La tirzepatide come nuova prospettiva terapeutica

Massimiliano Anzaldi
U.O.C. Malattie Endocrine
A.O.E. Cannizzaro
Catania

DISCLOSURE FORM

Ai sensi dell'art. 76 sul Conflitto di Interessi, pag. 34 dell'Accordo Stato-Regioni del 2 febbraio 2017, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

- Astra Zeneca
- Ely Lilly
- Novo Nordisk
- MSD
- Abbott
- Boeringher-Ingelheim
- Menarini
- Sanofi

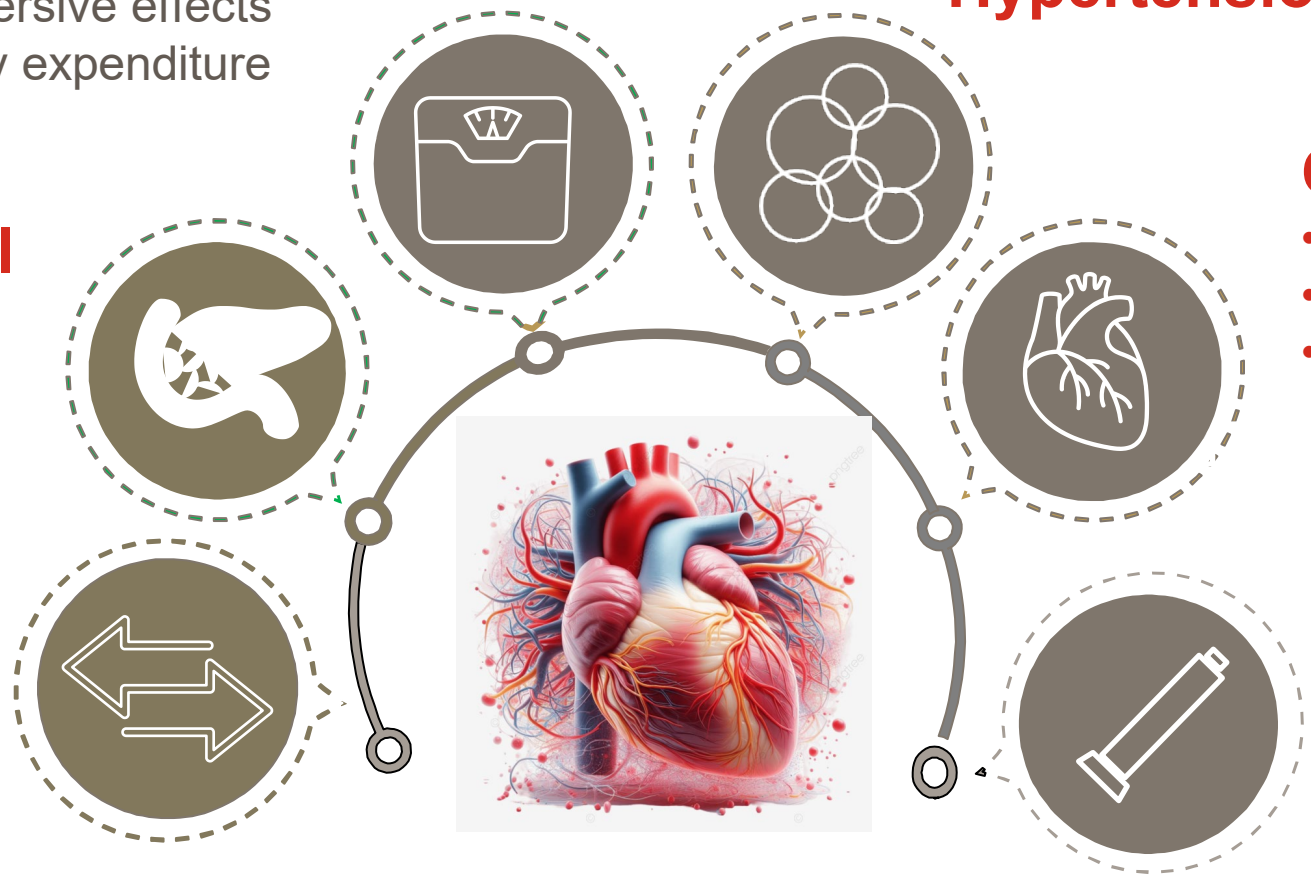
L'INNOVAZIONE dell' "IN-NOVA-AZIONE"

Weight loss
- Food intake
- Antiaversive effects
- Energy expenditure

Lipid metabolism and Hypertension

Glycemic control
- Effect on HbA1C

Cardiovascular
- Plasma lipid control
- Inflammation
- Endothelial function



Receptor pharmacology
Dual agonism

Dose escalation

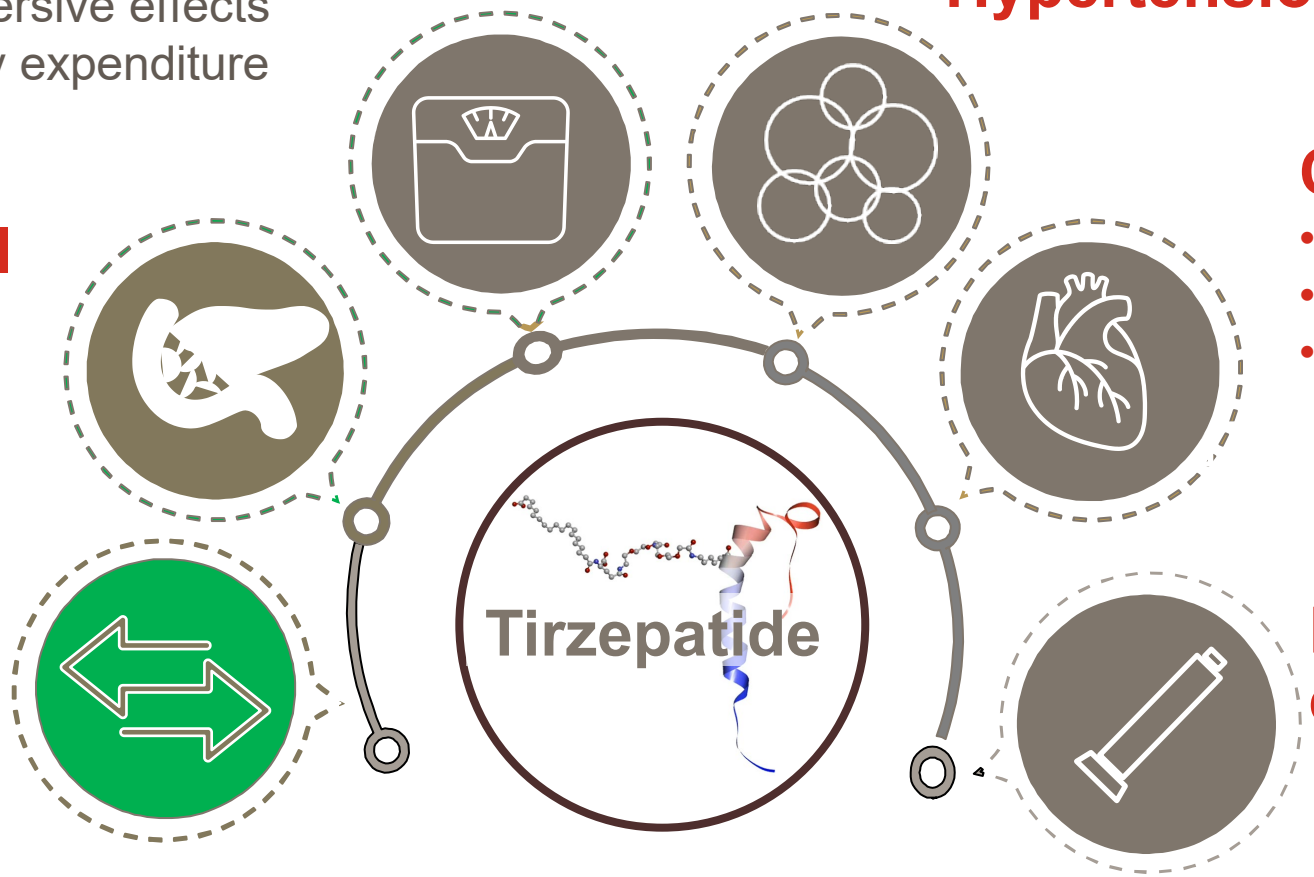
Tirzepatide: dual agonism

Weight loss
- Food intake
- Antiaversive effects
- Energy expenditure

Lipid metabolism and Hypertension

Glycemic control
- Effect on HbA1C

Cardiovascular
- Plasma lipid control
- Inflammation
- Endothelial function

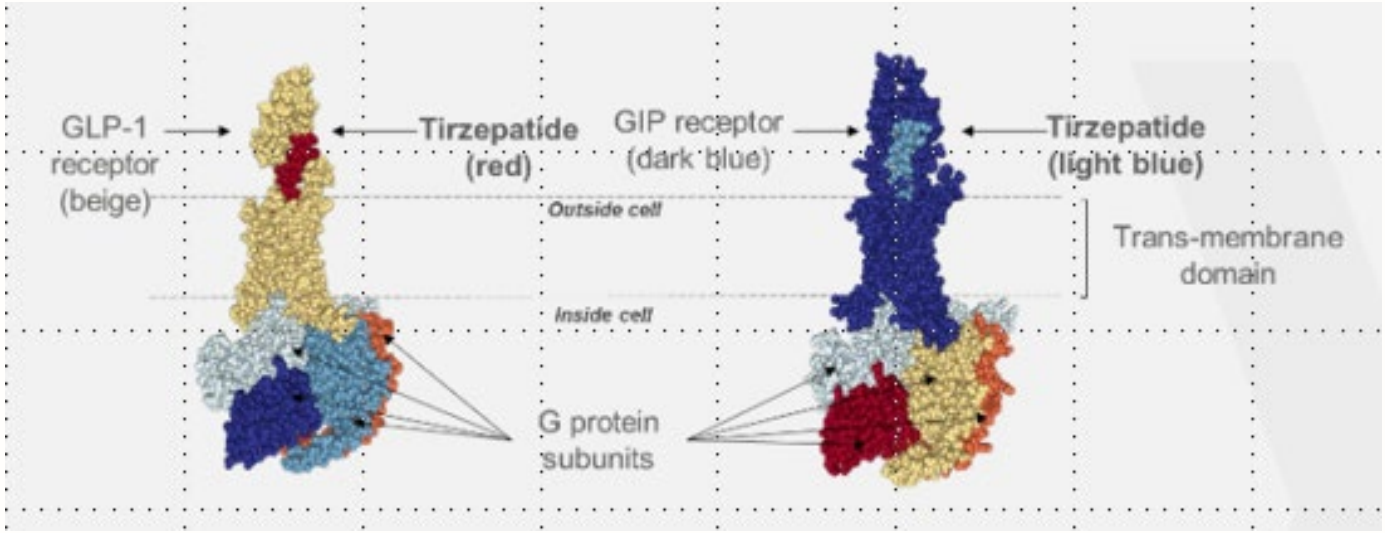


Receptor pharmacology
Dual agonism

Dose escalation

Tirzepatide: Unimolecular coagonist

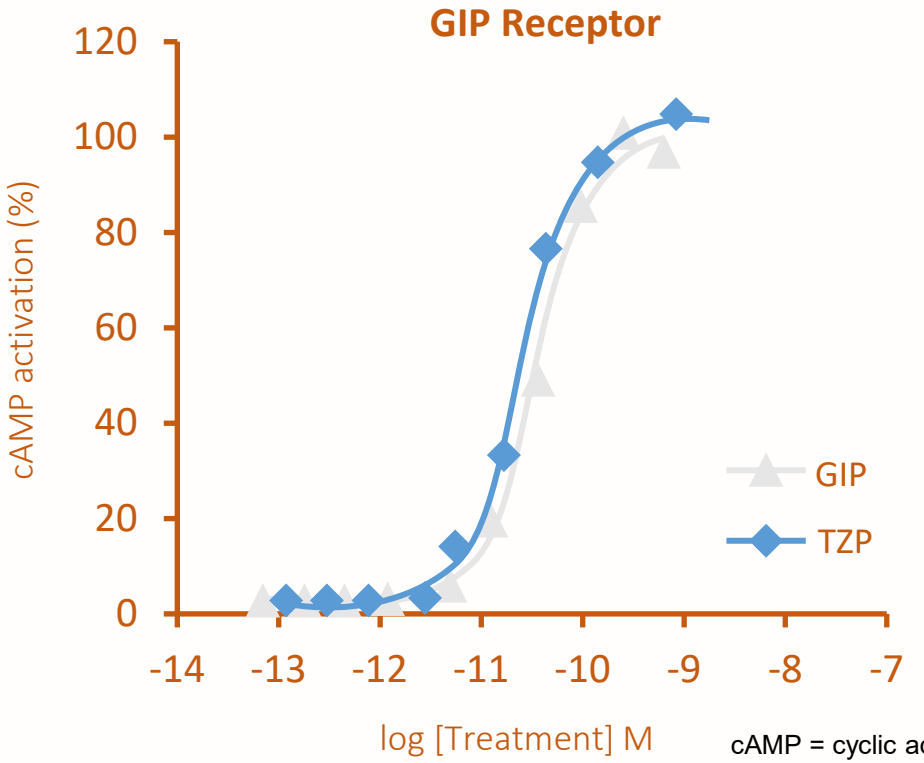
Single molecule possessing activity at 2 pharmacologic targets

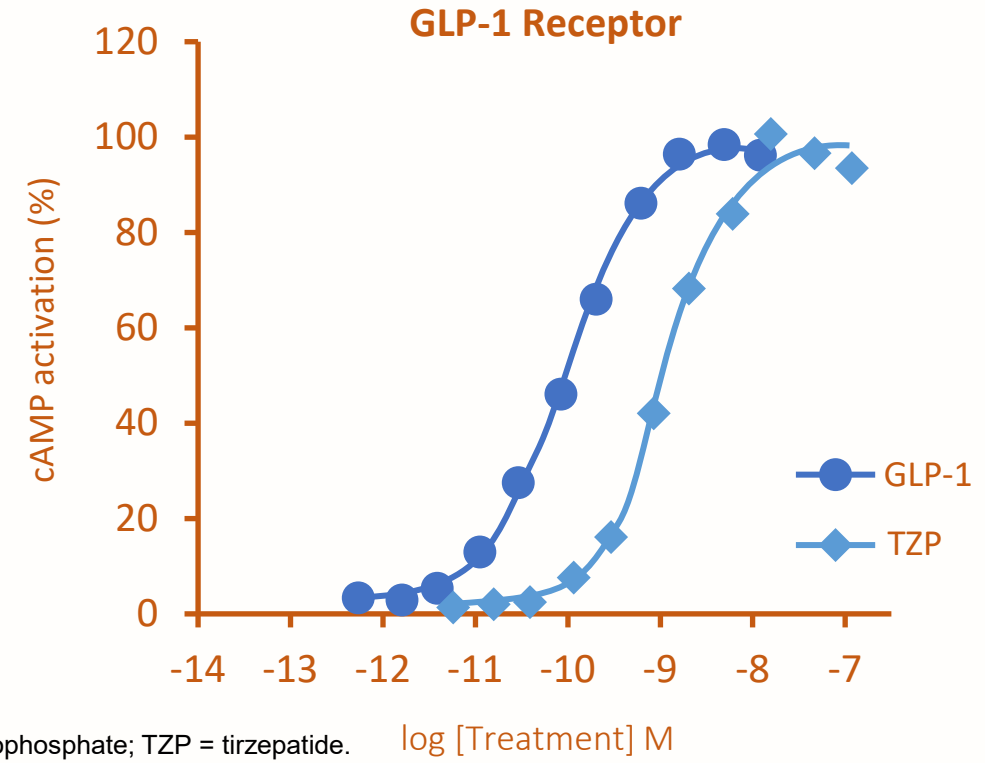


- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIPR and GLP-1R
- Tirzepatide is a 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- Tirzepatide has a mean half-life of approximately 5 days (116.7 hours), enabling **once-weekly dosing**
- Plasma concentrations in people with renal and hepatic impairment do not differ versus healthy people

Tirzepatide Potency and Affinity for GIP and GLP-1 Receptors

- In vitro, tirzepatide has a potency/affinity for the GIP receptor similar to native GIP
- Potency/affinity for the GLP-1 receptor is slightly weaker compared with native GLP-1

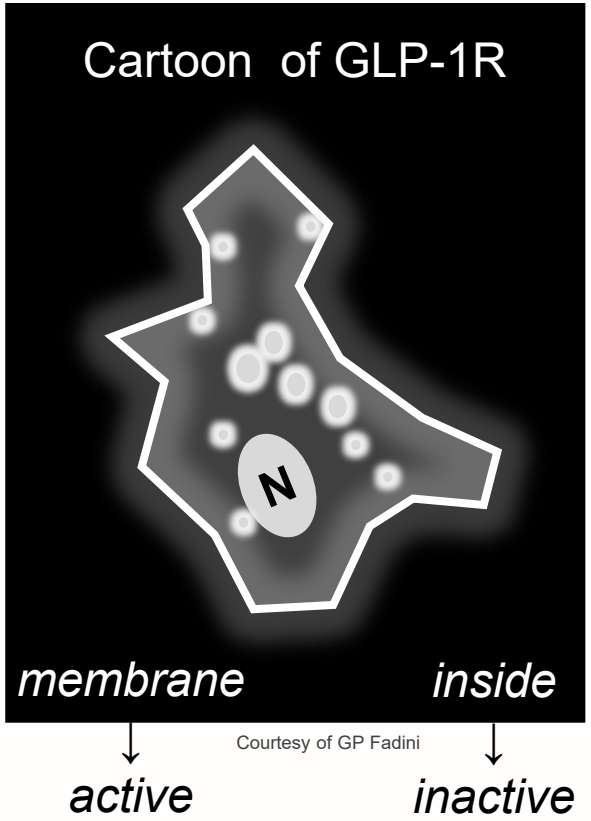




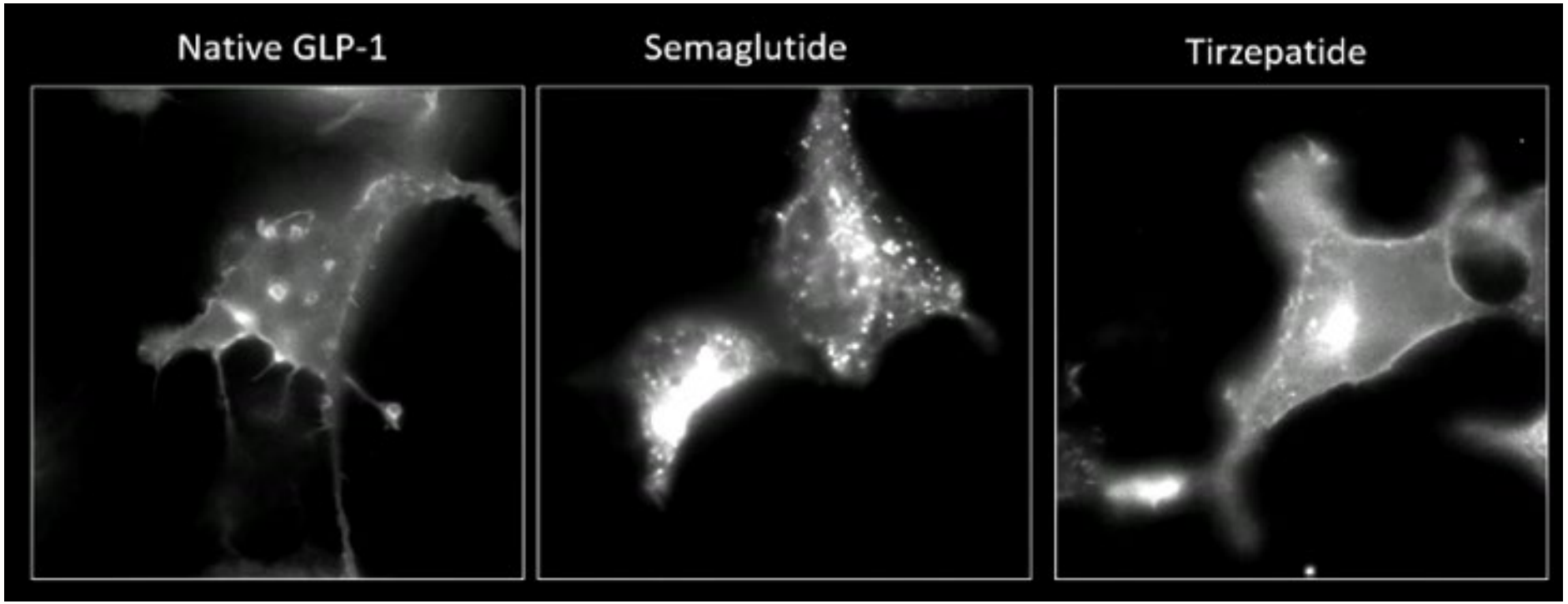
cAMP = cyclic adenosine monophosphate; TZP = tirzepatide.

