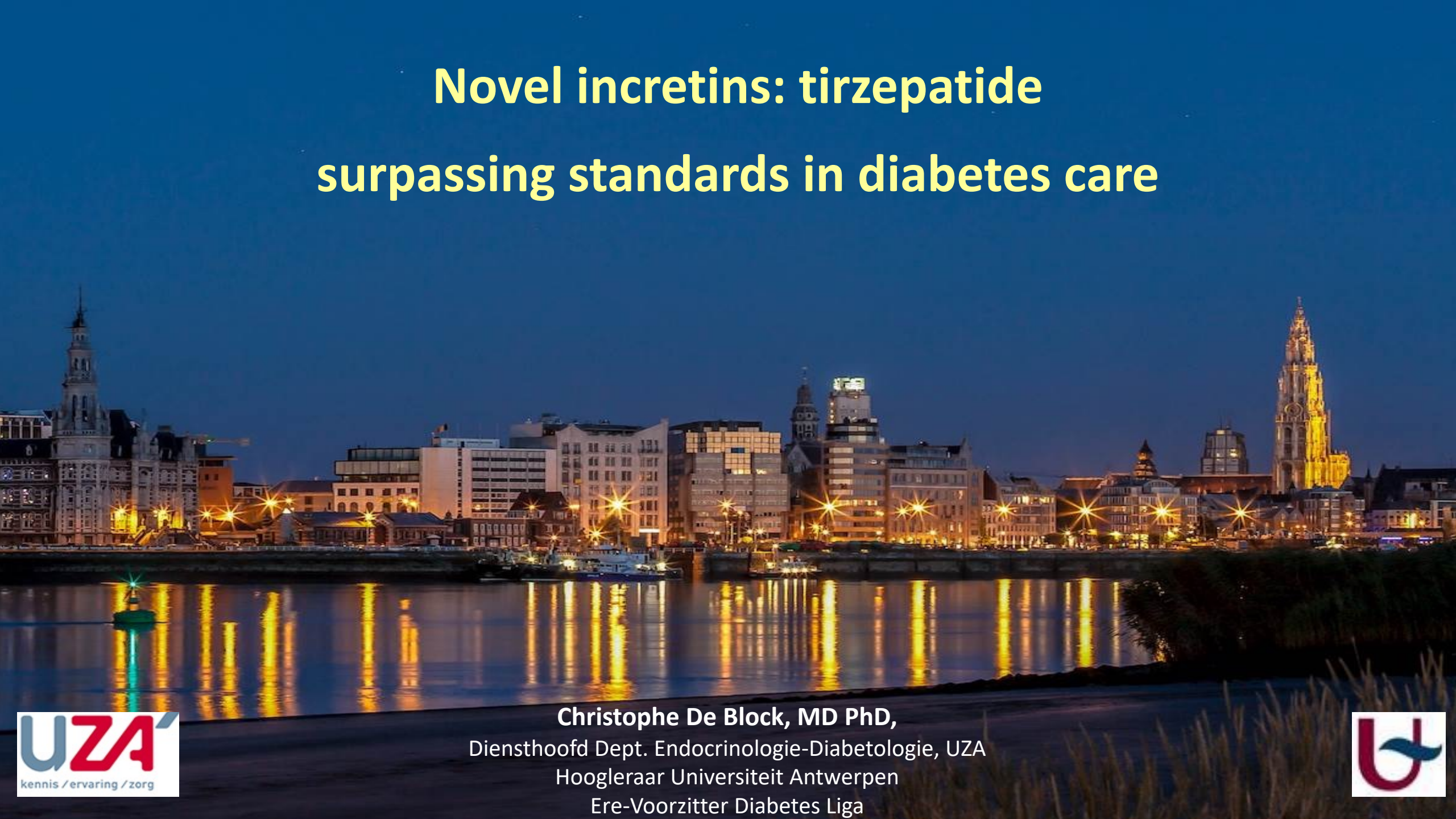
Novel incretins: tirzepatide surpassing standards in diabetes care



Christophe De Block, MD PhD,
Diensthoofd Dept. Endocrinologie-Diabetologie, UZA
Hoogleraar Universiteit Antwerpen
Ere-Voorzitter Diabetes Liga

Target achievement in type 2 diabetes

Unmet needs

Glycaemic control

~30-60% of people with diabetes are not at target HbA_{1c}

Hypoglycaemic events are **a barrier** to achieving target HbA_{1c}

Fear of hypo can also lead to some patients skipping medication

Weight

65-80% of subjects are overweight or obese

a 5-10% weight loss contributes to CV risk reduction

Patients often worry about **weight gain**, and this can lead to them skipping injections or reducing their dose

Cardiovascular risk factors

~50% reach BP targets

~60% for lipid targets

CVD disease accounts for 60-80% of total mortality

Complexity

avoid complex insulin regimens

improve therapy adherence and persistence

Fang M et al. NEJM 2021; 384: 2219-2228.

Mauricio D et al. Diabetes Obes Metab. 2017; 19(8): 1155-1164

Pedersen Bjergaard U et al. Diabetes Res Clin Pract. 2014;106(Suppl. 1):S104-106

Russell-Jones D, Khan R. Diabetes Obes Metab. 2007;9(6):799-812

Carver C. Diabetes Educ. 2006;32(6):910–7

Khunti, Ceriello, Cos, De Block. Diab Res Clin Pract 2018; 137; 137-148

Giugliano et al. Diabetes Care 2011;34:510–17

Peyrot et al. Diabet Med 2012;29:682–9

Hex et al. Diabet Med 2012;29:855–62

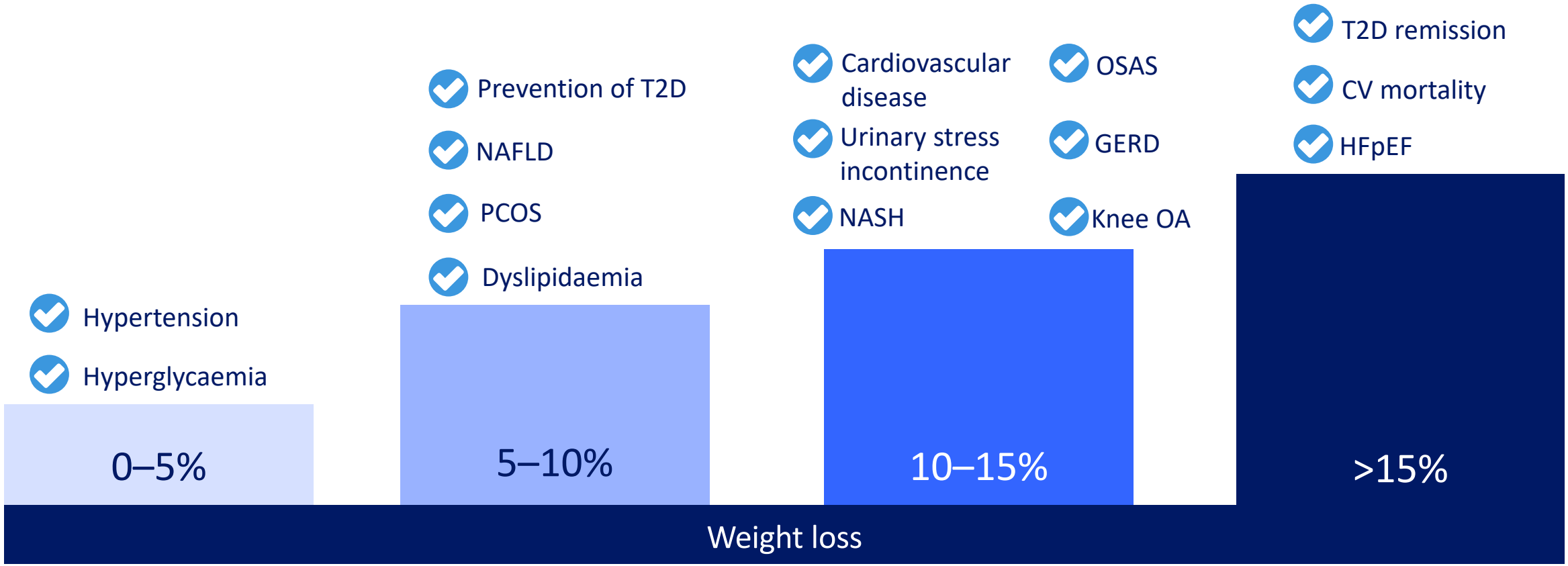
HbA1c and body weight target achievement

	HbA1c[1,4]	Body weight[1-9]	
		≥5% loss	≥10 loss
• Liraglutide (1.2 mg or 1.8 mg)	43–51%	18%	4%
• Exenatide extended release (2.0 mg)	63%	17%	4%
• Dulaglutide (0.75 mg or 1.5 mg)	62–63%	23–30%	3–8%
• Semaglutide (1.0 mg)	72–79%	45–66%	13–27%

HbA1c = glycated haemoglobin.

[1]Sorli C, et al. *Lancet Diabetes Endocrinol*. 2017;5(4):251–260; [2]Ahrén B, et al. *Lancet Diabetes Endocrinol*. 2017;5(5):341–354; [3]Ahmann AJ, et al. *Diabetes Care*. 2018;41(2):258–266; [4]Pratley RE, et al. *Lancet Diabetes Endocrinol*. 2018;6(4):275–286; [5]Lingvay I, et al. *Lancet Diabetes Endocrinol*. 2019;7(11):834–844; [6]Zinman B, et al. *Lancet Diabetes Endocrinol*. 2017;7(5):356–367; [7]Capehorn MS, et al. *Diabetes Metab*. 2020;46(2):100–109; [8]Aroda VR, et al. *Lancet Diabetes Endocrinol*. 2017;5(5):355–366; [9]Rodbard HW, et al. *J Clin Endocrinol Metab*. 2018;103(6):2291–2301.

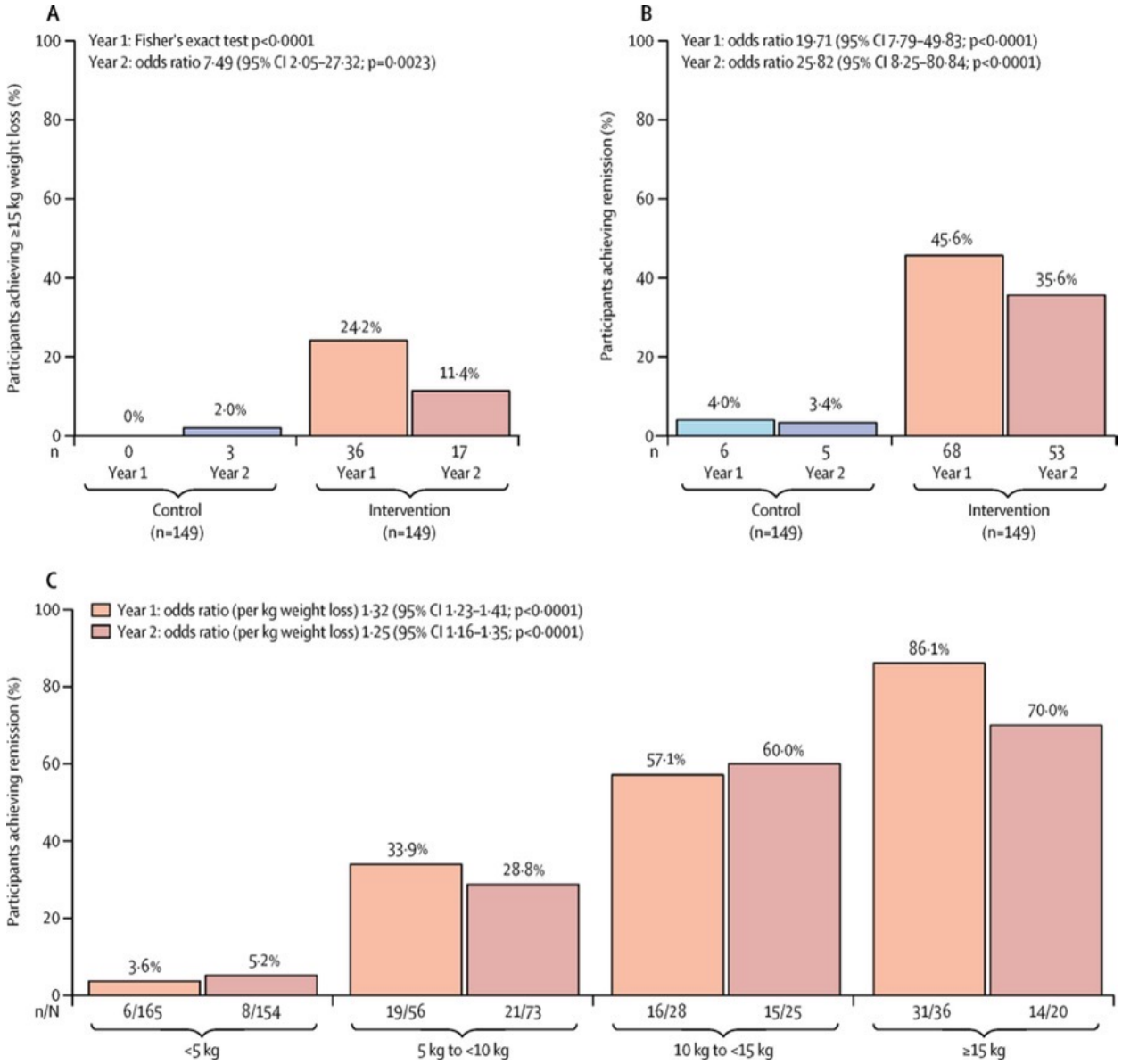
Benefits of weight loss



CV, cardiovascular; GERD, gastro-oesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome; TG, triglycerides.

Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21; Lean ME et al. Lancet 2018;391:541–51; Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61; Sundström J et al. Circulation 2017;135:1577–85.

