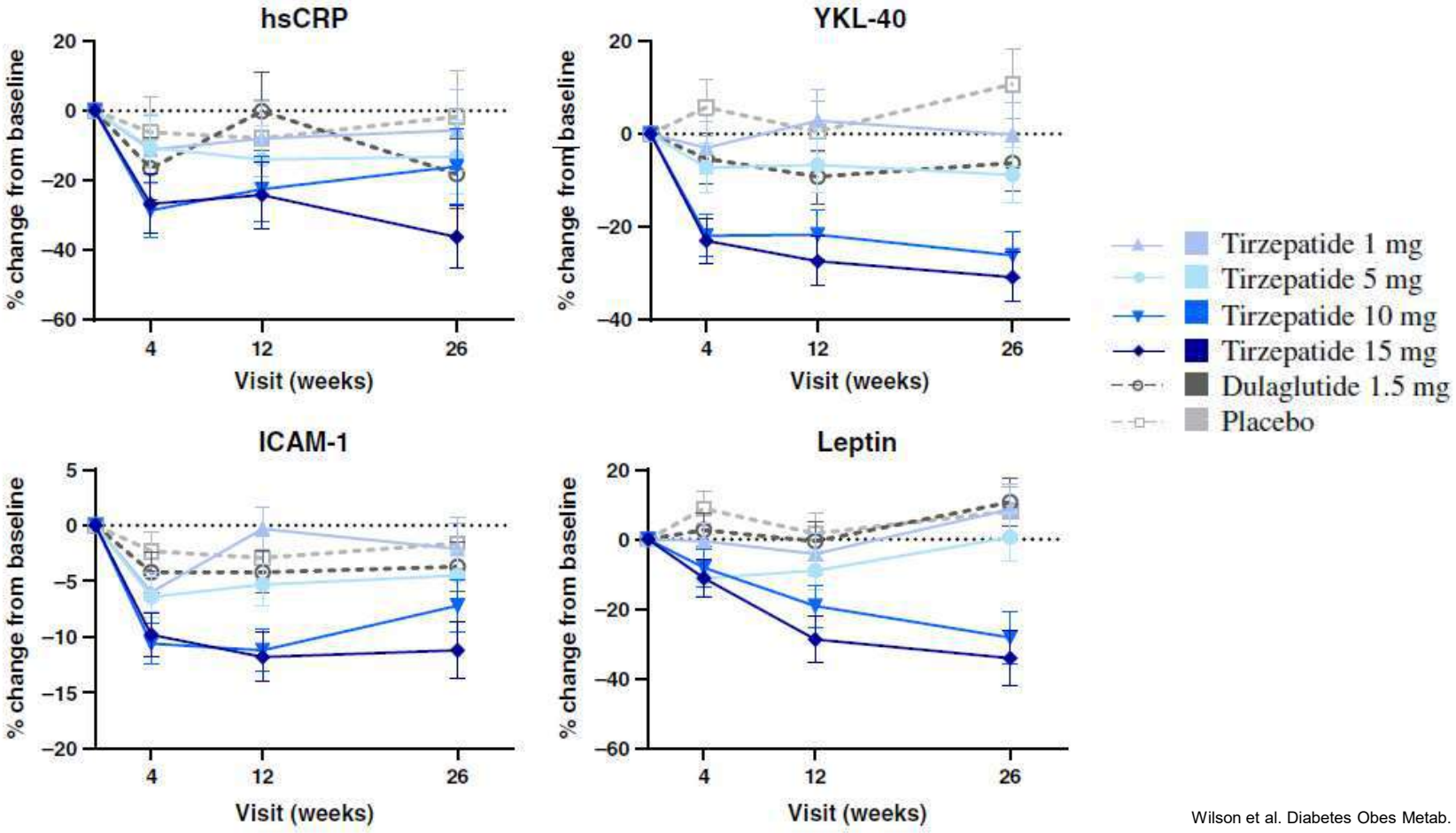
Rating of satiety as measured by fasting visual analog score. *p < 0.05 tirzepatide vs placebo; †p < 0.05 semaglutide vs placebo.