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

Tirzepatide-related GLP-1r overexpression

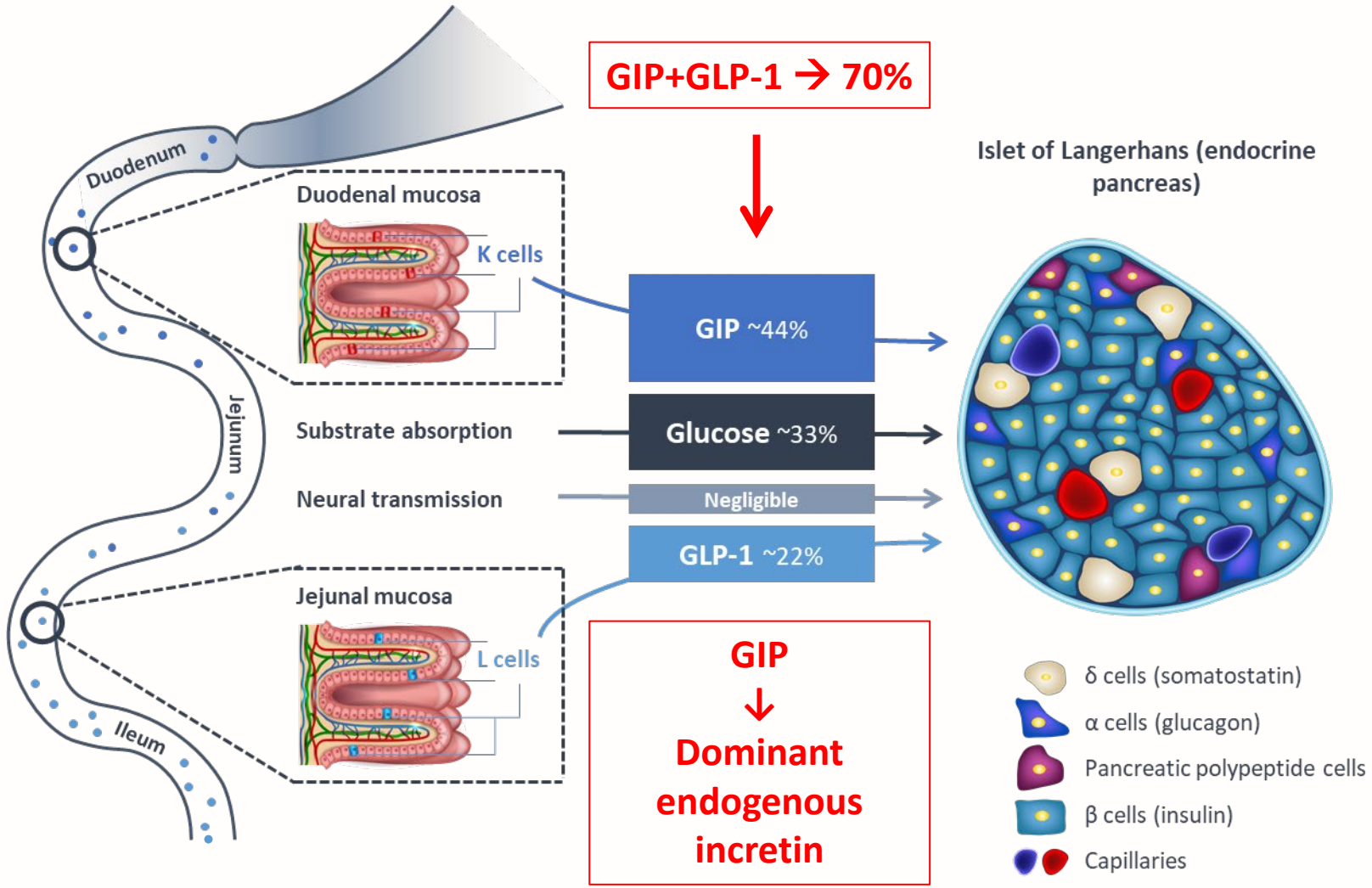


Courtesy of GP Fadini



Mol Metab. 2021 Jul;49:101181

The Gut-Pancreas Axis: preminent GIP role in insulin secretion



- ✓ 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
- ✓ This "incretin effect" is a major contributor to regulation of PPG clearance in healthy people

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

GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; PPG = postprandial glucose.

Fig. 1 from ref.1

GLP-1a and GIPa-mediated actions

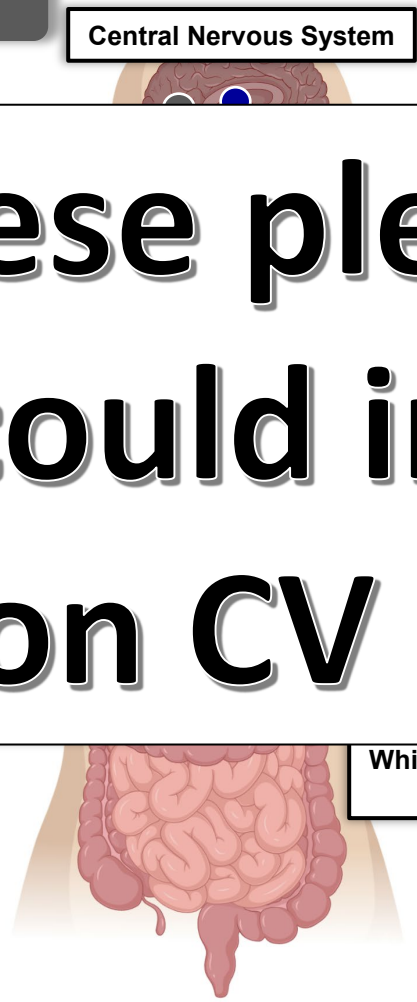
GLP-1 Receptor Agonism

Central Nervous System

- ↓ Ectopic Lipid Accumulation

GIP Receptor Agonism

Central Nervous System



Skeletal Muscle

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

How these pleiotropic actions could impact on DMT2 and on CV continuum?

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

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

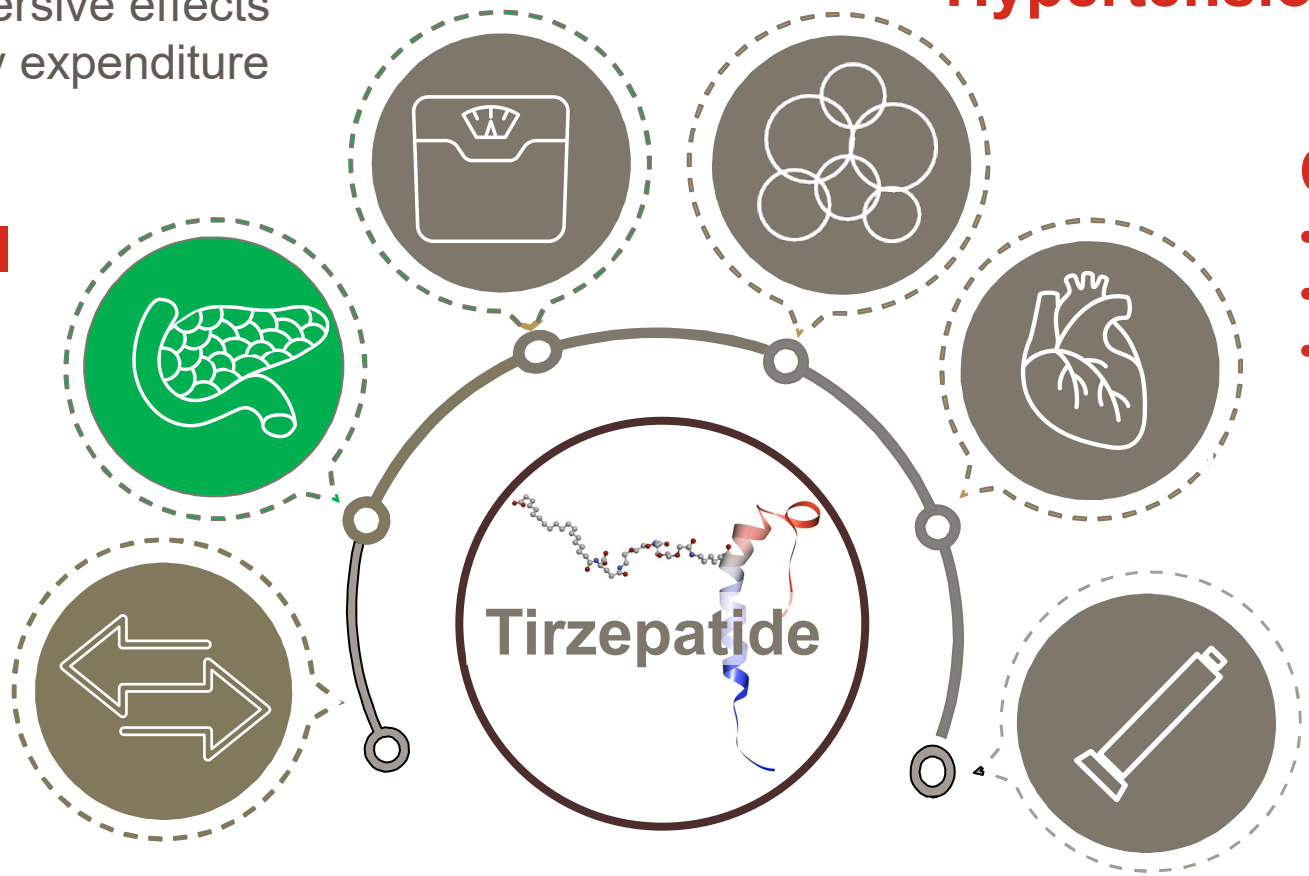
Tirzepatide: glycemic control

Weight loss
- Food intake
- Antiaversive effects
- Energy expenditure

Lipid metabolism and Hypertension

Glycemic control
- Effect on HbA1C

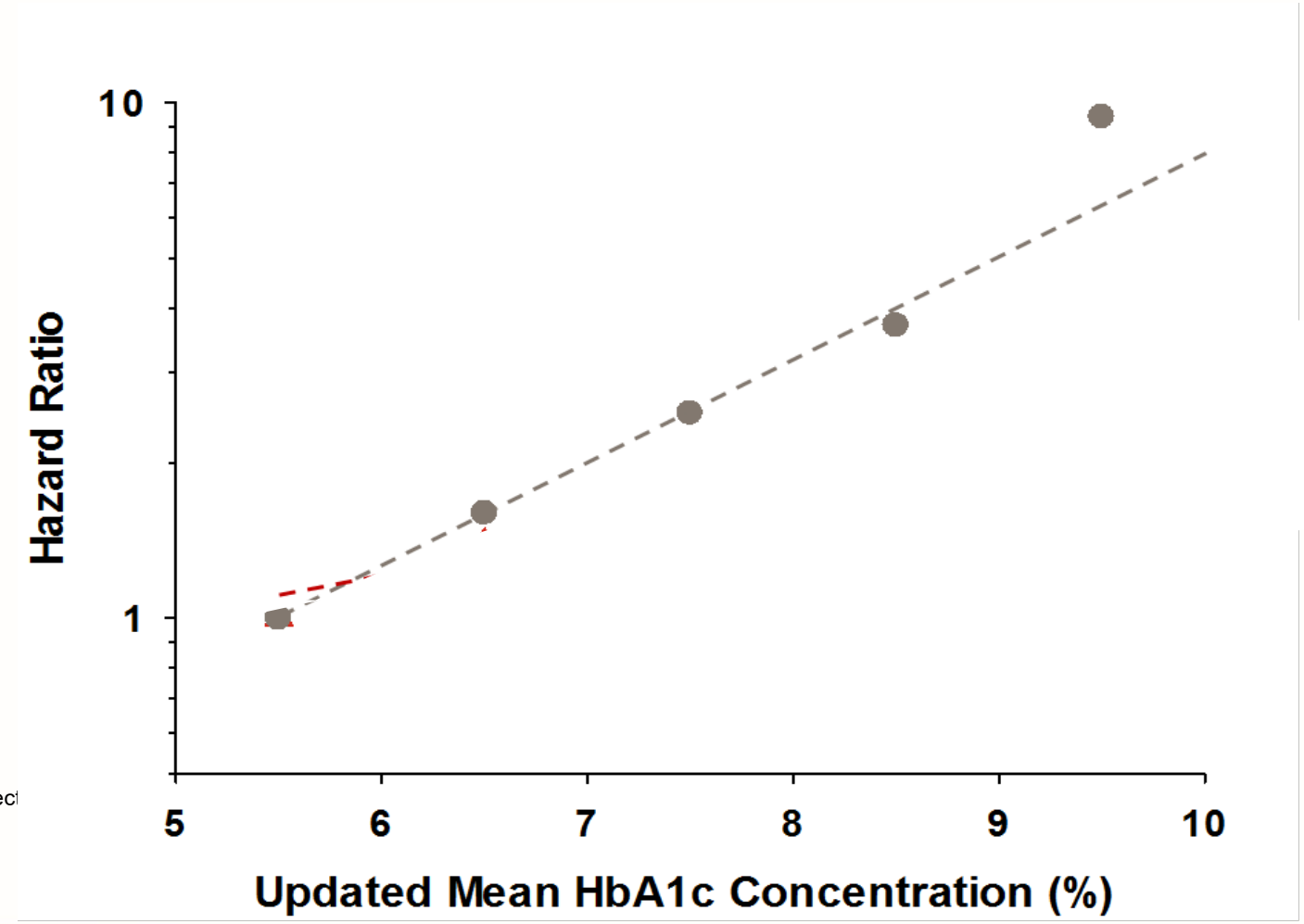
Cardiovascular
- Plasma lipid control
- Inflammation
- Endothelial function



Receptor pharmacology
Dual agonism

Dose escalation

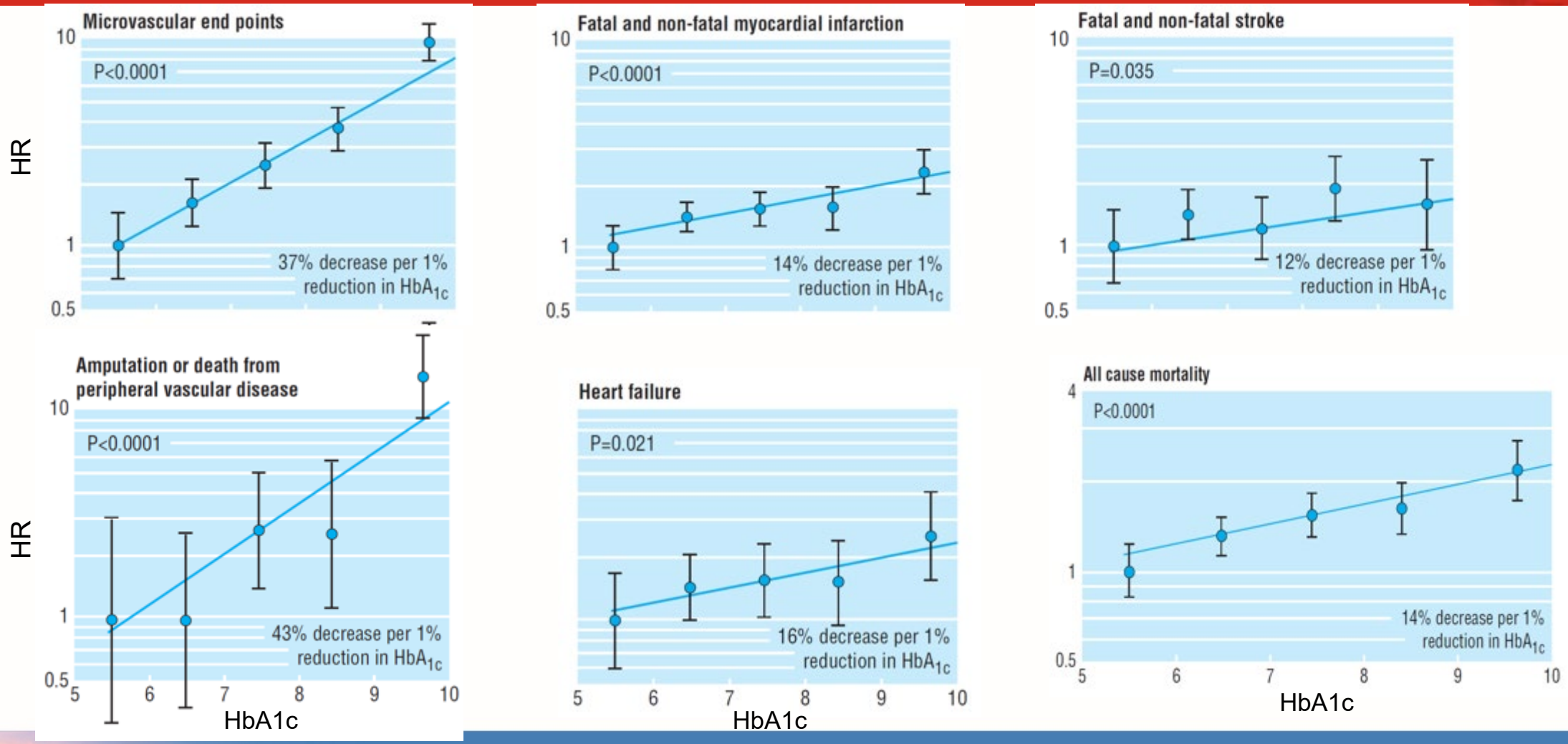
L'iperglicemia contribuisce indipendentemente alle complicazioni micro- e macrovascolari nel diabete di tipo 2



HbA1c=glycated hemoglobin; UKPDS=UK Prospect
Study

Stratton IM, et al. *BMJ*. 2000;321:405–412.