Intensive Structured Weight Management: the DiRect RCT



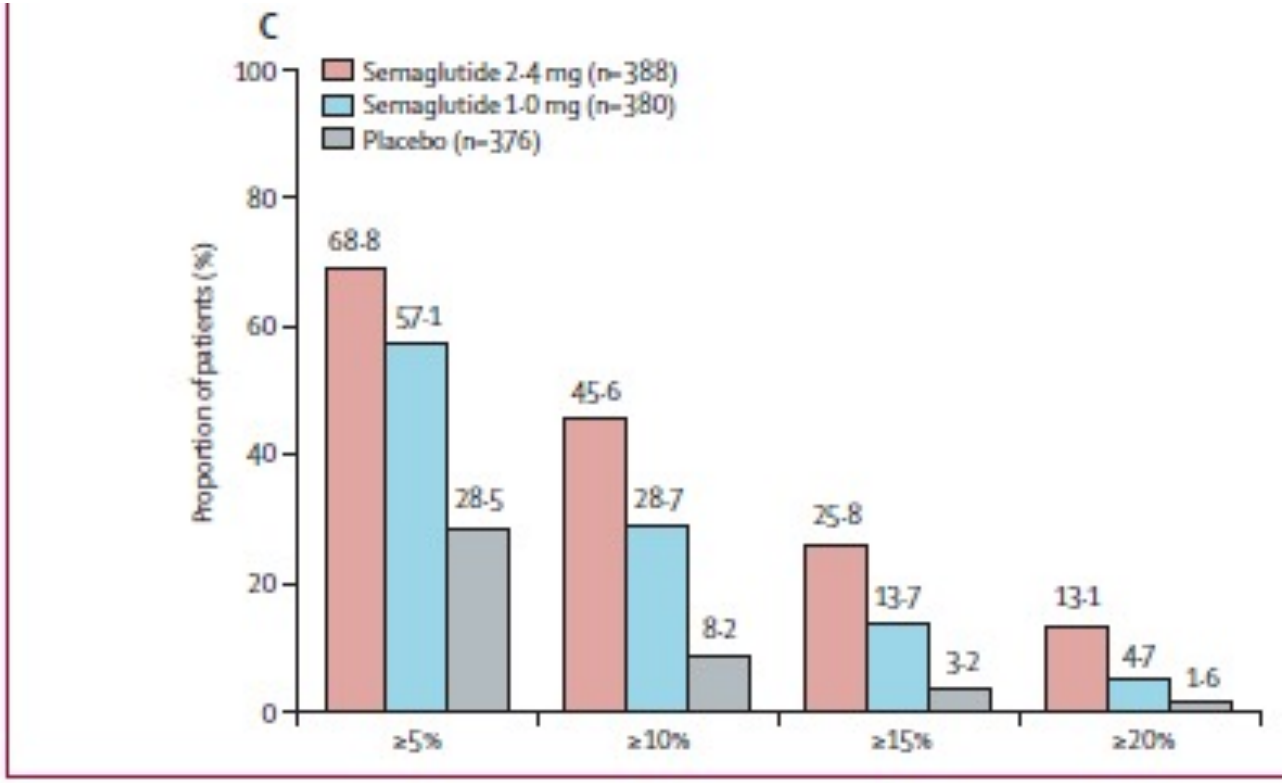
- 10 kg at 2 year follow-up = 64% diabetes remission

Lean et al. *The Lancet Diabetes & Endocrinology* 2019;7:344-355.

Weight Management in Type 2 Diabetes

Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial

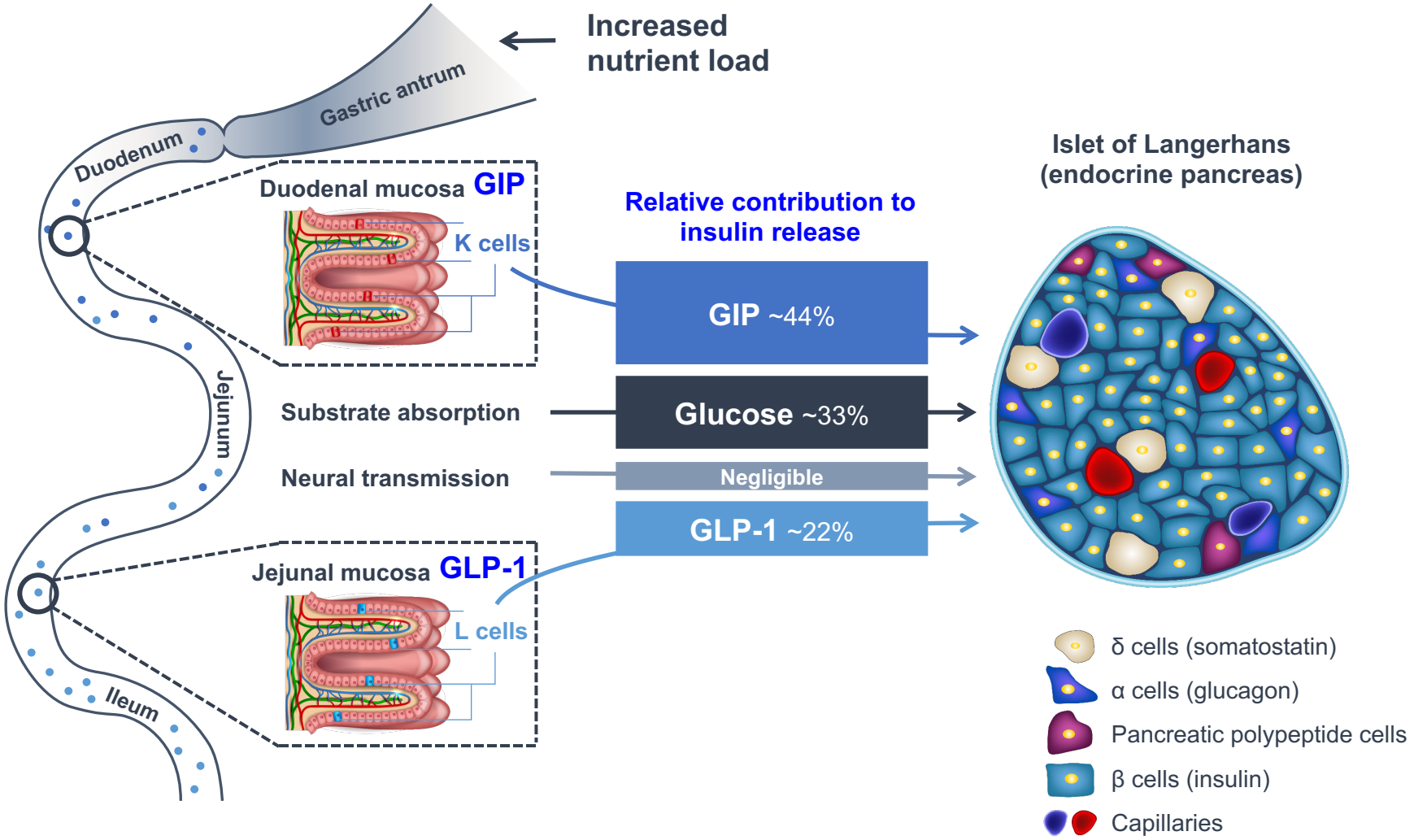
*Melanie Davies, Louise Færch, Ole K Jeppesen, Arash Pakseresht, Sue D Pedersen, Leigh Perreault, Julio Rosenstock, Iichiro Shimomura, Adie Viljoen, Thomas A Wadden, Ildiko Lingvay, for the STEP 2 Study Group**



Davies M *et al; Lancet* 2021; 397: 971-84

Incretins: recapitulation

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

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

Actions of GLP-1 and GIP

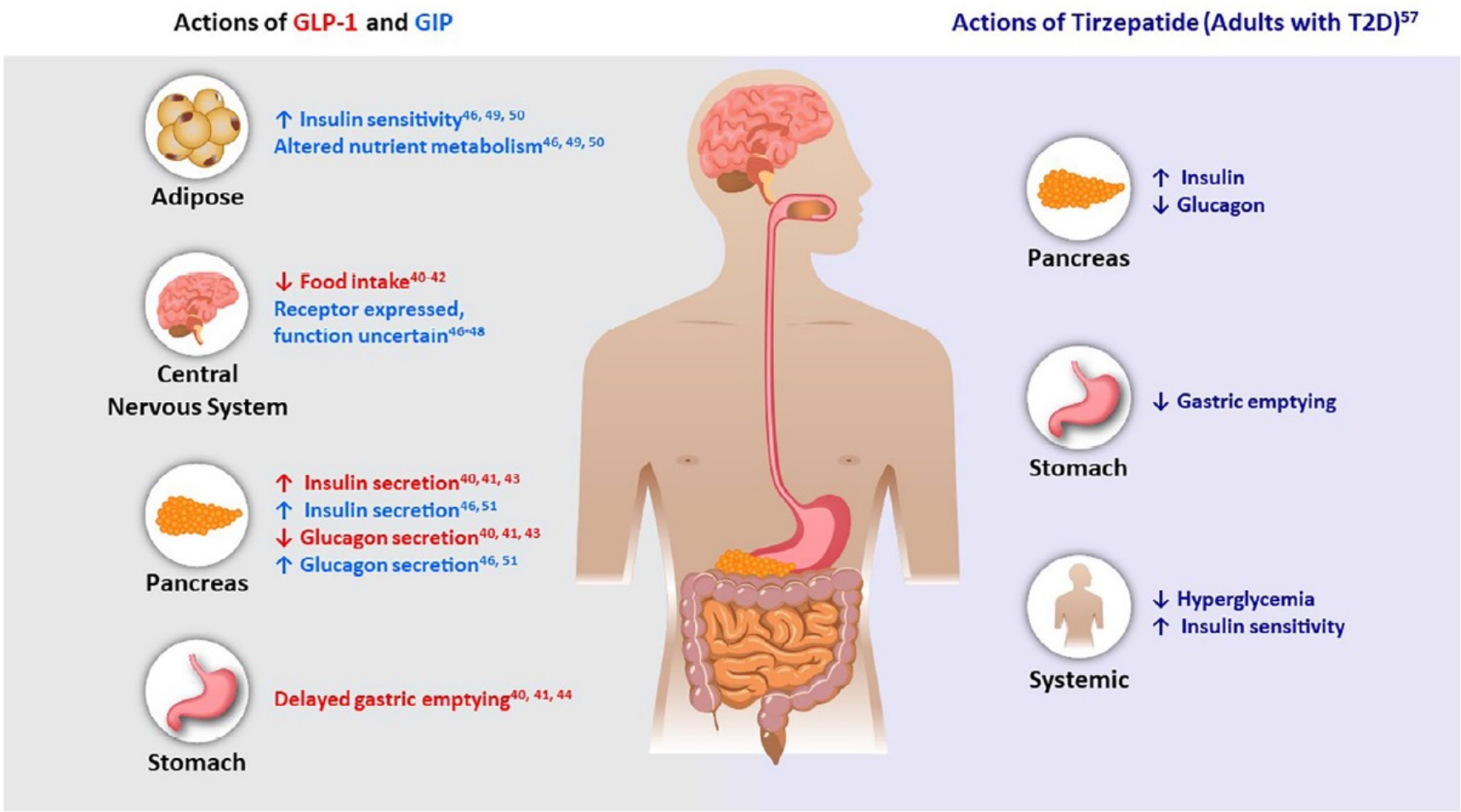
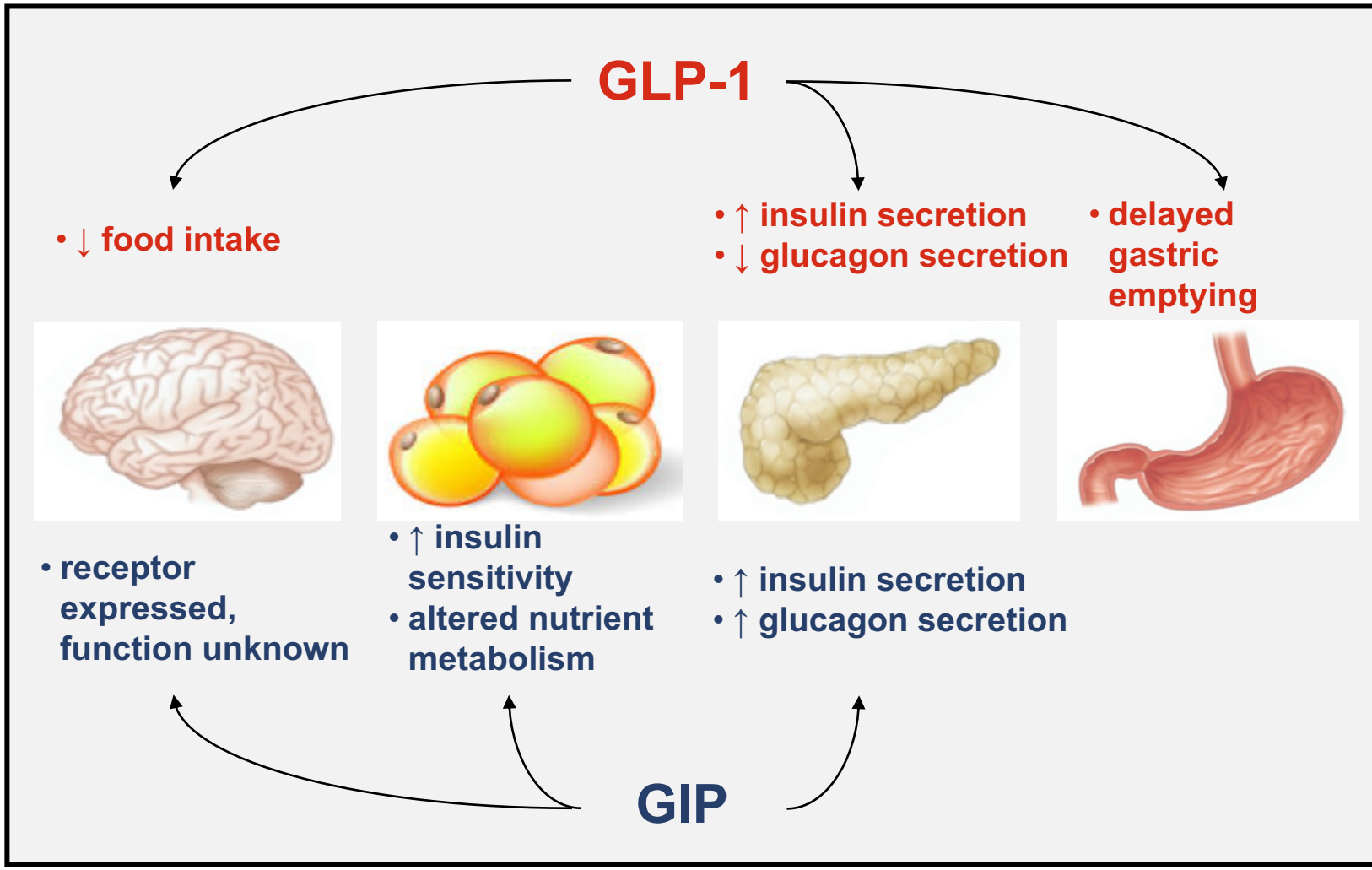


FIGURE 1 Gluco-regulatory actions of GIP and GLP-1 proposed based on preclinical and clinical studies, and actions of tirzepatide in adults with type 2 diabetes. GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; T2D, type 2 diabetes

De Block C et al. Diab Obes Metab 2022

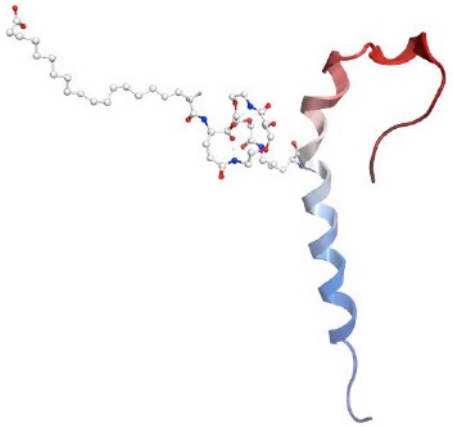
Tirzepatide: a dual GIP and GLP-1 receptor agonist

