Twincretin and triple G drugs in management of diabetes

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Professor of Endocrinology and Metabolism

Agenda

- Introduction
- Dual agonist structure
- Tirzepatide a promising drug studies
- Triple agonist in treatment of diabetes

Three decades ago

The (impossible?) Mission:

Discover a new class of drugs that safely reduce body weight by 20-30% to overcome obesity and prevent type 2 diabetes.

Munich University Hospital 1993

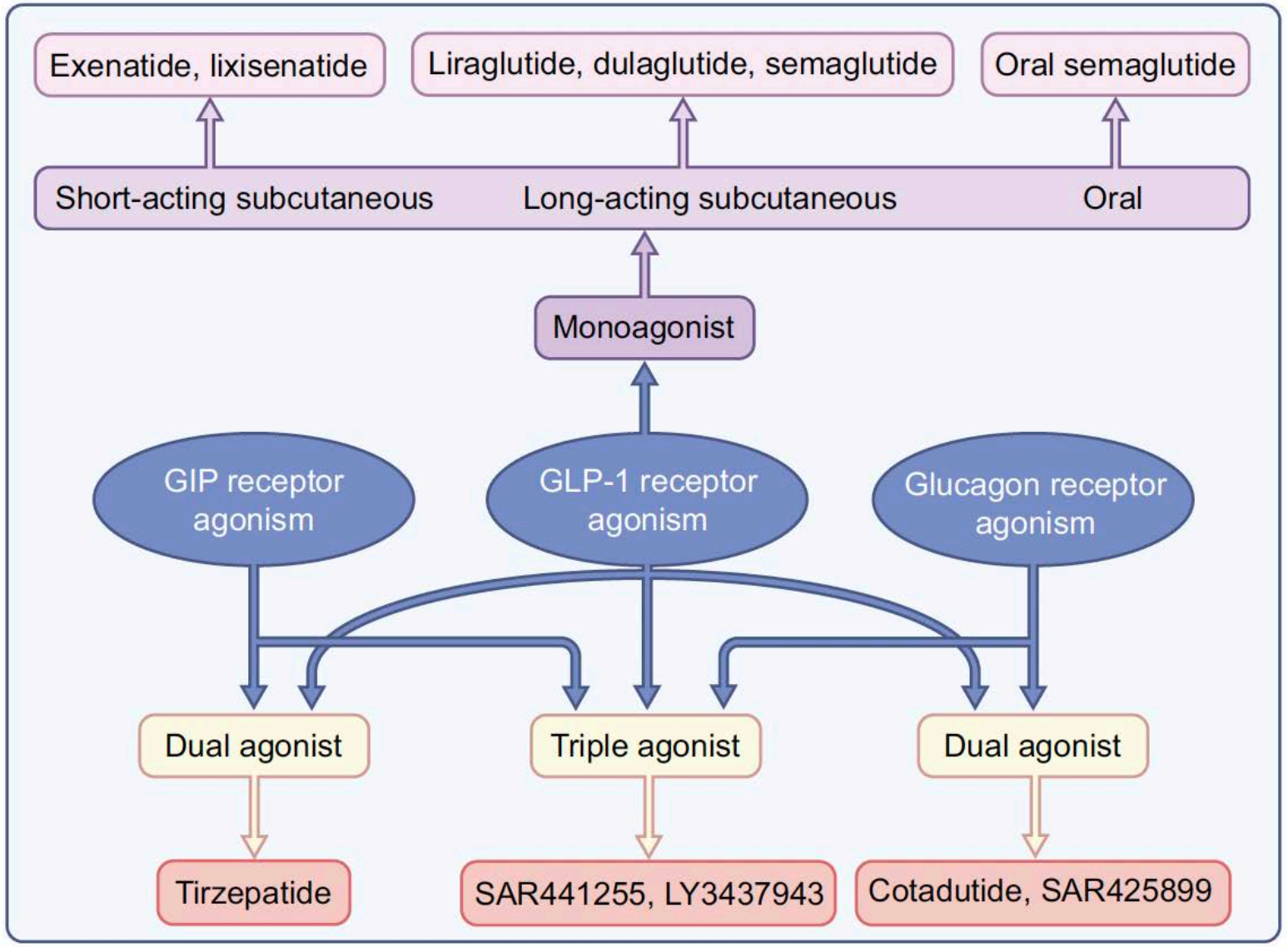
Introduction

- The diabetes pandemic is still here and still growing.
- The **twin epidemics** of obesity and type 2 DM will continue to pose major health challenges in coming decades.
- Despite numerous scientific advances bringing improvement to patients' life over last 100 years, since Banting discovered insulin, we have not managed to control, reverse or to prevent diabetes worldwide.
- RCTS of new IBT showed promising reductions in HbA1c and body weight and have been hailed as a game- changers in the diabesity community.

Schematic illustration of :

- Monoagonists
- Dual agonists
- Triple agonists

- Based on GLP-1, GIP and glucagon receptor activation alone or in combination



Twincretin

- Co- administration of GIP and GLP1 has an additive insulinotropic effect in healthy individuals and in those with T2DM2

The first ‘twincretin’ was a **unimolar** dual agonist of GIP and GLP1 receptors, which induced:

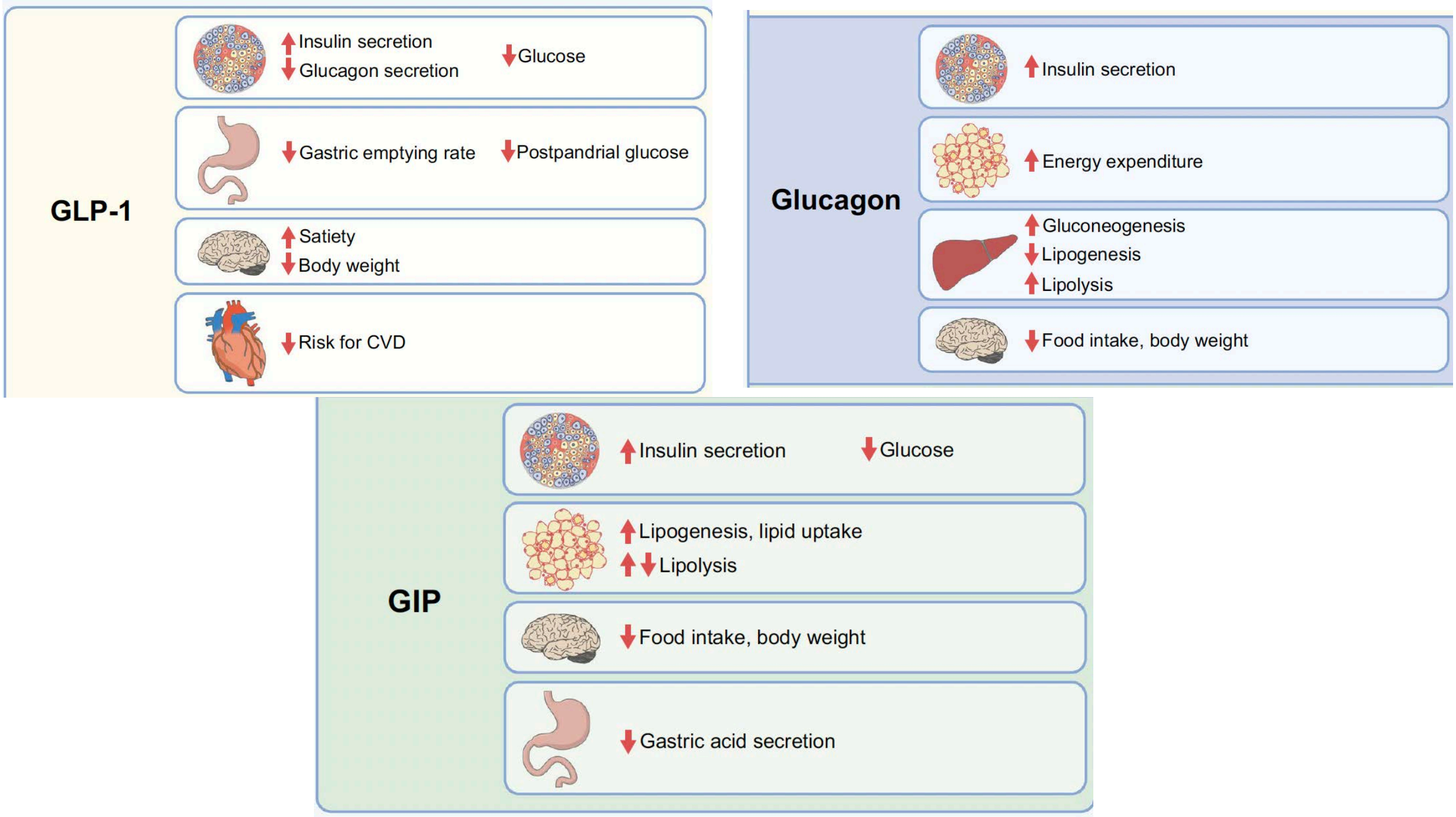
1. Superior dose- dependent weight loss
2. Reductions in blood glucose
3. Reduced food intake

Single molecule dual agonist

- Initial studies adding a second incretin hormone, GIP, to GLP-1 receptor agonism did not suggest any amplification of the metabolic effects.

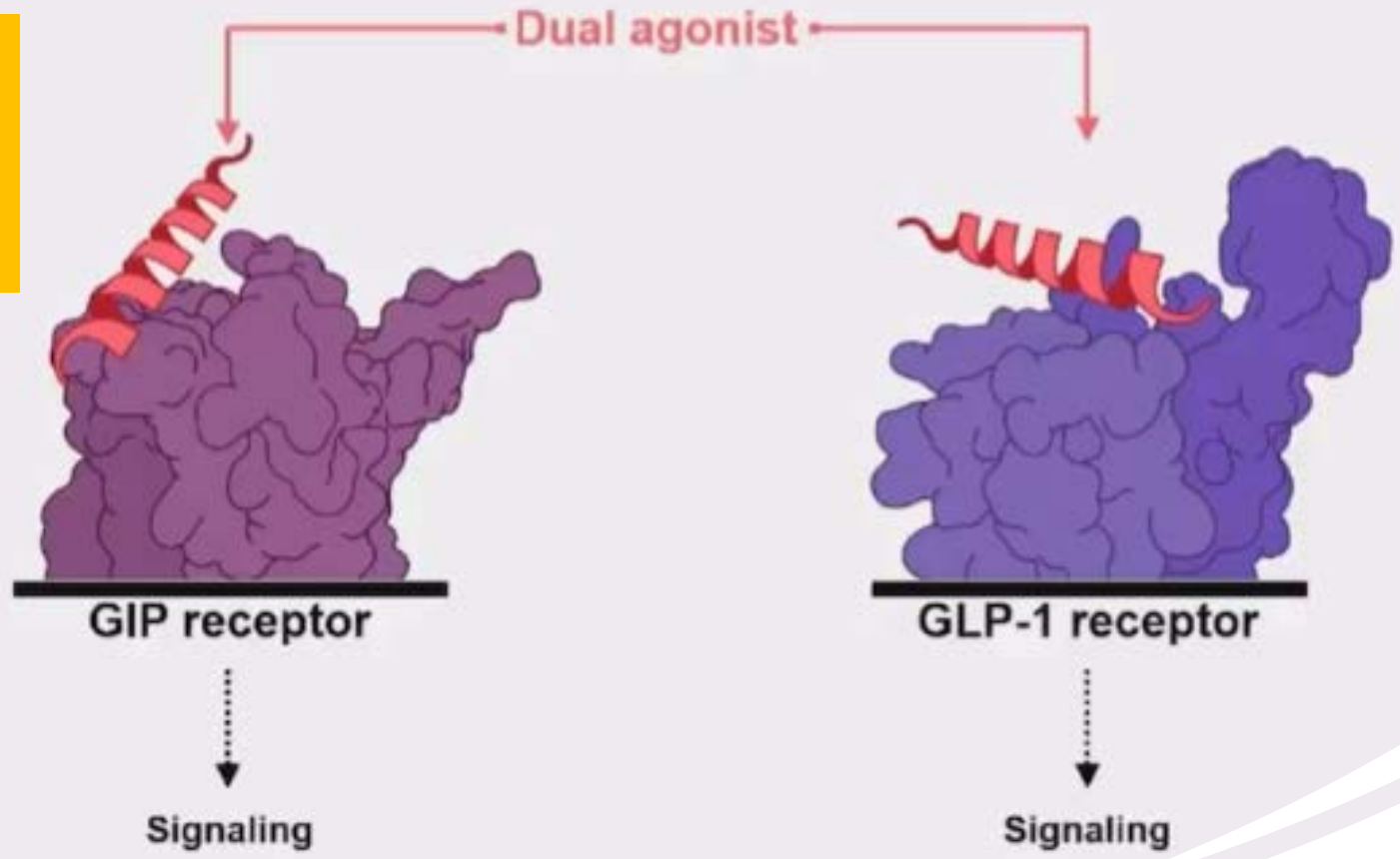
- Combining physiology, biology, chemistry ,and pharmacology toward one common goal, discovering drugs that allows safe and effective drugs to control DM and obesity.