Tirzepatide improves lipid biomarkers in phase II study



*P<.05 vs baseline; †P<.05 vs placebo; ‡P<.05 vs dulaglutide.
apo = apolipoprotein; DU = dulaglutide; PL = placebo; LDL-C = low-density lipoprotein cholesterol; LDLP = low-density lipoprotein particles; TRLP = triglyceride-rich lipoprotein particles; TZP = tirzepatide.
Wilson JM, et al. *Diabetes Obes Metab*. 2019;13(5):910-918.

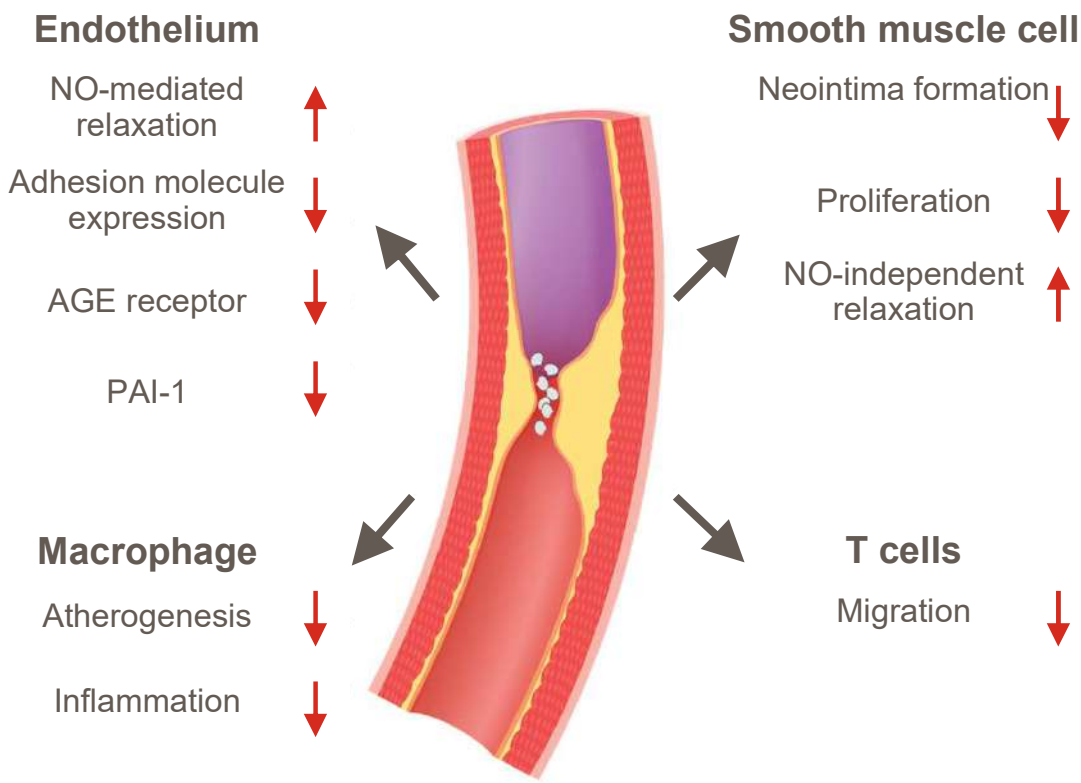
Tirzepatide improves inflammatory biomarkers in phase 2 study



Wilson et al. Diabetes Obes Metab. 2021;1–6.