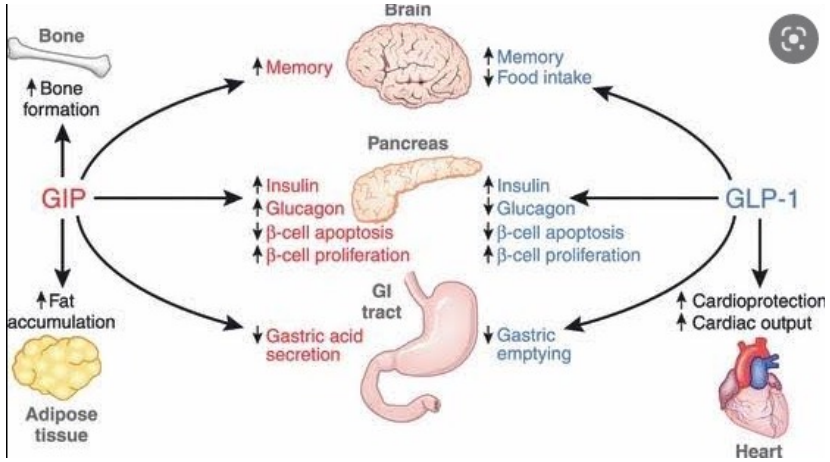
- GLP-1 has suggested direct actions in CNS, islets, and stomach[1-3]
- GIP has suggested direct actions in CNS, adipose, and islets[1-3]
- A single molecule GIP/GLP-1 receptor dual agonist may enable improved physiology over the sum of its individual agonist components[2,3]
- Normal postprandial physiology (GIP plasma levels are 3-5 times higher than GLP-1) was mimicked while creating the receptor dual agonist[2,3]



CNS, central nervous system; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1

[1]Seino Y, et al. *J Diabetes Investig.* 2010;1(1-2):8–23; [2]Frias JP, et al. *Lancet*. 2018;391(10160):2180–93; [3]Coskun T, et al. *Mol Metab*. 2019;18:3–14





Tirzepatide & SURPASS studies

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Endocrinology-Diabetology
Antwerp University Hospital

kennis / ervaring / zorg

SURPASS Clinical Trial Program covers a whole spectrum

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 Add-on to ≥ 1 and ≤ 3 OAMs (metformin, SGLT-2i, or SU)	**SURPASS-5** vs placebo Both with insulin glargine with or without metformin **SURPASS-6** vs insulin lispro (TID) Both with insulin glargine with or without metformin (ongoing)

	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]
Mean T2D duration (yrs)	4.7	8.6	8.4	10.5	13.3
Mean HbA1c (%)	7.94	8.28	8.17	8.52	8.3

SURPASS-CVOT[7]
H2H comparing TZP vs. dulaglutide, >12,000 participants (ongoing)

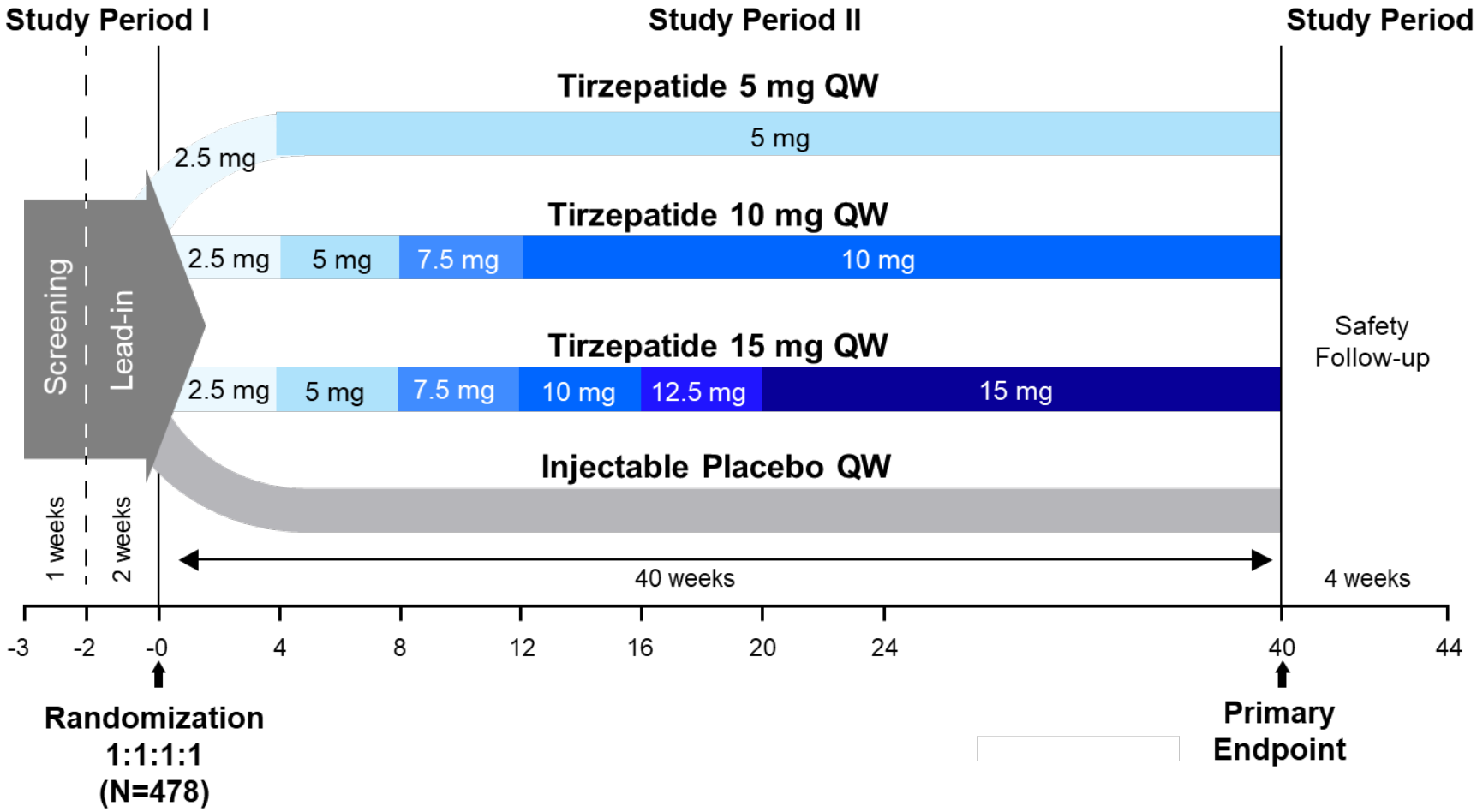
- OAM = oral antihyperglycaemic medication; SU = sulphonylurea; TID = thrice daily.

- 1. SURPASS-1. Available at: https://clinicaltrials.gov/ct2/show/NCT03954834. Accessed April 2021. 2. SURPASS-2. Available at: https://clinicaltrials.gov/ct2/show/NCT03987919. Accessed April 2021. 3. SURPASS-3. Available at: https://clinicaltrials.gov/ct2/show/NCT03882970. Accessed April 2021. 4. SURPASS-4. Available at: https://clinicaltrials.gov/ct2/show/NCT03730662. Accessed April 2021. 5. SURPASS-5. Available at: https://clinicaltrials.gov/ct2/show/NCT04039503. Accessed April 2021. 6. SURPASS-6. Available at: https://clinicaltrials.gov/ct2/show/NCT04537923. Accessed April 2021. 7. SURPASS-CVOT. Available at: https://clinicaltrials.gov/ct2/show/NCT04255433. Accessed April 2021.

General Study Design

Key inclusion criteria

- T2DM
- HbA1c ≥7.0 to ≤9.5%
- BMI ≥23 kg/m^2 stable weight
- Naïve to T2DM injectable therapy[a]
- Have not used any oral antihyperglycaemic medication in the 3 months before screening



[a]Except for the use of insulin for treatment of gestational diabetes, or short-term use (≤14 days) for acute conditions such as acute illness, hospitalization, or elective surgery.

BMI, body mass index; HbA1c, glycated haemoglobin A1c; QW, once weekly; T2DM, type 2 diabetes mellitus.

Rosenstock J, et al. Lancet. 2021;398(10295): 143–155.

SURPASS Program – Overview of Efficacy Findings

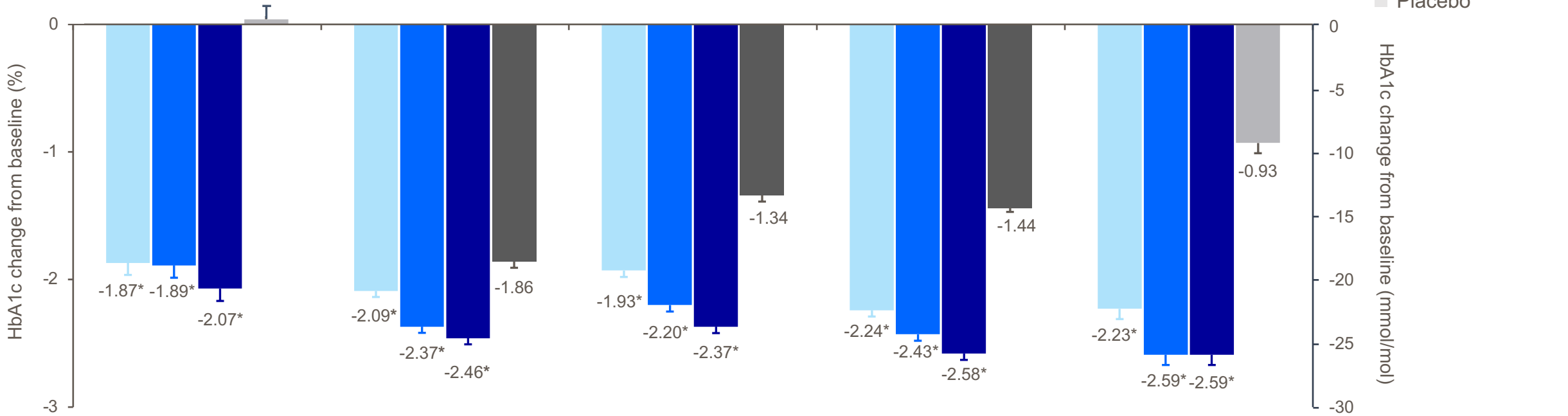
Efficacy Estimand

Treatment difference in the change from baseline to Week 40 for randomized patients, had all patients completed treatment without rescue therapy

HbA1c Change From Baseline to Primary Endpoint

Efficacy Estimand

Study	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]
Duration	40 Weeks	40 Weeks	52 Weeks	52 Weeks	40 Weeks
Baseline HbA1c	7.9%	8.3%	8.2%	8.5%	8.3%
N	478	1878	1437	1995	475

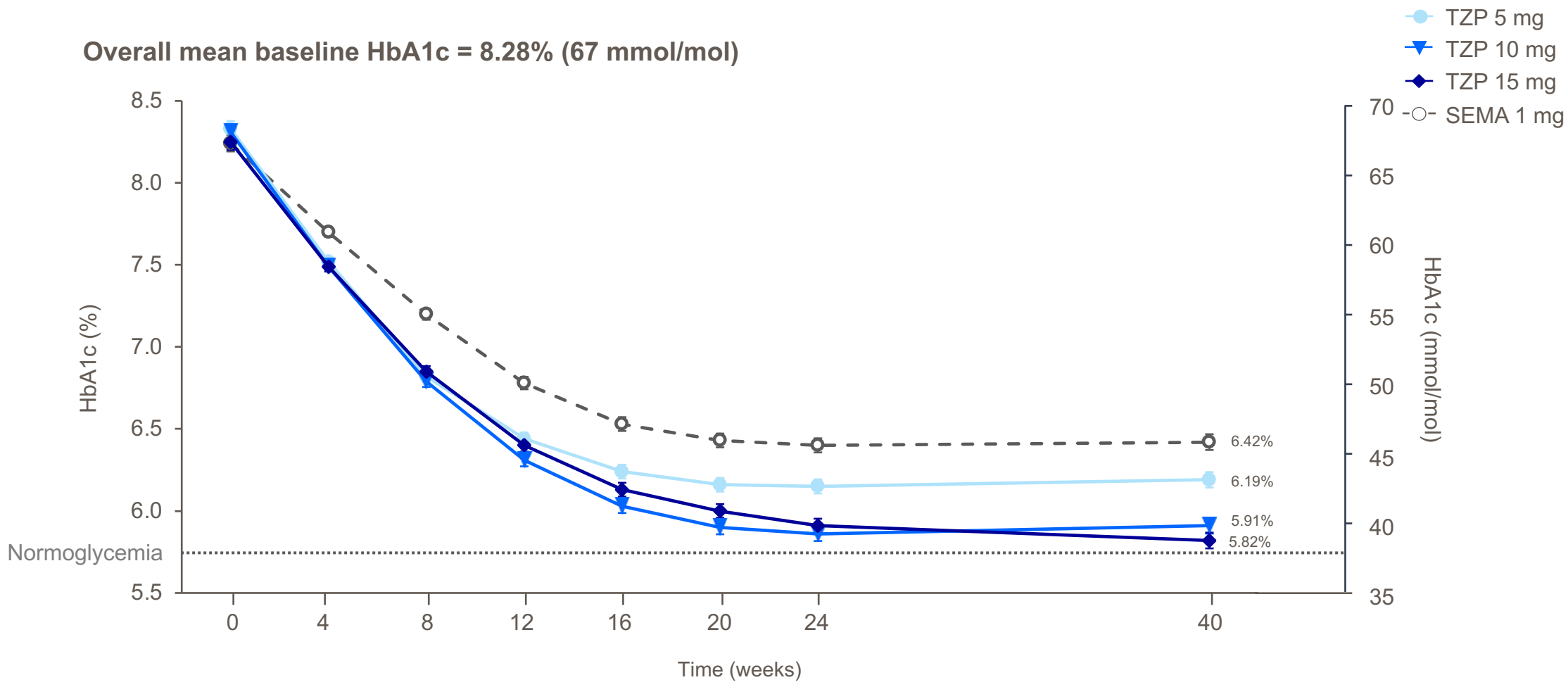


Superiority vs.	Placebo	SEMA 1 mg	Insulin degludec	Insulin glargine	Placebo
Background therapy	Monotherapy	Add-on to MET	Add-on to MET or MET + SGLT2i	Add-on to MET, SGLT2i, or SU	Add-on to insulin glargine ± MET

*P<.001 vs. placebo or active comparator.
Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c.
LSM = least squares mean; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed model repeated measures;
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;(Accepted). 5. Dahl D, et al. Poster presented at: *ADA* 2021. Poster LB-20.