UKPDS: Un controllo glicemico intensivo precoce riduce il rischio a lungo termine di complicanze croniche nel diabete di tipo 2



Stratton IM et al. BMJ. 2000;321:405-412

SURPASS Program:
Clinical Trials Across the T2D Spectrum

Total studied population: 7699 T2 diabetic patients

Monotherapy	2-Drug Combination	2-3 Drug Combinations	2-4 Drug Combinations	Combination With Insulin
SURPASS-1 vs. placebo[1] Drug-naïve or washout from any OAM	**SURPASS-2** vs. semaglutide[2] Add-on to metformin	**SURPASS-3** vs. insulin degludec[3] Add-on to metformin with or without SGLT-2i	**SURPASS-4** vs. insulin glargine[4] Add-on to ≥1 and ≤3 OAMs (metformin, SGLT-2i, or SU)	**SURPASS-5** vs. placebo[5] Both with insulin glargine with or without metformin **SURPASS-6** vs. insulin lispro[6] (TID) Both with insulin glargine with or without metformin

SURPASS-CVOT[7]

H2H comparing TZP vs. dulaglutide >12,000 participants (ongoing)

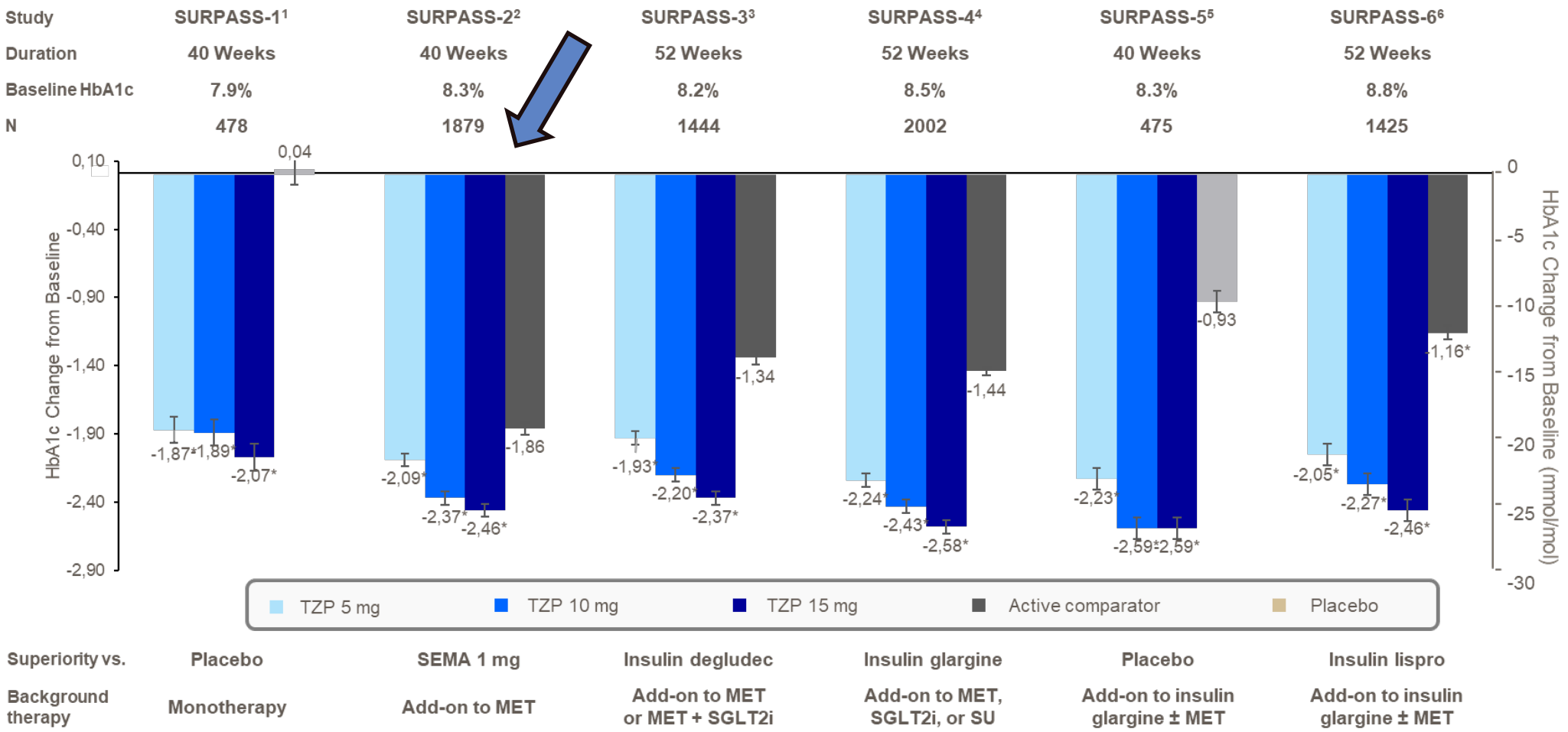
SURPASS-EARLY

to understand the effect of TZP when used early in the treatment paradigm compared to Intensified Conventional Care for the treatment of T2D (ongoing)

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).

Tirzepatide all doses are associated to superior HbA1c reduction vs comparators

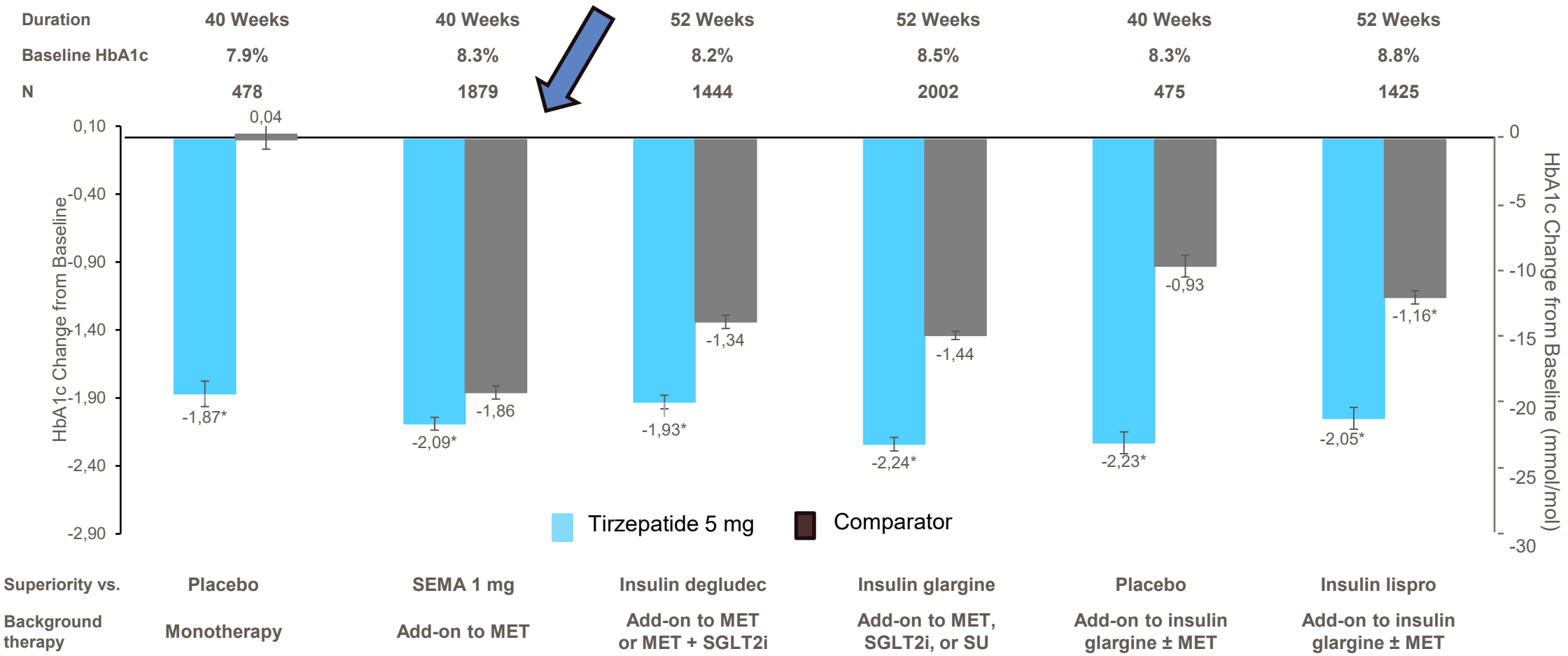


***p<0.001 vs. placebo or active comparator.**

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

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

Tirzepatide already at 5 mg provide clinically relevant HbA1c reduction superior both to placebo and active comparators

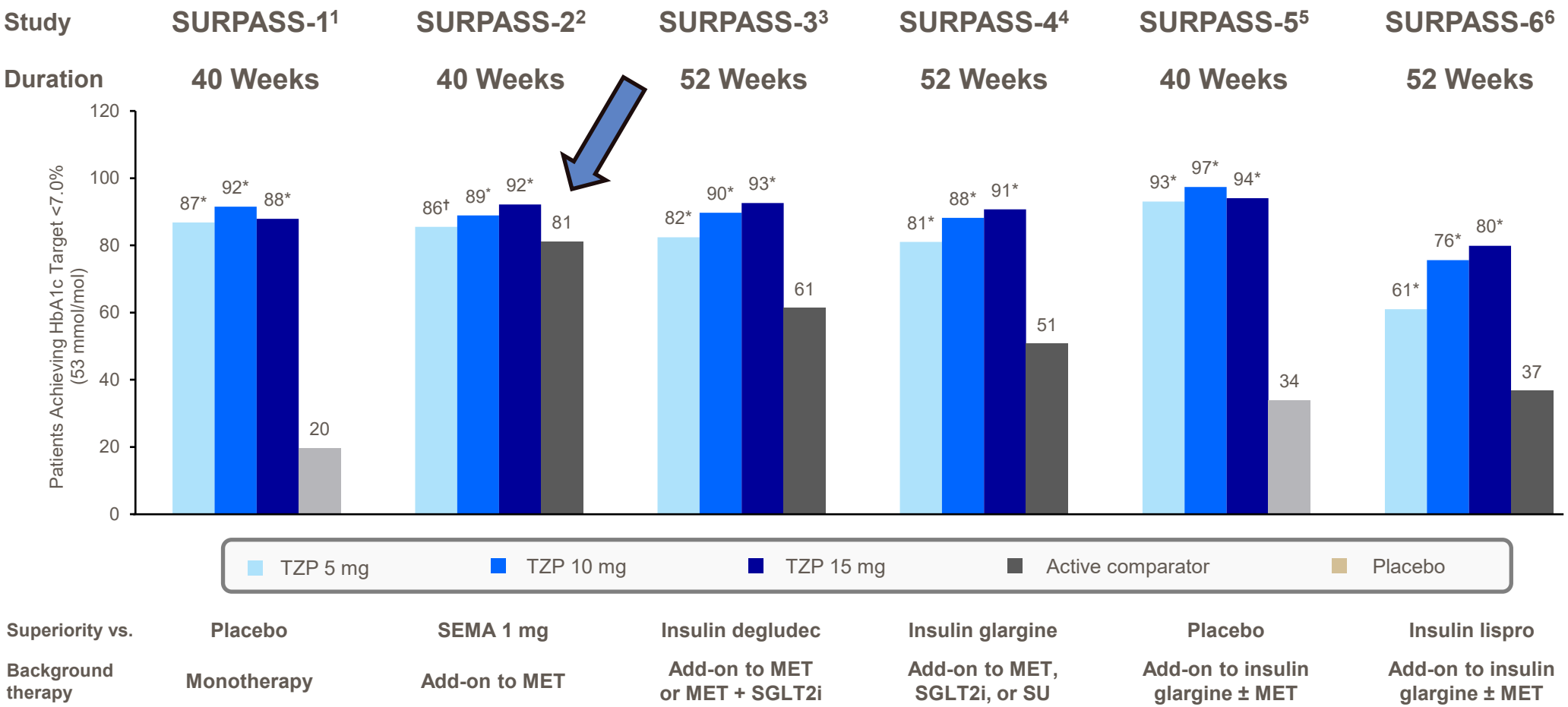


***p<0.001 vs. placebo or active comparator.**

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

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

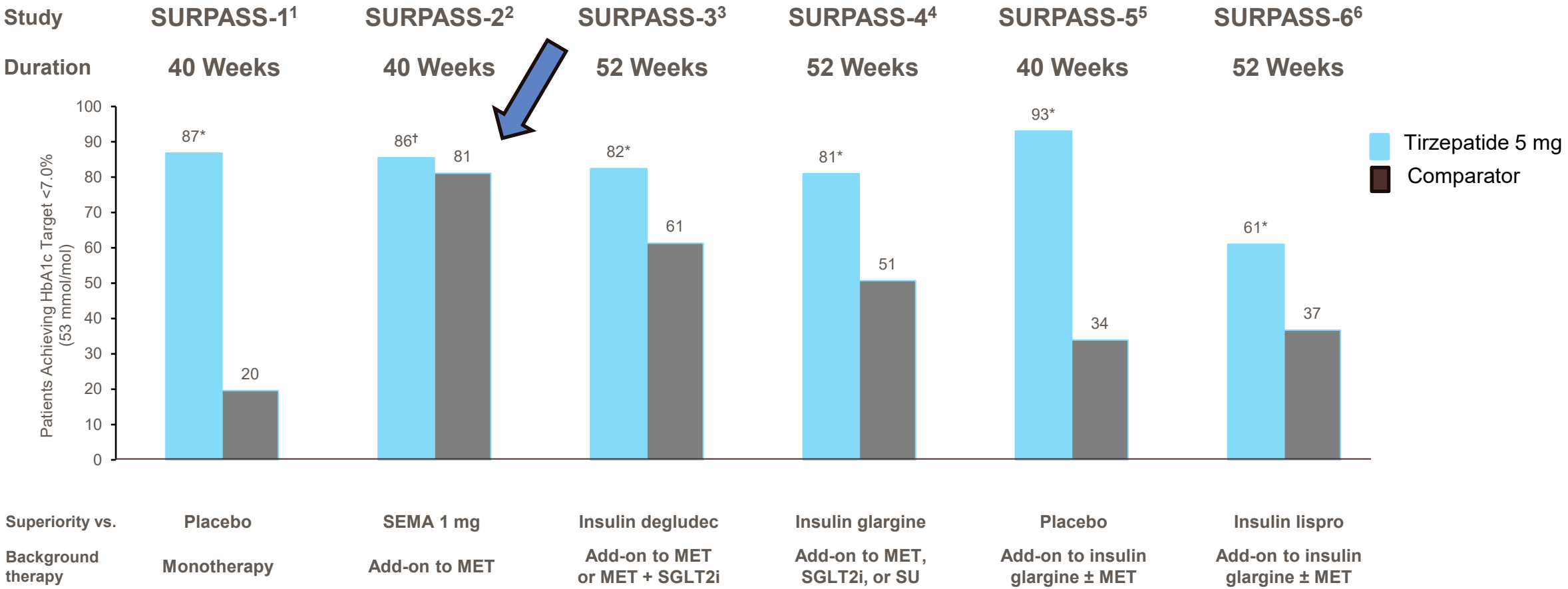
Tirzepatide all doses are associated with higher percentage of patients reaching HbA1c target (< 7,0%)



*p<0.001, †p<0.05 vs. placebo or active comparator.
Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.

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

Tirzepatide already at 5 mg allows majority of patients to achieve HbA1c target (HbA1c < 7.0%)

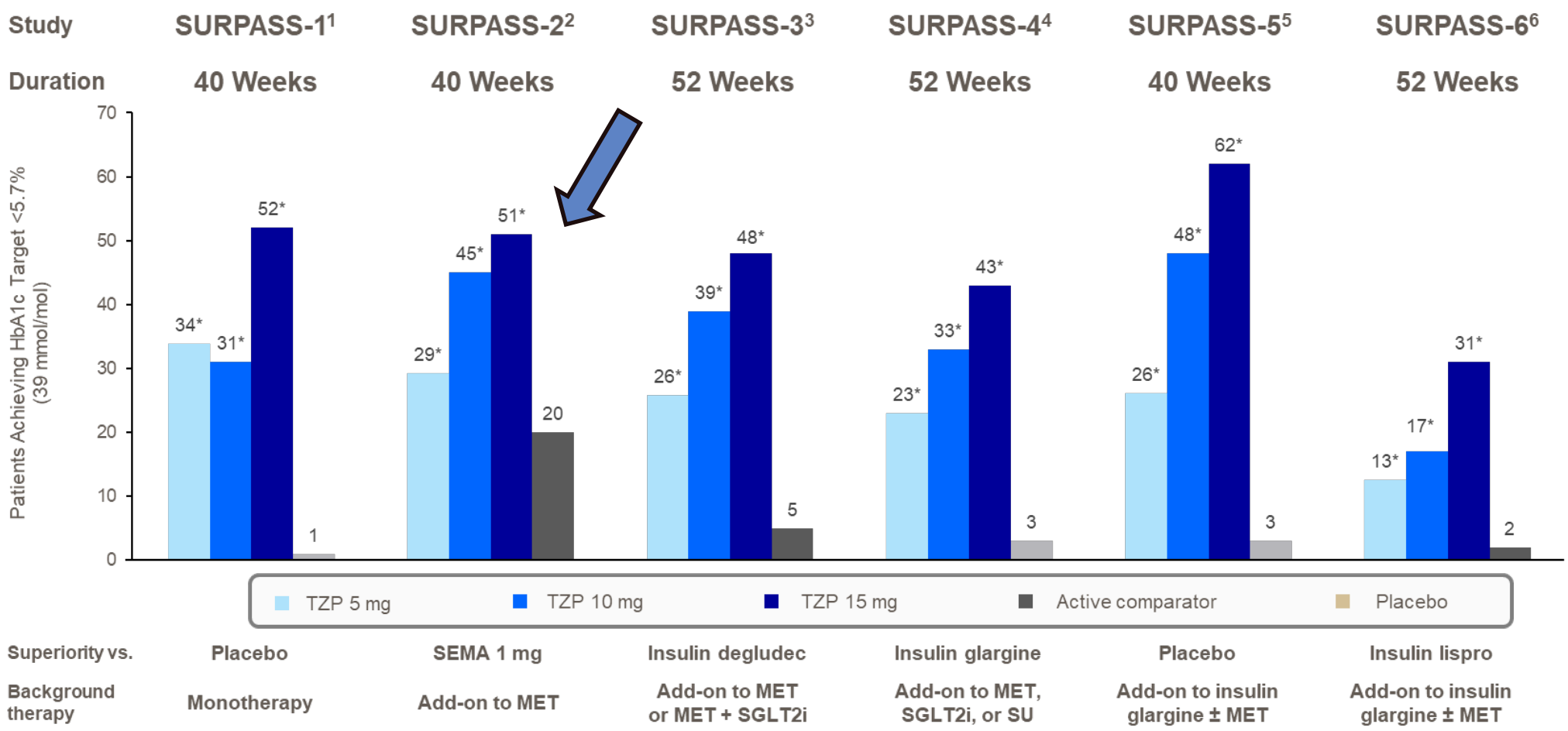


*p<0.001, †p<0.05 vs. placebo or active comparator.

Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.

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

Higher percentages of tirzepatide treated subjects achieved normal HbA1c level (< 5,7%)