Vascular Protective Effects of GLP-1 and GIP

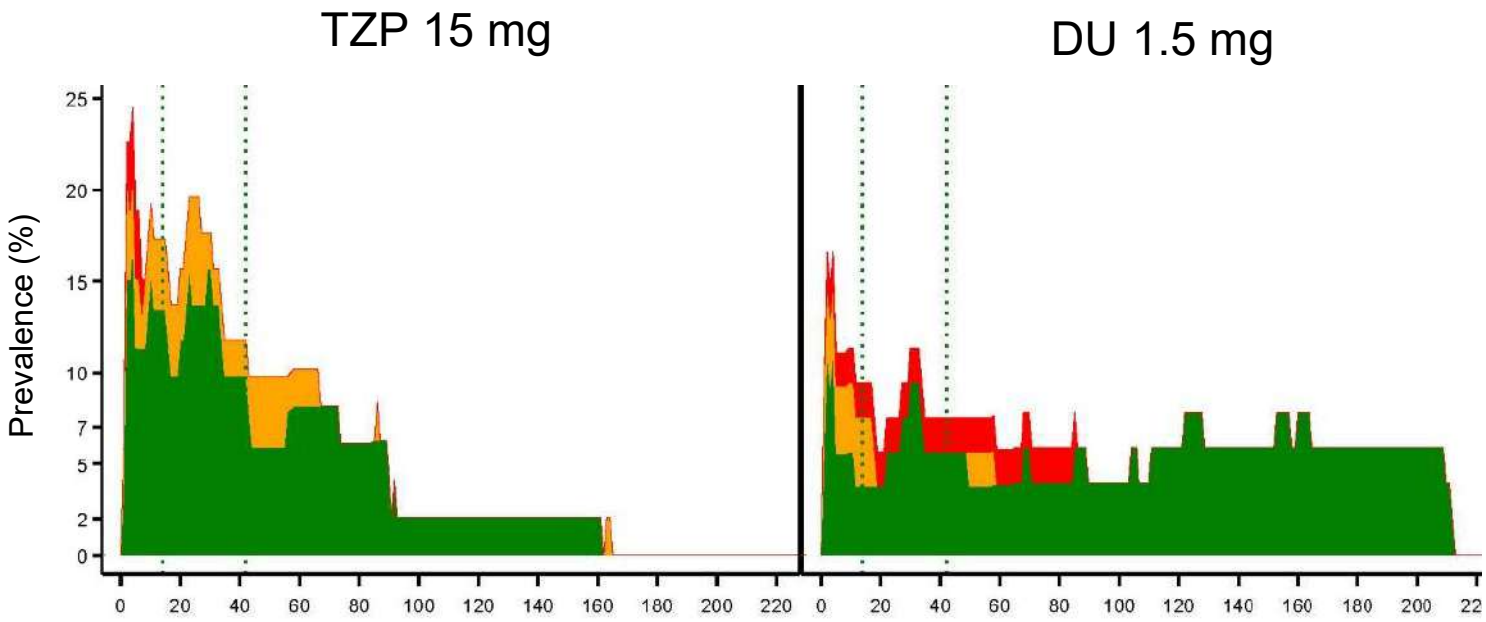
- Long-acting GLP-1RAs have demonstrated benefit in large CVOTs in humans[1]
- Preclinical research suggests a similar mechanistic role for GLP-1 and GIP in vascular biology[2,3]
- Preclinical data suggest that GLP-1 and GIP have beneficial effects on the vasculature[2,3]
- The clinical relevance of these effects, particularly for GIP, will be evaluated in the tirzepatide CVOT



AGE = advanced glycation end product; CVOT = cardiovascular outcomes trial; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; GLP-1RA = glucagon-like peptide-1 receptor agonist; NO = nitric oxide; PAI = plasminogen activator inhibitor.

1. American Diabetes Association. *Diabetes Care*. 2021;44(suppl 1):S1-S232. 2. Lehrke M, Marx N. *Rev Diabet Stud*. 2011;8(3):382-391. 3. Mori Y, et al. *Int J Mol Sci*. 2020;21(4):1509.

Prevalence and severity of nausea over time

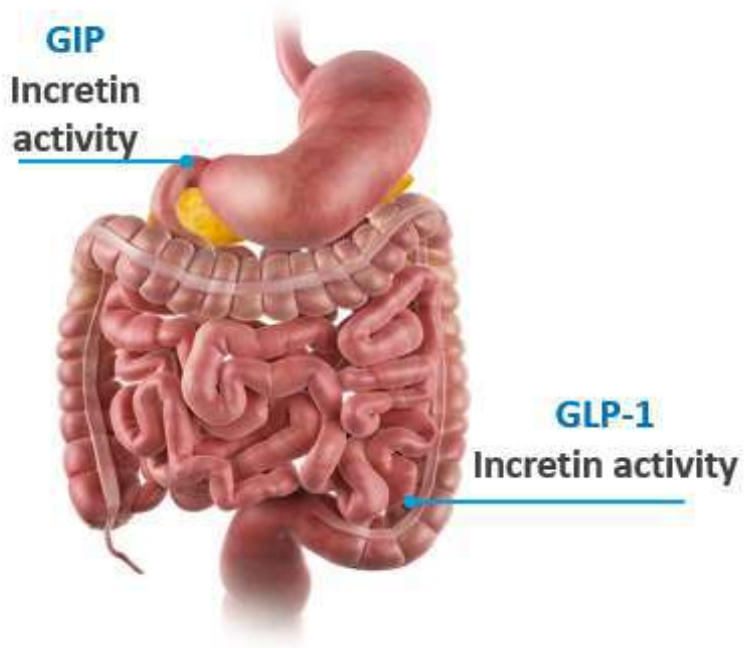


- The majority gastrointestinal AEs with tirzepatide treatment were mild to moderate in intensity and transient
- Despite significantly increased efficacy, GI AEs with tirzepatide 15 mg were comparable overtime to dulaglutide 1.5mg