HbA1c Over Time (SURPASS-2): TZP vs SEMA 1 mg

Efficacy Estimand



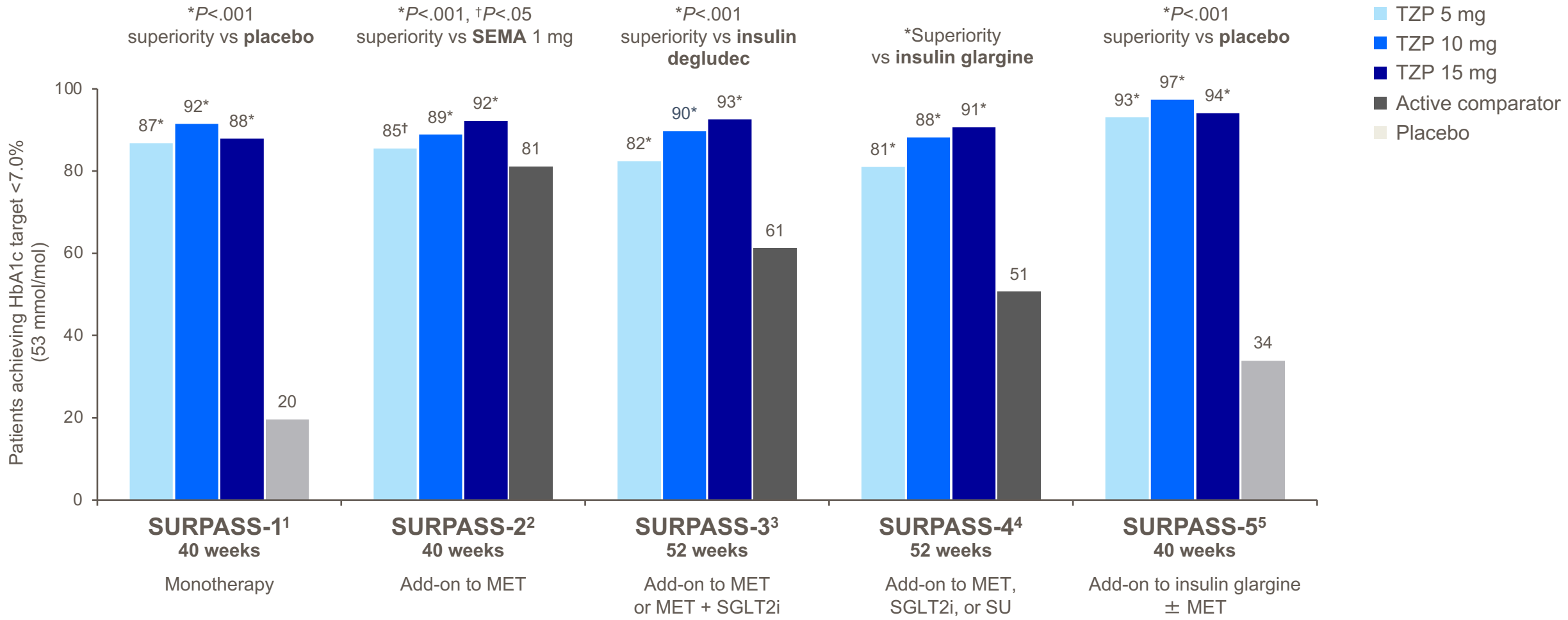
Data are LSM (SE); mITT population (efficacy analysis set). ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the dose of TZP 5 mg, 10 mg, and 15 mg and SEMA 1 mg were achieved. Data labels are % HbA1c.

ANOVA = analysis of variance; HbA1c = glycated hemoglobin; LSM = least squares mean; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide.

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

Proportion of patients achieving HbA1c <7.0% (53 mmol/mol)

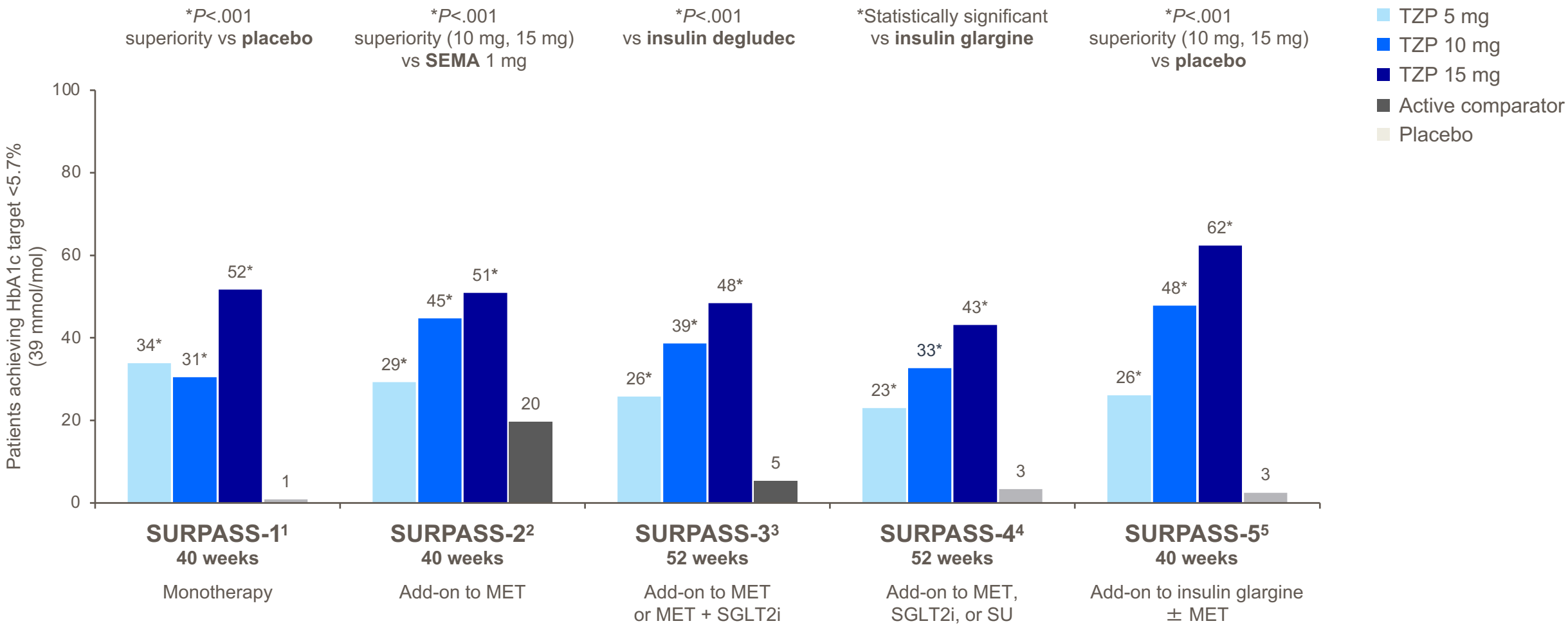
Efficacy Estimand



Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
HbA1c = glycated haemoglobin; MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TZP = tirzepatide.
[1]Rosenstock J, et al. *Lancet*. 2021;398(10295):143–155; [2]Frias JP, et al. *N Engl J Med.* 2021;385(6):503–515; [3]Ludvik B, et al. *Lancet.* 2021;398(10300):583–598; [4]Eli Lilly and Company, 2021. Accessed June 2022. https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study; [5]Dahl D, et al. Poster 80-LB presented at the 81st Scientific Sessions of the ADA. 2021.

Proportion of patients achieving HbA1c <5.7% (39 mmol/mol)

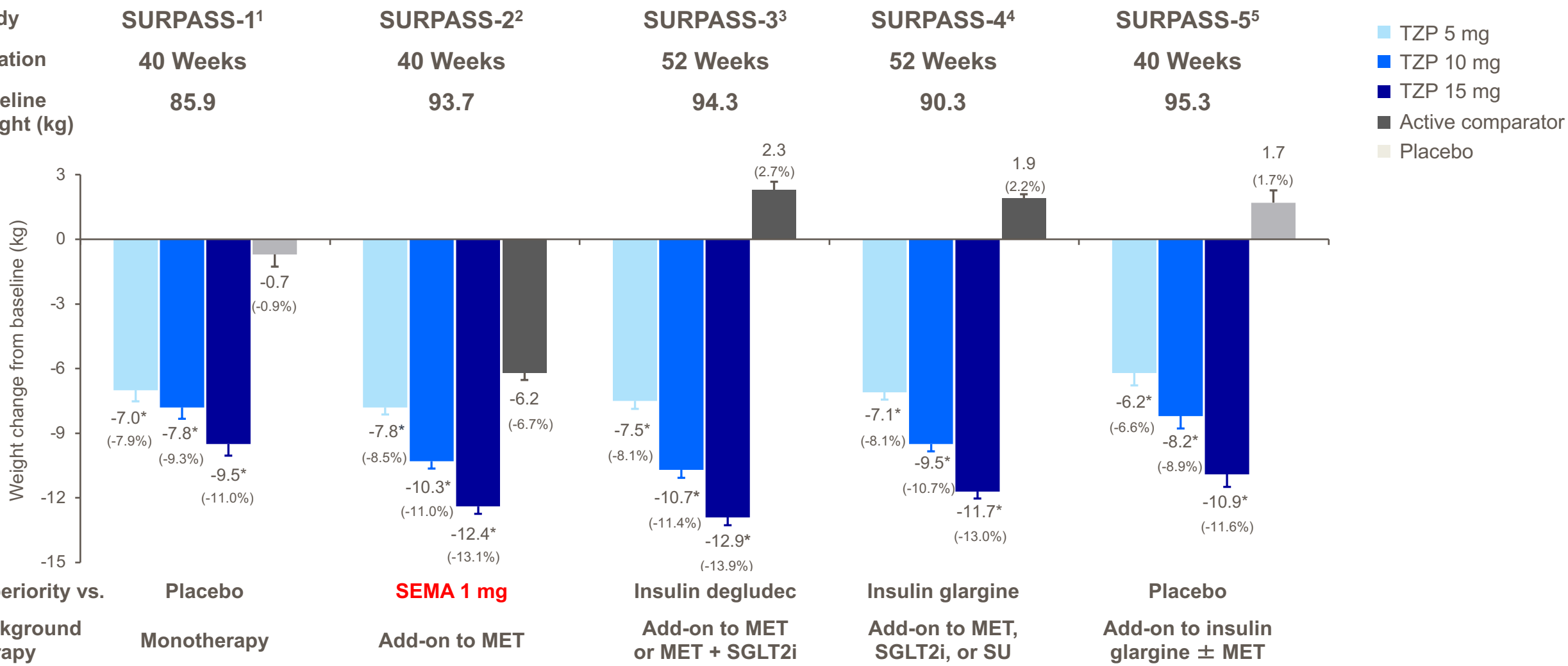
Efficacy Estimand



Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
HbA1c = glycated haemoglobin; MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; SU = sulphonylurea; TZP = tirzepatide.
[1]Rosenstock J, et al. *Lancet*. 2021;398(10295):143–155; [2]Frias JP, et al. *N Engl J Med.* 2021;385(6):503–515; [3]Ludvik B, et al. *Lancet.* 2021;398(10300):583–598; [4]Eli Lilly and Company, 2021. Accessed June 2022. https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study; [5]Dahl D, et al. Poster 80-LB presented at the 81st Scientific Sessions of the ADA. 2021.

Body Weight Change From Baseline to Primary Endpoint

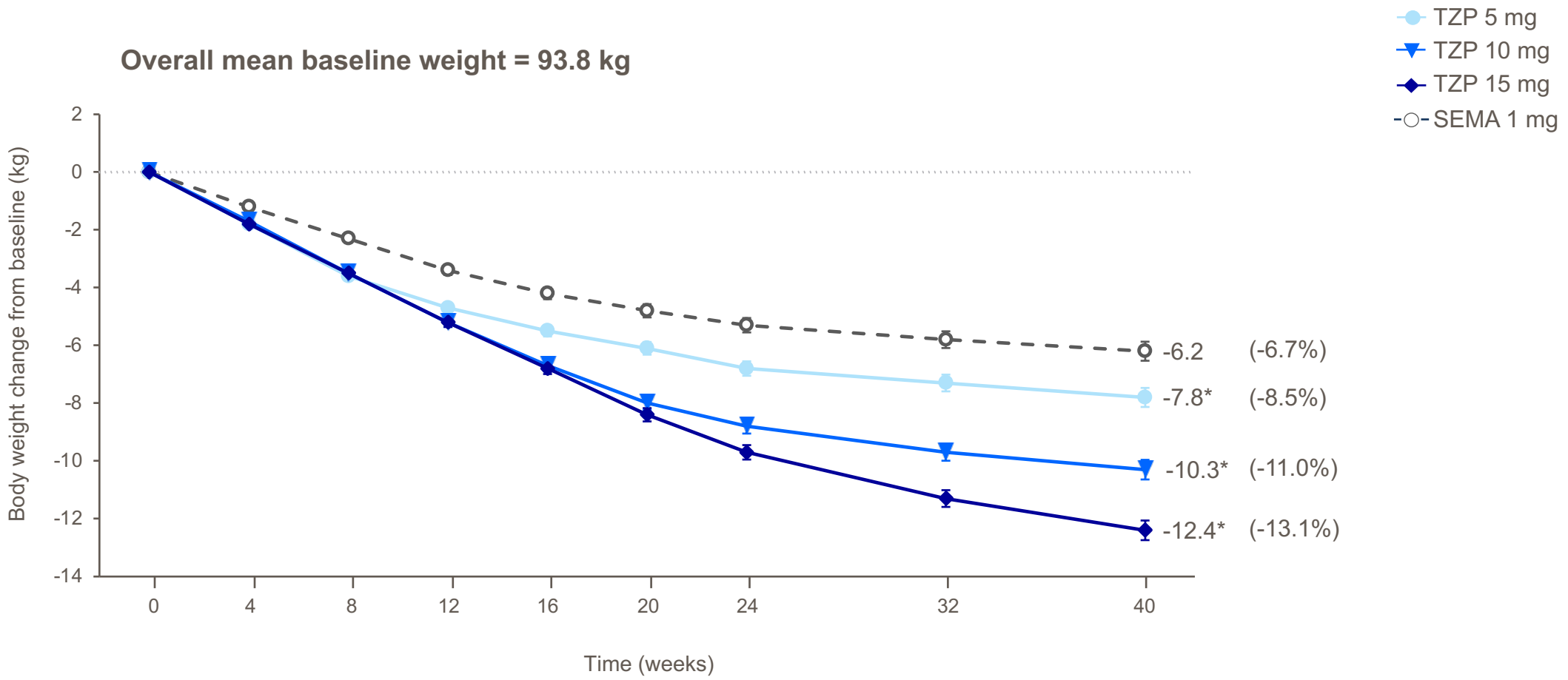
Efficacy Estimand



*P<.001 vs. placebo or active comparator.
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; SEMA = semaglutide; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TZP = tirzepatide.
1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;(Accepted). 5. Dahl D, et al. Poster presented at: *ADA* 2021. Poster LB-20.