***p<0.001 vs. placebo or active comparator.**
Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.

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

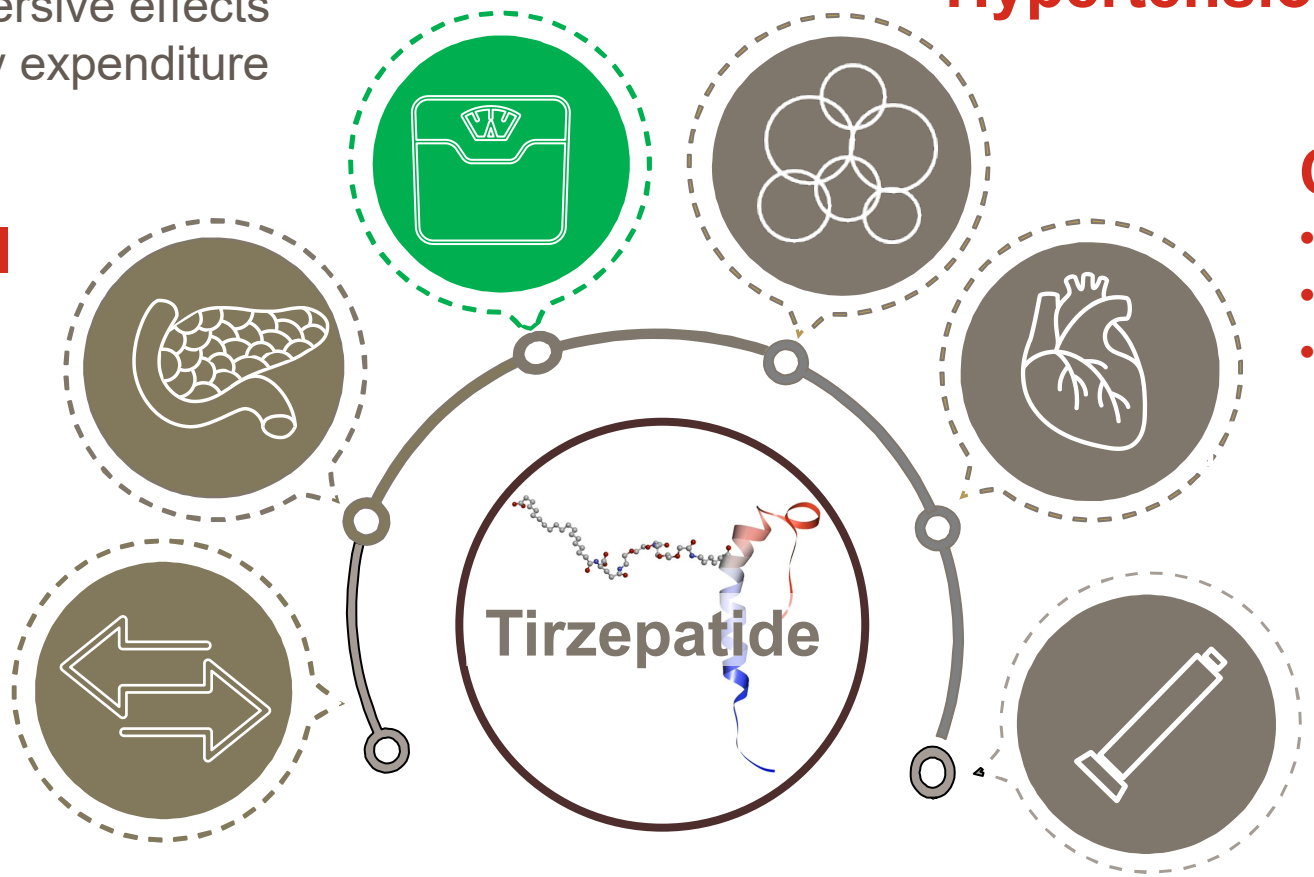
Tirzepatide: weight loss

Weight loss
- Food intake
- Antiaversive effects
- Energy expenditure

Lipid metabolism and Hypertension

Glycemic control
- Effect on HbA1C

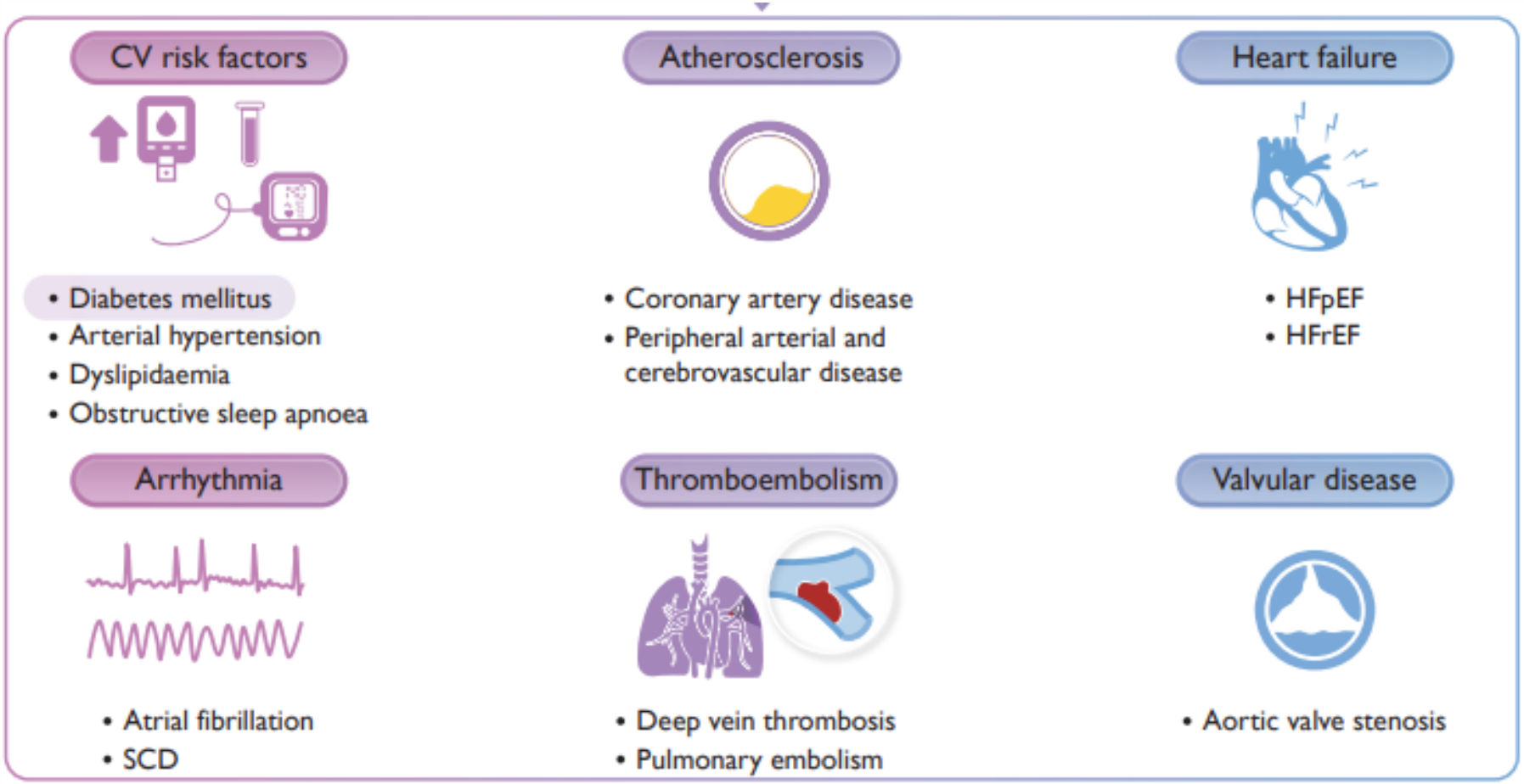
Cardiovascular
- Plasma lipid control
- Inflammation
- Endothelial function



Receptor pharmacology
Dual agonism

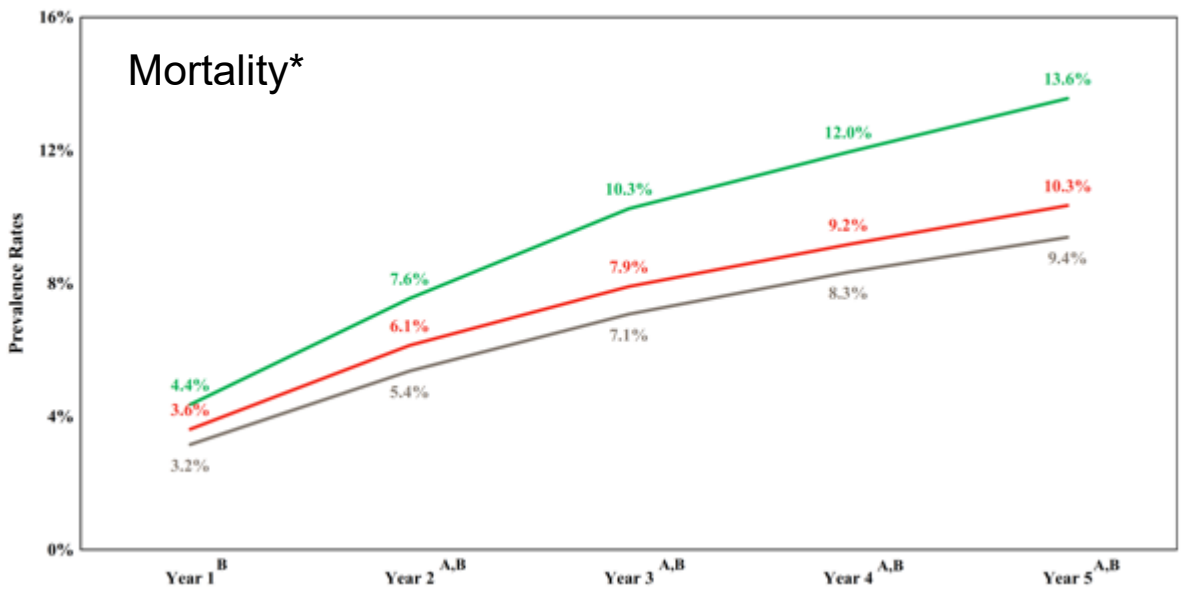
Dose escalation

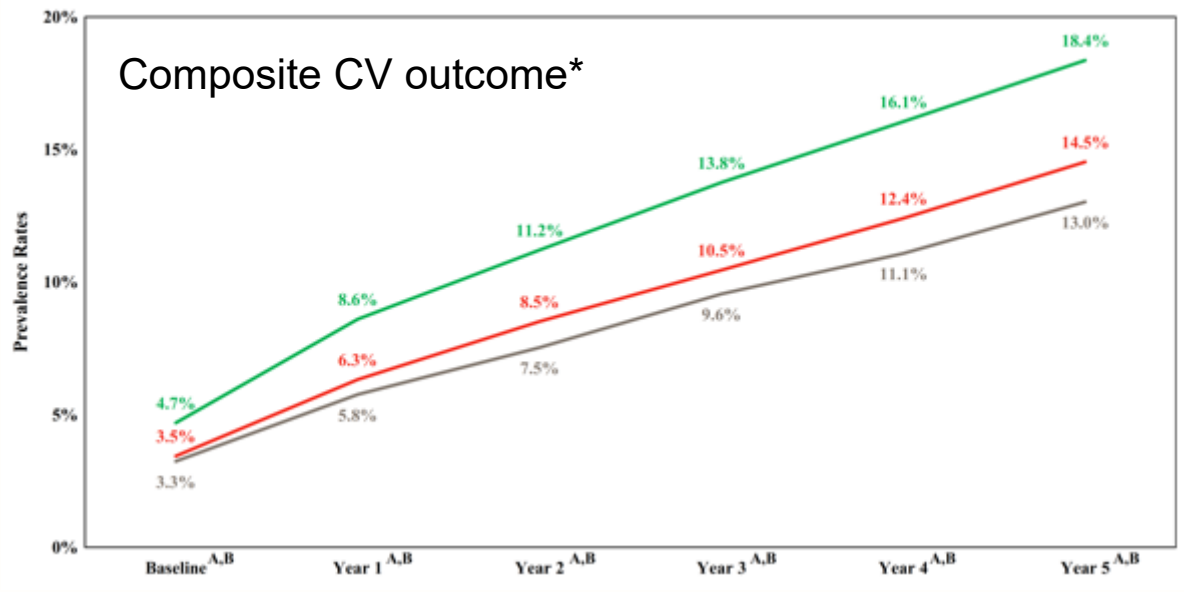
Direct/indirect negative effects of obesity on CV system



Koskinas KC. Obesity and cardiovascular disease: an ESC clinical consensus statement. European Heart Journal (2024) 00, 1–36

Associazione tra obesità e prevalenza a 5 anni di morbilità e mortalità in adulti con diabete di tipo 2





Acute care visit suggesting AMI, HF or stroke

Class 1 obesity Class 2 obesity Class 3 obesity

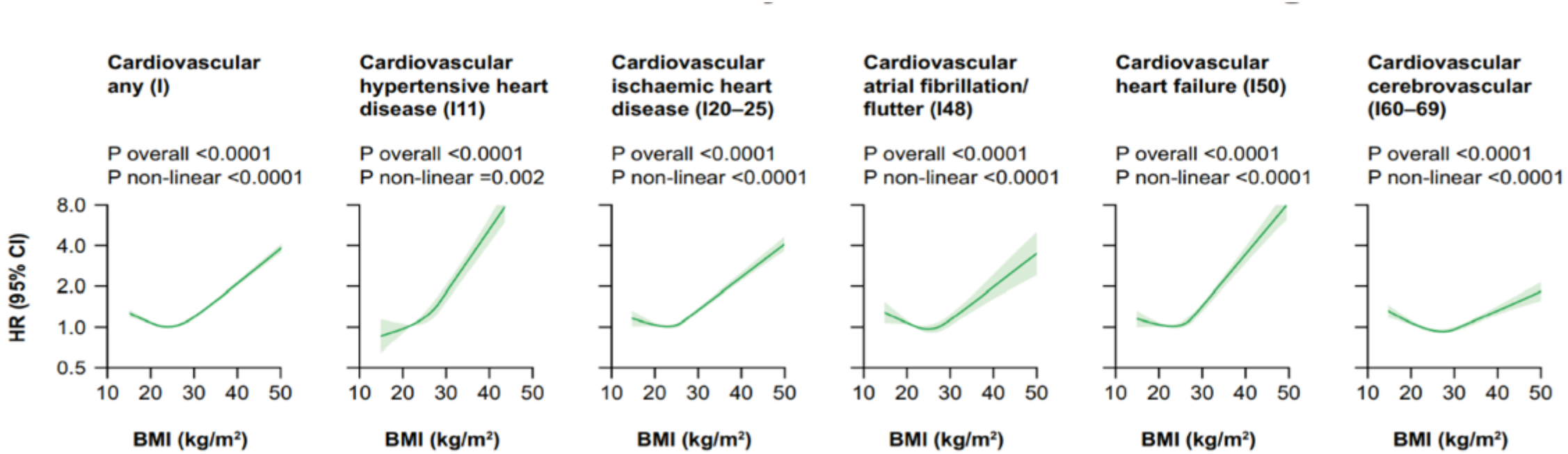
Boye KS et al ***Diabetes Ther*** 2023;14:709–721

*5-year age- and sex-adjusted prevalence

Il rischio di malattia cardiovascolare aumenta con l'aumentare del BMI

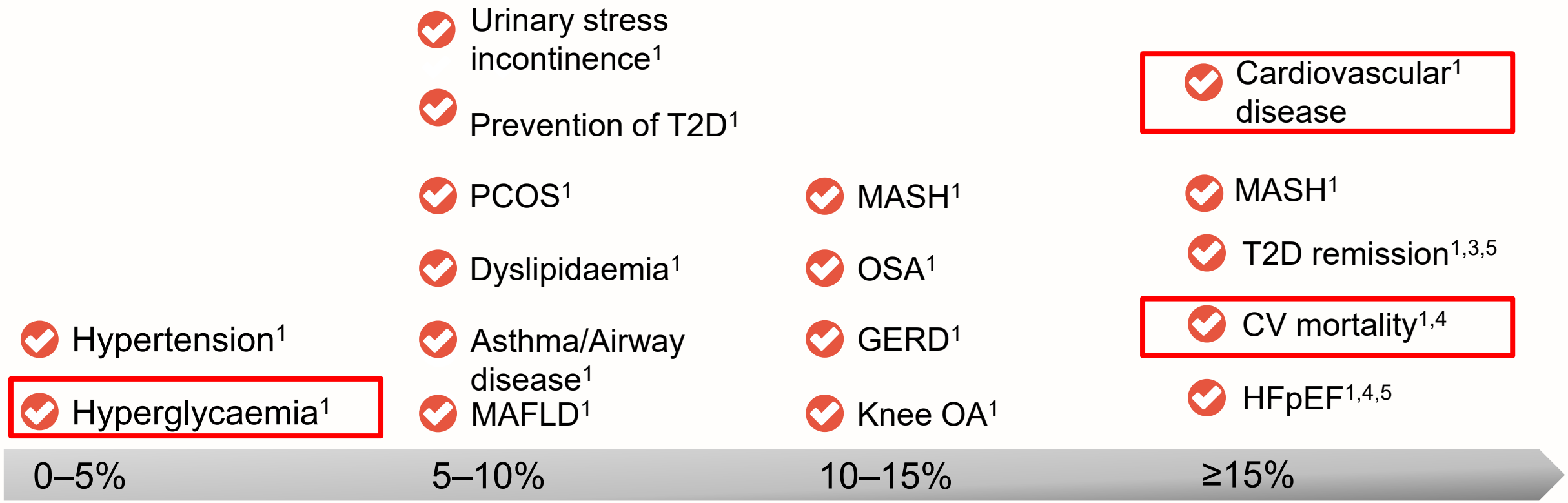
29% di incremento di rischio di malattia cardiovascolare per ogni 5 unità di BMI al di sopra di 25 kg/m^2

Studio di popolazione su 3,6 milioni di adulti nel Regno Unito



Krishnan Bhaskaran, Lancet Diabetes Endocrinol 2018

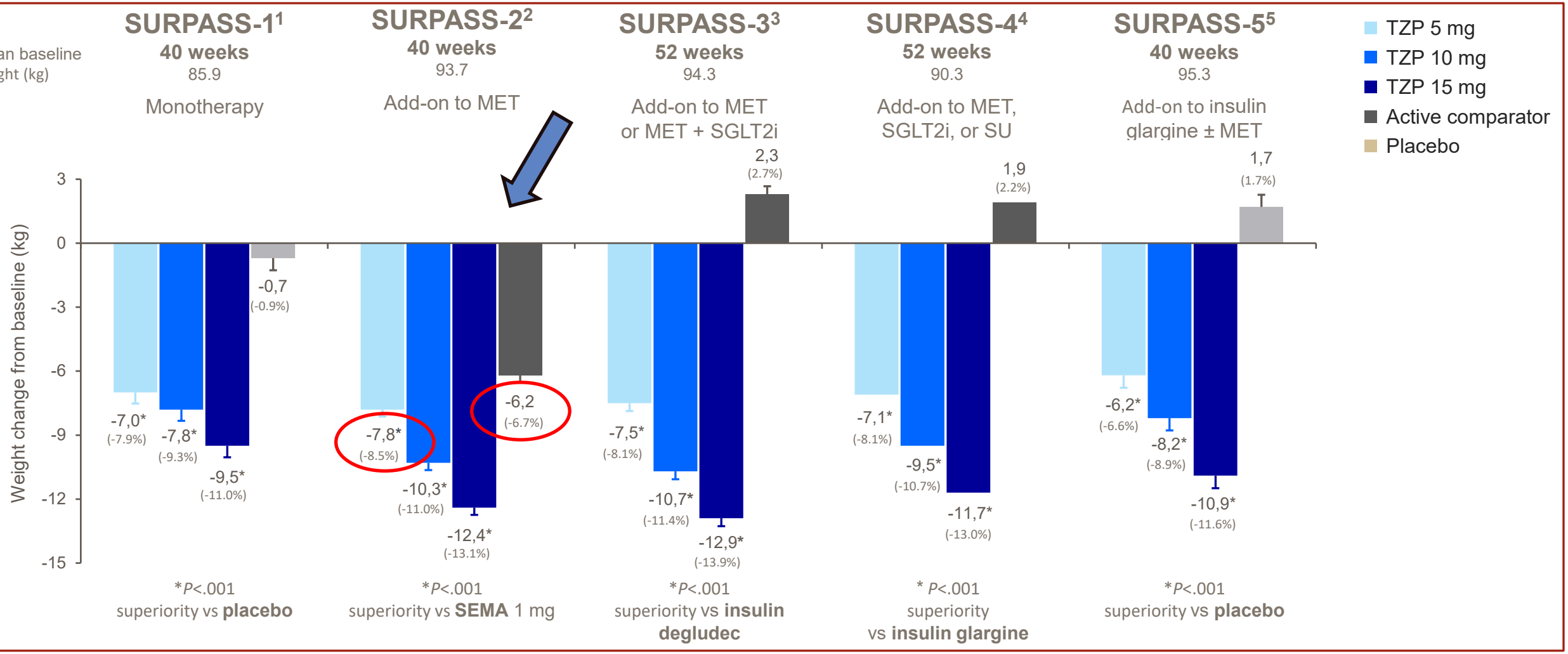
Clinical benefit of weight loss



CV, cardiovascular; GERD, gastroesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA, osteoarthritis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome

1. Garvey WT, et al. Endocr Pract 2016;22(Suppl. 3): 1–203; 2. Look AHEAD Research Group. Lancet Diabetes Endocrinol. 2016;4(11): 913–921; 3. Lean ME, et al. Lancet. 2018;391(10120): 541–551; 4. Benraoune F and Litwin SE. Curr Opin Cardiol. 2011;26(6): 555–561; 5. Sundström J, et al. Circulation. 2017;135(17): 1577–1585.