- However, the development of a **single-molecule** dual agonist, which binds to both the GLP-1 and GIP receptors, has had different outcomes.


GLP-1
Insulin secretion
Glucagon secretion
Glucose
Gastric emptying rate
Postpandrial glucose
Satiety
Body weight
Risk for CVD
Glucagon
Insulin secretion
Energy expenditure
Gluconeogenesis
Lipogenesis
Lipolysis
Food intake, body weight
GIP
Insulin secretion
Glucose
Lipogenesis, lipid uptake
Lipolysis
Food intake, body weight
Gastric acid secretion

Discovery of a 2nd dual gut hormone receptor agonist for treatment of obesity and diabetes

Maximize beneficial effect on satiety, energy balance and glucose metabolism

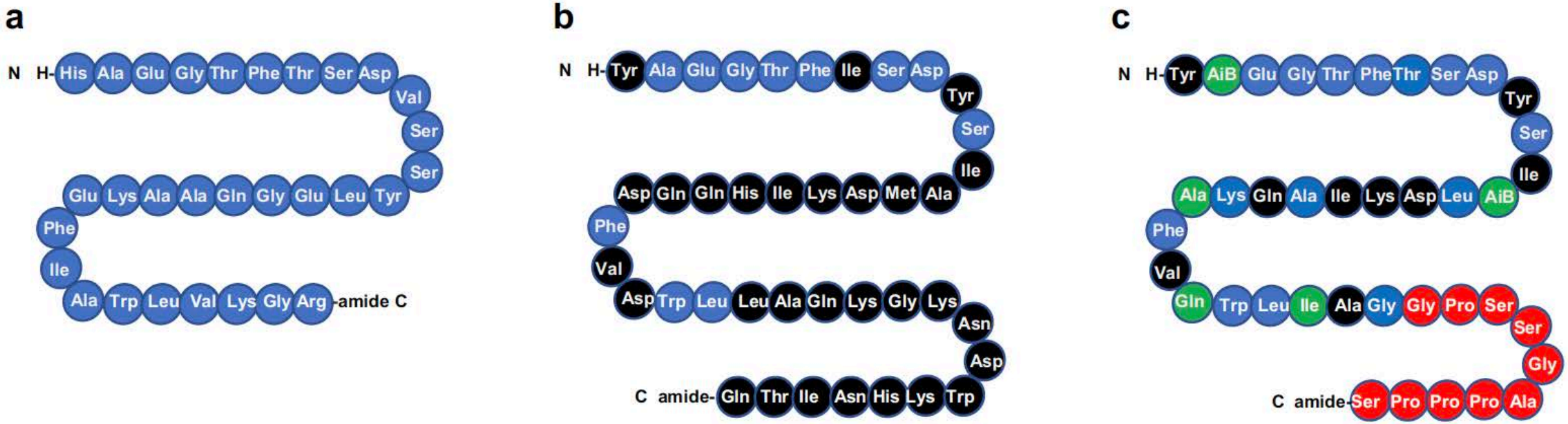


Activating multiple receptors

Tirzepatide is a synthetic linear peptide molecule containing 39 amino acids

Structures of (a) GLP-1, (b) GIP and (c) tirzepatide

In early 2016 Eli Lilly first applied a method of glycemic control using tirzepatide



Residues derive from GLP-1, GIP and semaglutide, and a few residues are unique

Green circles show amino acids that are present in tirzepatide but not in GLP-1, GIP or exenatide

Tirzepatide: A Promising Drug for T2DM and Beyond

- Tirzepatide is a promising drug with dual-acting GIP and GLP-1 receptor activation that has revolutionized the treatment of T2DM as an adjunct to diet and exercise.

It is conjugated to a C20 fatty diacid moiety which reversibly binds to albumin, prolonging its half-life to approximately 5 days, which allows for once-weekly subcutaneous dosing

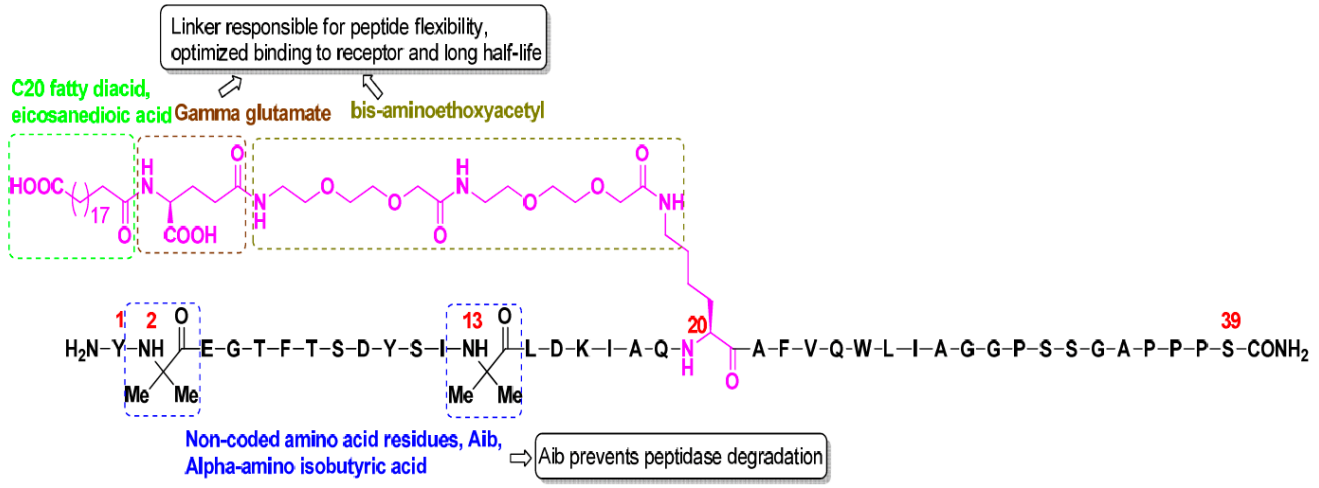
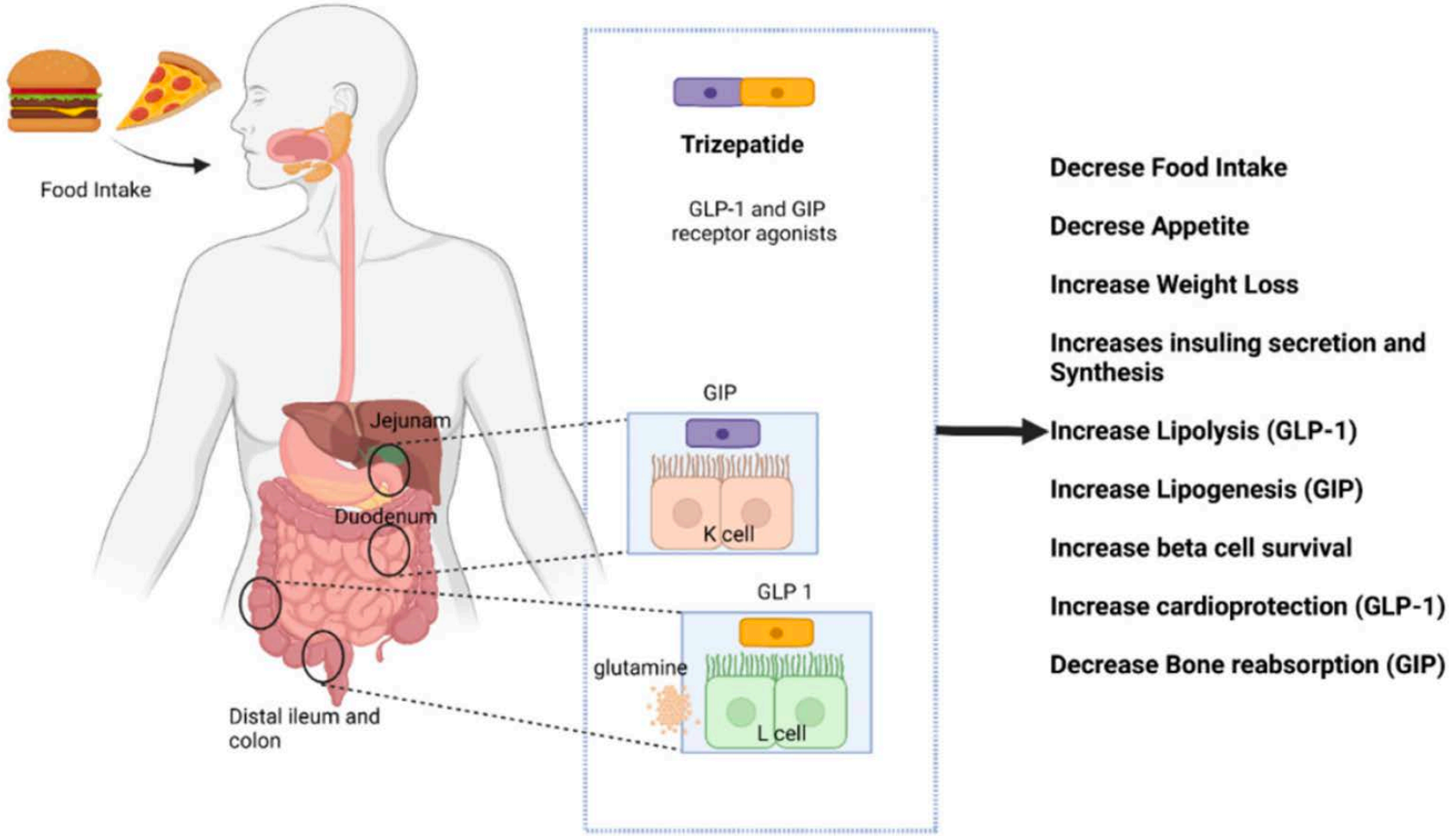


Figure 2. Structural features of tirzepatide, amino acids are denoted as single-letter codes.

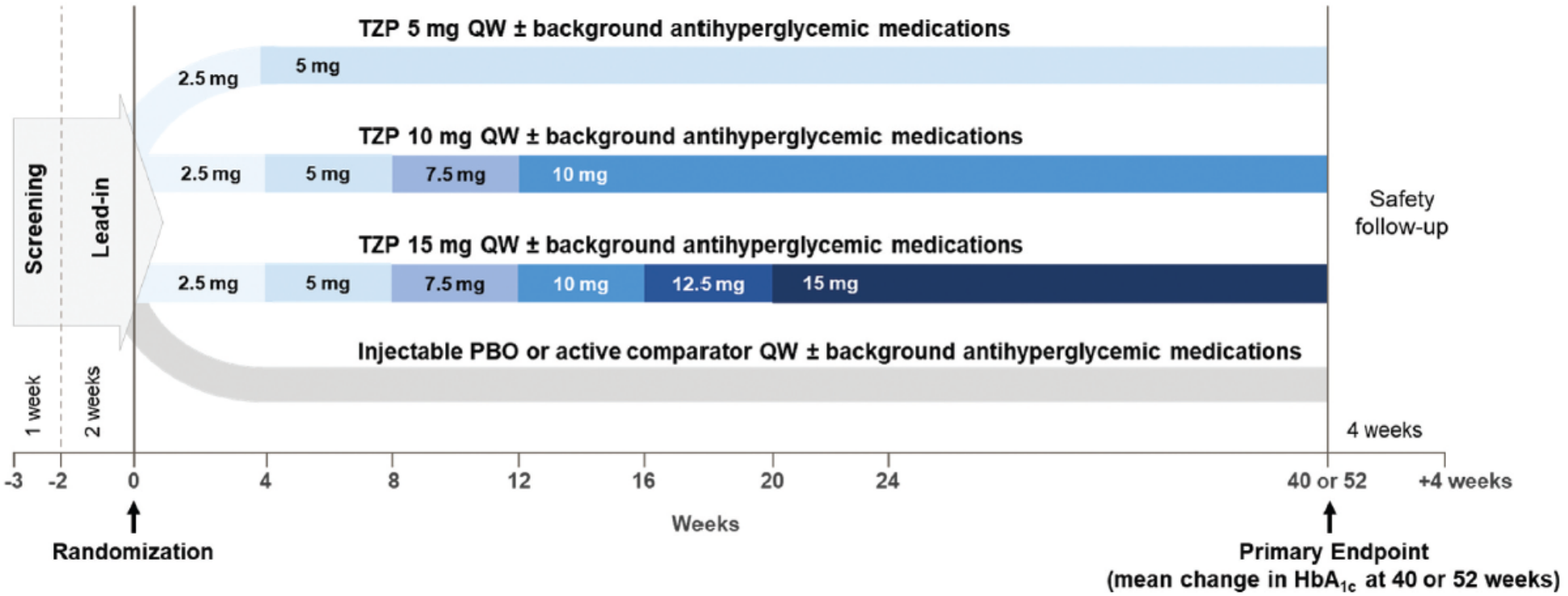
Mechanisms of action of tirzepatide within the human body