Body Weight Change Over Time (SURPASS-2)

Efficacy Estimand

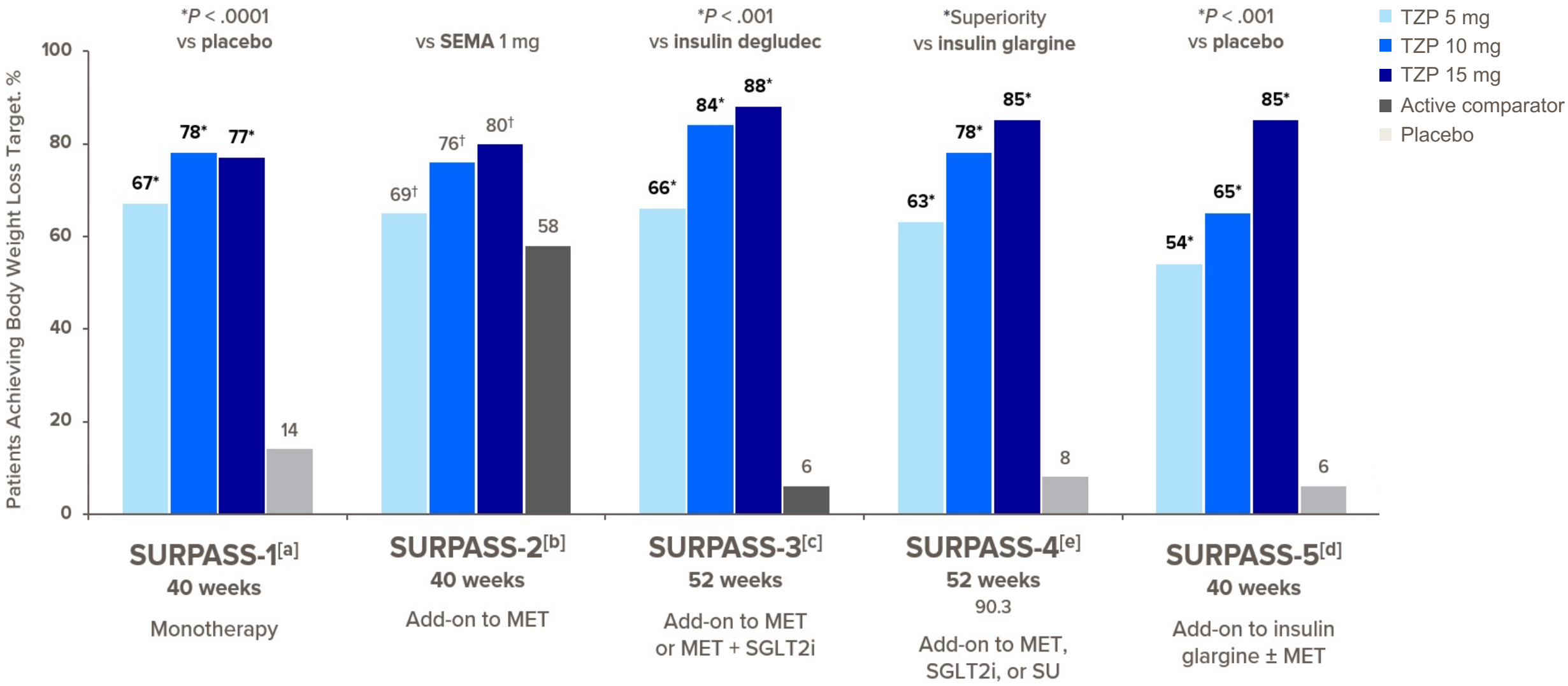


Data are LSM (SE); mITT population (efficacy analysis set). ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the dose of TZP 5 mg, 10 mg, 15 mg, and SEMA 1 mg were achieved. Data labels are weight in kg (% change from baseline). *P<001 vs. SEMA.

ANOVA = analysis of variance; LSM = least squares mean; mITT = modified intent to treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide.

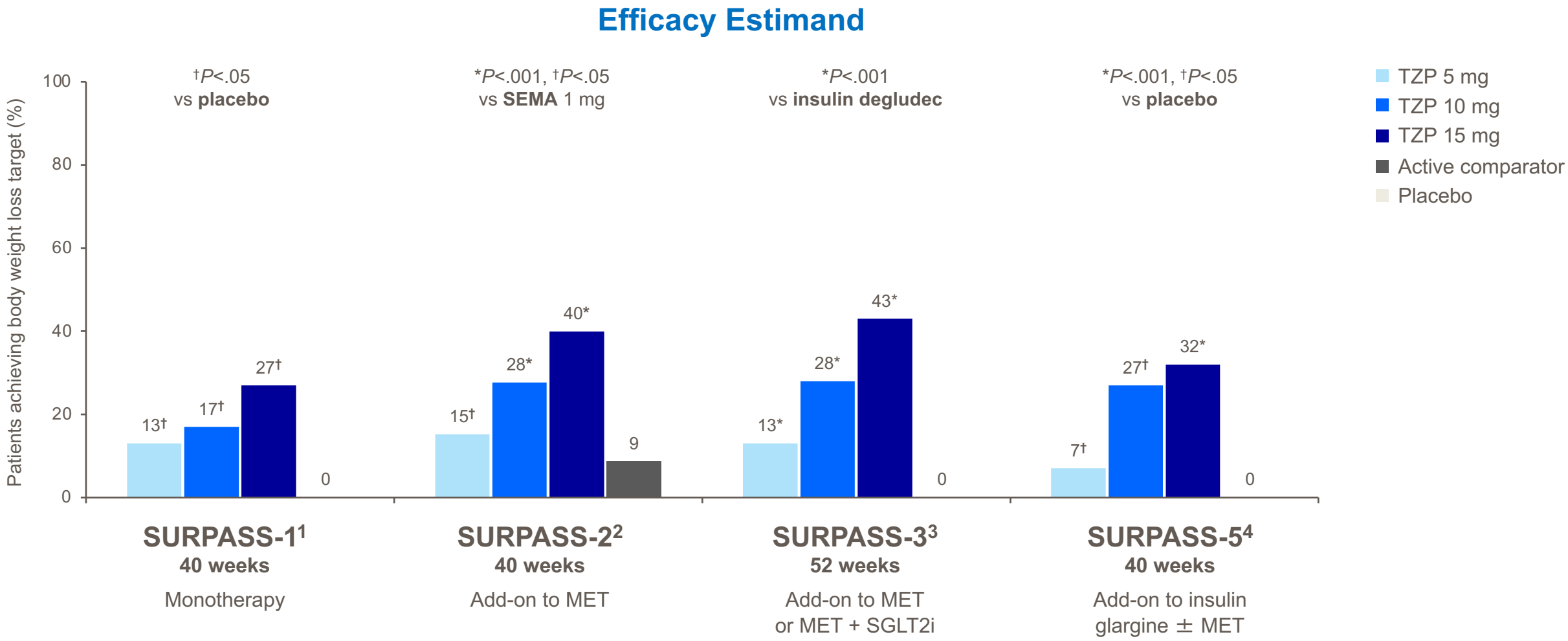
Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515.

Proportion of Patients Achieving ≥ 5% Weight Loss



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. 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. Eli Lilly and Company, 2021. Accessed 5 June 2021. https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study. 5. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

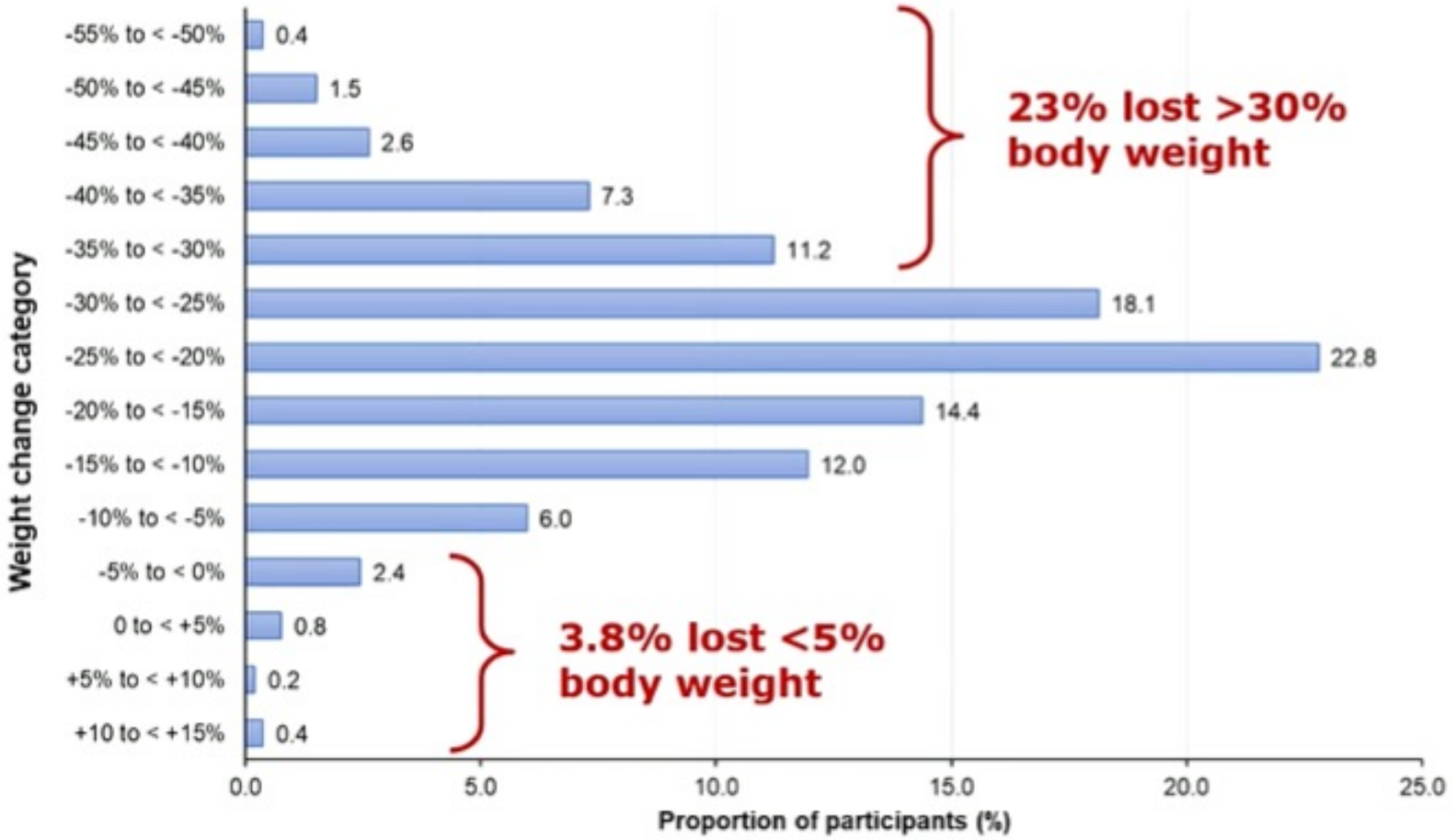
Proportion of patients achieving ≥15% weight loss



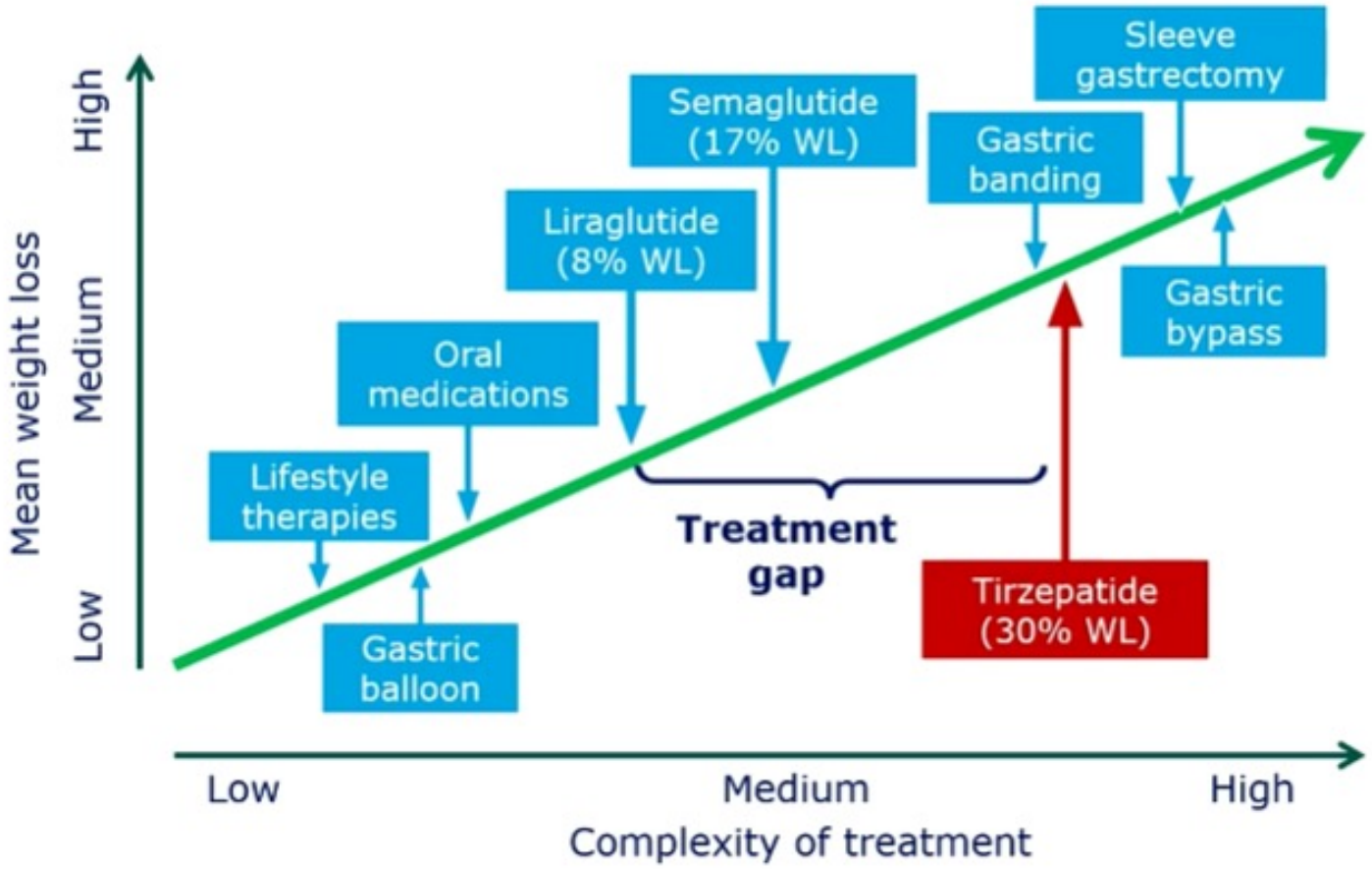
Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
MET = metformin; mITT = modified intent-to-treat; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SEMA = semaglutide; TZP = tirzepatide.
[1]Rosenstock, et al. *Lancet*. 2021;398(10295):143–155; [2]Frias JP, et al. *N Engl J Med.* 2021;385(6):503–515; [3]Ludvik B, et al. *Lancet.* 2021;398(10300):583–598; [4]Dahl D, et al. Poster 80-LB presented at the 81st Scientific Sessions of the ADA. 2021.