Up to 12.9 kg of Weight Change From Baseline to Primary Endpoint

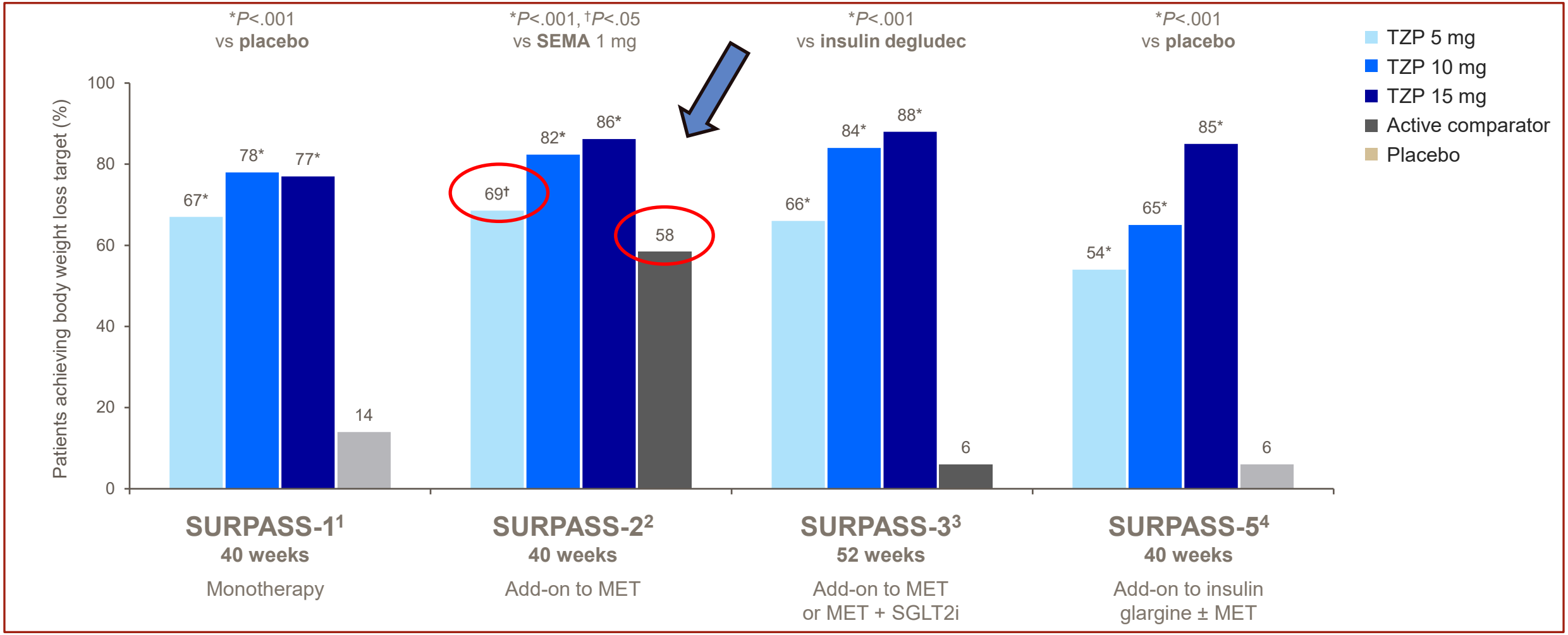


Data are LSM (SE); mITT population (efficacy analysis set). MMRM analysis.

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.

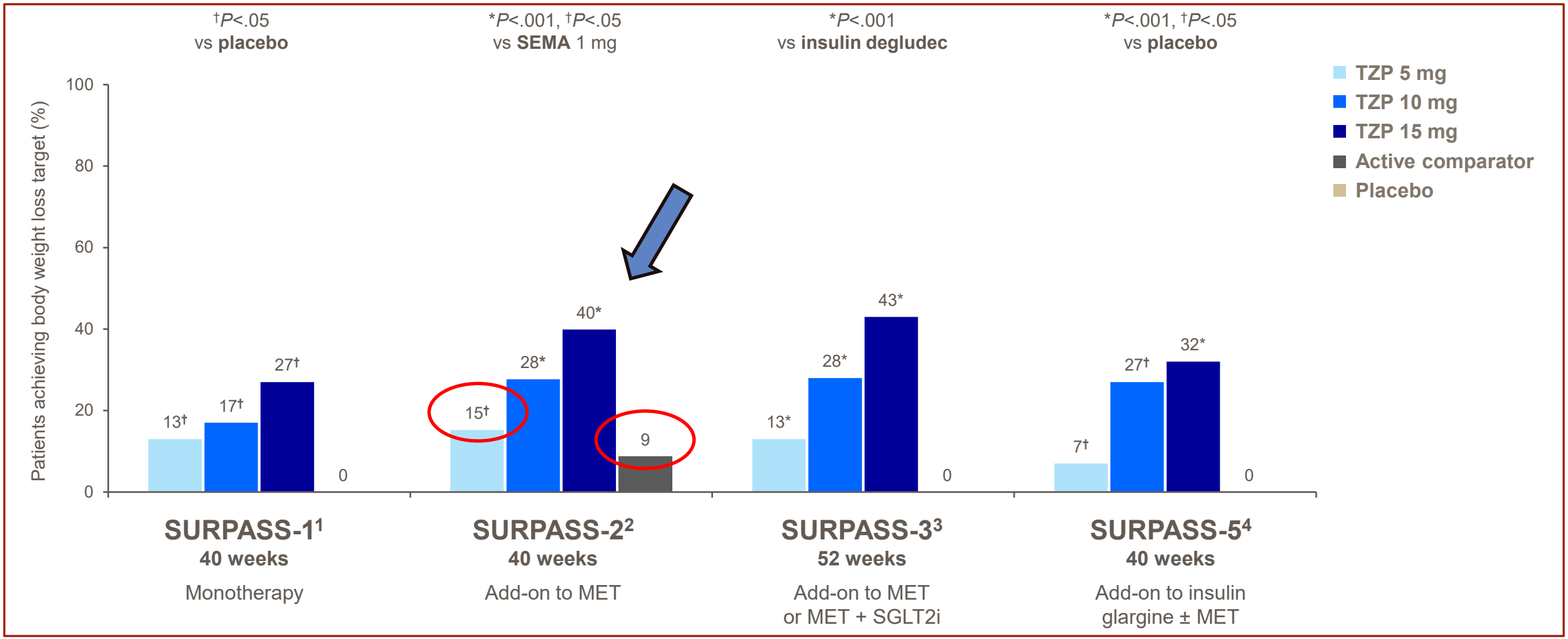
1. 1Rosenstock J et al, *Lancet* 2021; Frias JP et al, *N Eng J Med* 2021; Ludvik B et al, *Lancet* 2021; Del Prato S et al, *Lancet* 2021; Dahl D et al, *JAMA* 2022

Up to 88% of Patients Achieving ≥5% Weight Loss



Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; 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

Up to 43% of Patients Achieving ≥15% Weight Loss



Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; TZP = tirzepatide.

11Rosenstock 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

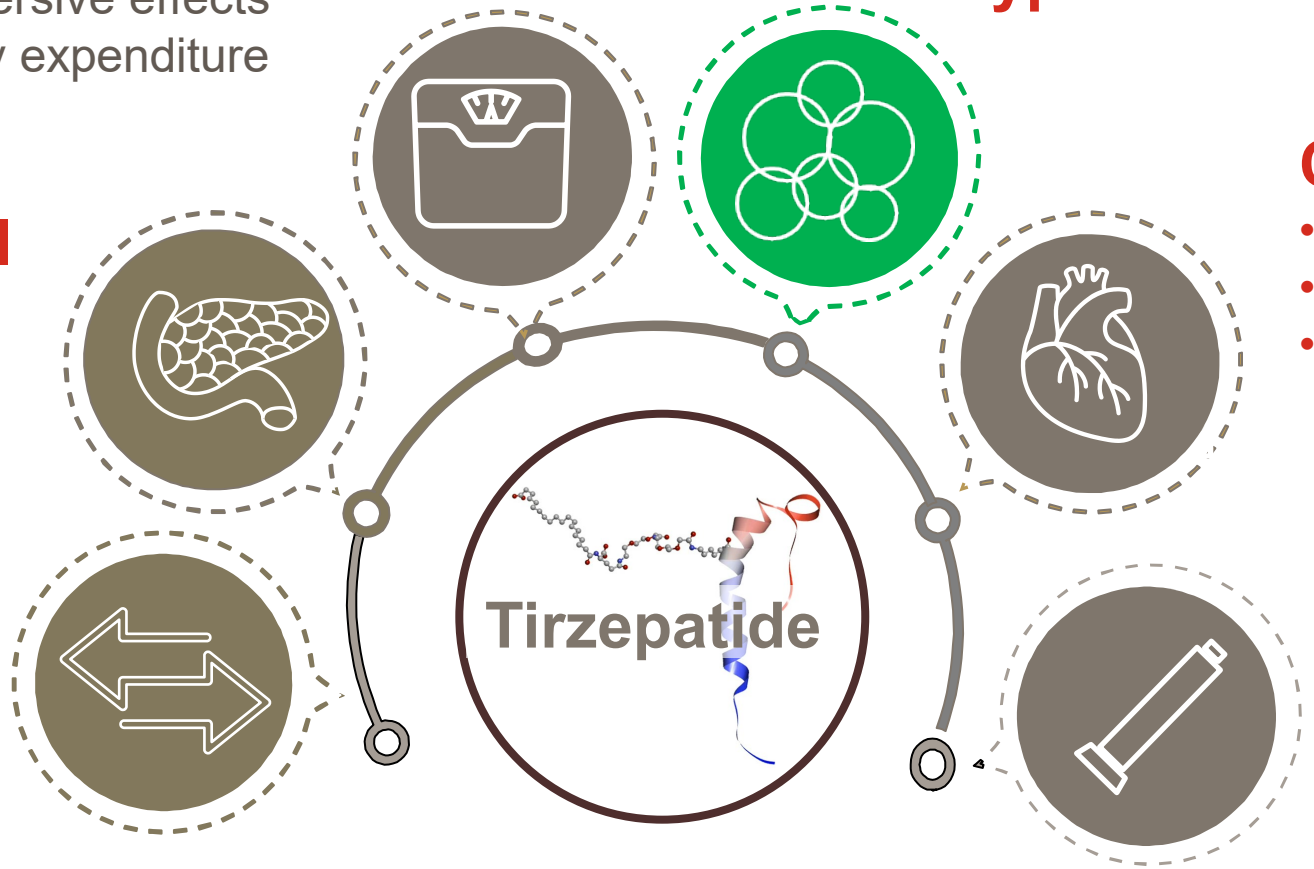
Tirzepatide: Lipid metabolism and Hypertension

Weight loss
- Food intake
- Antiaversive effects
- Energy expenditure

Lipid metabolism and Hypertension

Glycemic control
- Effect on HbA1C

Cardiovascular
- Plasma lipid control
- Inflammation
- Endothelial function



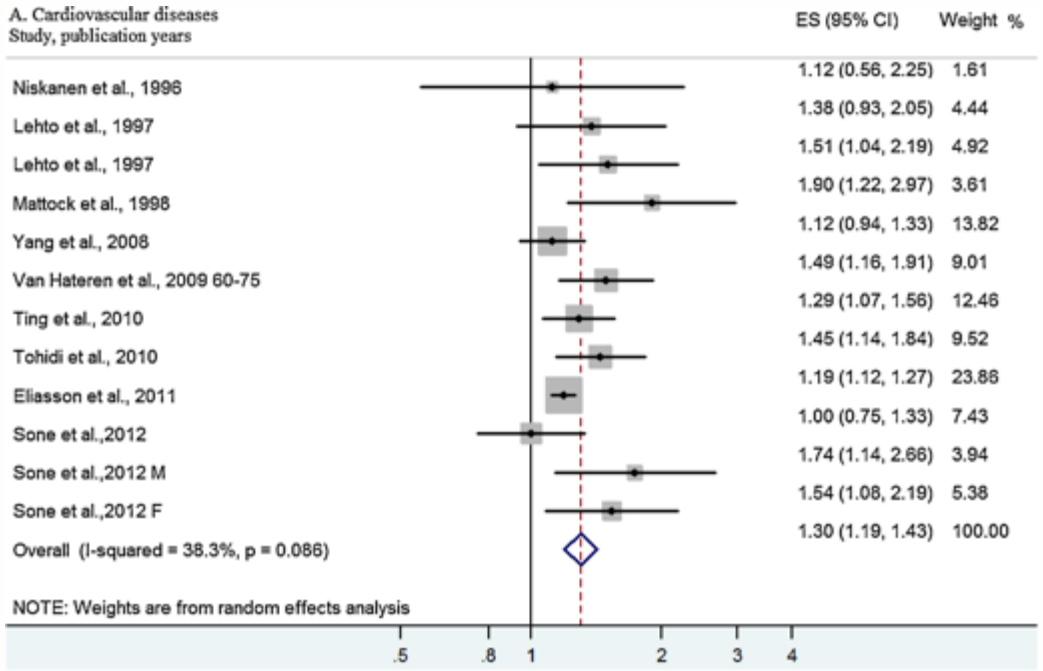
Receptor pharmacology
Dual agonism

Dose escalation

Lipid profile and CV outcomes in diabetes

CV disease

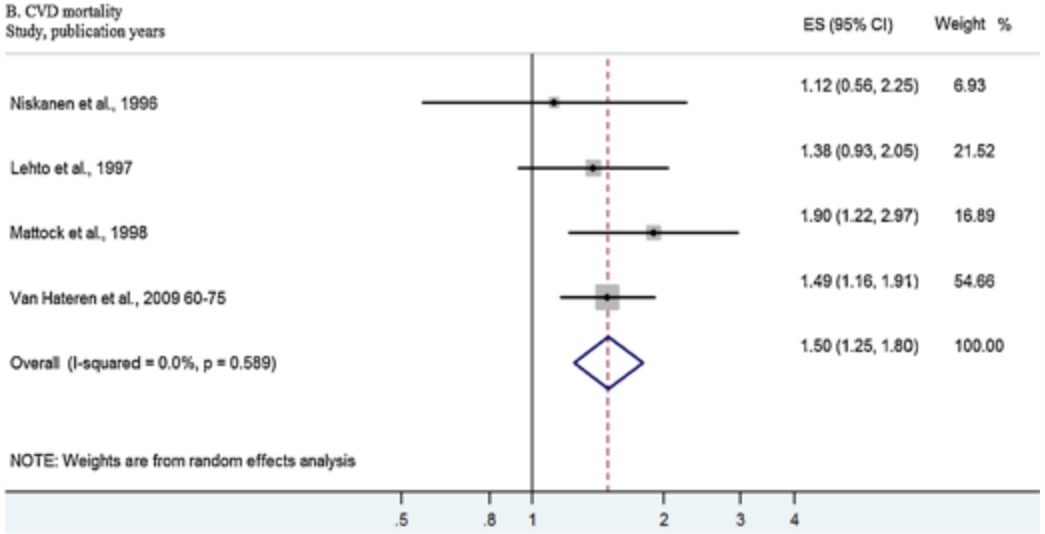
+1 mmol/L (39 mg/dL) LDL→ +30% di RR



Wang Y et al, *Diabetes Res Clin Pract* 2013

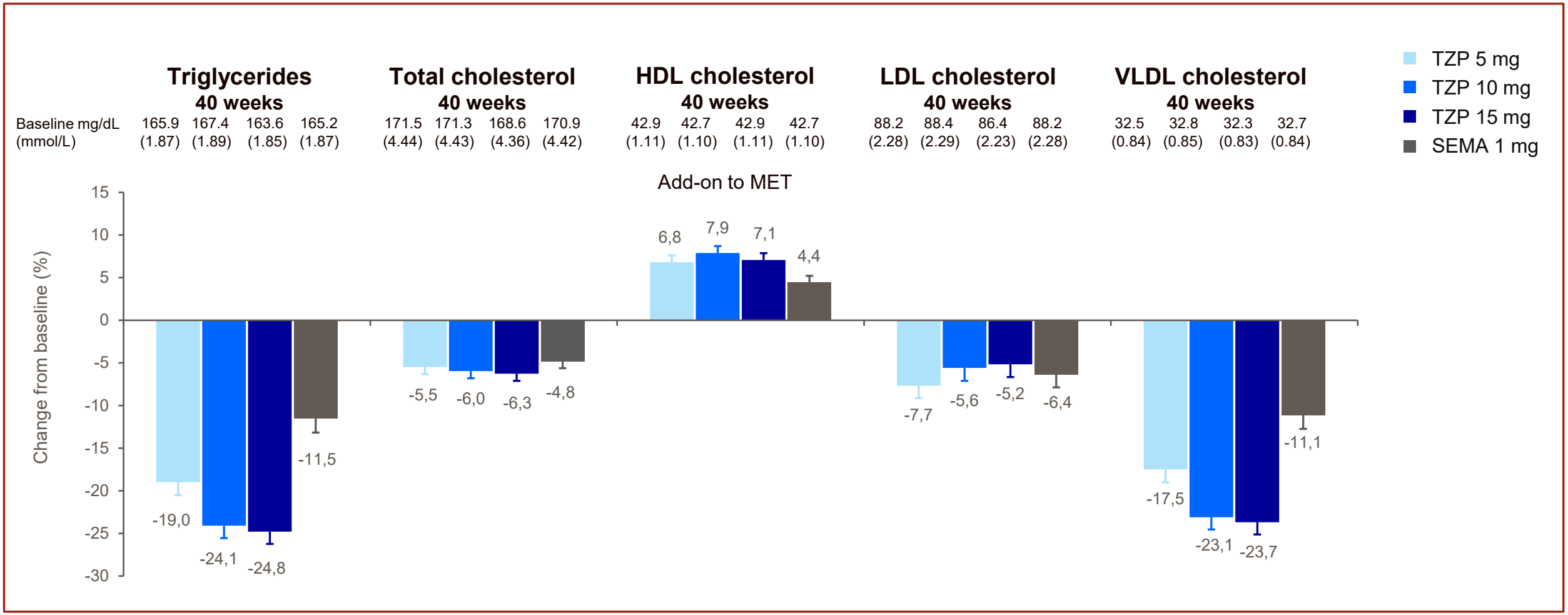
CV mortality

+1 mmol/L (39 mg/dL) LDL→ +50% di RR



Meta-analysis of prospective cohort studies in people with T2D

SURPASS-2: Tirzepatide Improves Serum Lipid Profile at 40 Weeks vs Semaglutide 1.0 mg



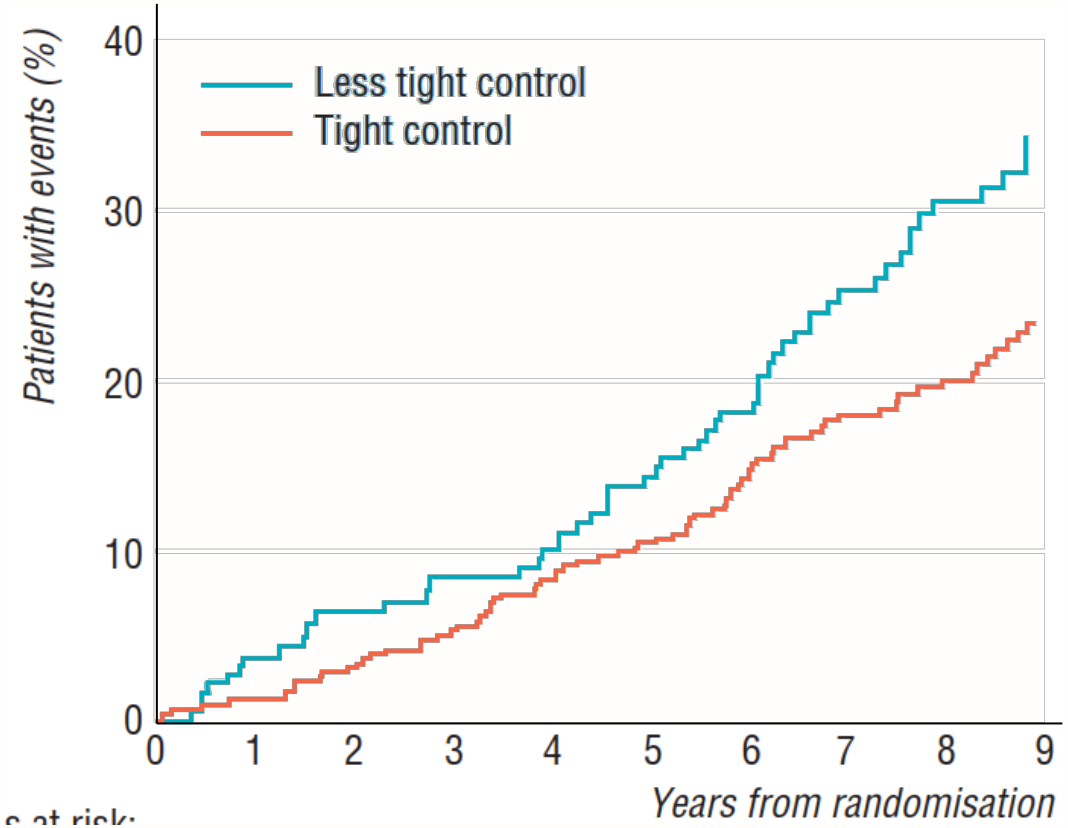
Data are estimated percentage means (SE) from MMRM analysis using log transformation; mITT population (efficacy analysis set).
HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide; VLDL = very-low-density lipoprotein.