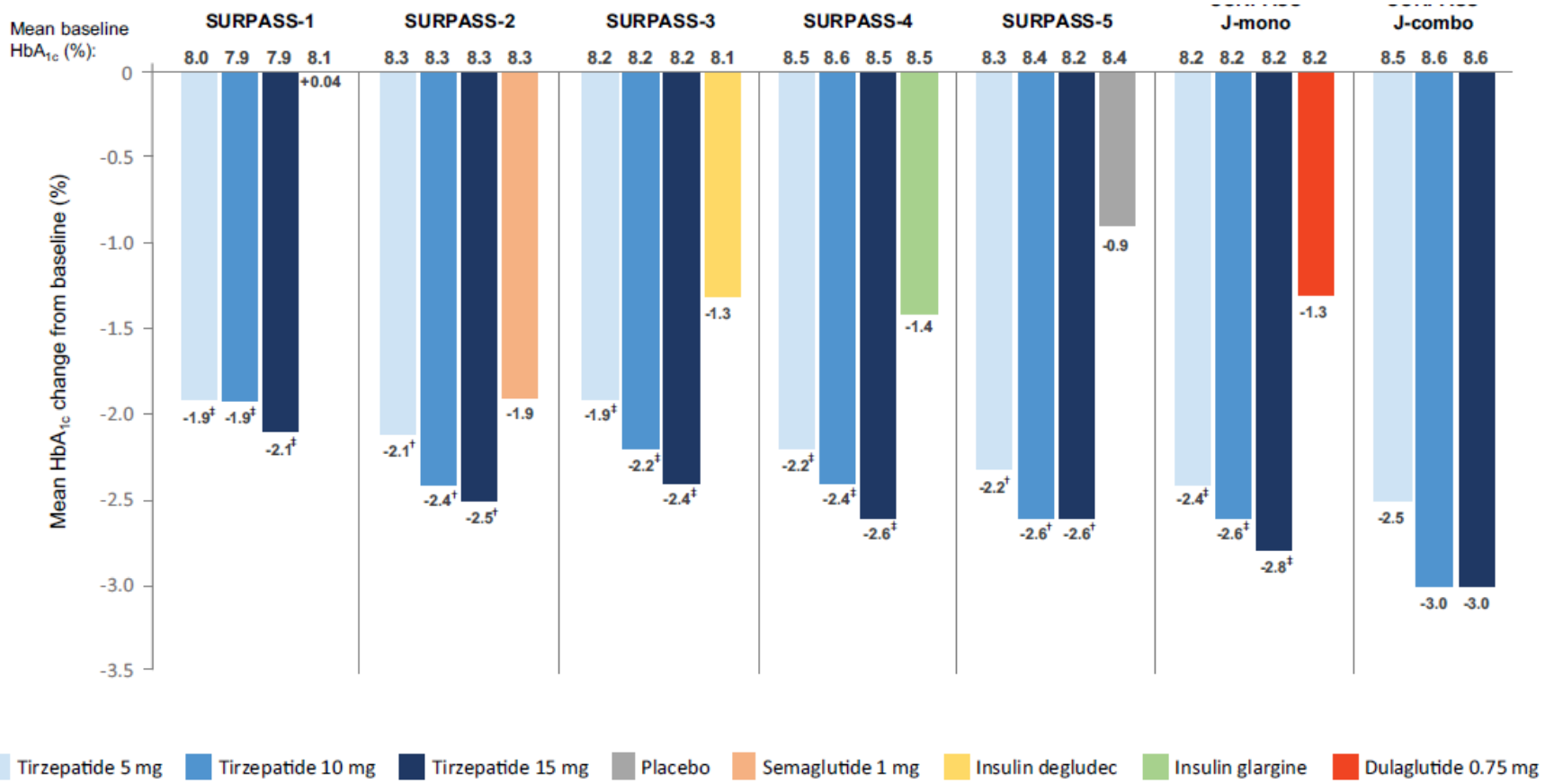
Tirzepatiden in SURPASS trials

Study	comparator	
SURPASS-1	placebo-controlled trial	
SURPASS-2	semaglutide	
SURPASS-3	insulin degludec	Metformin +/- SGLT2 -I
SURPASS-4	Insulin glargine	High CVD Risk
SURPASS-5	Insulin glargine	placebo
SURPASS-6	Prandial insulin	
SURPASS-J mono	Dulaglutide	
SURPASS-J combo	OAD	

Study design and dose escalation of SURPASS trials

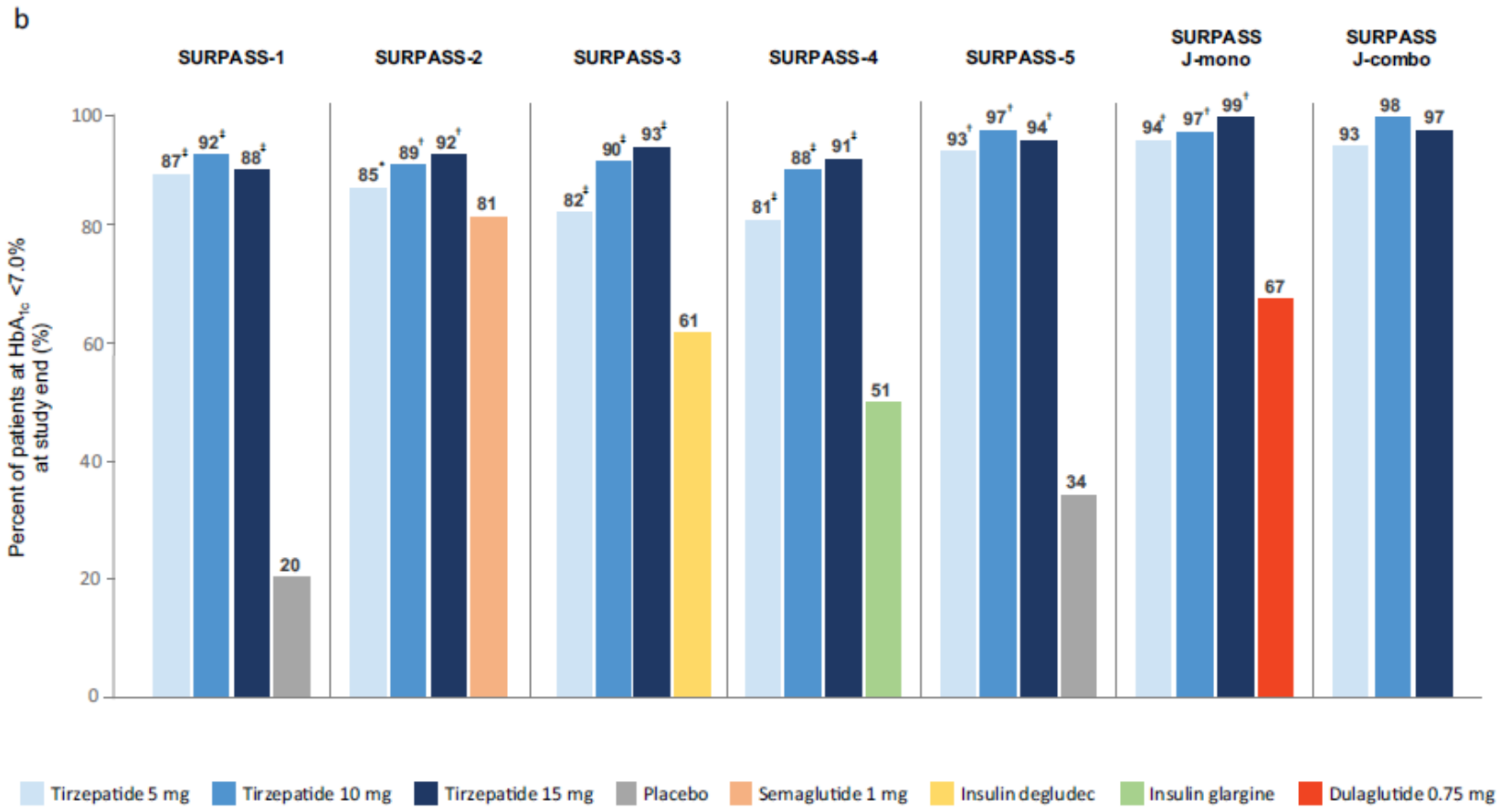


Change in HbA1c from baseline at study end



EXPERT REVIEW OF ENDOCRINOLOGY & METABOLISM 2023, VOL. 18, NO. 2, 111–130

Proportion of patients achieving a HbA1c <7.0% at study end



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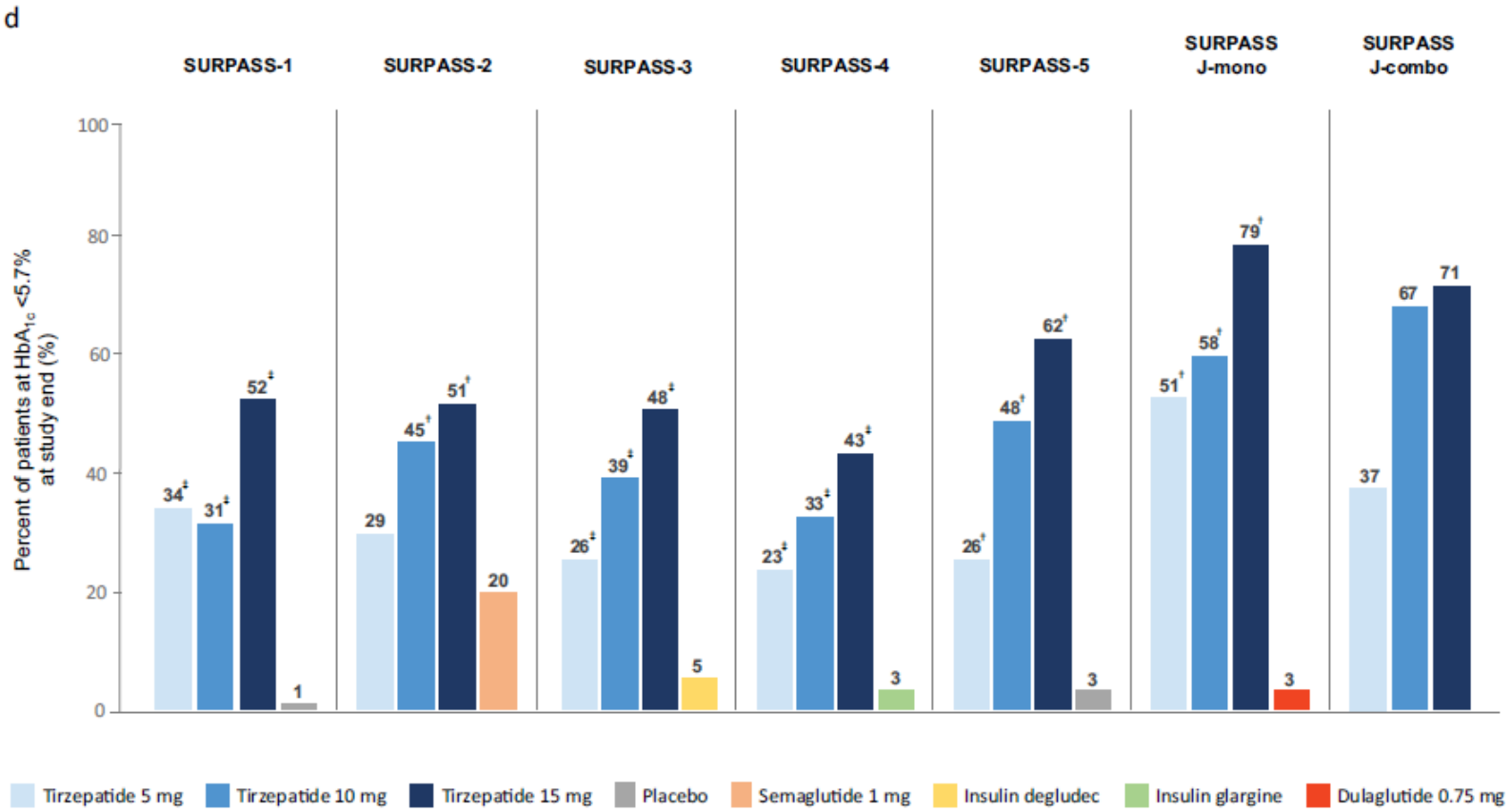
Proportion of patients achieving a HbA1c <5.7% at study end