Variability of weight loss with Tirzepatide

Data on file. Eli Lilly and Company

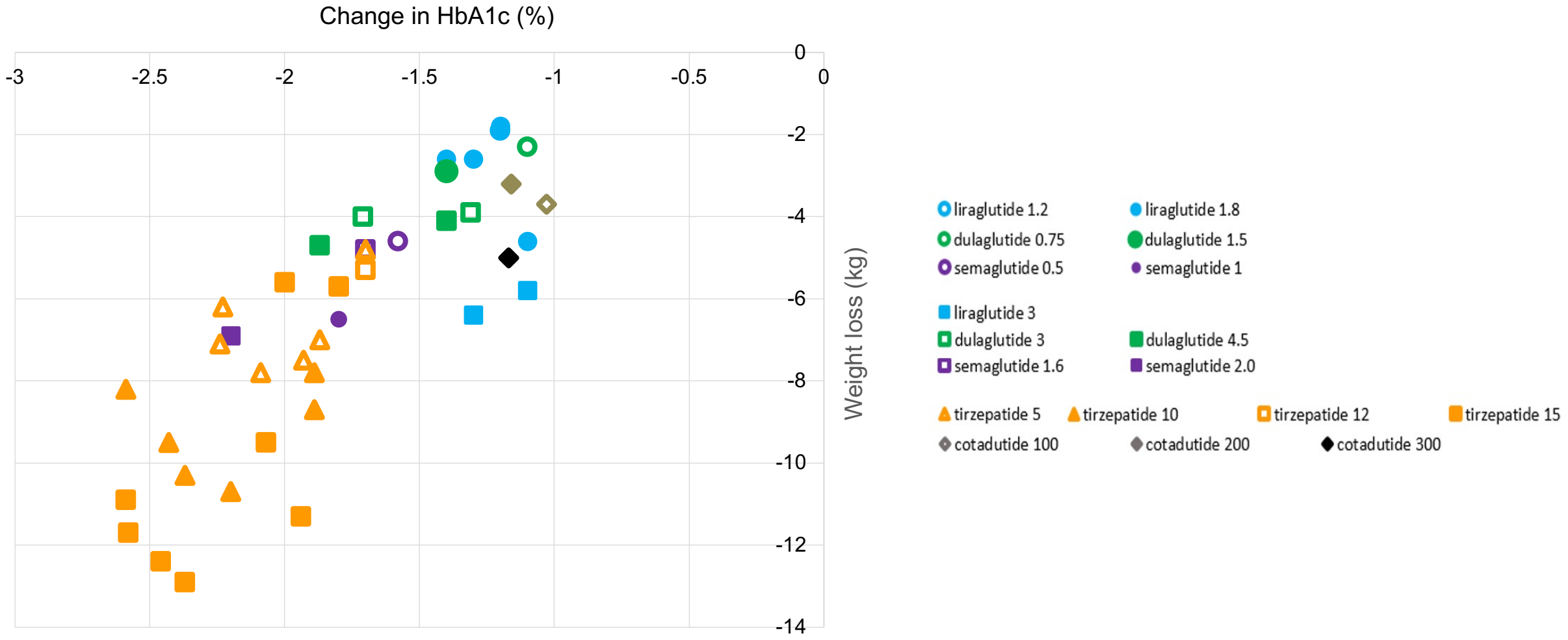


Perspectives on weight loss: closing the gap…



US CDC, Decision Resources 2012; Martin *et al. Surg Obes Relat Dis* 2010;6:8–15; GWU. Obesity Drug Outcome Measures: A Consensus Report of Considerations Regarding Pharmacologic Intervention. 2012. http://sphhs.gwu.edu/pdf/releases/obesitydrugmeasures.pdf

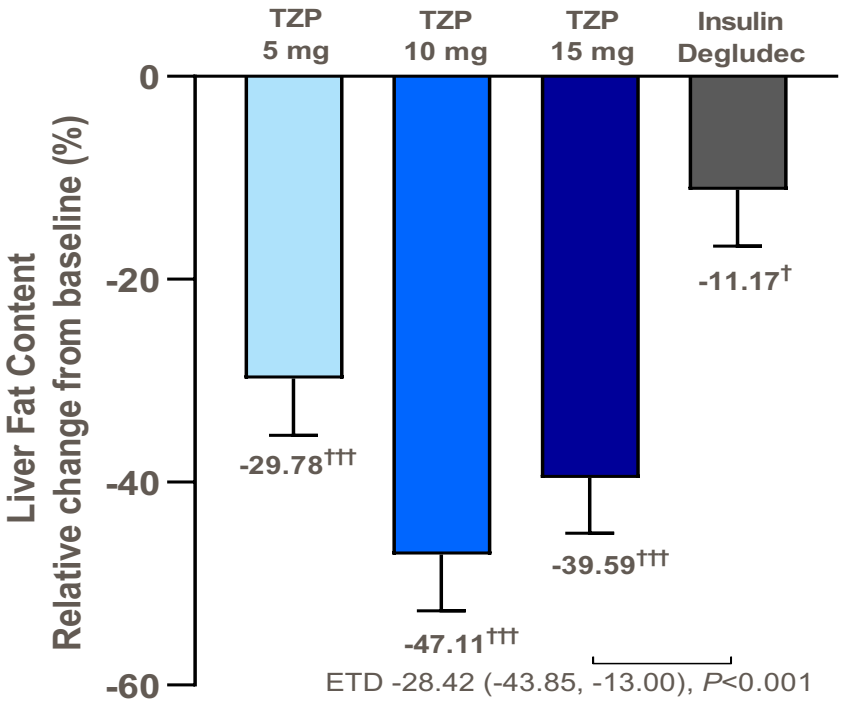
Tirzepatide vs other GLP1 RAs: effect on HbA1c and weight



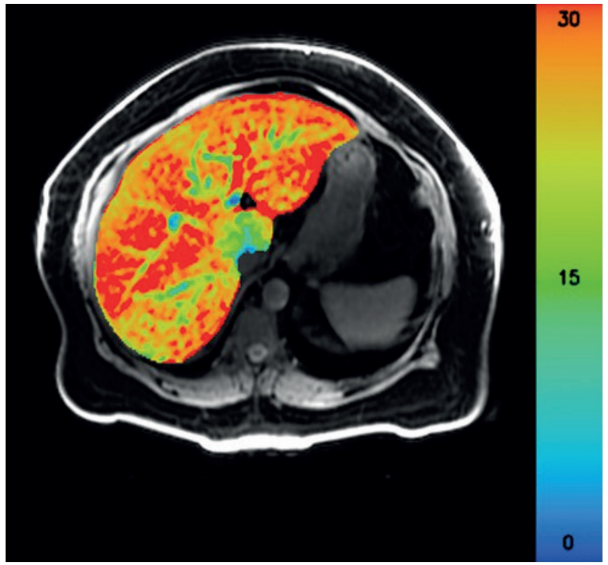
GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated haemoglobin.

De Block, et al. *Diabetes Obes Metab.* 2022;24(7):1185–1407; Davies MJ, et al. *JAMA*. 2015;314(7):687–699 (SCALE); Garvey WT, et al. *Diabetes Care.* 2020;43(5):1085–1093; Pratley RE, et al. *Lancet Diabetes Endocrinol.* 2018;6(4):275–286; Frias JP, et al. *Diabetes Care.* 2021;44(3):765–773; Frias JP, et al. *Lancet.* 2021;9(9):563–574; Davies M, et al. *Lancet.* 2021;397(10278):971–984; Rosenstock J, et al. *Lancet.* 2021;398(10295):143–155; Frias JP, et al. *N Engl J Med.* 2021;385(6):503–515; Ludvik B, et al. *Lancet.* 2021;398(10300):583–598.

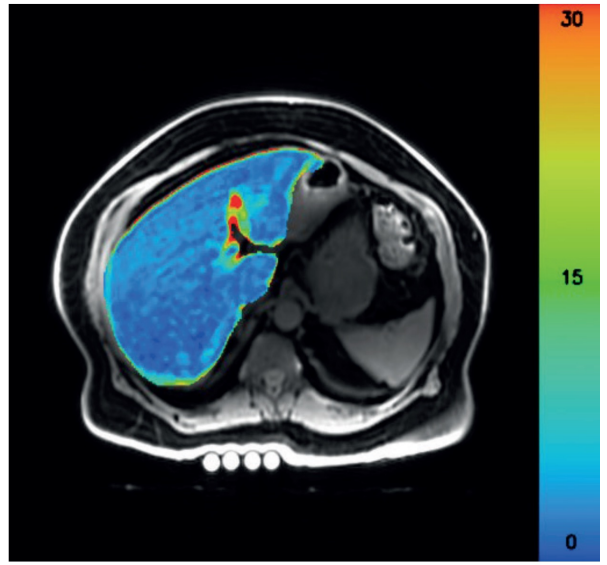
Liver Fat Content (LFC) vs. Titrated Insulin Degludec (SURPASS-3)



Mean Baseline value	TZP 5 mg	TZP 10 mg	TZP 15 mg	IDeg
	14.86%	14.78%	16.65%	16.58%



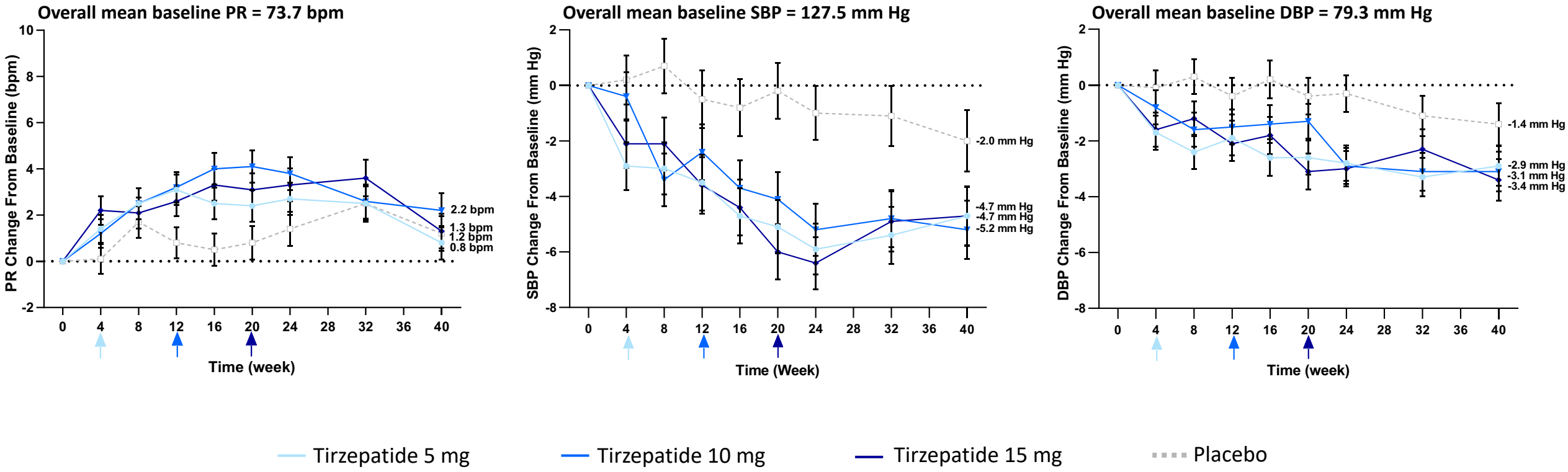
LFC at baseline: 27·3%



LFC at week 52: 2·6%

Data are LSM (SE) at 52 weeks. Estimated treatment differences (ETD) at 52 weeks are LSM (95% CI); mITT (MRI analysis set). ANCOVA analysis. †P<0.05; †††P<0.001 vs. baseline within the treatment group. ANCOVA = analysis of covariance; CI = confidence interval; ETD = estimated treatment difference; LSM = least square mean; mITT = modified intention to treat; SE = standard error;
Gastaldelli A, et al. *Lancet Diabetes Endocrinol.* 2022;10(6):393–406.

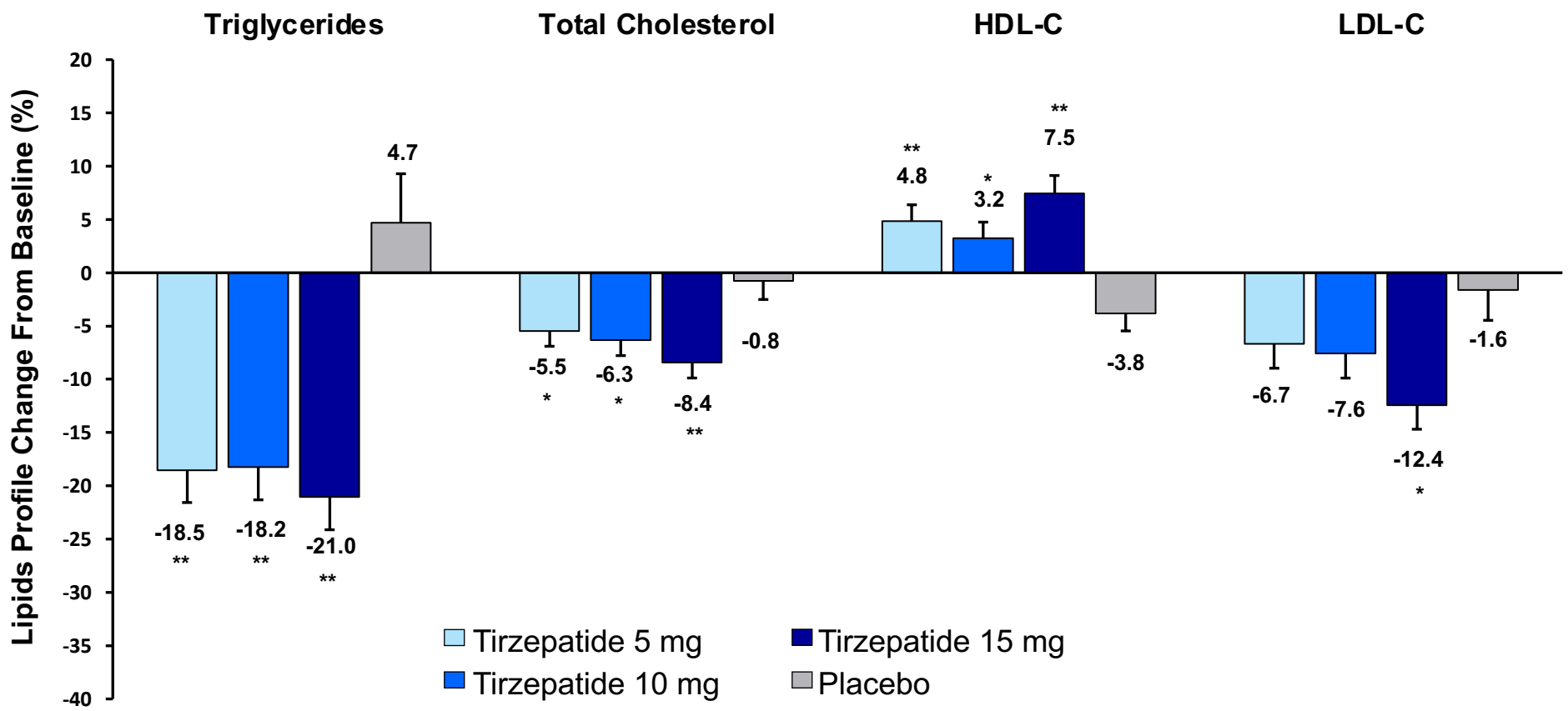
Change from baseline in pulse rate and blood pressure over time: SURPASS-1



Data are least squares mean (standard error) and are based on the modified intent-to-treat population (safety analysis set); arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg are achieved
bpm, beats per minute; DBP, diastolic blood pressure; PR, pulse rate; SBP, systolic blood pressure.

Rosenstock J, et al. Lancet. 2021;398(10295): 143–155.

Percent Change From Baseline in Lipids at 40 Weeks: SURPASS-1



Data presented are estimated percentage means (SE) from MMRM analysis calculated using log transformation and are based on the mITT population (efficacy analysis set); *p<0.05 and **p<0.0001 vs placebo

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; mITT=modified intent-to-treat; MMRM=mixed model repeated measures

Rosenstock J, et al. *Lancet.* 2021; doi:10.1016/S0140-6736(21)01324-6 (Ahead of print).