.Frias JP, et al. *Lancet.* 2018;392(10160):2180-2193.

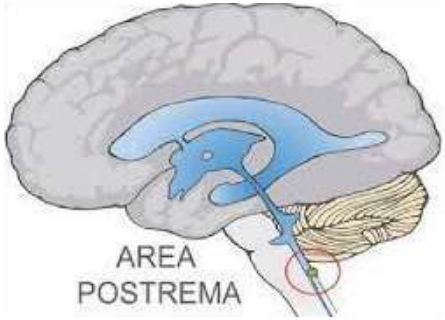
Why an increase in efficacy does not produce the same increase in GI adverse events?

Hormone site of production may impact differently gastric emptying



1. Aronoff SL, et al. Diabetes Spectr. 2004;17(3):183-190.
2. .Nauck Lancet Diabetes Endocrinol2016 Jun;4(6):525-36.
3. Kim W, Egan JM. Pharmacol Rev. 2008;60(4):470-512.
4. Gasbjerg L S et al Peptides. 2020 Mar;125:170183.

GIP receptor agonism attenuates GLP-1 - induced nausea and emesis



The area postrema and nucleus tractus solitaries

- Regulates food intake
- Mediates body weight suppression by GLP-1RA
- Contains different cells expressing GIPR and GLP1R
- GIPR is expressed on GABAergic neurons

Other AEs

Pancreatitis

- 4 adjudication-confirmed cases of pancreatitis were reported with TZP (10 mg, n=2; 15 mg n=2) across the SURPASS clinical trial programme, but none of the events were serious[1-4]

Antidrug antibodies

- There was no evidence of a diminished effect of TZP in TZP pharmacokinetics or HbA1c (SURPASS-1)
  - None of the treatment-emergent antidrug antibody-positive participants experienced severe or serious hypersensitivity or injection-site reactions[1]

Medullary thyroid carcinoma

- No clinically relevant changes in mean calcitonin concentrations were observed, and no cases of medullary thyroid cancer were reported*[,1-3]

Diabetic retinopathy

- Cases of treatment-emergent diabetic retinopathy were reported in SURPASS-2 (n=2) and SURPASS-3 (n=3)*[,1-3]

*These results do not yet include data from the SURPASS-4 or SURPASS-5 clinical trials.
HbA1c = glycated haemoglobin; TZP = tirzepatide.
1. Rosenstock J, et al. *Lancet*. Published online June 26, 2021. 2. Frias JP, et al. *N Engl J Med*. Published online June 25, 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

Maneggevolezza

Controllo glicemico

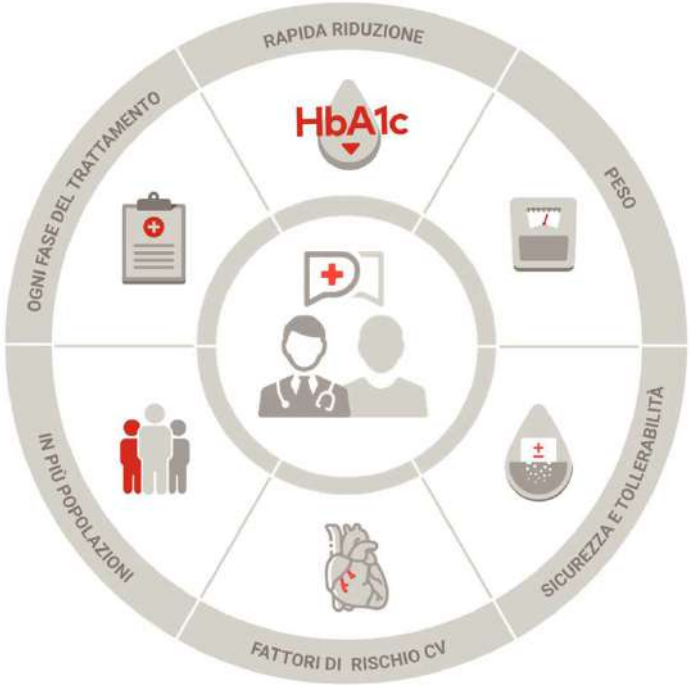
- Fino a **9 pazienti su 10** raggiungono il target raccomandato dalle linee guida internazionali di HbA1c<7%
- **Rapida riduzione dell'HbA1c** già dopo 4 settimane
- **Persistenza** fino a 104 settimane
- **Efficacia superiore** sin dal dosaggio più basso (5 mg) rispetto a GLP- 1 RAs