Frias JP, et al. *N Engl J Med*. 2021

UKPDS: Blood pressure and CV mortality in diabetes

tight control: 144/82 mmHg
less tight control: 154/87 mmHg

Diabetes-related mortality causes

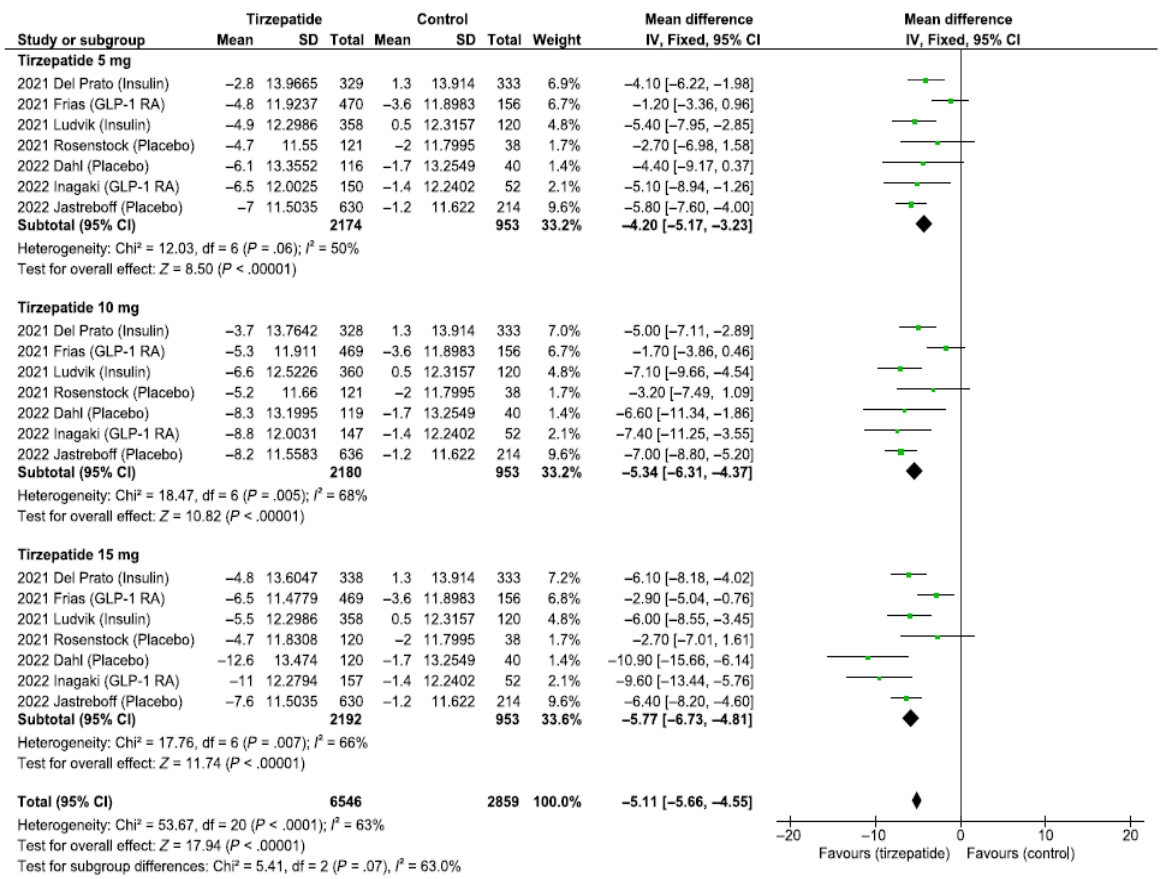


Risk reduction
32% (95%CI 6-51%)

** AMI, Sudden Death , Stroke, PAD, CKD*

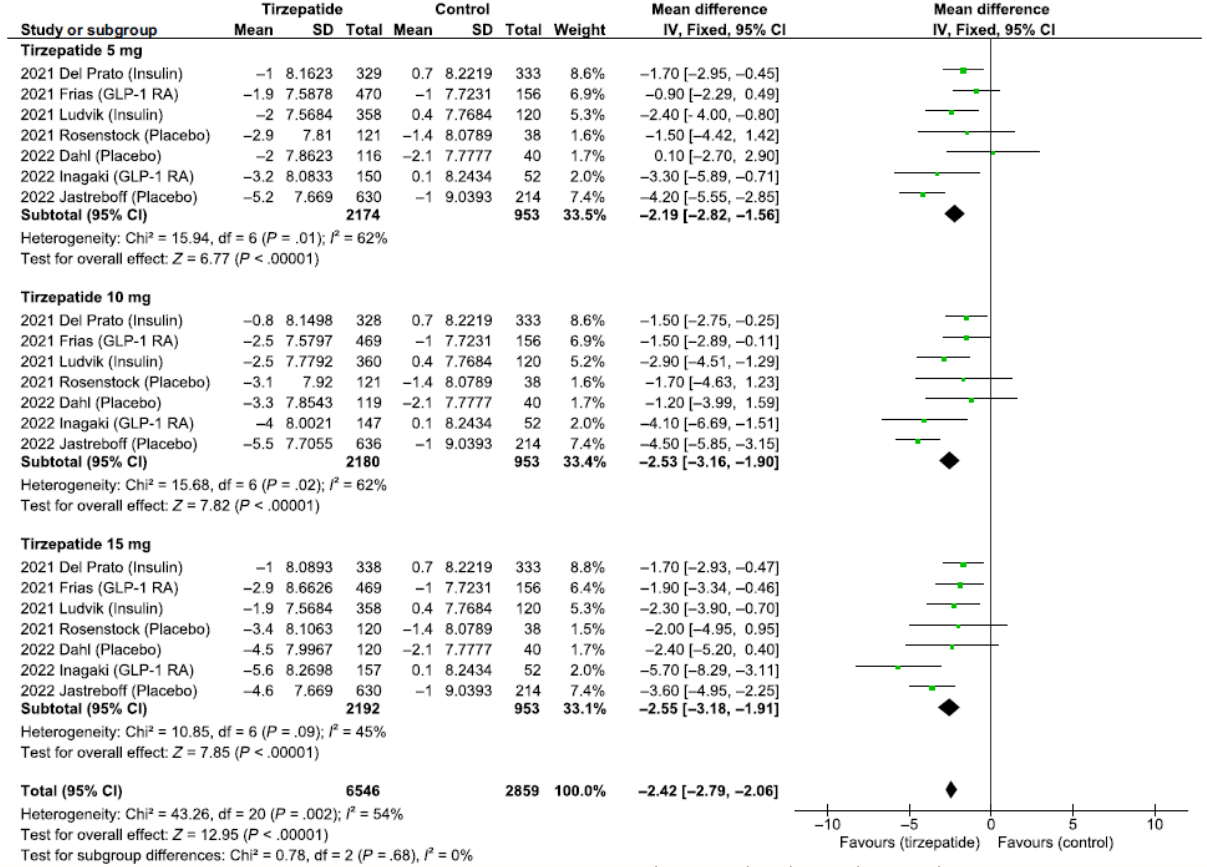
Effect of tirzepatide on blood pressure: metanalysis of the SURPASS program

systolic blood pressure



Study or subgroup	Tirzepatide Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Fixed, 95% CI
Tirzepatide 5 mg								
2021 Del Prato (Insulin)	−2.8	13.9665	329	1.3	13.914	333	6.9%	−4.10 [−6.22, −1.98]
2021 Frias (GLP-1 RA)	−4.8	11.9237	470	−3.6	11.8983	156	6.7%	−1.20 [−3.36, 0.96]
2021 Ludvik (Insulin)	−4.9	12.2986	358	0.5	12.3157	120	4.8%	−5.40 [−7.95, −2.85]
2021 Rosenstock (Placebo)	−4.7	11.55	121	−2	11.7995	38	1.7%	−2.70 [−6.98, 1.58]
2022 Dahl (Placebo)	−6.1	13.3552	116	−1.7	13.2549	40	1.4%	−4.40 [−9.17, 0.37]
2022 Inagaki (GLP-1 RA)	−6.5	12.0025	150	−1.4	12.2402	52	2.1%	−5.10 [−8.94, −1.26]
2022 Jastreboff (Placebo)	−7	11.5035	630	−1.2	11.622	214	9.6%	−5.80 [−7.60, −4.00]
Subtotal (95% CI)			**2174**			**953**	**33.2%**	**−4.20 [−5.17, −3.23]**
Heterogeneity: Chi² = 12.03, df = 6 (P = .06); I² = 50%								
Test for overall effect: Z = 8.50 (P < .00001)								
Tirzepatide 10 mg								
2021 Del Prato (Insulin)	−3.7	13.7642	328	1.3	13.914	333	7.0%	−5.00 [−7.11, −2.89]
2021 Frias (GLP-1 RA)	−5.3	11.911	469	−3.6	11.8983	156	6.7%	−1.70 [−3.86, 0.46]
2021 Ludvik (Insulin)	−6.6	12.5226	360	0.5	12.3157	120	4.8%	−7.10 [−9.66, −4.54]
2021 Rosenstock (Placebo)	−5.2	11.66	121	−2	11.7995	38	1.7%	−3.20 [−7.49, 1.09]
2022 Dahl (Placebo)	−8.3	13.1995	119	−1.7	13.2549	40	1.4%	−6.60 [−11.34, −1.86]
2022 Inagaki (GLP-1 RA)	−8.8	12.0031	147	−1.4	12.2402	52	2.1%	−7.40 [−11.25, −3.55]
2022 Jastreboff (Placebo)	−8.2	11.5583	636	−1.2	11.622	214	9.6%	−7.00 [−8.80, −5.20]
Subtotal (95% CI)			**2180**			**953**	**33.2%**	**−5.34 [−6.31, −4.37]**
Heterogeneity: Chi² = 18.47, df = 6 (P = .005); I² = 68%								
Test for overall effect: Z = 10.82 (P < .00001)								
Tirzepatide 15 mg								
2021 Del Prato (Insulin)	−4.8	13.6047	338	1.3	13.914	333	7.2%	−6.10 [−8.18, −4.02]
2021 Frias (GLP-1 RA)	−6.5	11.4779	469	−3.6	11.8983	156	6.8%	−2.90 [−5.04, −0.76]
2021 Ludvik (Insulin)	−5.5	12.2986	358	0.5	12.3157	120	4.8%	−6.00 [−8.55, −3.45]
2021 Rosenstock (Placebo)	−4.7	11.8308	120	−2	11.7995	38	1.7%	−2.70 [−7.01, 1.61]
2022 Dahl (Placebo)	−12.6	13.474	120	−1.7	13.2549	40	1.4%	−10.90 [−15.66, −6.14]
2022 Inagaki (GLP-1 RA)	−11	12.2794	157	−1.4	12.2402	52	2.1%	−9.60 [−13.44, −5.76]
2022 Jastreboff (Placebo)	−7.6	11.5035	630	−1.2	11.622	214	9.6%	−6.40 [−8.20, −4.60]
Subtotal (95% CI)			**2192**			**953**	**33.6%**	**−5.77 [−6.73, −4.81]**
Heterogeneity: Chi² = 17.76, df = 6 (P = .007); I² = 66%								
Test for overall effect: Z = 11.74 (P < .00001)								
Total (95% CI)			**6546**			**2859**	**100.0%**	**−5.11 [−5.66, −4.55]**
Heterogeneity: Chi² = 53.67, df = 20 (P < .0001); I² = 63%								
Test for overall effect: Z = 17.94 (P < .00001)								
Test for subgroup differences: Chi² = 5.41, df = 2 (P = .07), I² = 63.0%								

diastolic blood pressure



Study or subgroup	Tirzepatide Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Fixed, 95% CI
Tirzepatide 5 mg								
2021 Del Prato (Insulin)	−1	8.1623	329	0.7	8.2219	333	8.6%	−1.70 [−2.95, −0.45]
2021 Frias (GLP-1 RA)	−1.9	7.5878	470	−1	7.7231	156	6.9%	−0.90 [−2.29, 0.49]
2021 Ludvik (Insulin)	−2	7.5684	358	0.4	7.7684	120	5.3%	−2.40 [- 4.00, −0.80]
2021 Rosenstock (Placebo)	−2.9	7.81	121	−1.4	8.0789	38	1.6%	−1.50 [−4.42, 1.42]
2022 Dahl (Placebo)	−2	7.8623	116	−2.1	7.7777	40	1.7%	0.10 [−2.70, 2.90]
2022 Inagaki (GLP-1 RA)	−3.2	8.0833	150	0.1	8.2434	52	2.0%	−3.30 [−5.89, −0.71]
2022 Jastreboff (Placebo)	−5.2	7.669	630	−1	9.0393	214	7.4%	−4.20 [−5.55, −2.85]
Subtotal (95% CI)			**2174**			**953**	**33.5%**	**−2.19 [−2.82, −1.56]**
Heterogeneity: Chi² = 15.94, df = 6 (P = .01); I² = 62%								
Test for overall effect: Z = 6.77 (P < .00001)								
Tirzepatide 10 mg								
2021 Del Prato (Insulin)	−0.8	8.1498	328	0.7	8.2219	333	8.6%	−1.50 [−2.75, −0.25]
2021 Frias (GLP-1 RA)	−2.5	7.5797	469	−1	7.7231	156	6.9%	−1.50 [−2.89, −0.11]
2021 Ludvik (Insulin)	−2.5	7.7792	360	0.4	7.7684	120	5.2%	−2.90 [−4.51, −1.29]
2021 Rosenstock (Placebo)	−3.1	7.92	121	−1.4	8.0789	38	1.6%	−1.70 [−4.63, 1.23]
2022 Dahl (Placebo)	−3.3	7.8543	119	−2.1	7.7777	40	1.7%	−1.20 [−3.99, 1.59]
2022 Inagaki (GLP-1 RA)	−4	8.0021	147	0.1	8.2434	52	2.0%	−4.10 [−6.69, −1.51]
2022 Jastreboff (Placebo)	−5.5	7.7055	636	−1	9.0393	214	7.4%	−4.50 [−5.85, −3.15]
Subtotal (95% CI)			**2180**			**953**	**33.4%**	**−2.53 [−3.16, −1.90]**
Heterogeneity: Chi² = 15.68, df = 6 (P = .02); I² = 62%								
Test for overall effect: Z = 7.82 (P < .00001)								
Tirzepatide 15 mg								
2021 Del Prato (Insulin)	−1	8.0893	338	0.7	8.2219	333	8.8%	−1.70 [−2.93, −0.47]
2021 Frias (GLP-1 RA)	−2.9	8.6626	469	−1	7.7231	156	6.4%	−1.90 [−3.34, −0.46]
2021 Ludvik (Insulin)	−1.9	7.5684	358	0.4	7.7684	120	5.3%	−2.30 [−3.90, −0.70]
2021 Rosenstock (Placebo)	−3.4	8.1063	120	−1.4	8.0789	38	1.5%	−2.00 [−4.95, 0.95]
2022 Dahl (Placebo)	−4.5	7.9967	120	−2.1	7.7777	40	1.7%	−2.40 [−5.20, 0.40]
2022 Inagaki (GLP-1 RA)	−5.6	8.2698	157	0.1	8.2434	52	2.0%	−5.70 [−8.29, −3.11]
2022 Jastreboff (Placebo)	−4.6	7.669	630	−1	9.0393	214	7.4%	−3.60 [−4.95, −2.25]
Subtotal (95% CI)			**2192**			**953**	**33.1%**	**−2.55 [−3.18, −1.91]**
Heterogeneity: Chi² = 10.85, df = 6 (P = .09); I² = 45%								
Test for overall effect: Z = 7.85 (P < .00001)								
Total (95% CI)			**6546**			**2859**	**100.0%**	**−2.42 [−2.79, −2.06]**
Heterogeneity: Chi² = 43.26, df = 20 (P = .002); I² = 54%								
Test for overall effect: Z = 12.95 (P < .00001)								
Test for subgroup differences: Chi² = 0.78, df = 2 (P = .68), I² = 0%								

Kanbay M et al. Diabetes Obes Metab. 2023;1–13.