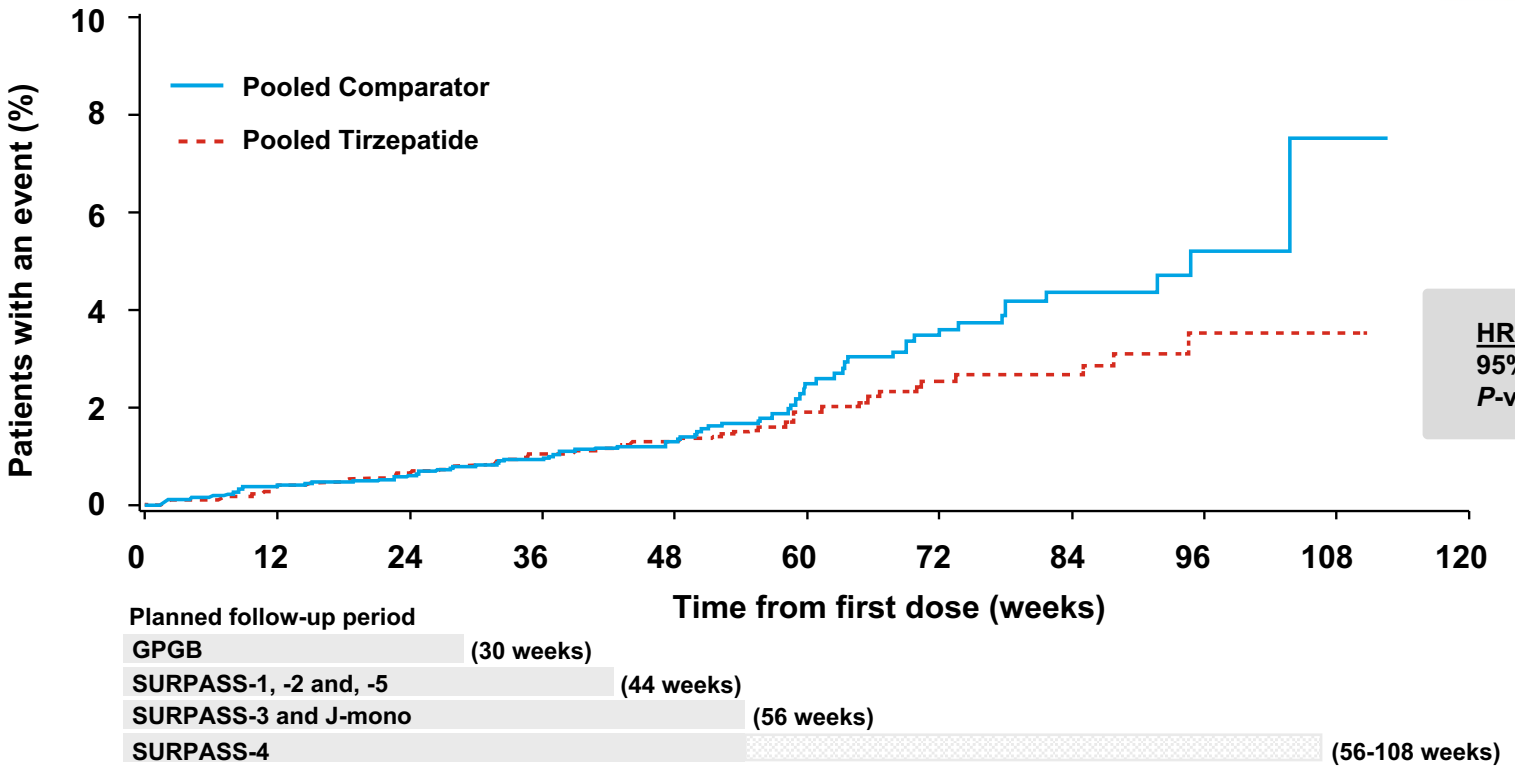
Cardiovascular assessment of TZP

nature medicine
ANALYSIS
https://doi.org/10.1038/s41591-022-01707-4
Check for updates

OPEN

Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis

Naveed Sattar[1,6], Darren K. McGuire[2], Imre Pavo[3], Govinda J. Weerakkody[4], Hiroshi Nishiyama[4], Russell J. Wiese[4] and Sophia Zoungas[5,6]



Cumulative number of events: Number of patients at risk

Pooled Tirzepatide:	0:4887	15:4813	28:4726	43:4477	53:2477	62:960	68:832	69:515	72:188	72:19	72:0
Pooled Comparator:	0:2328	13:2292	19:2250	28:2118	36:1438	52:914	62:794	67:496	69:172	70:14	70:0

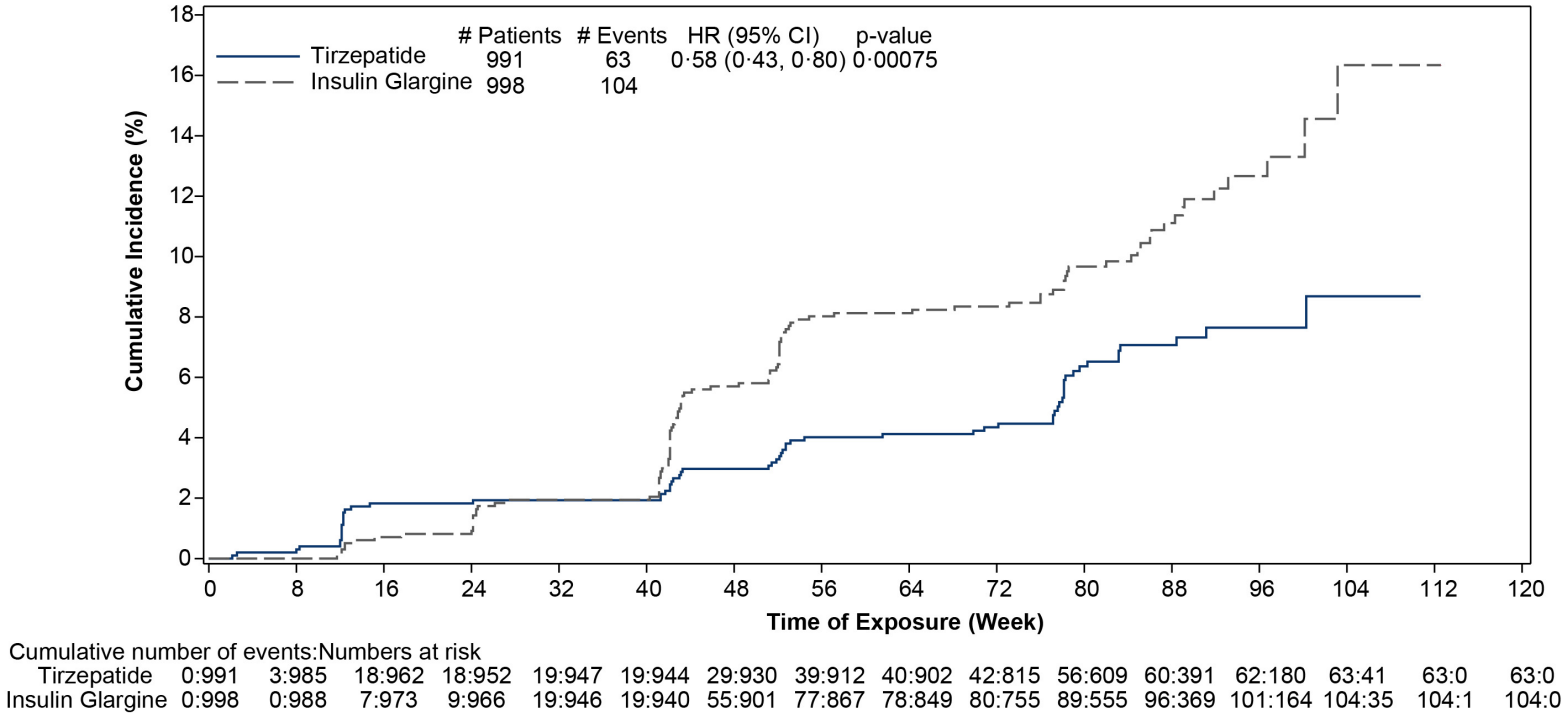
Note: *P* values are based on the Wald Chi-square test. Gray bars represent the planned follow-up period for trials GPGB (30 weeks), SURPASS-1, SURPASS-2 and SURPASS-5 (44 weeks), SURPASS-3 and SURPASS J-mono (56 weeks), and SURPASS-4 (56-108 weeks).

HR=Hazard Ratio; CI=Confidence Interval; MACE=Major Adverse Cardiovascular Event. - Sattar N, et al. *Nat Med*. 2022

Tirzepatide Reduces the Risk of the Composite Kidney Endpoint (Macroalbuminuria, 40% eGFR Decline, ESKD, Renal Death)

SURPASS-4 Exploratory Analysis

Incidence composite kidney endpoint



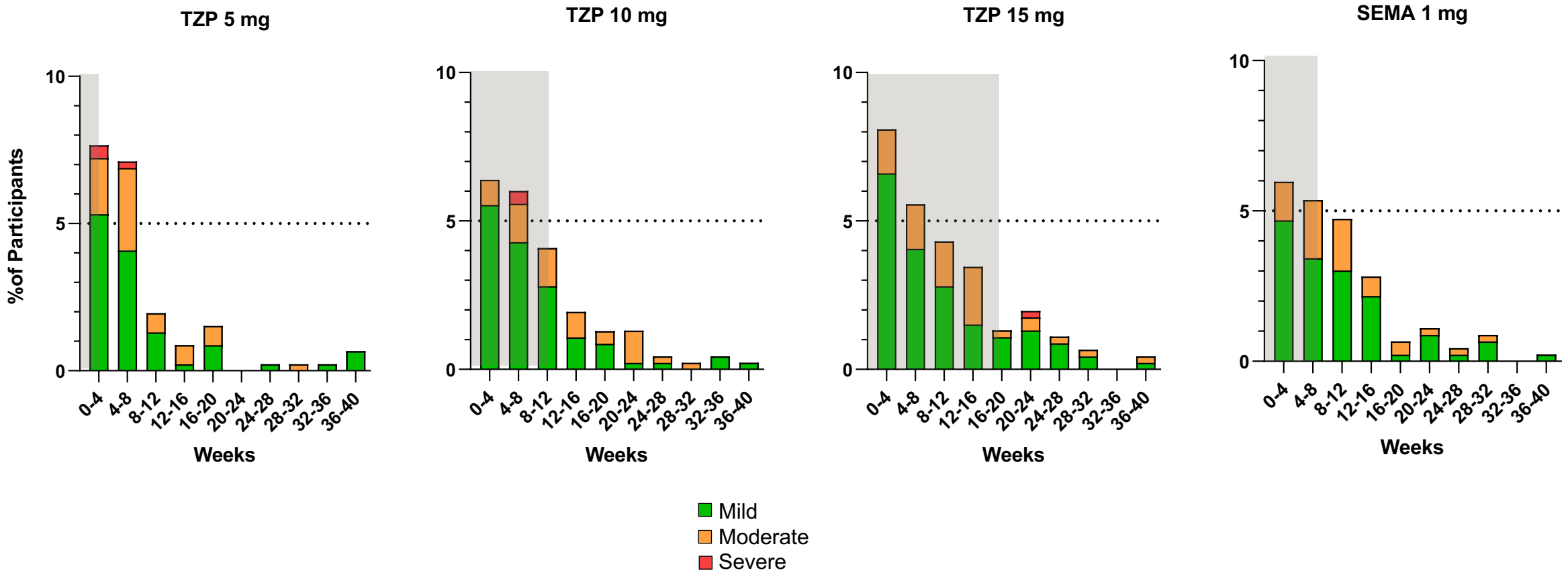
Component	Treatment	N (%)	HR (95%CI)
eGFR decline ≥40% from baseline	TZP	38 (3.8%)	**0.87 (0.56,1.33)**
	iGLAR	45 (4.5%)	
Renal death	TZP	0	-
	iGLAR	0	
Progression to ESKD	TZP	0	-
	iGLAR	5 (0.5%)	
New onset macroalbuminuria[a]	TZP	25 (2.5%)	**0.41 (0.26,0.66)***
	iGLAR	61 (6.1%)	

For left-side graph: Cumulative incidence of time to renal composite endpoint HR, CI, and p-value are derived from a Cox proportional-hazards model with treatment (tirzepatide vs. insulin glargine) as a fixed effect. For right-side graph: HR estimate with CI is not calculated when either the TZP or iGLAR arm has no event. [a]UACR ≥30 mg/g. *p<0.05 versus iGLAR.

Heerspink HJL, et al. Oral presentation at: *ADA 2022*. Abstract 17-OR.

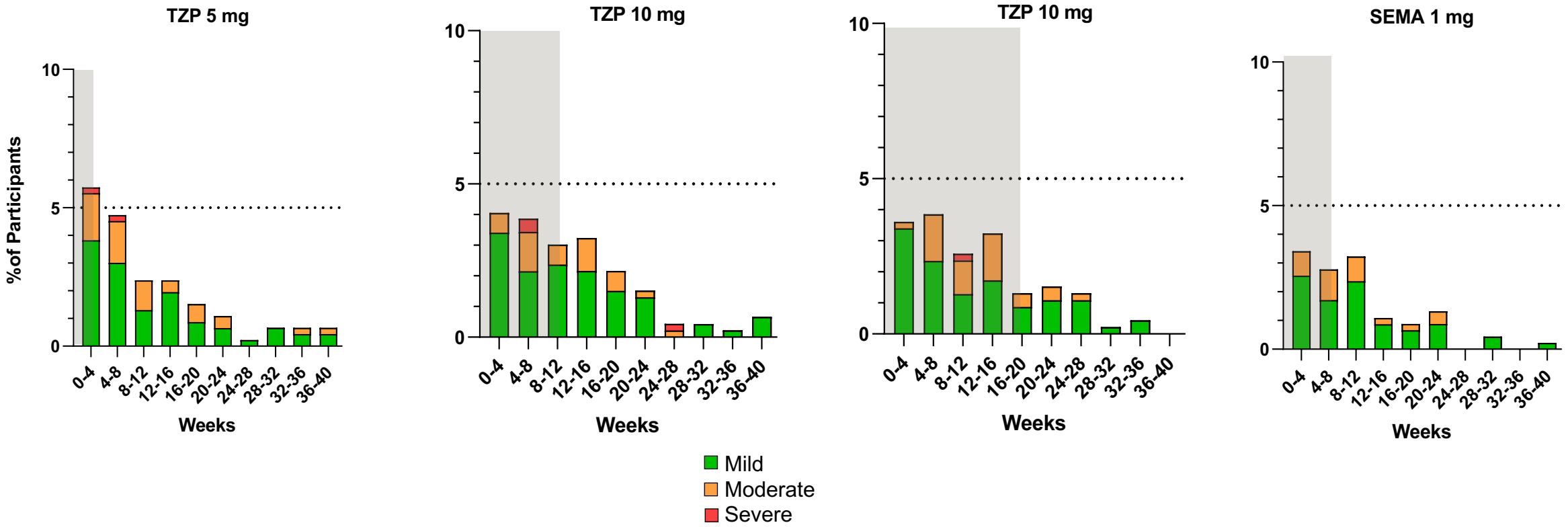
SURPASS Program – Overview of Safety Endpoints

Incidence of nausea: SURPASS-2



Note: Data are percent of participants who reported a new event relative to participants at risk during a time interval; mITT population (safety analysis set). Incidence refers to the proportion of participants who have a new event during a time interval. Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments.
mITT = modified intent-to-treat; SEMA = semaglutide; TZP = tirzepatide.
Frias JP, et al. *N Engl J Med.* 2021;385(6):503–515.