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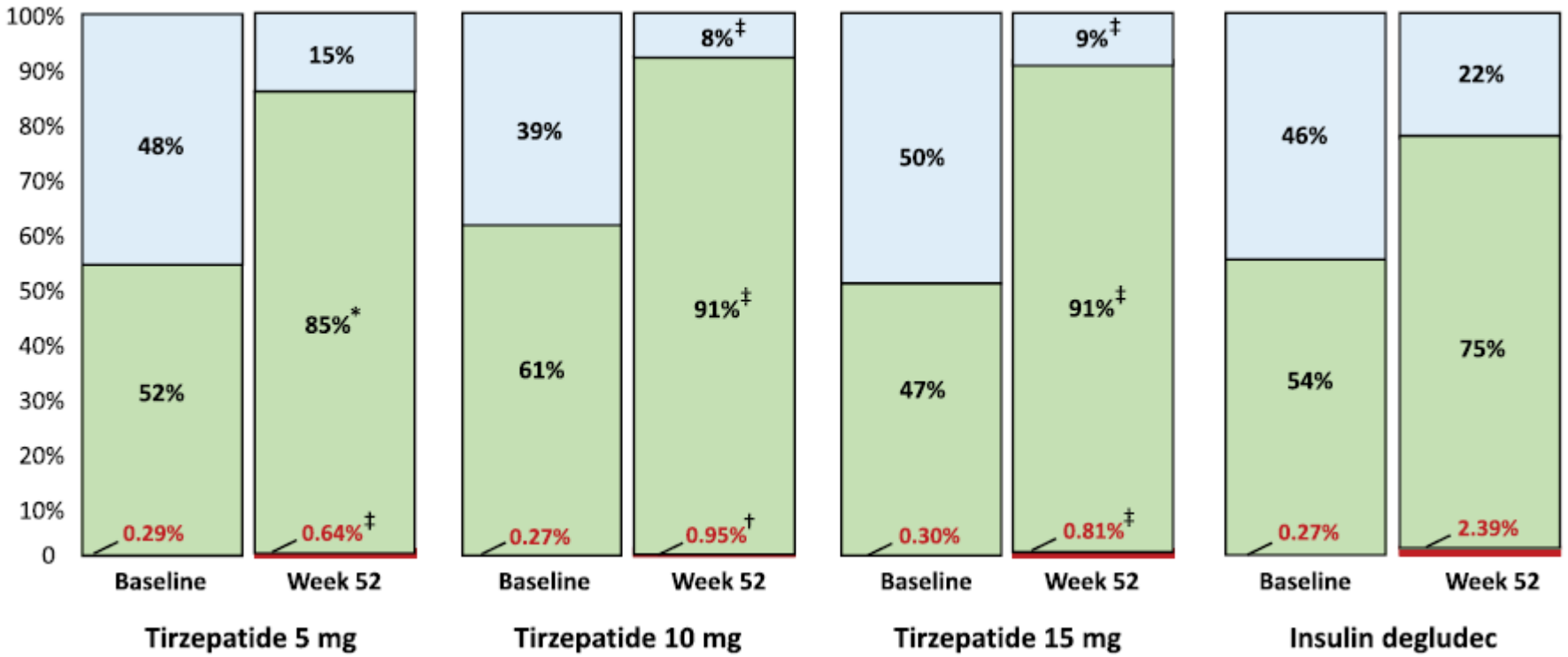
Proportion of TAR (>180) , TIR (71–180), TBR (≤70) during a 24-hour period at baseline and week 52 for tirzepatide

The improvement in HbA_{1c} was due to reduction in both fasting/preprandial and postprandial glucose, as demonstrated by 7-point SMBG profiles and CGM



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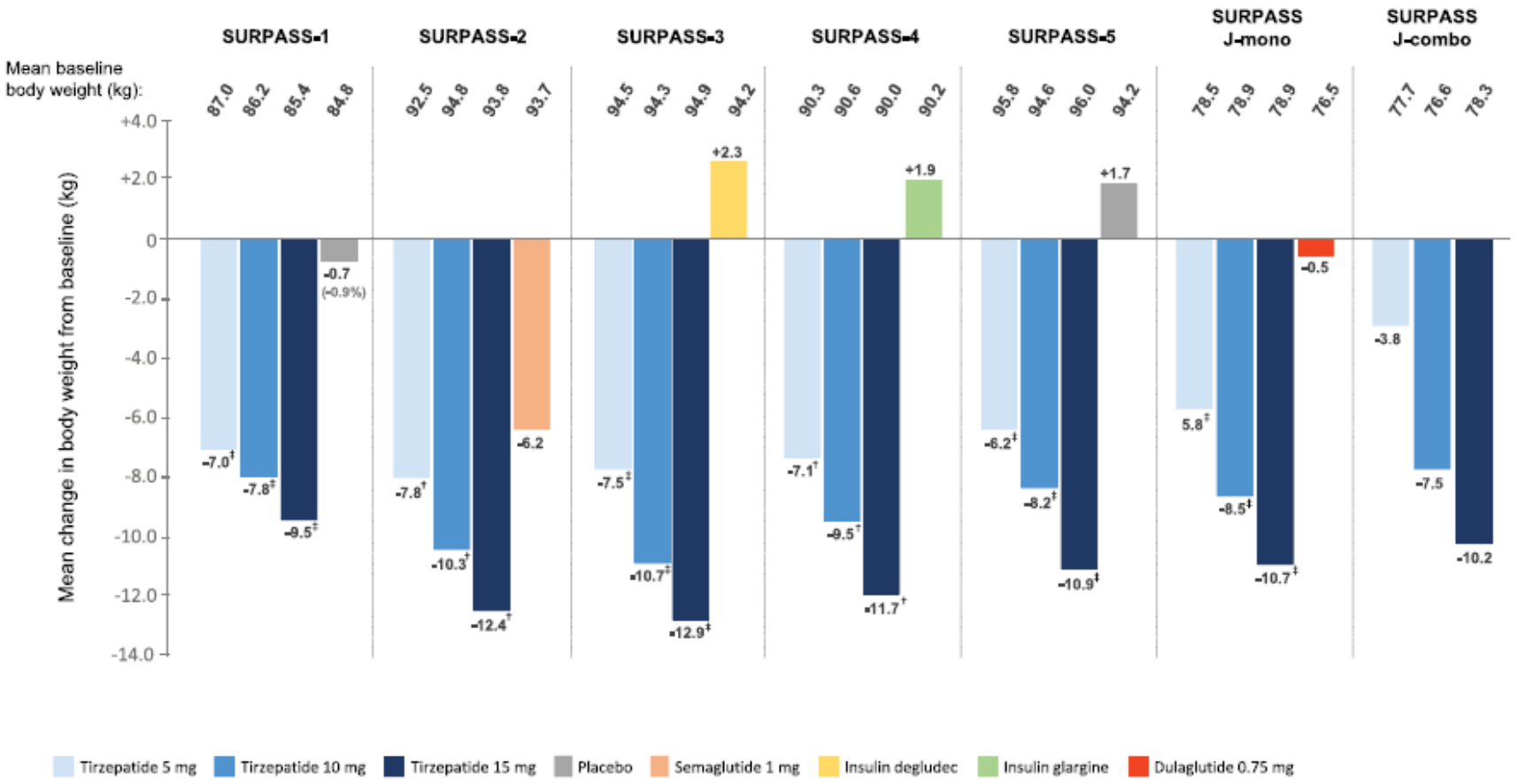
Change in body weight from baseline at study end



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Most reported adverse events

	Nausea (%)	Diarrhea (%)	Vomiting (%)
SURPASS-1	12–18	12–14	2–6
SURPASS-2	17–22	13–16	6–10
SURPASS-3	12–24	15–17	6–10
SURPASS-4	12–23	13–22	5–9
SURPASS-5	13–18	12–21	7–13
SURMOUNT-1	25–33	19–23	8–12

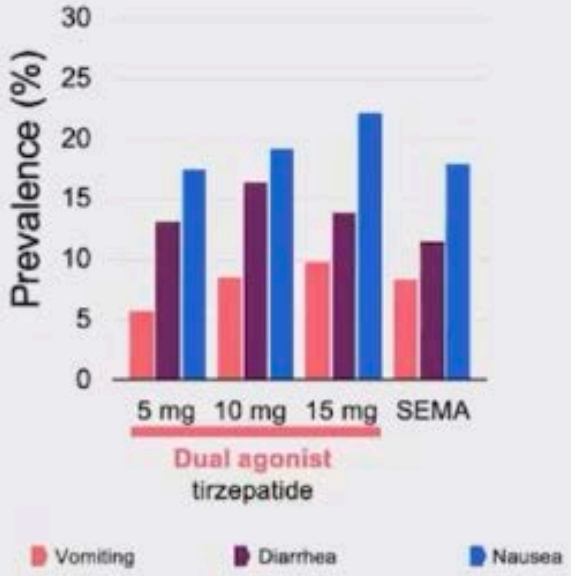
The GIP-GLP-1 receptor agonist tirzepatide: Superior efficacy without increasing side effects

2

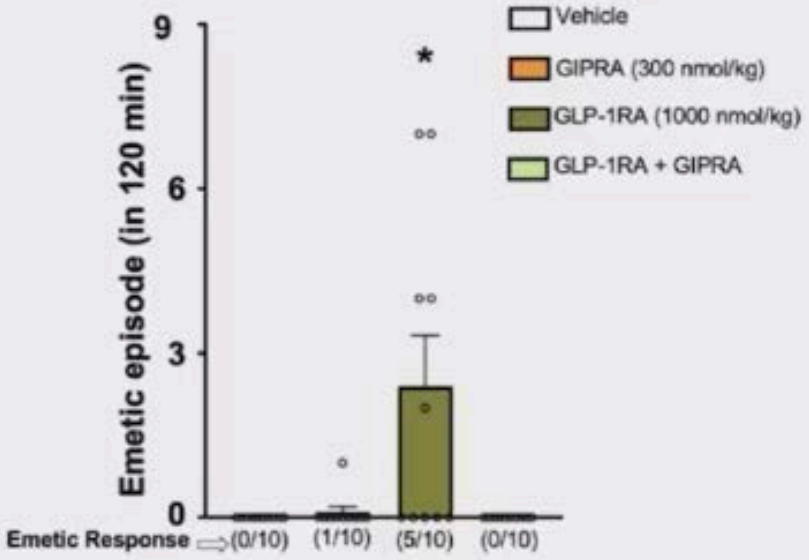
SURPASS-2[2]

40 weeks

Add-on to MET



GIP Receptor Agonism Attenuates GLP-1 Receptor Agonist-Induced Nausea and Emesis in Preclinical Models



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. Dahl D, et al. *JAMA*. 2022;327(6):534-545.

Borner,...Grill,..Samms,..Hayes., Diabetes (2021)

JAMA | Original Investigation

Tirzepatide vs Insulin Lispro Added to Basal Insulin in Type 2 Diabetes

The SURPASS-6 Randomized Clinical Trial

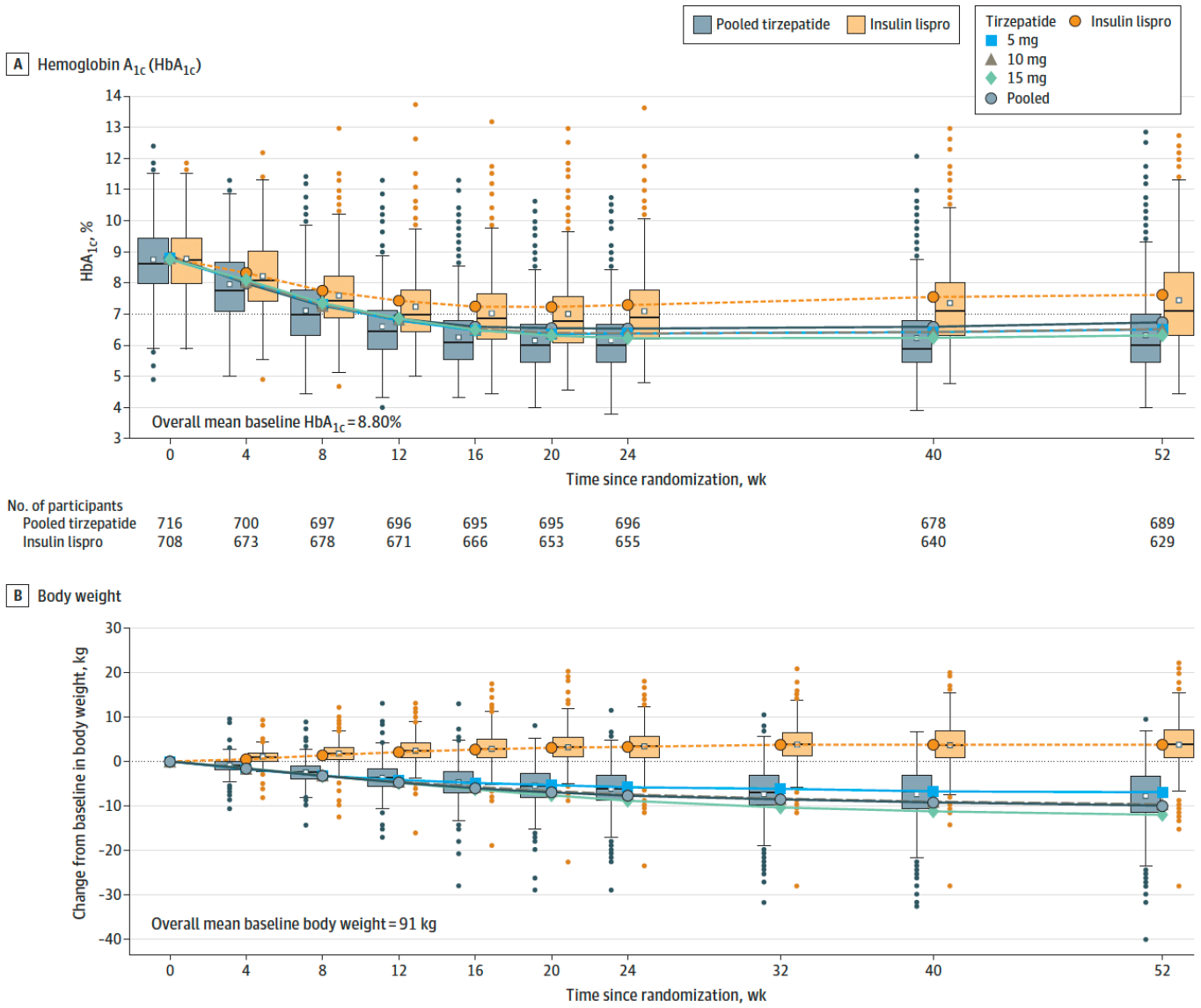
Julio Rosenstock, MD; Juan P. Frías, MD; Helena W. Rodbard, MD; Santiago Tofé, MD; Emmalee Sear
Ruth Huh, PhD; Laura Fernández Landó, MD; Hiren Patel, MPharm