Peso

- **Calo ponderale dipendente dal BMI iniziale**
- **8 pazienti su 10** raggiungono almeno il 5% di riduzione del peso come raccomandato da linee guida internazionali

Fattori di rischio CV

- **Riduce la pressione arteriosa sistolica** fino a -12,6 mmHg e la **diastolica** fino a -4,5 mmHg
- **Migliora il profilo lipidico**, riducendo trigliceridi e colesterolo VLDL e aumentando il colesterolo HDL
- **Riduce la circonferenza vita**
- **Riduce il grasso intraepatico**



Sicurezza e tollerabilità

- **Minimo rischio di ipoglicemia**
- **Profilo di tollerabilità più vantaggioso rispetto ai GLP1-RAs** al dosaggio di 5 mg
- **Tollerabilità simile** ai GLP-1 RAs, nonostante la maggiore efficacia
- **Gli effetti avversi gastrointestinali sono transitori, di entità da lieve a moderata** e si verificano soprattutto quando si aumenta il dosaggio

Ogni fase del trattamento

- Possibilità di **impiego in diversi momenti dell'evoluzione della malattia** e **in combinazione con differenti regimi terapeutici**

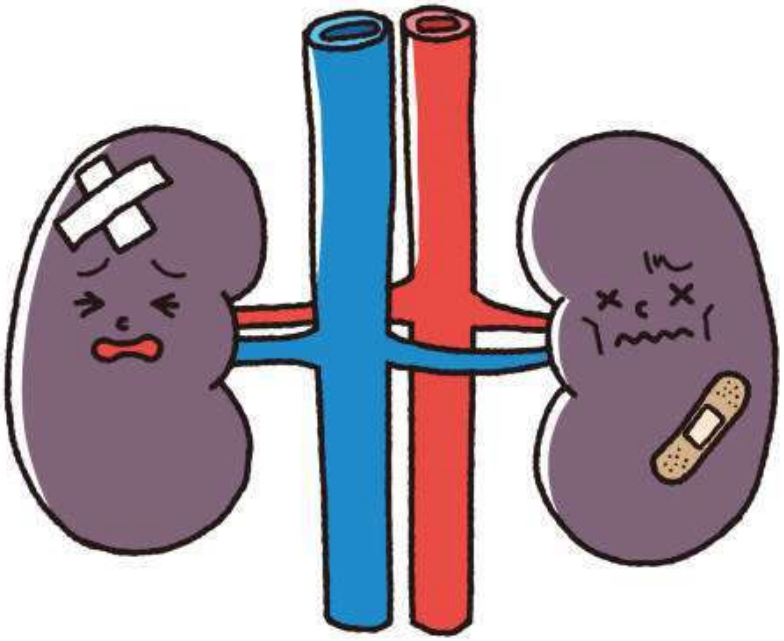
In più popolazioni

- **Non è necessario aggiustare la dose** sulla base di età, genere, razza, etnia o peso corporeo
- **Possibilità di scegliere tra i dosaggi quello** più adeguato in base agli obiettivi terapeutici