Incidence of diarrhoea: SURPASS-2



Note: Data are percent of participants who reported a new event relative to participants at risk during a time interval; mITT population (safety analysis set). Incidence refers to the proportion of participants who have a new event during a time interval. Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments.
mITT = modified intent-to-treat; SEMA = semaglutide; TZP = tirzepatide.
Frias JP, et al. *N Engl J Med.* 2021;385(6):503–515.

Incidence of Hypoglycemia

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
SURPASS-4[4]	**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[5] (combination with insulin glargine)	**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

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. Semaglutide and insulin glargine are active comparators in the SURPASS-2 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. 4. Del Prato S, et al. *Lancet*. 2021;(Accepted). 5. Dahl D, et al. Poster presented at: *ADA* 2021. Poster LB-20.

Other AEs

Parameters	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]
Pancreatitis[a]	**0**	**2** (TZP 10 mg) **2** (TZP 15 mg) **3** (SEMA 1 mg)	**0**	**3** (TZP 5 mg) **2** (TZP 10 mg) **1** (TZP 15 mg) **1** (Insulin Glargine)	**0**
Cholelithiasis	**1** (TZP 5 mg)	**4** (TZP 5 mg) **4** (TZP 10 mg) **4** (TZP 15 mg) **2** (SEMA 1 mg)	**2** (TZP 5 mg) **1** (TZP 10 mg) **1** (TZP 15 mg)	**3** (TZP 5 mg) **1** (TZP 10 mg) **1** (TZP 15 mg) **4** (Insulin Glargine)	**1** (TZP 5 mg)
Medullary Thyroid Carcinoma	**0**	**0**	**0**	**0**	N/A*
Diabetic Retinopathy	**0**	**2** (TZP 10 mg)	**2** (TZP 5 mg) **1** (TZP 15 mg)	**2** (TZP 5 mg) **1** (TZP 10 mg) **1** (TZP 15 mg) **1** (Insulin Glargine)	N/A*

[a]Adjudication-Confirmed.
*Not Available at time of slide deck compilation.
AEs = adverse events; 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. 4. Del Prato S, et al. *Lancet*. 2021;(Accepted). 5. Dahl D, et al. Poster presented at: *ADA* 2021. Poster LB-20.

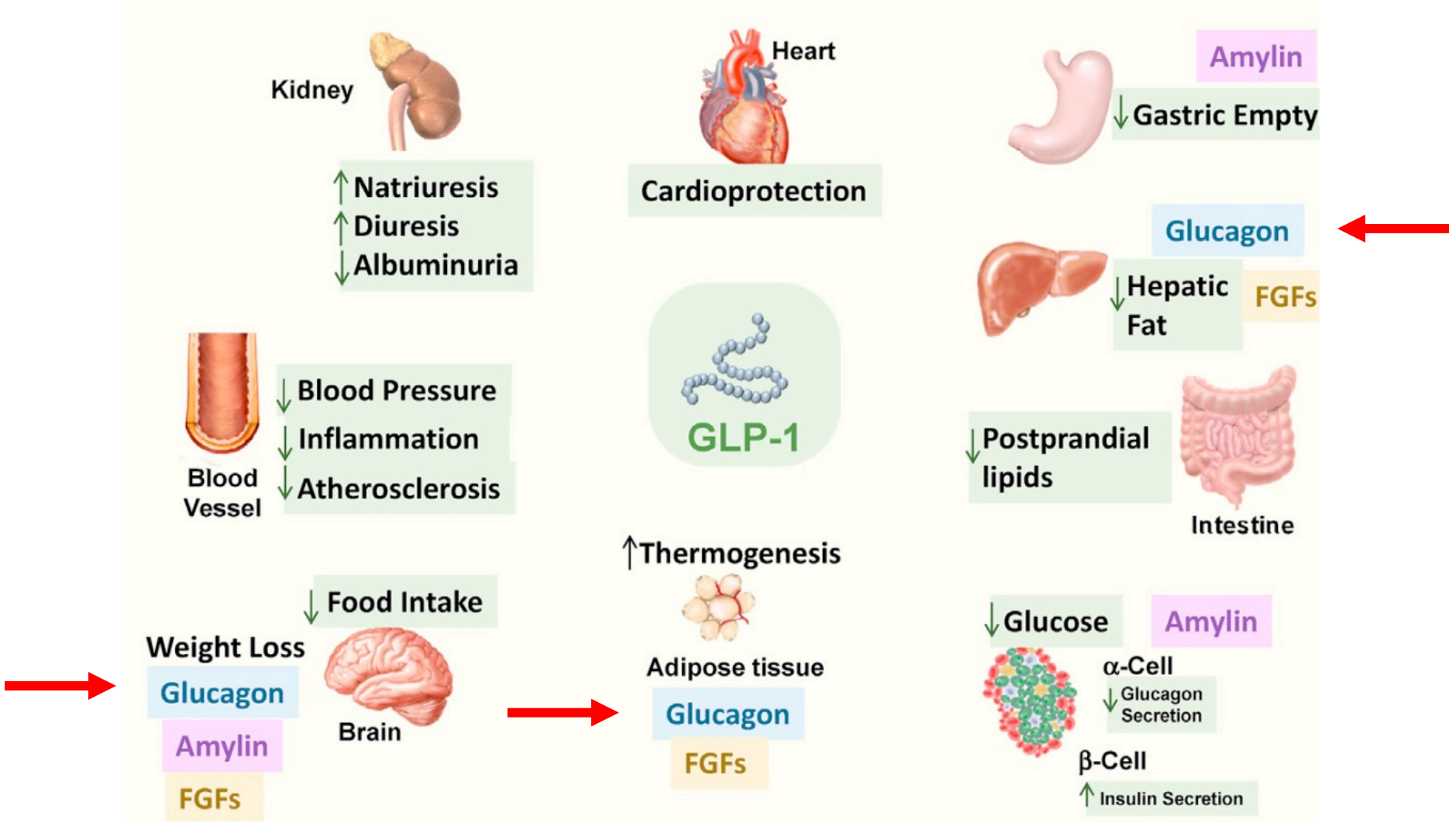
Summary of Results

- The results of the phase 3 clinical programme with Tirzepatide across a wide spectrum of people with T2D (both early stages and well-advanced disease) SURPASS those of all comparators (including semaglutide 1.0 mg QW, insulin glargine, insulin degludec, …) in terms of …
  - HbA1c reduction
    - Approx. 80% (with TZP 5) to up to 95% (with TZP 15) reach an HbA1c target < 7.0%
    - Approx. 25% (with TZP 5) to up to 60% (with TZP 15) reach an HbA1c target < 5.7%
  - Weight lowering
    - Approx. 60% (with TZP 5) to up to 90% (with TZP 15) achieve ≥ 5% weight loss
    - Approx. 10% (with TZP 5) to up to 40% (with TZP 15) achieve ≥ 15% weight loss
- Whether this will translate in better cardiovascular outcome remains to be determined

Summary of Results

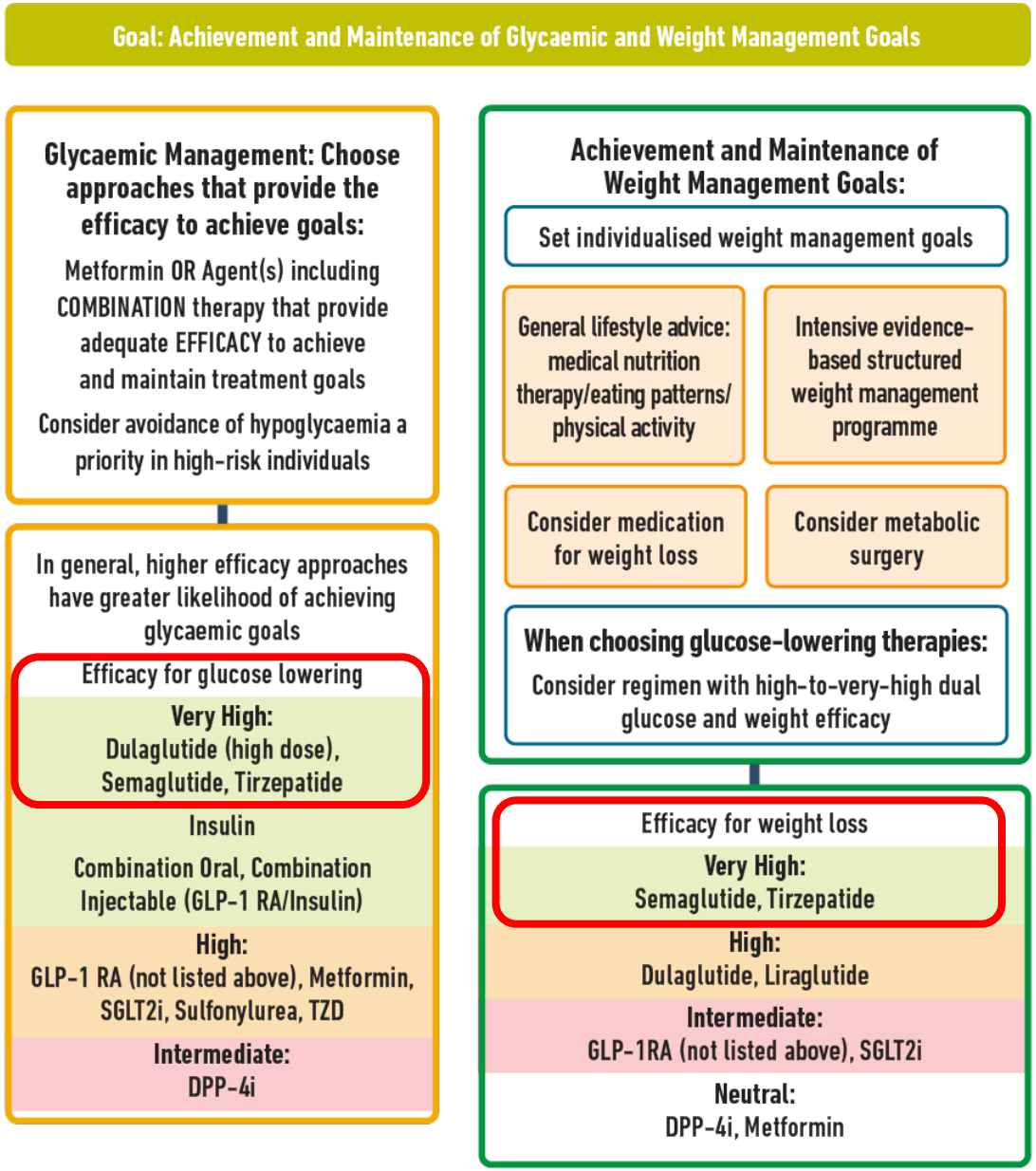
- As expected, GI-AEs are the major barrier of using a dual GIP/GLP-1 receptor agonist.
- Adverse events were dose- and time-dependent, and mild to moderate in severity, usually occurring during the dose escalation period and decreasing with continued dosing.
- Tirzepatide has a reassuring safety profile.

Actions of GLP-1, amylin, FGFs, leptin and glucagon on key target organs relevant to metabolism



GLP-1 = glucagon-like peptide-1; FGF = fibroblast growth factor

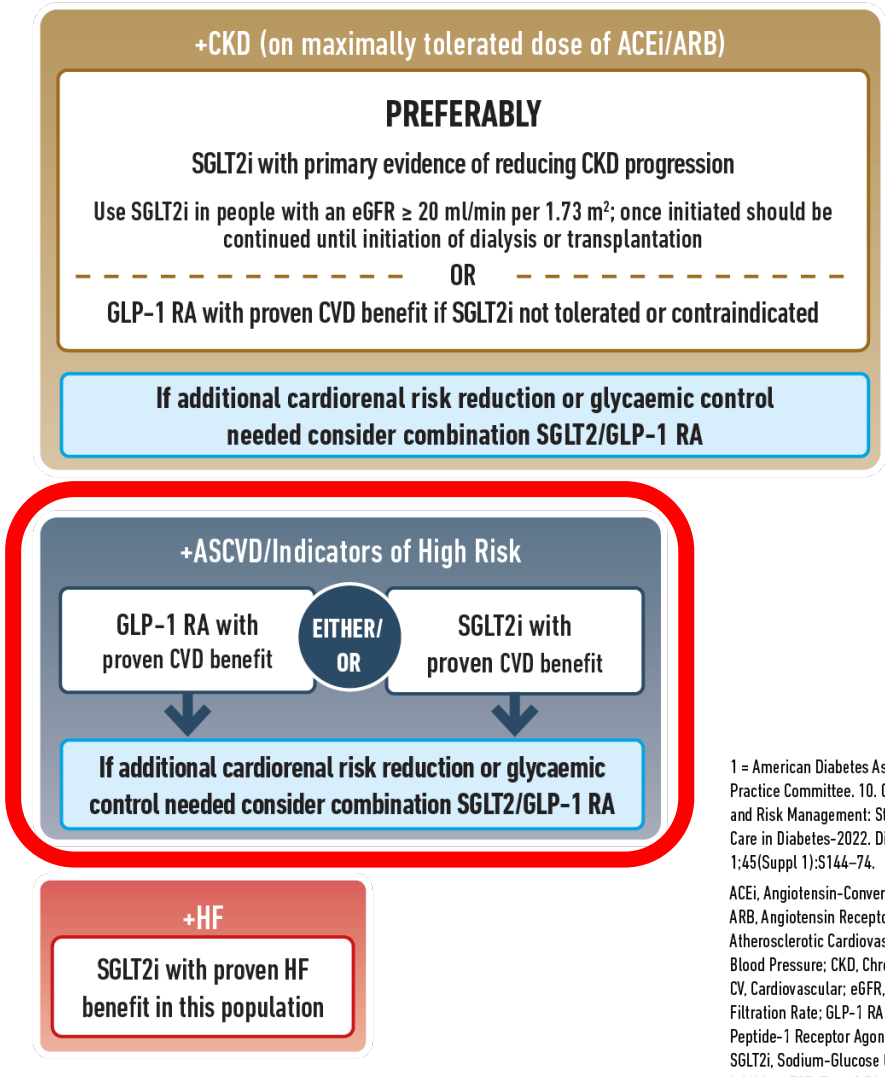
Baggio LL, Drucker DJ. *Mol Metab.* 2021;46:101090.



Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT



1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

Incretin-based therapies: conclusions

- GLP-1/GIP receptor agonist tirzepatide
- Future agents: GLP-1/glucagon, GLP-1/amylin, oxyntomodulin analogues, GLP-1/GIP/glucagon RA, oral GLP-1

Might be able to bring more people to target

Not only focussing on glycaemic control,

But applying a holistic approach: glucose, weight, BP, lipids, cardiorenal, NAFLD, …

Exciting times, the future looks bright

BP = blood pressure; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; NAFLD = non-alcoholic fatty liver disease.

Thank you for your attention