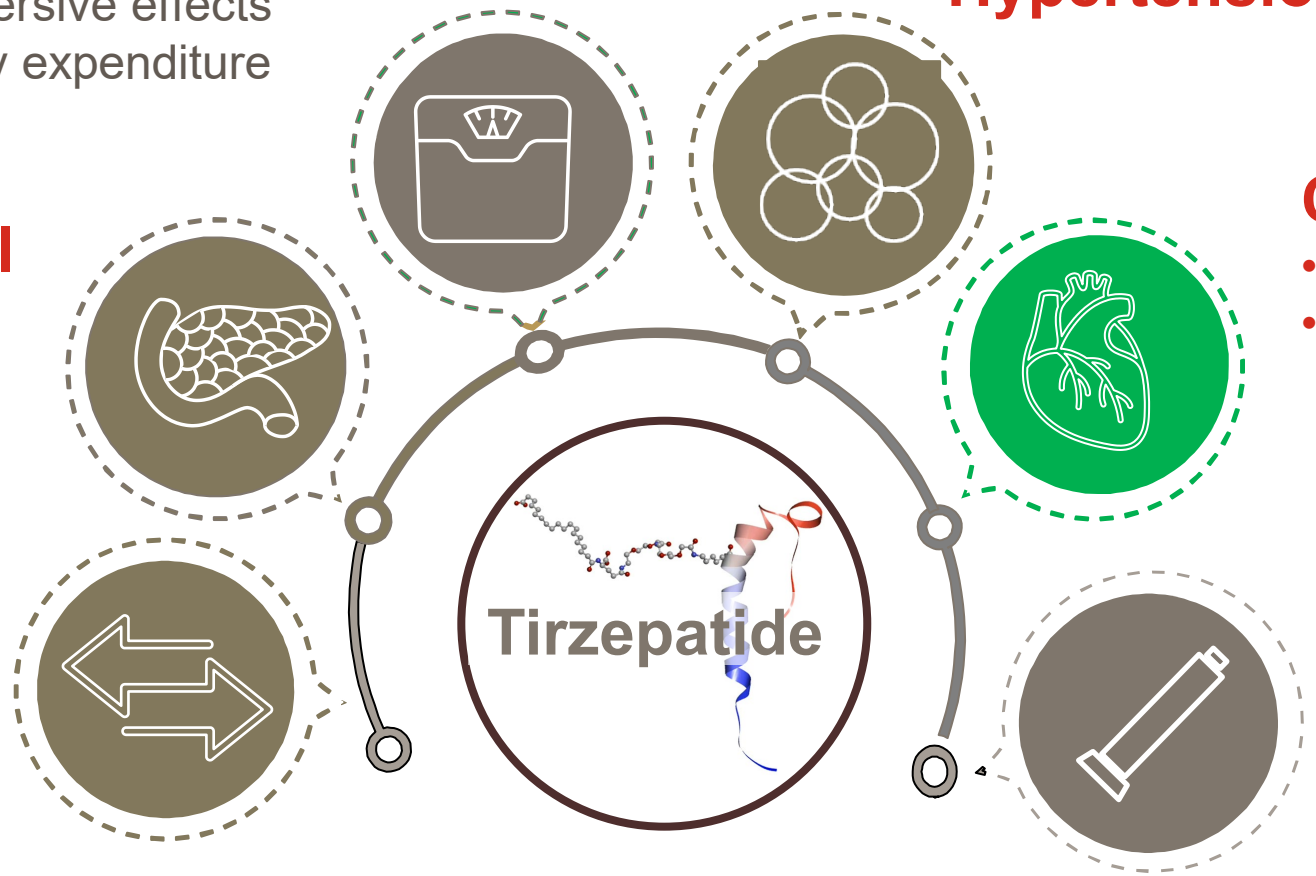
Tirzepatide: cardiovascular effect

Weight loss
- Food intake
- Antiaversive effects
- Energy expenditure

Lipid metabolism and Hypertension

Glycemic control
- Effect on HbA1C

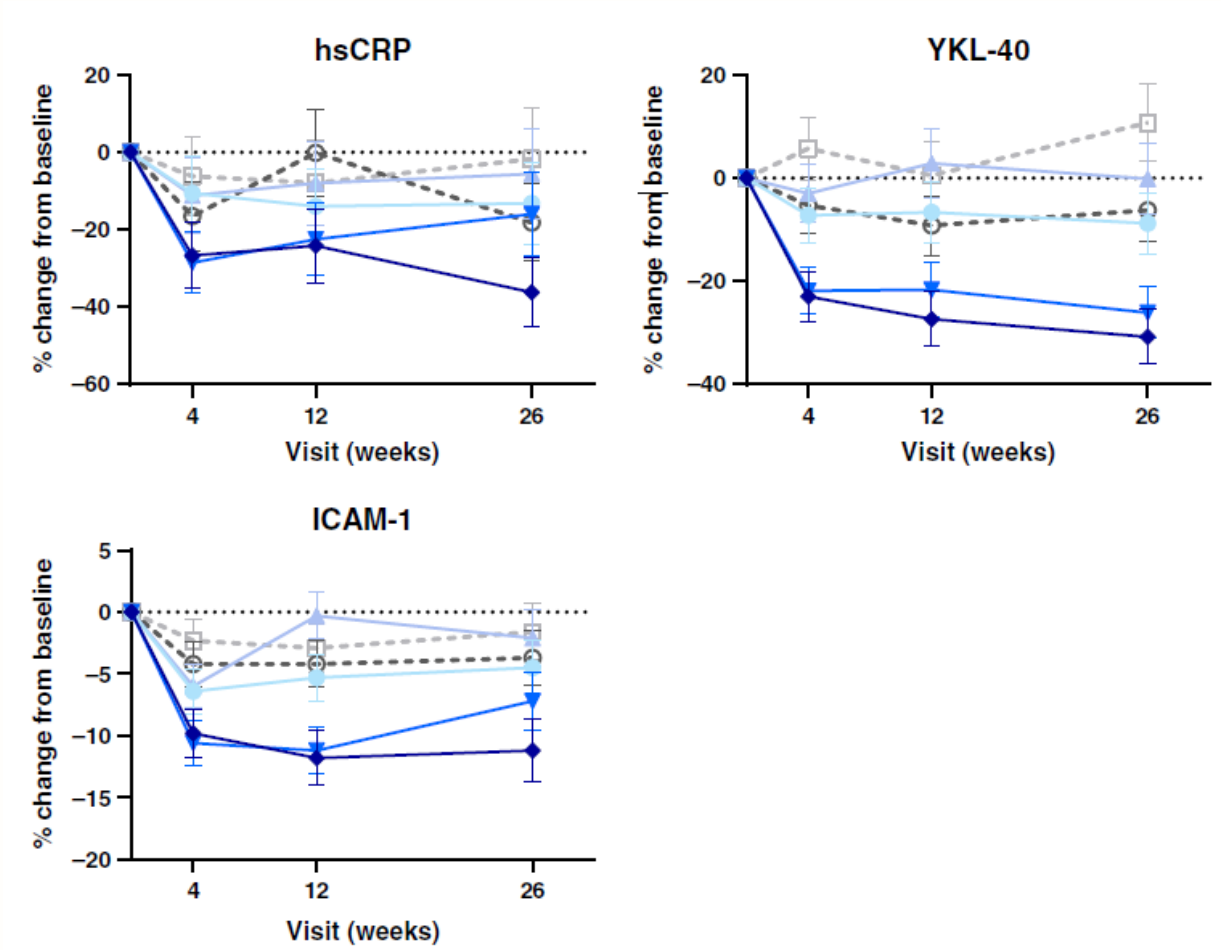
Cardiovascular
- Inflammation
- Endothelial function



Receptor pharmacology
Dual agonism

Dose escalation

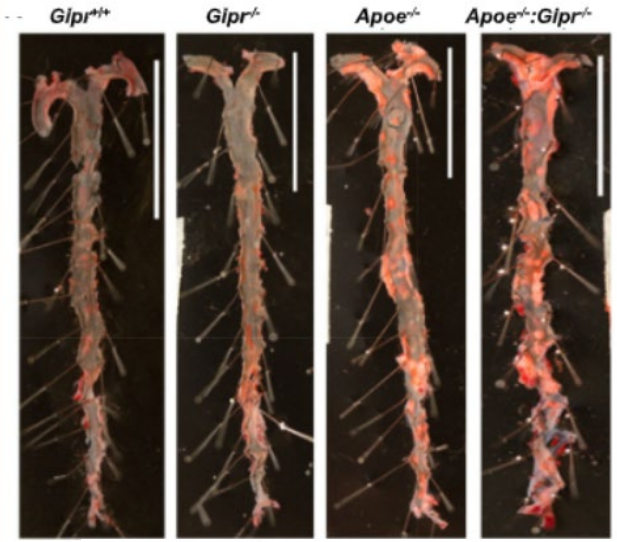
Tirzepatide improves inflammatory biomarkers in phase 2 study

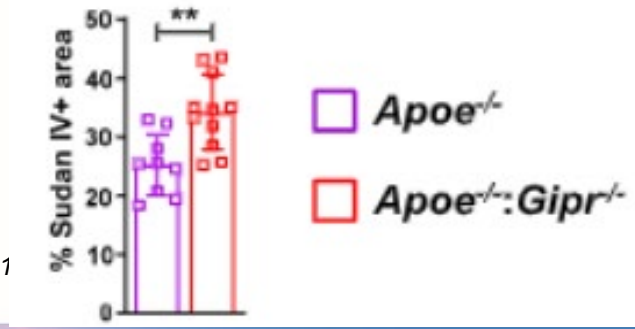


Wilson et al. Diabetes Obes Metab. 2021;1–6.

GIP protects from atherosclerosis in mice

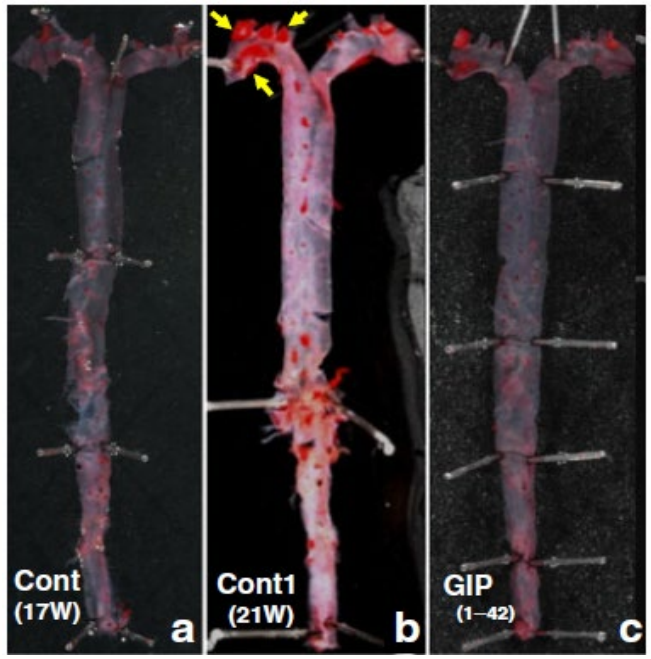
GIPR deletion increases atherosclerotic area

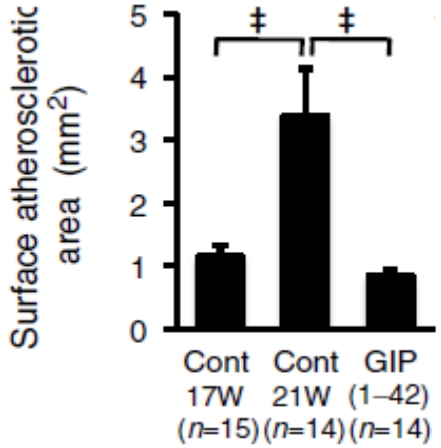




Mol Metab. 2022 Aug 31

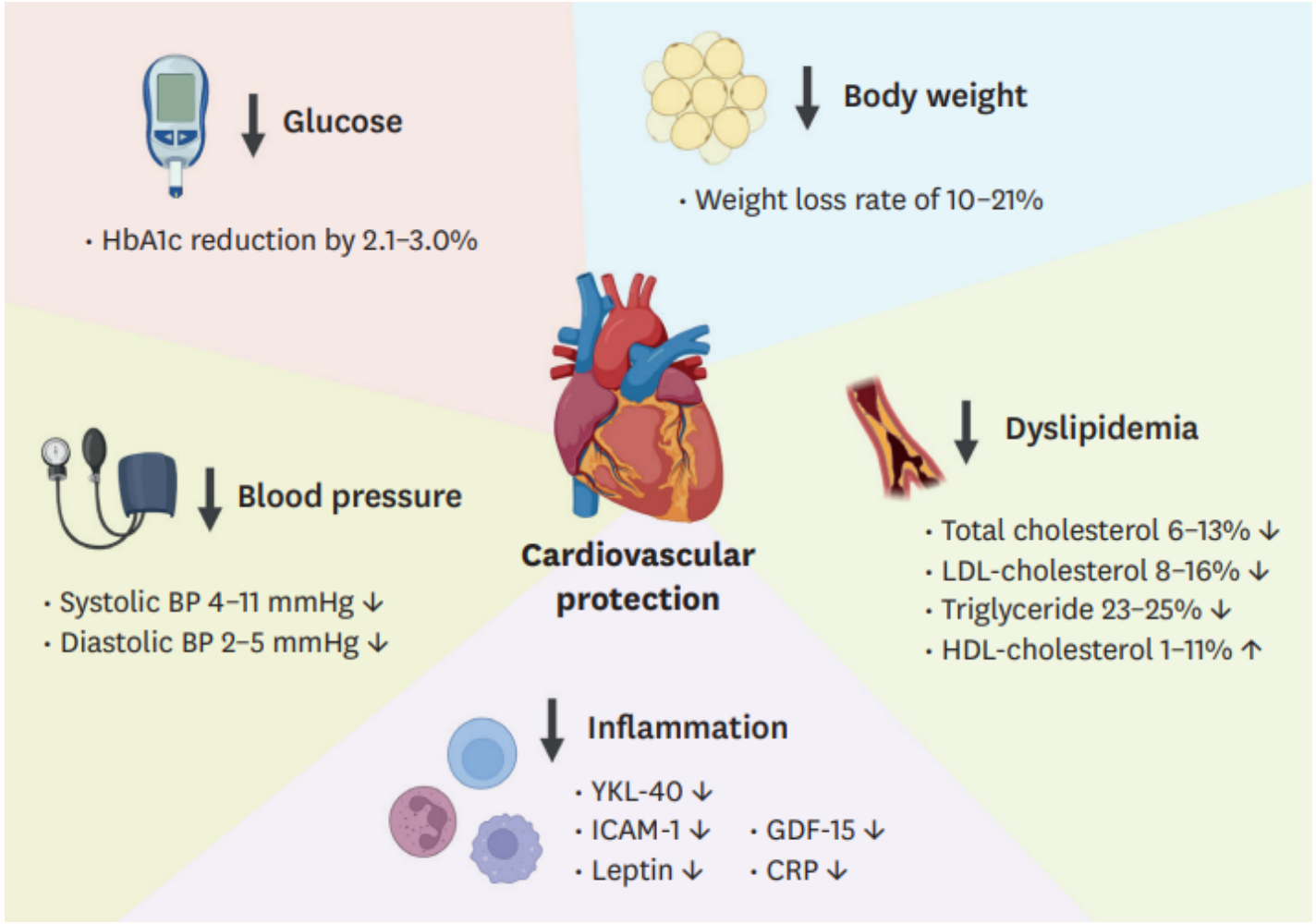
GIP administration decreases surface atherosclerotic area





Diabetologia (2011) 54:2649–2659

Tirzepatide- induced CV risk factors reduction: summary.



Cho YK. The Cardiovascular Effect of Tirzepatide: A Glucagon-Like Peptide-1 and Glucose-Dependent Insulinotropic Polypeptide Dual Agonist. J Lipid Atheroscler. 2023 Sep;12(3):213-222

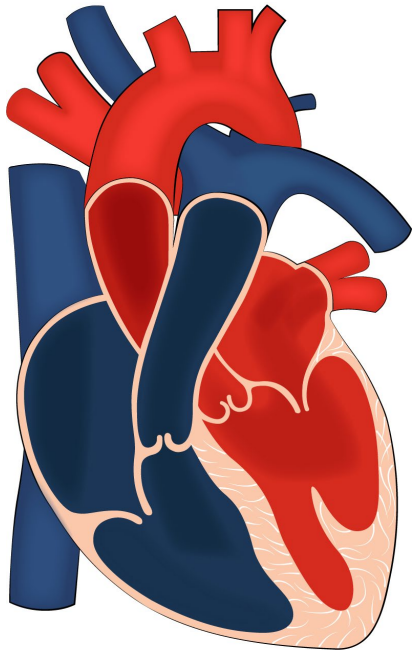
SURPASS-CVOT: Background

ELIXA
Lixisenatide

AMPLITUDE-O
Efpeglenatide

LEADER
Liraglutide

SUSTAIN-6
Semaglutide



HARMONY OUTCOMES
Albiglutide

SURPASS-CVOT
Tirzepatide

EXSCEL
Exenatide-ER

REWIND
Dulaglutide

PIONEER-6
Semaglutide

SOUL
Semaglutide

Superior vs. placebo for MACE

Non-inferior vs. placebo for MACE

Study ongoing

Several GLP-1RAs showed macrovascular protection by reducing the occurrence of MACE in participants with T2D and increased CV risk

Earlier studies demonstrated that TZP did not increase CV risk in people with T2D.
However, it's effect on reducing risk of atherosclerotic cardiovascular events in T2D has not been established

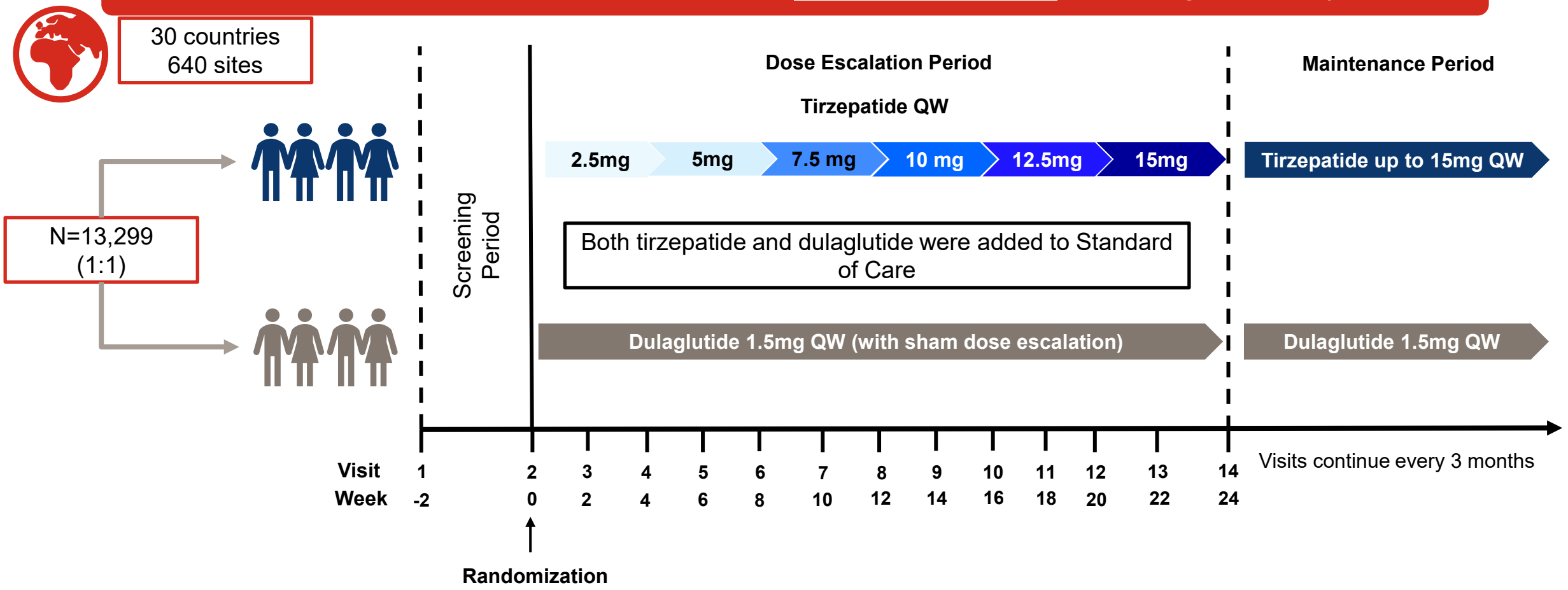
SURPASS-CVOT is designed to confirm the CV safety of TZP and assess the cardioprotective effect of TZP in patients with T2DM **in comparison with dulaglutide**, a GLP-1RA with established CV benefit

ASCVD=Atherosclerotic Cardiovascular Disease; CV=Cardiovascular; CVOT=Cardiovascular Outcomes Trial; GLP-1RA=Glucagon-like Peptide 1 Receptor Agonist; MACE=Major Adverse Cardiovascular Event; T2D=Type 2 Diabetes; TZP=Tirzepatide.

Nicholls SJ, et al. *Am Heart J.* 2023;S0002-8703(23)00280-6.

SURPASS-CVOT: Study Design

Event driven, randomized, double blind, **active comparator**, parallel group study



QW=Once Weekly.

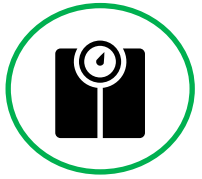
Nicholls SJ, et al. *Am Heart J.* 2023;S0002-8703(23)00280-6.

Key Inclusion and Exclusion Criteria

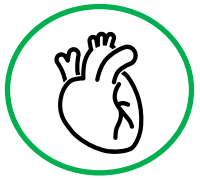
Inclusion Criteria

Men or women aged ≥40 years

T2D (HbA1c ≥7% and ≤10.5%)



BMI ≥25kg/m^2

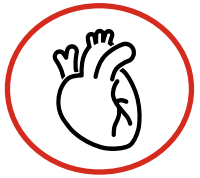


Established ASCVD, including ≥1 of the following

- Coronary artery disease
- Cerebrovascular disease
- Peripheral artery disease

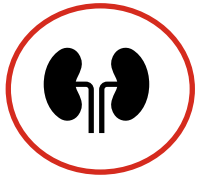
Exclusion Criteria

HbA1c > 10.5%



- Hospitalization for CHF, chronic NYHA class IV HF and planned coronary, carotid or peripheral revascularization
- CV event or intervention <60 days prior to screening

History of acute or chronic pancreatitis



eGFR <15 mL/minute/1.73m^2 or on chronic dialysis

GLP-1RA or pramlintide treatment within 3 months prior to visit 1

ASCVD=Atherosclerotic cardiovascular disease; BMI=Body Mass Index; CHF=Congestive Heart Failure; CV=Cardiovascular; eGFR=Estimated Glomerular Filtration Rate; GLP-1RA=Glucagon-like Peptide 1 Receptor Agonist; HbA1c=Glycated Hemoglobin; HF=Heart Failure; NYHA=New York Heart Association; T2D=Type 2 Diabetes.

Nicholls SJ, et al. *Am Heart J.* 2023;S0002-8703(23)00280-6.

SURPASS-CVOT: Objectives and Endpoints

Primary Objective

Time to first occurrence of any component of MACE, which includes the following

- CV Death
- Myocardial Infarction
- Stroke

Key Secondary Objective

- Time to death due to any cause
- Time to CV death
- Time to first occurrence of MI, stroke and expanded composite CV outcome
- Cumulative number of CV deaths and total HF events requiring hospitalization and/or urgent HF visits

CV=Cardiovascular; MACE=Major Adverse Cardiovascular Event; TZP=Tirzepatide.
Nicholls SJ, et al. *Am Heart J.* 2023

Three Scenarios of Possible Trial Results

Upper Limit of 95% CI of HR for MACE-3 for TZP vs. Dulaglutide	Interpretation	Clinical Implications
≥1.05 but <1.23	TZP non-inferior to putative placebo	TZP confers no increased CV risk
≥1.00 but <1.05	TZP non-inferior to dulaglutide, and superior to putative placebo	TZP and dulaglutide are cardioprotective
<1.00	TZP is superior to dulaglutide	TZP has more cardioprotective effects than dulagluide

CI=Confidence Interval; HR=Hazard Ratio; MACE-3=3-Point Major Adverse Cardiovascular Event; TZP=Tirzepatide.
Nicholls SJ, et al. *Am Heart J.* 2023;S0002-8703(23)00280-6.