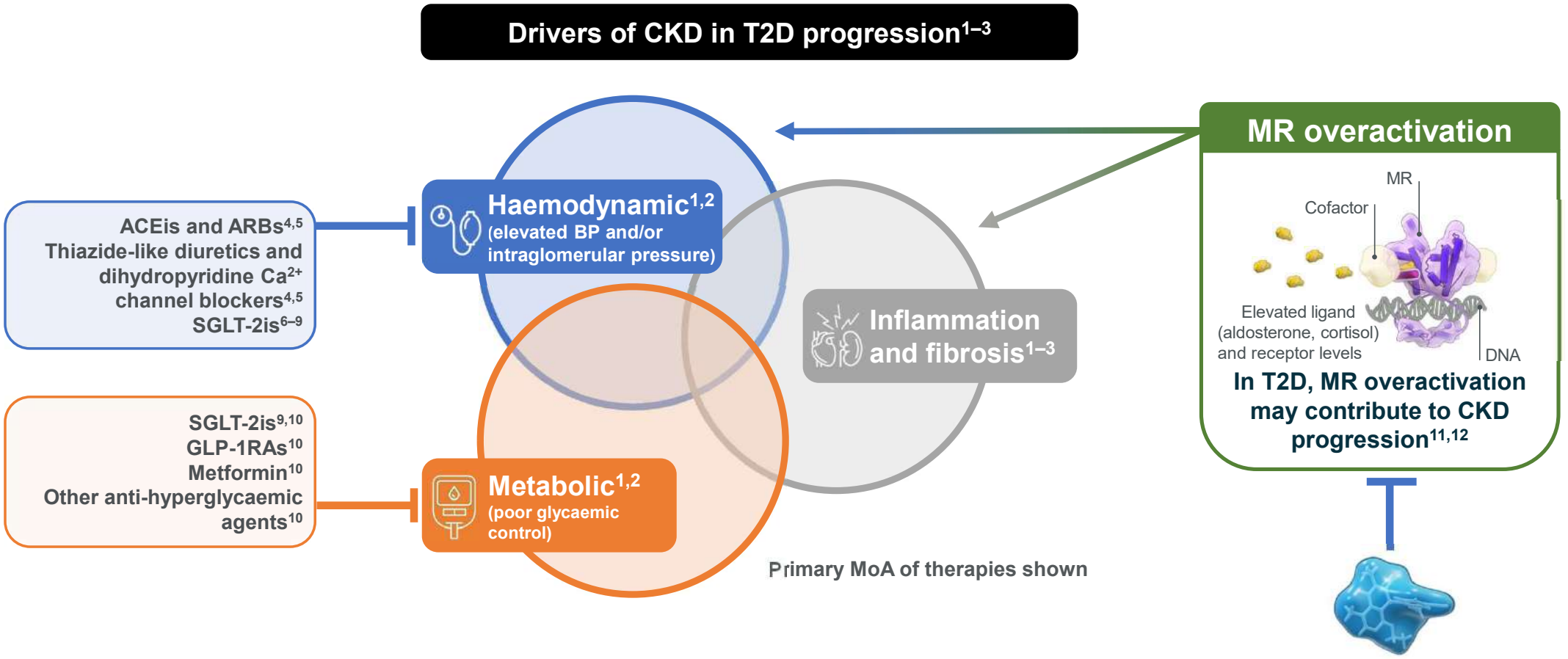
Rosenstock J et al, Lancet 2021; Frias JP et al, N Eng J Med 2021; Ludvik B et al, Lancet 2021; Del Prato S et al, Lancet 2021; Dahl D et al, JAMA 2022; RCP Tirzepatide 2022

Whath else ?