CONCLUSIONS AND RELEVANCE

In people with inadequately controlled T2DM treated with basal insulin

weekly tirzepatide compared with prandial insulin as an additional treatment with insulin glargine demonstrated:
Reductions in HbA1c and body weight with less hypoglycemia.

Figure 2. Effect of Tirzepatide vs Insulin Lispro on Hemoglobin A_{1c} (HbA_{1c}) and Body Weight



First FDA-approved version of a dual GIPR/GLP-1R agonist: Mounjaro™ (tirzepatide, Eli Lilly)

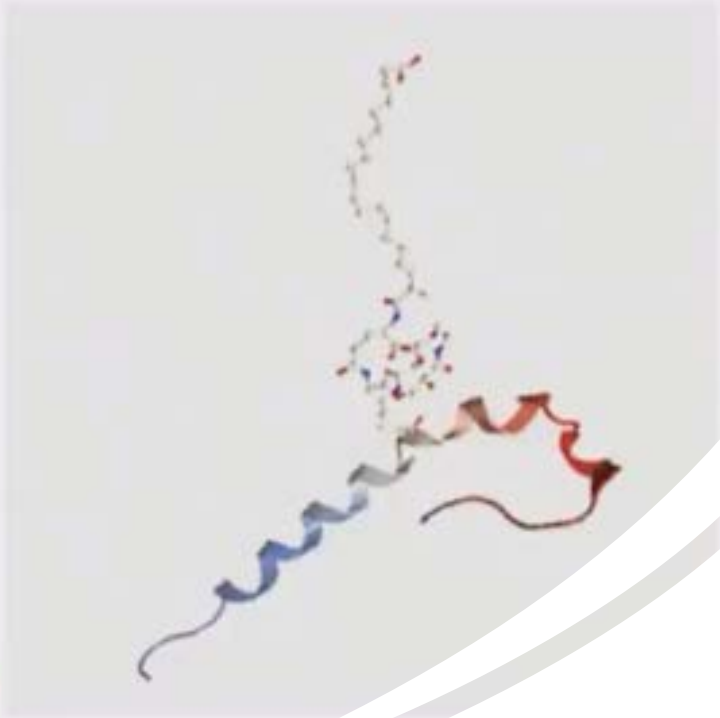

Lilly

FDA approves Lilly's Mounjaro™ (tirzepatide) injection, the first and only GIP and GLP-1 receptor agonist for the treatment of adults with type 2 diabetes

May 13, 2022

FIERCE Pharma:

In another note to clients, a team of analysts at UBS recently opined that tirzepatide could become **"the biggest drug ever,"**.[2]



APPROVED FDA APPROVED

FDA approves Lilly's Mounjaro™ (tirzepatide) injection. http://lilly.mediaroom.com/ ... FDA fast lane for obesity. www.fiercepharma.com.

- A dose-dependent superiority on glycemic efficacy and body weight reduction was evident with tirzepatide vs placebo, GLP-1 RAs and basal insulin.

- Tirzepatide did not increase the odds of hypoglycemia

- It was associated with increased incidence of GI adverse events.

Seven trials (6609 participants) were included

Diabetologia (2022) 65:1251–1261
https://doi.org/10.1007/s00125-022-05715-4

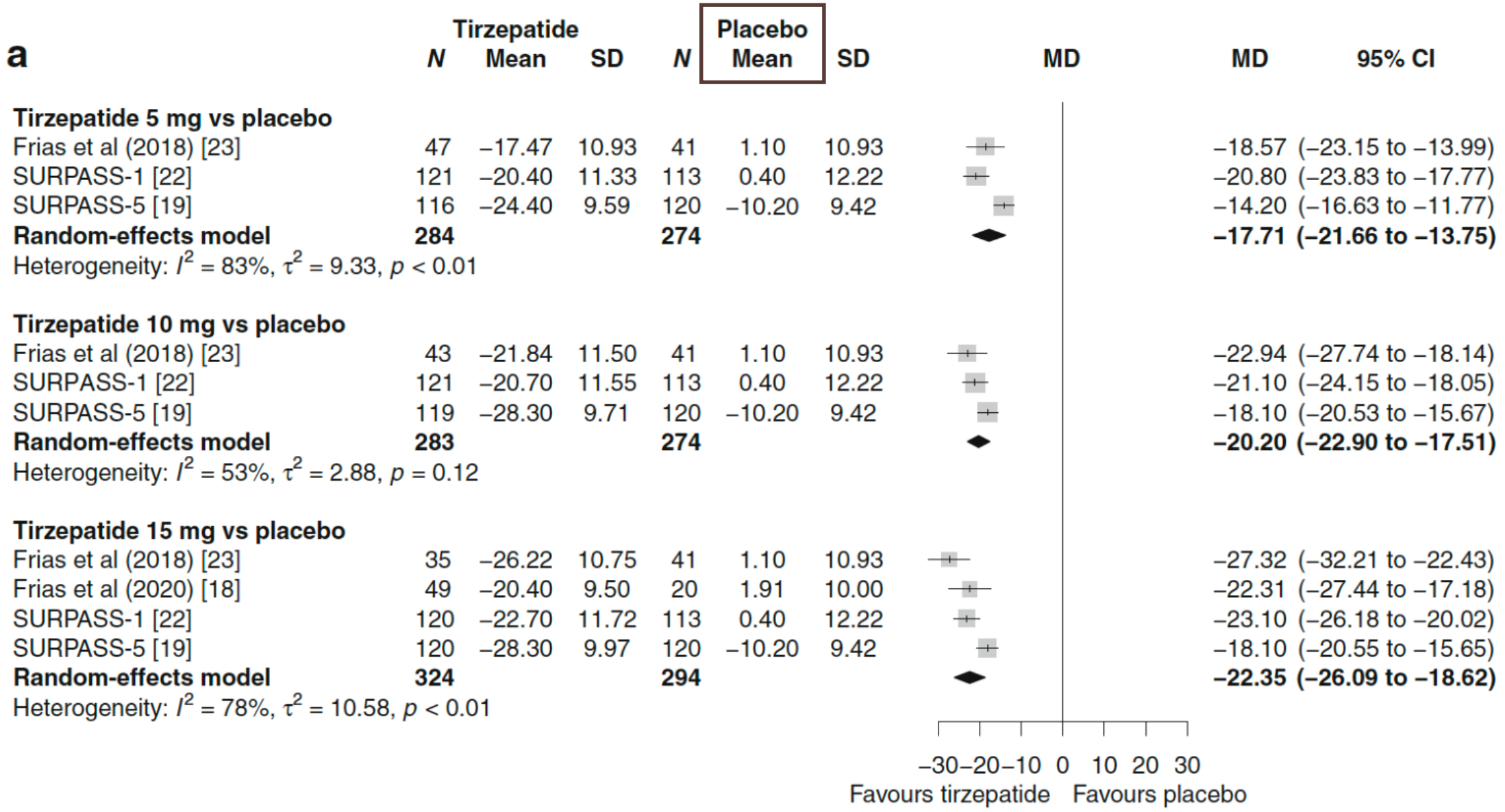
ARTICLE

Check for updates

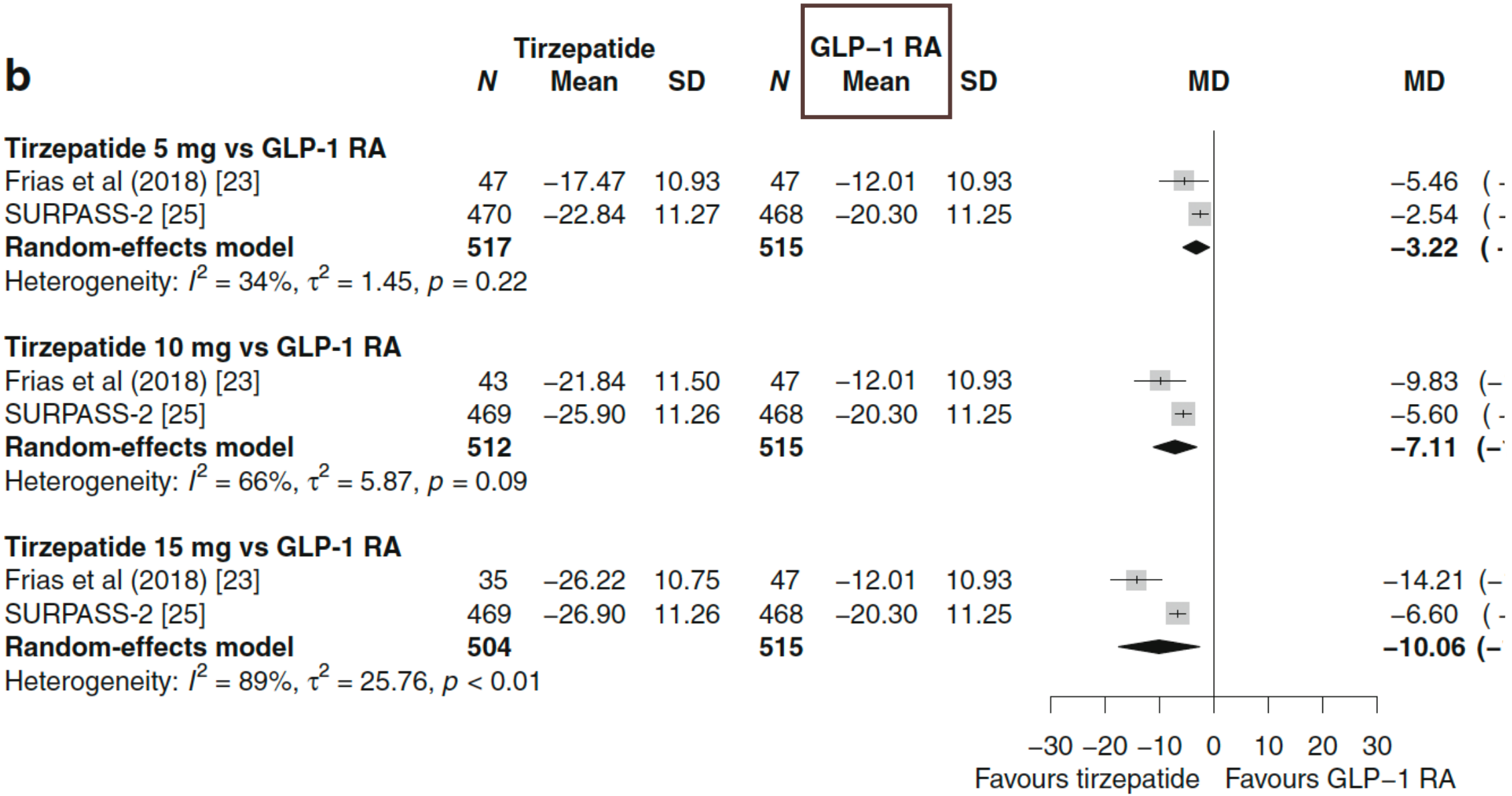
Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis

Thomas Karagiannis[1,2] · Ioannis Avgerinos[1,2] · Aris Liakos[1,2] · Stefano Del Prato[3] · David R. Matthews[4,5] · Apostolos Tsapas[1,2,4] · Eleni Bekiari[1,2]

Received: 10 December 2021 / Accepted: 21 February 2022 / Published online: 17 May 2022



Meta-analysis results for tirzepatide vs placebo (a) and vs GLP1-RAs (b) for change in HbA1c



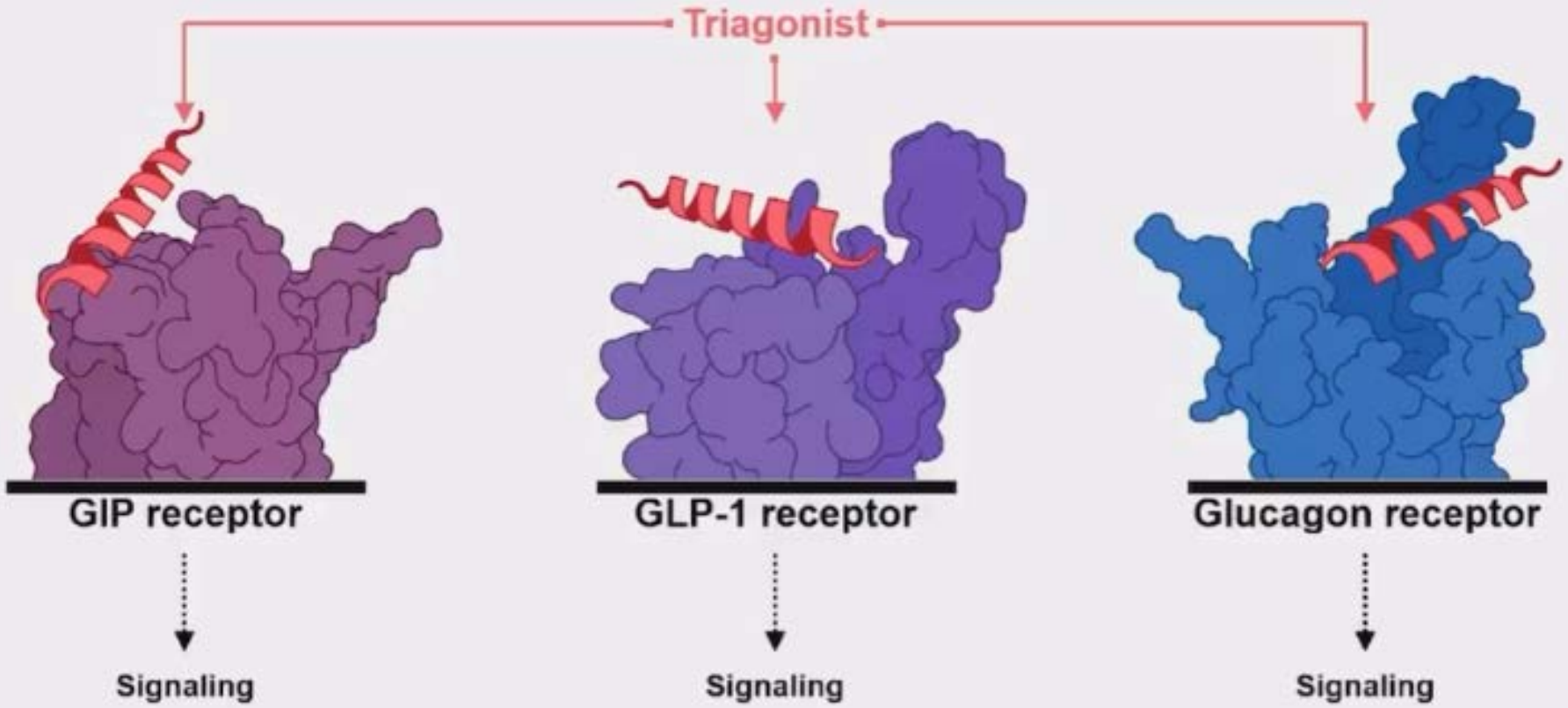
Meta-analysis results for tirzepatide vs placebo (a) and vs GLP1-RAs (b) for change in HbA1c

Triple agonist drugs

A new class of glucose-lowering therapy for type 2 diabetes: the latest development in the incretin arena

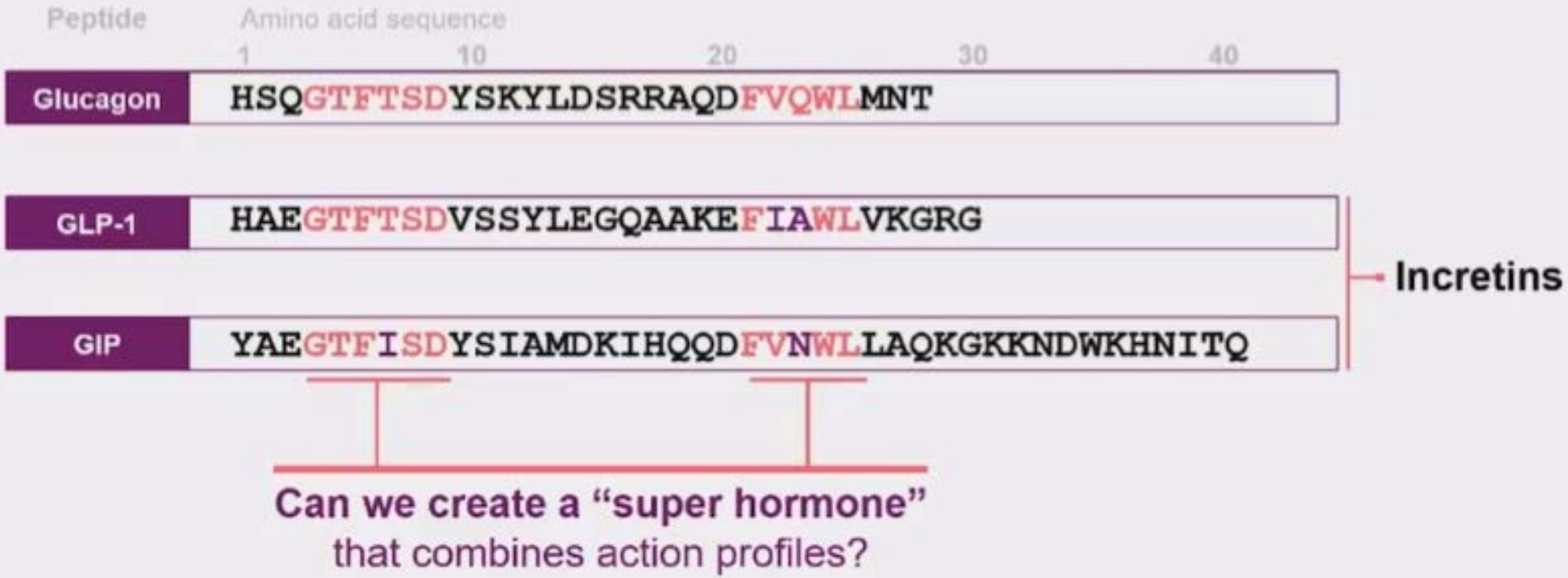
Discovery of the 1st triple gut hormone receptor agonist for obesity and diabetes

3



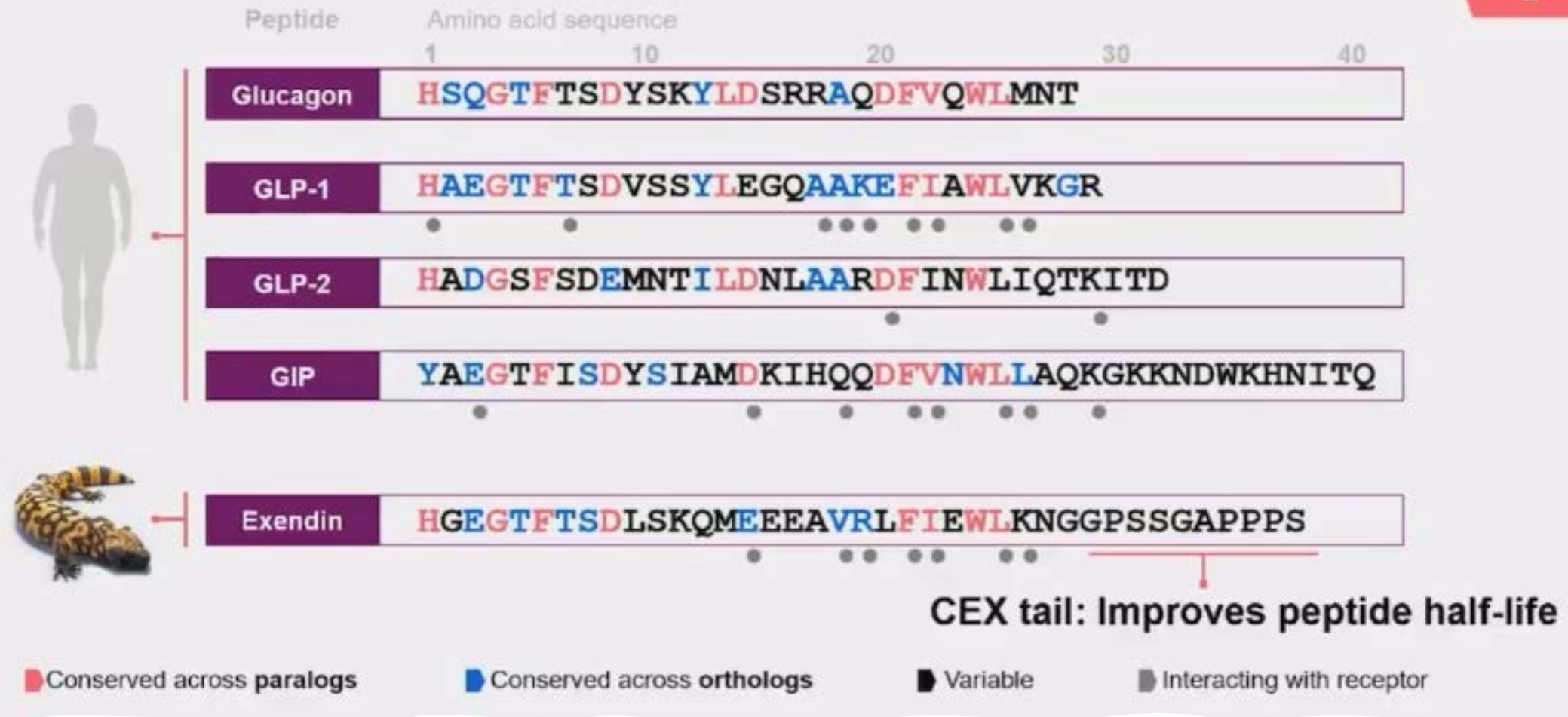
The main question is in which ratio of these 3 components be present?

Repositioning glucagon: The peptide family



Discovery of new synthetic glucagon receptor agonists

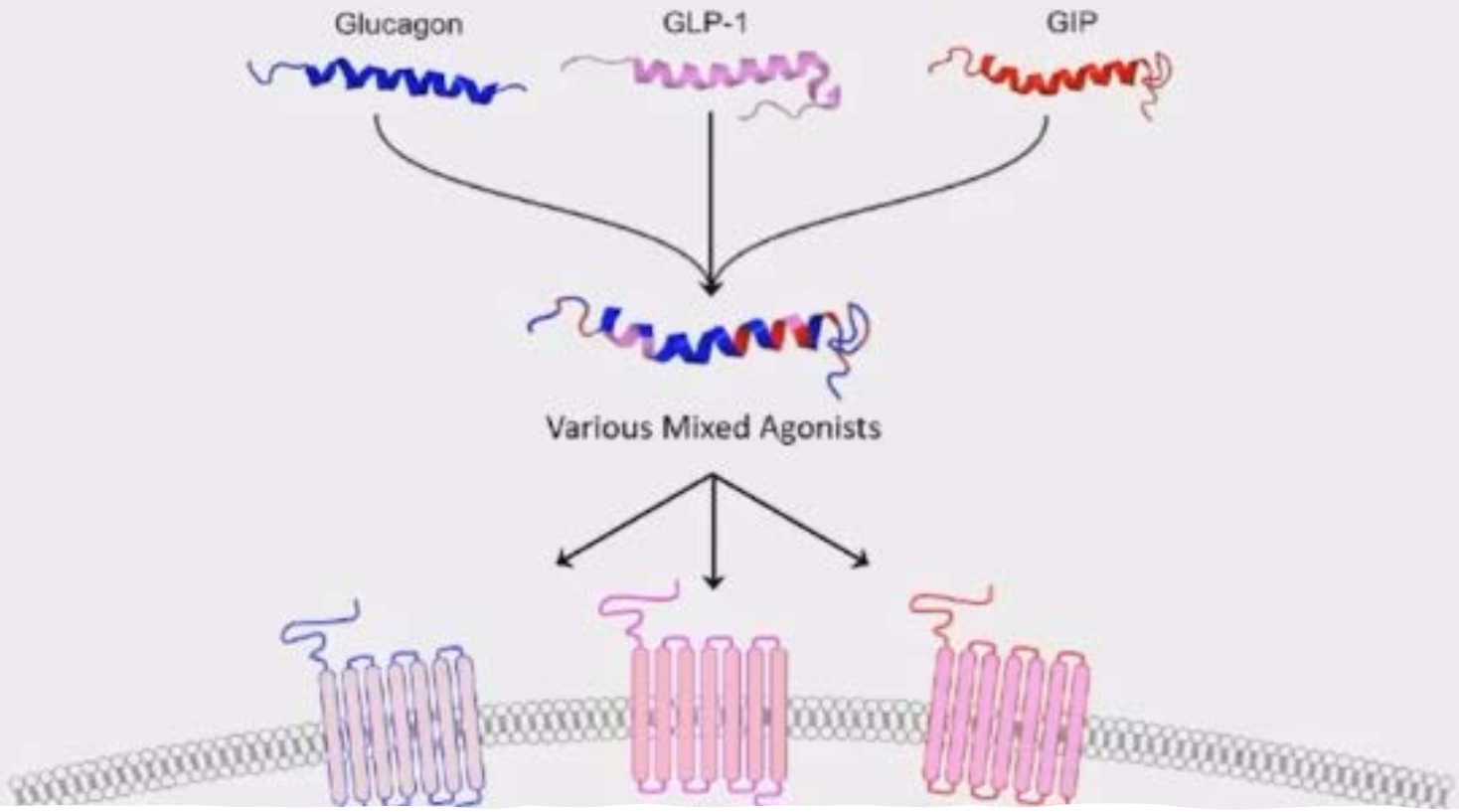
1



Orthologous genes keep the same function , paralogous genes often develop different functions