TIRZEPATIDE CV PROFILE IN REAL LIFE

Original Investigation | Diabetes and Endocrinology

Clinical Outcomes of Tirzepatide or GLP-1 Receptor Agonists in Individuals With Type 2 Diabetes

Min-Hsiang Chuang, MD; Jui-Yi Chen, MD; Hsien-Yi Wang, MD; Zheng-Hong Jiang, MD; Vin-Cent Wu, MD, PhD

Abstract

IMPORTANCE Despite its demonstrated benefits in improving cardiovascular risk profiles, the association of tirzepatide with mortality and cardiovascular and kidney outcomes compared with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) remains unknown.

OBJECTIVE To investigate the association of tirzepatide with mortality and adverse cardiovascular and kidney outcomes compared with GLP-1 RAs in patients with type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used US Collaborative Network of TriNetX data collected on individuals with type 2 diabetes aged 18 years or older initiating tirzepatide or GLP-1 RA between June 1, 2022, and June 30, 2023; without stage 5 chronic kidney disease or kidney failure at baseline; and without myocardial infarction or ischemic or hemorrhagic stroke within 60 days of drug initiation.

EXPOSURES Treatment with tirzepatide compared with GLP-1 RA.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality, and secondary outcomes included major adverse cardiovascular events (MACEs), the composite of MACEs and all-cause mortality, kidney events, acute kidney injury, and major adverse kidney events. All outcomes were analyzed using Cox proportional hazards regression models.

RESULTS There were 14 834 patients treated with tirzepatide (mean [SD] age, 55.4 [11.8] years; 8444 [56.9%] female) and 125 474 treated with GLP-1 RA (mean [SD] age, 58.1 [13.3] years; 67 474 [53.8%] female). After a median (IQR) follow-up of 10.5 (5.2-15.7) months, 95 patients (0.6%) in the tirzepatide group and 166 (1.1%) in the GLP-1 RA group died. Tirzepatide treatment was associated with lower hazards of all-cause mortality (adjusted hazard ratio [AHR], 0.58; 95% CI, 0.45-0.75), MACEs (AHR, 0.80; 95% CI, 0.71-0.91), the composite of MACEs and all-cause mortality (AHR, 0.76; 95% CI, 0.68-0.84), kidney events (AHR, 0.52; 95% CI, 0.37-0.73), acute kidney injury (AHR, 0.78; 95% CI, 0.70-0.88), and major adverse kidney events (AHR, 0.54; 95% CI, 0.44-0.67). Treatment with tirzepatide was associated with greater decreases in glycated hemoglobin (treatment difference, −0.34 percentage points; 95% CI, −0.44 to −0.24 percentage points) and body weight (treatment difference, −2.9 kg, 95% CI, −4.8 to −1.1 kg) compared with GLP-1 RA. An interaction test for subgroup analysis revealed consistent results stratified by estimated glomerular filtration rate, glycated hemoglobin level, body mass index, comedications, and comorbidities.

CONCLUSIONS AND RELEVANCE In this study, treatment with tirzepatide was associated with lower hazards of all-cause mortality, adverse cardiovascular events, acute kidney injury, and adverse kidney events compared with GLP-1 RA in patients with type 2 diabetes. These findings support the integration of tirzepatide into therapeutic strategies for this population.

Key Points

Question What is the association of tirzepatide vs glucagon-like peptide 1 receptor agonist (GLP-1 RA) treatment with all-cause mortality and adverse cardiovascular or kidney events in US patients with type 2 diabetes?

Findings In this cohort study of 140 308 patients with type 2 diabetes, treatment with tirzepatide was associated with significantly lower hazards of all-cause mortality and major adverse cardiovascular and kidney events compared with GLP-1 RA.

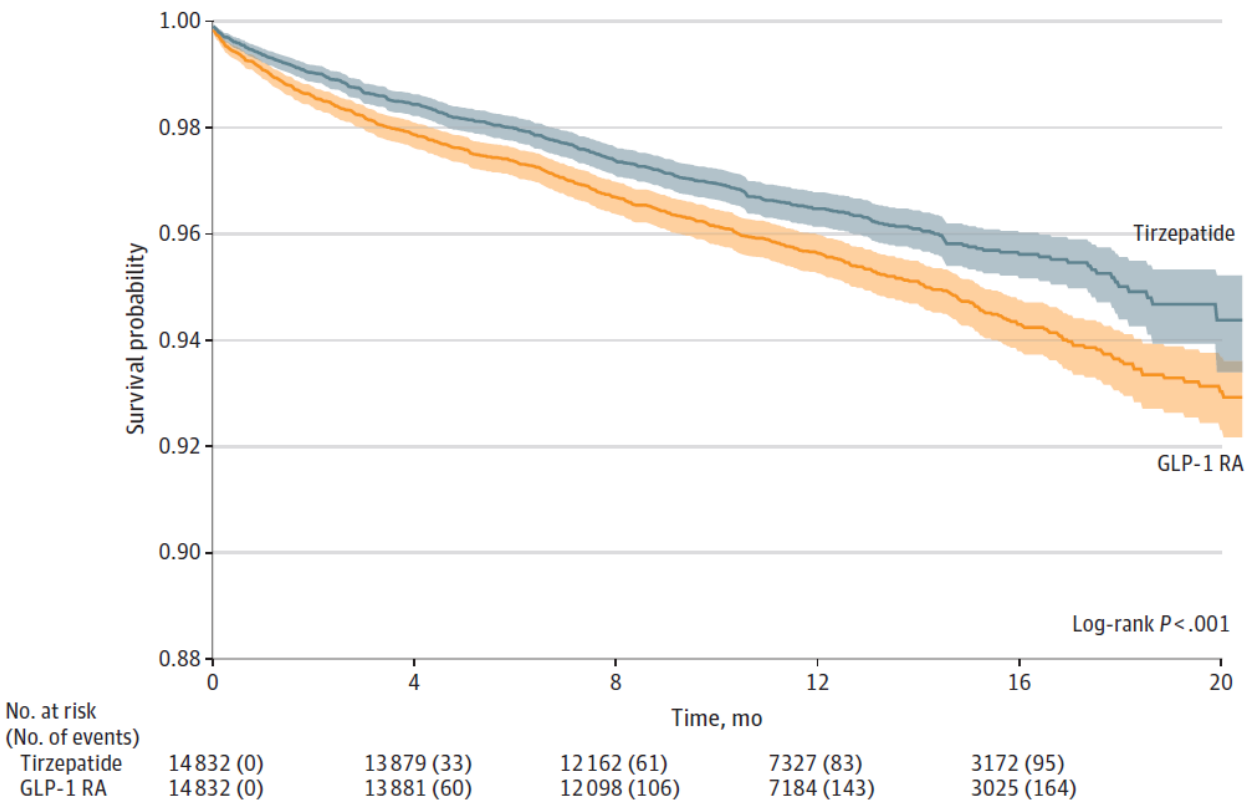
Meaning These findings suggest that treatment with tirzepatide may confer additional clinical benefits for patients with type 2 diabetes.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Tirzepatide and Real World Evidence

All-Cause Mortality



No. at risk (No. of events)					
Tirzepatide	14832 (0)	13879 (33)	12162 (61)	7327 (83)	3172 (95)
GLP-1 RA	14832 (0)	13881 (60)	12098 (106)	7184 (143)	3025 (164)

- Mortalità per tutte le cause (HR 0,58; 95% CI, 0,45-0,75)
- MACE (HR 0,80; 95% CI, 0,71-0,91)
- MACE e mortalità per tutte le cause (HR, 0,76; 95% CI, 0,68-0,84)
- Eventi renali (HR, 0,52; 95% CI, 0,37-0,73)
- Lesioni renali acute (HR, 0,78; 95% CI, 0,70-0,88)
- Eventi renali avversi maggiori (HR 0.54; 95% CI, 0.44-0.67)

Clinical Outcomes of Tirzepatide or GLP-1 Receptor Agonists in Individuals With Type 2 Diabetes- Min-Hsiang Chuang, et al- Jama Open Network

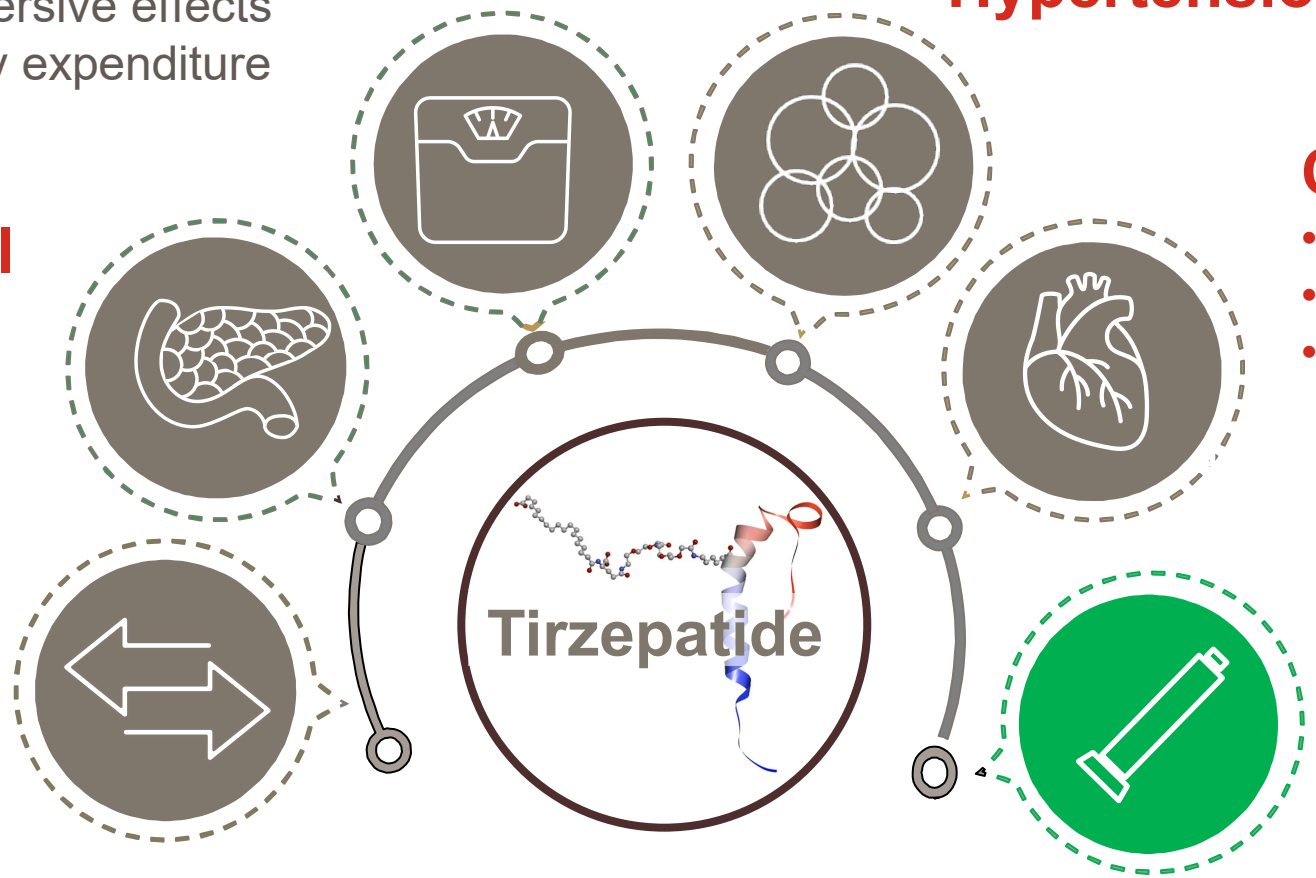
Tirzepatide: dose escalation

Weight loss
- Food intake
- Antiaversive effects
- Energy expenditure

Lipid metabolism and Hypertension

Glycemic control
- Effect on HbA1C

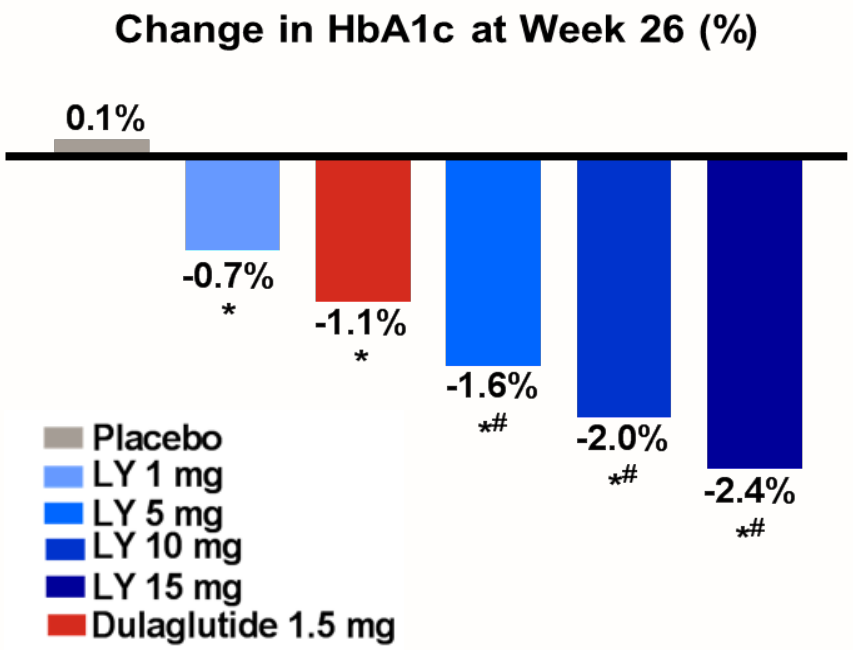
Cardiovascular
- Plasma lipid control
- Inflammation
- Endothelial function

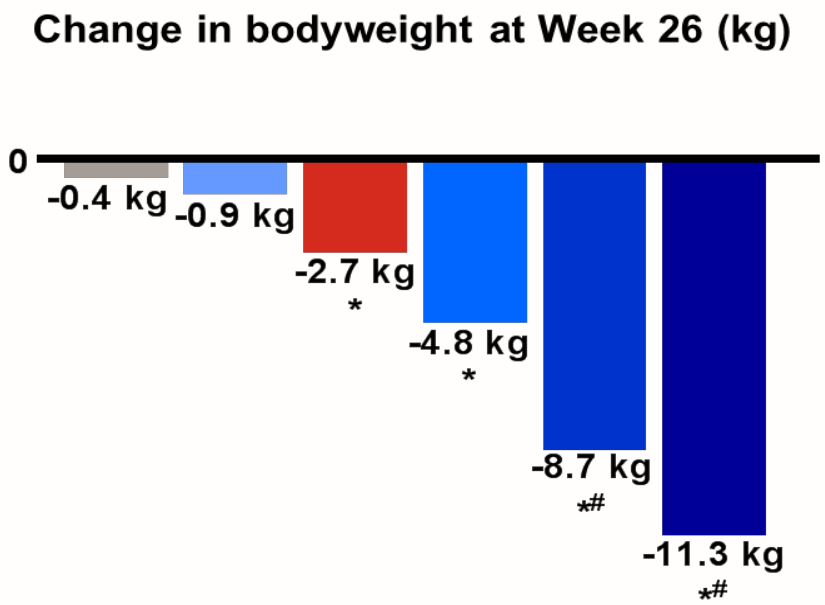


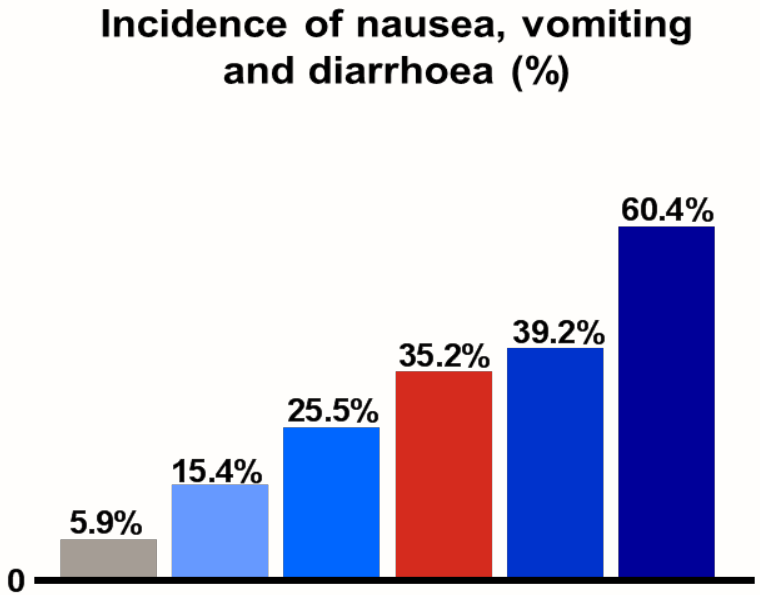
Receptor pharmacology
- Dual agonism

Dose escalation

Is the efficacy balanced with tolerability?





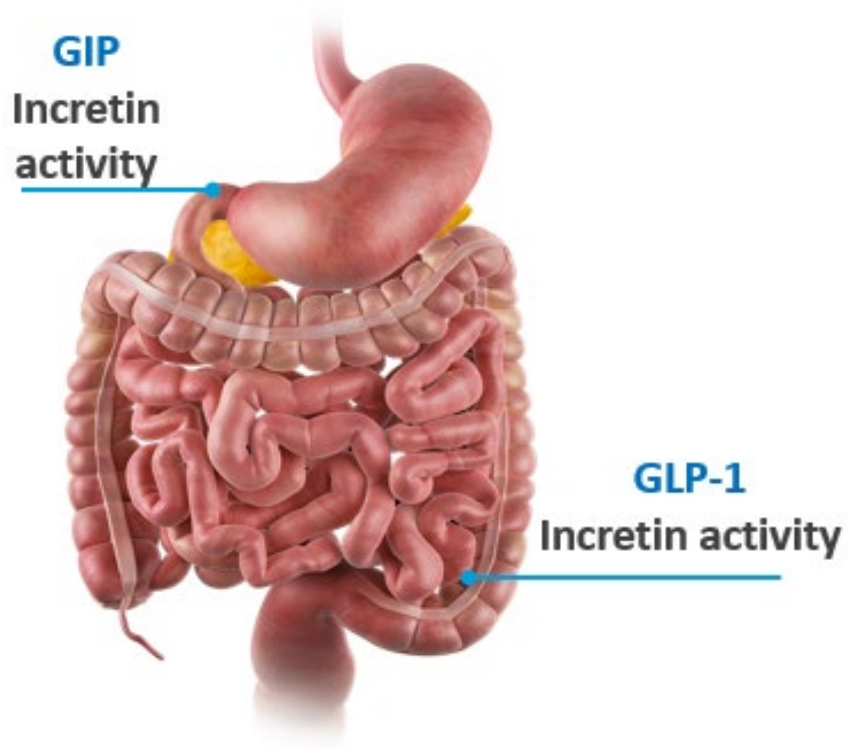


Upon a significantly higher efficacy with tirzepatide beginning from 5 mg, there is not a proportional increased incidence of GI EAs

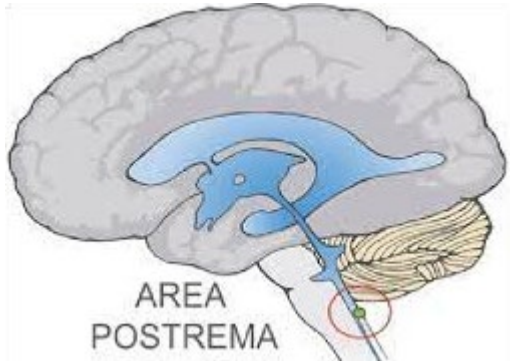
Data for change in HbA1c and bodyweight presented are LS mean ± SE, MMRM on treatment analysis. *,#p<.05 vs placebo and vs. dulaglutide 1.5 mg, respectively.
Frias JP et al. *Lancet* 2018; (in press) DOI: 10.1016/S0140-6736(18)32260-8

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

Hormone site of production may impact differently gastric emptying



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

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.

Take Home Messages

- Ad oggi tirzepatide rappresenta nel paziente diabetico, anche a dosaggi non massimali, la terapia più efficace in termini di compenso glicemico e di calo ponderale senza determinare incrementi significativi di AEs.
- L'utilizzo di Tirzepatide ha mostrato effetti benefici sulle singole determinanti e sui markers laboratoristici di rischio CV.
- In attesa dei risultati del SURPASS-CVOT, i dati provenienti da studi di RWE su larga scala attribuirebbero a tirzepatide effetti cardio- e nefroprotettivi.