Mineralocorticoid receptor in CKD and T2D



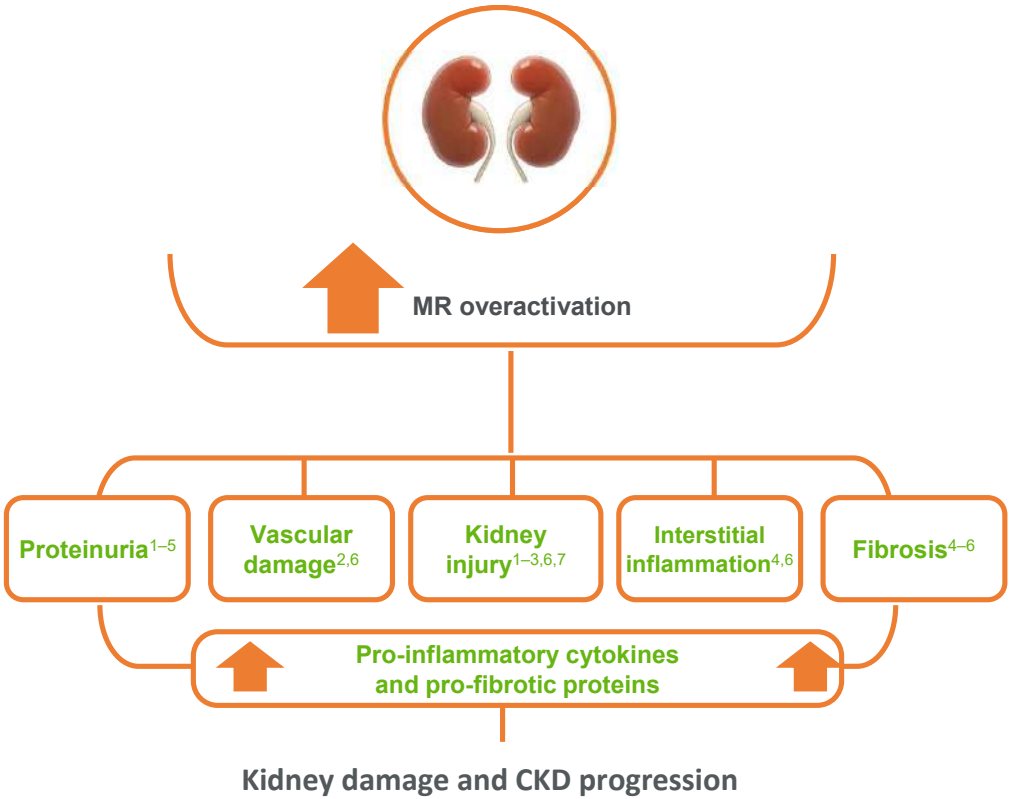
CKD in T2D progression is driven by the combined effects of metabolic, haemodynamic and inflammatory and fibrotic factors

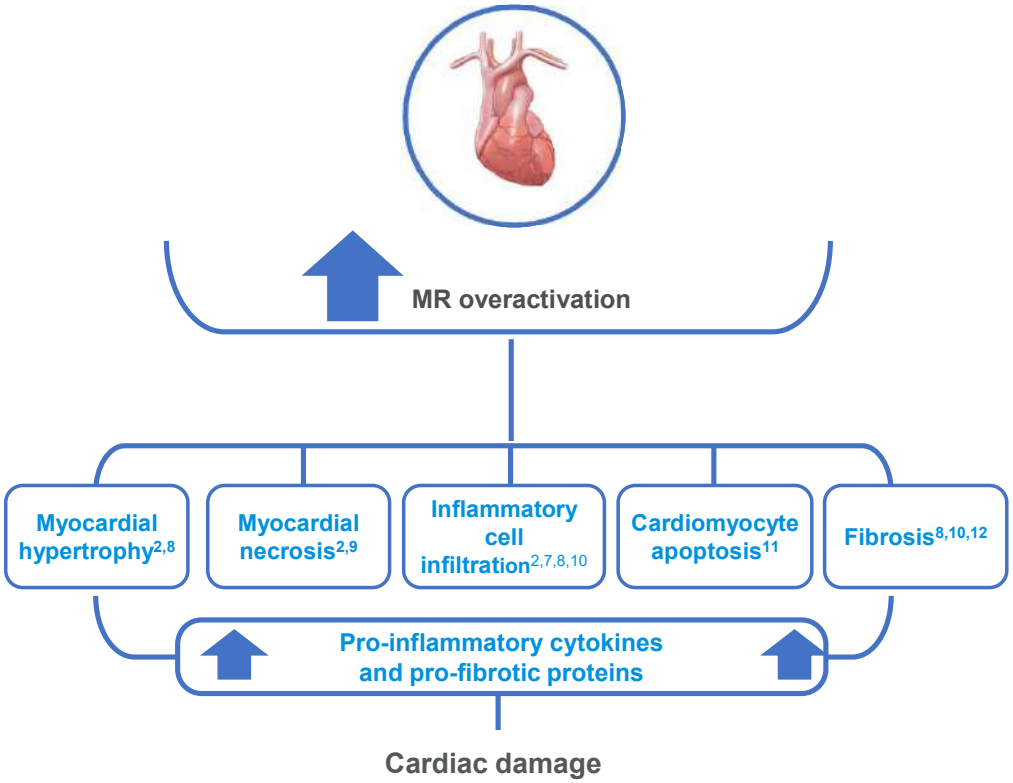


BP, blood pressure; GLP-1RA, glucagon-like peptide-1 receptor agonist; MoA, mechanism of action

1. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Mora-Fernández C, *et al. J Physiol* 2014;18:3997; 3. Bauersachs J, *et al. Hypertension* 2015;65:257–263;
4. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S175–S184; 5. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S144–S174;
6. Kidokoro K, *et al. Circulation* 2019:140;303–315; 7. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2018;72:1845–1855; 8. Heerspink HJ, *et al. Circulation* 2016;134:752–772; 9. Zelniker TA & Braunwald E. J *Am Coll Cardiol* 2020;75:422–434; 10. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S125–S143;
11. Agarwal R, *et al. Eur Heart J* 2021;42:152–162; 12. Agarwal R, *et al. Nephrol Dial Transplant* 2022;37:1014–1023

MR overactivation is thought to be a major driver of end-organ damage through inflammation and fibrosis in preclinical animal models





Evidence cited is based on data from preclinical animal models

1. Brown NJ, *et al. Kidney Int* 2000;58:1219–1227; 2. Rocha R, *et al. Endocrinology* 2000;141:3871–3878; 3. Shibata S, *et al. Hypertension* 2007;49:355–364;
4. Siragy HM & Xue C. *Exp Physiol* 2008;93:817–824; 5. Nishiyama A, *et al. Hypertension* 2004;24:841–848; 6. Blasi ER, *et al. Kidney Int* 2003;63:1791–1800; 7. Ma J, *et al. Kidney Int* 2006;69:1064–1072;
8. Yoshida K, *et al. Hypertension Res* 2005;28:447–455; 9. Rocha R, *et al. Am J Physiol Heart Circ Physiol* 2002;283:H1802–H1810; 10. Sun Y, *et al. Am J Path* 2002;161:1773–1781;
11. De Angelis N, *et al. J Mol Cell Cardiol* 2002;34:1655–1665; 12. Shen JZ, *et al. Endocrinology* 2016;157:3213–3223

Finerenone reducing **kidney failure and disease progression** in patients with CKD and T2D

Finerenone reducing **cardiovascular mortality and morbidity** in patients with CKD and T2D

Summary of Recommendations of Finerenone use in the management of CKD in T2D

Scientific Society	Year	Recommendation	Grade
American Diabetes Association	2023	For people with type 2 diabetes and chronic kidney disease with albuminuria treated with maximum tolerated doses of ACE inhibitor or angiotensin receptor blocker, addition of finerenone is recommended to improve cardiovascular outcomes and reduce the risk of chronic kidney disease progression	A
		In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m2) additionally for cardiovascular risk reduction	A
		In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events	A
American Diabetes Association & KDIGO consensus	2022	A nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) with proven kidney and cardiovascular benefit is recommended for patients with T2D, eGFR ≥25 mL/min/1.73m2, normal serum potassium concentration, and albuminuria (albumin-to-creatinine ratio [ACR] ≥30 mg/g) despite maximum tolerated dose of renin-angiotensin system (RAS) inhibitor	-
KDIGO	2022	We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min per 1.73 m2, normal serum potassium concentration, and albuminuria (≥30 mg/g [≥3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor [recommendation 1.4.1]	2A
AACE American Association of Clinical Endocrinology	2022	A non-steroidal mineralocorticoid receptor antagonist (finerenone) with proven kidney and CVD benefit is recommended for persons with T2D, an eGFR ≥25 mL/min/1.73 m2, normal serum potassium concentration, and albuminuria (ACR ≥30 mg/g) despite a maximum tolerated dose of a renin-angiotensin system inhibitor [recommendation 6.6]	1A

1. De Boer HI et al., *Diabetes Care* 2022; DOI: 10.2337/dci22-0027; 2. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease, *Kidney Int* 2022; 102(55); 3. American Diabetes Association Professional Practice Committee, *Diabetes Care* 2023;46(1); https://doi.org/10.2337/dc23-S011; 4. Blonde L et al., Endocrine Practice 2022;28(10):923-1049; https://doi.org/10.1016/j.eprac.2022.08.002

Grazie per l'attenzione !