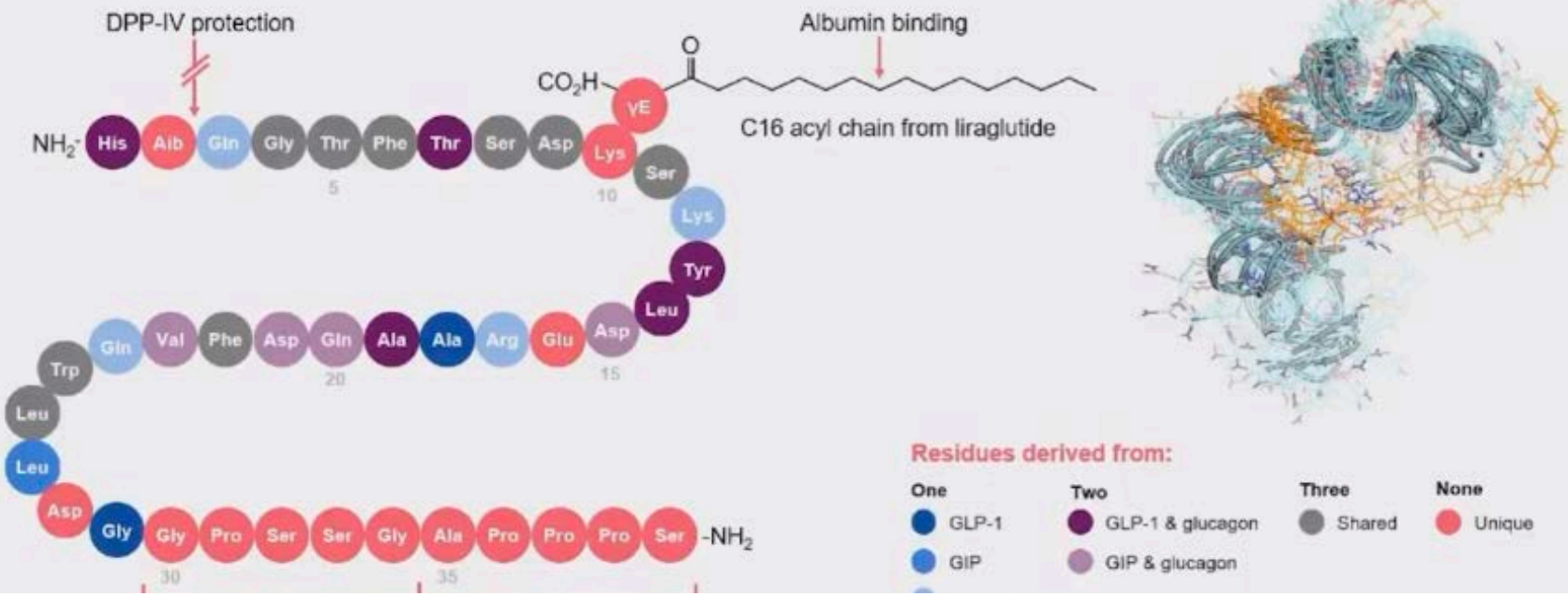
Discovery of triple receptor agonists: Structural engineering

3



Discovery of triple receptor agonists: Structural engineering

3



Residues derived from:

One	Two	Three	None
GLP-1	GLP-1 & glucagon	Shared	Unique
GIP	GIP & glucagon		

Compared with the native hormones, retatrutide is more potent at human GIP receptors and less potent at human glucagon and GLP-1 receptors.

Cell Metab 2022; **34:** 1234–1247.e9.

Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA

Julio Rosenstock, Juan Frias, Ania M Jastreboff, Yu Du, Jitong Lou, Sirel Gurbuz, Melissa K Thomas, Mark L Hartman, Axel Haupt, Zvonko Milicevic, Tamer Coskun

Once-weekly injections of:
placebo
1·5 mg dulaglutide
retatrutide maintenance doses of 0·5 mg
4 mg (starting dose 2 mg)
4 mg (no escalation)
8 mg (starting dose 2 mg)
8 mg (starting dose 4 mg)
12 mg (starting dose 2 mg)

- The primary endpoint was change in HbA1c from baseline to 24 weeks
- Secondary endpoints included change in HbA1c and bodyweight at 36 weeks

281 participants (mean age 56·2 years [SD 9·7]
mean duration of diabetes 8·1 years [7·0]
156 [56%] female

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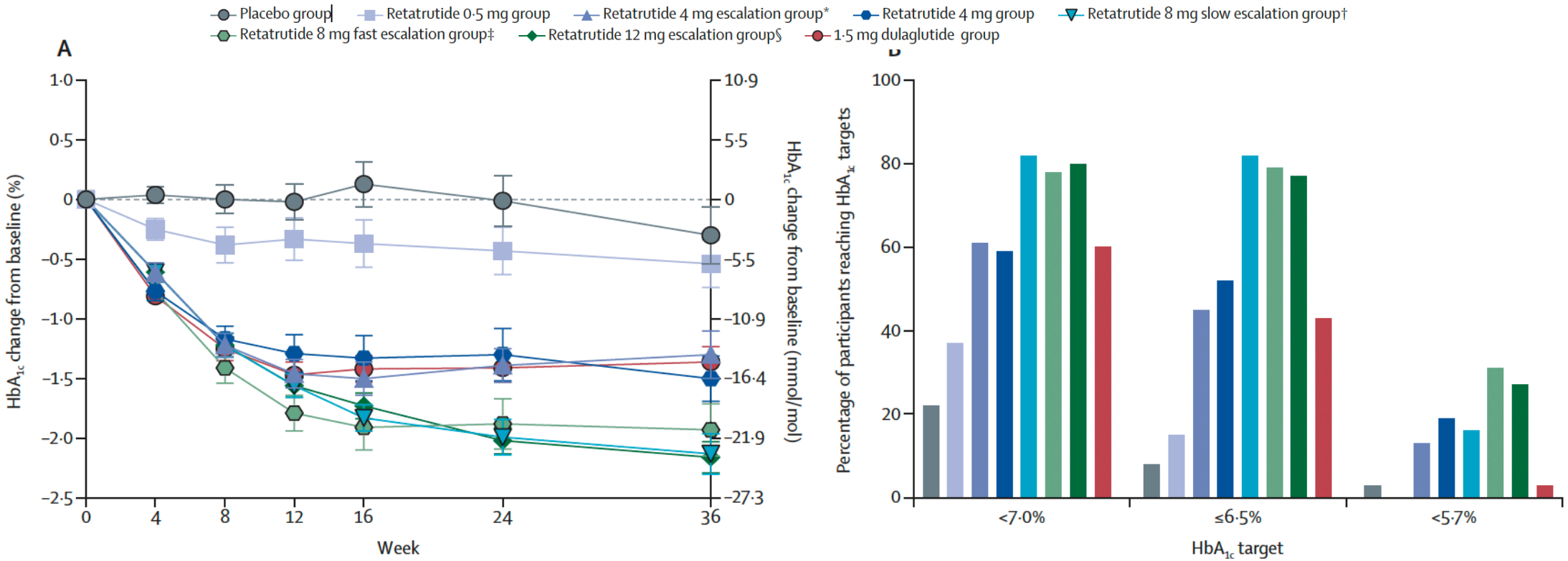
42 research and health-care centers in the USA



HbA1c results

	Placebo group (n=45)	Retatrutide 0·5 mg group (n=46)	Retatrutide 4 mg escalation group* (n=22)	Retatrutide 4 mg group (n=24)	Retatrutide 8 mg slow escalation group† (n=25)	Retatrutide 8 mg fast escalation group‡ (n=24)	Retatrutide 12 mg escalation group§ (n=43)	1·5 mg dulaglutide group (n=46)
HbA_{1c}, %								
Baseline	8·39 (0·17)	8·38 (0·17)	8·01 (0·18)	8·20 (0·24)	8·30 (0·22)	8·20 (0·25)	8·28 (0·16)	8·22 (0·13)
Change at 24 weeks	−0·01 (0·21); p=0·9580	−0·43 (0·20); p=0·0298	−1·39 (0·14); p<0·0001	−1·30 (0·22); p<0·0001	−1·99 (0·15); p<0·0001	−1·88 (0·21); p<0·0001	−2·02 (0·11); p<0·0001	−1·41 (0·12); p<0·0001
Versus placebo	..	−0·42 (−0·98 to 0·15); p=0·1470	−1·38 (−1·88 to −0·89); p<0·0001	−1·29 (−1·89 to −0·69); p<0·0001	−1·98 (−2·49 to −1·48); p<0·0001	−1·87 (−2·46 to −1·28); p<0·0001	−2·01 (−2·48 to −1·54); p<0·0001	..
Versus dulaglutide 1·5 mg		0·98 (0·53 to 1·43); p<0·0001	0·01 (−0·34 to 0·37); p=0·9370	0·11 (−0·39 to 0·60); p=0·6655	−0·58 (−0·95 to −0·22); p=0·0019	−0·47 (−0·95 to 0·01); p=0·0558	−0·61 (−0·93 to −0·29) p=0·0002	..
Change at 36 weeks	−0·30 (0·24); p=0·2091	−0·54 (0·20); p=0·0057	−1·30 (0·20); p<0·0001	−1·50 (0·19); p<0·0001	−2·13 (0·17); p<0·0001	−1·93 (0·22); p<0·0001	−2·16 (0·13); p<0·0001	−1·36 (0·13); p<0·0001
Versus placebo	..	−0·24 (−0·85 to 0·38); p=0·4481	−0·99 (−1·60 to −0·38); p=0·0014	−1·20 (−1·80 to −0·59); p=0·0001	−1·83 (−2·41 to −1·24); p<0·0001	−1·63 (−2·27 to −0·99); p<0·0001	−1·85 (−2·39 to −1·31); p<0·0001	..
Versus dulaglutide 1·5 mg	..	0·82 (0·35 to 1·29); p=0·0006	0·06 (−0·41 to 0·53); p=0·7964	−0·14 (−0·61 to 0·32); p=0·5483	−0·77 (−1·19 to −0·36); p=0·0003	−0·57 (−1·08 to −0·07); p=0·0250	−0·80 (−1·16 to −0·44); p<0·0001	..

Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA

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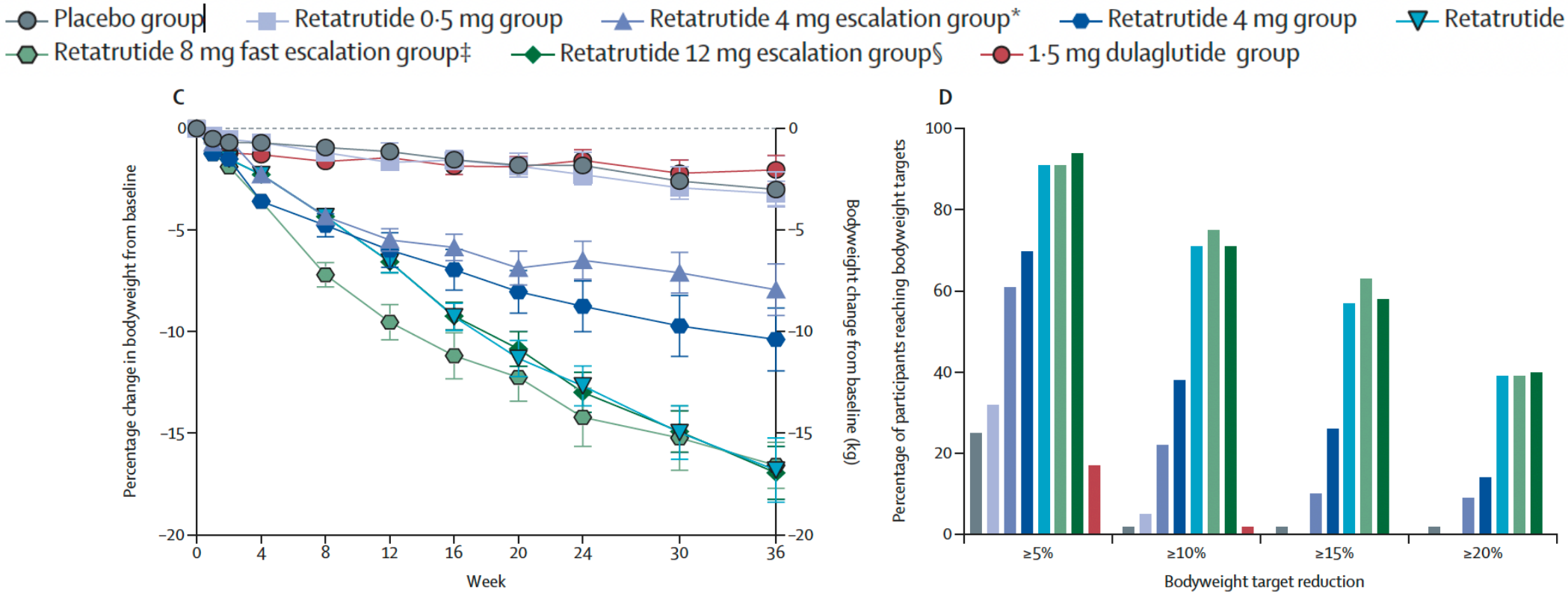


Adults aged 18–75 years T2DM, HbA1c of 7·0–10·5%, and BMI of 25–50 kg/m²

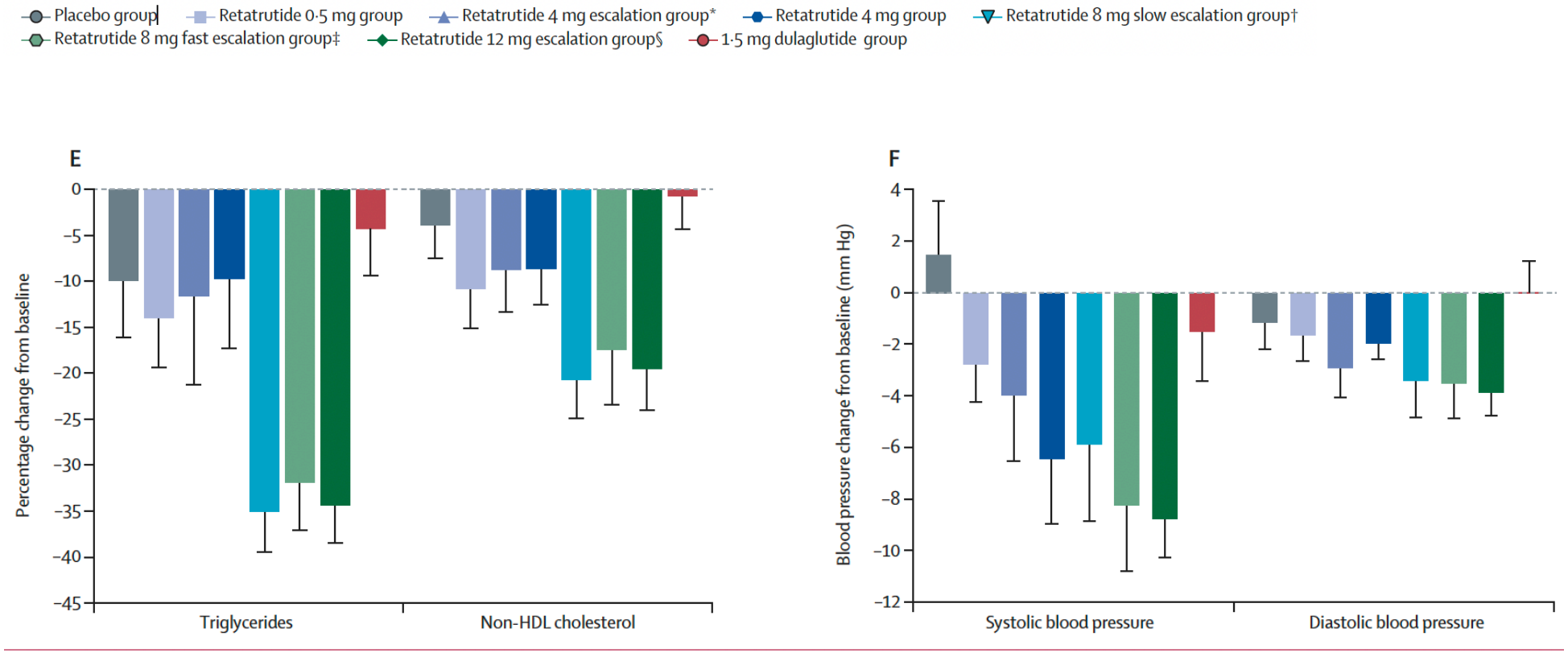
Weight reduction results

Bodyweight, kg								
Baseline	94·56 (2·44)	96·74 (2·67)	109·85 (5·46)	93·09 (3·94)	99·43 (4·09)	95·88 (4·20)	99·83 (3·53)	100·27 (3·42)
Change at 36 weeks	−3·28 (0·92); p=0·0004	−3·31 (0·62); p<0·0001	−7·28 (1·39); p<0·0001	−10·37 (1·49); p<0·0001	−16·48 (1·55); p<0·0001	−16·12 (1·63); p<0·0001	−17·18 (1·32); p<0·0001	−1·97 (0·87); p=0·0242
Versus placebo	..	−0·03 (−2·18 to 2·12); p=0·9789	−4·00 (−7·32 to −0·68); p=0·0181	−7·09 (−10·46 to −3·71); p<0·0001	−13·20 (−16·74 to −9·66); p<0·0001	−12·84 (−16·50 to −9·18); p<0·0001	−13·91 (−17·10 to −10·71); p<0·0001	..
Versus dulaglutide 1·5 mg	..	−1·34 (−3·45 to 0·77); p=0·2133	−5·31 (−8·66 to −1·97); p=0·0019	−8·40 (−11·76 to −5·04); p<0·0001	−14·51 (−18·00 to −11·01); p<0·0001	−14·15 (−17·77 to −10·54); p<0·0001	−15·22 (−18·36 to −12·07); p<0·0001	..

Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA

Julio Rosenstock, Juan Frias, Ania M Jastreboff, Yu Du, Jitong Lou, Sirel Gurbuz, Melissa K Thomas, Mark L Hartman, Axel Haupt, Zvonko Milicevic, Tamer Coskun

meaningful improvements in glucose control and lipid metabolism, as well as robust bodyweight reductions via decreased energy intake and increased energy expenditure.



Added value of this study Retatrutide treatment

- significant and clinically meaningful improvements in glycemic control.
- Robust bodyweight reductions ,did not plateaued by 36 weeks.
- Improved lipid profile and reduced BP, improved cardiometabolic outcomes.
- The safety profile was consistent with the GLP-1 RA and GIP and GLP-1 RA classes, with mild-to-moderate and transient GI adverse events , commonly reported.

Take home message

What are clinicians to make of these early results?

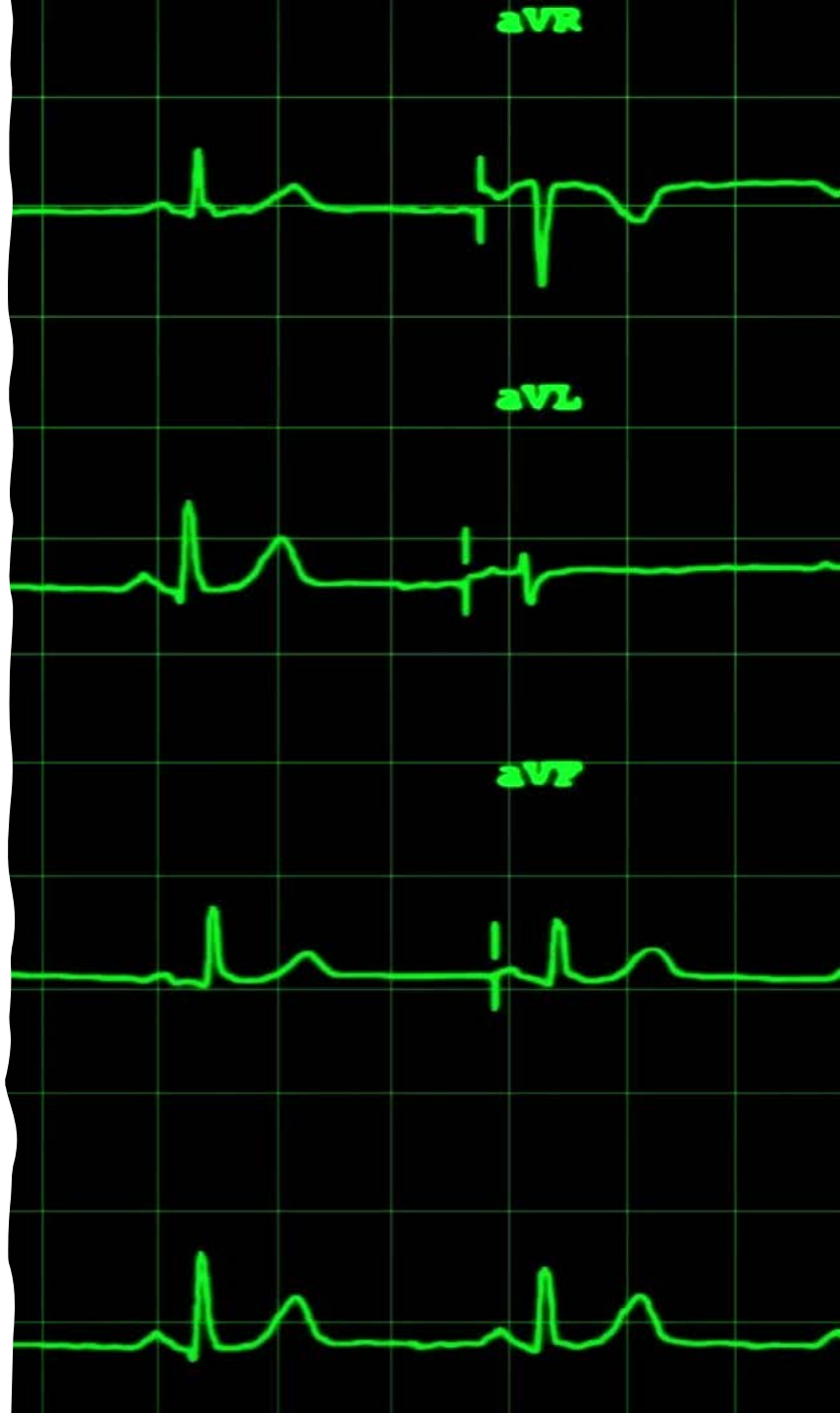
- The glucose-lowering effect of retatrutide is certainly substantial, but we now have large focus on weight management.
- Although the weight reduction of >16% with retatrutide at 36 weeks is impressive
- active comparator was dulaglutide 1·5 mg, which is not renowned for weight loss

- Lower than the highest licensed weekly dose 4·5 mg

What are clinicians to make of these early results?

challenges

- If glucagon agonism induces increased energy expenditure, a mechanism quite different to the satiety induced by GLP-1, then long-term cardiovascular outcome trials will almost certainly be requested by regulators, slowing the pathway to clinical use.



What are clinicians to make of these early results?

- phase 3 clinical trial programme of retatrutide to include comparisons with

1. higher dose GLP-1 RA
2. dual incretin agonists

is needed, and other triple agonists will continue to be developed.

- Safety is always crucial in the assessment of new therapies but, if confirmed, then the efficacy of glucose lowering, and weight reduction could prove to be valuable in the management of people with type 2 diabetes.

Take home message

- The discovery of triple receptor agonist drugs established yet another class of novel therapeutics which at least preclinically and it seems clinically may outperform mono and dual agonist as highly effective diabetes and obesity drugs.

- Of course, there are numerous other multireceptor drugs are now being tested , have the potential to transform the metabolic medicine.