Farmaci anti-obesità: molecole a confronto

UNIVERSITÀ CATTOLICA del Sacro Cuore

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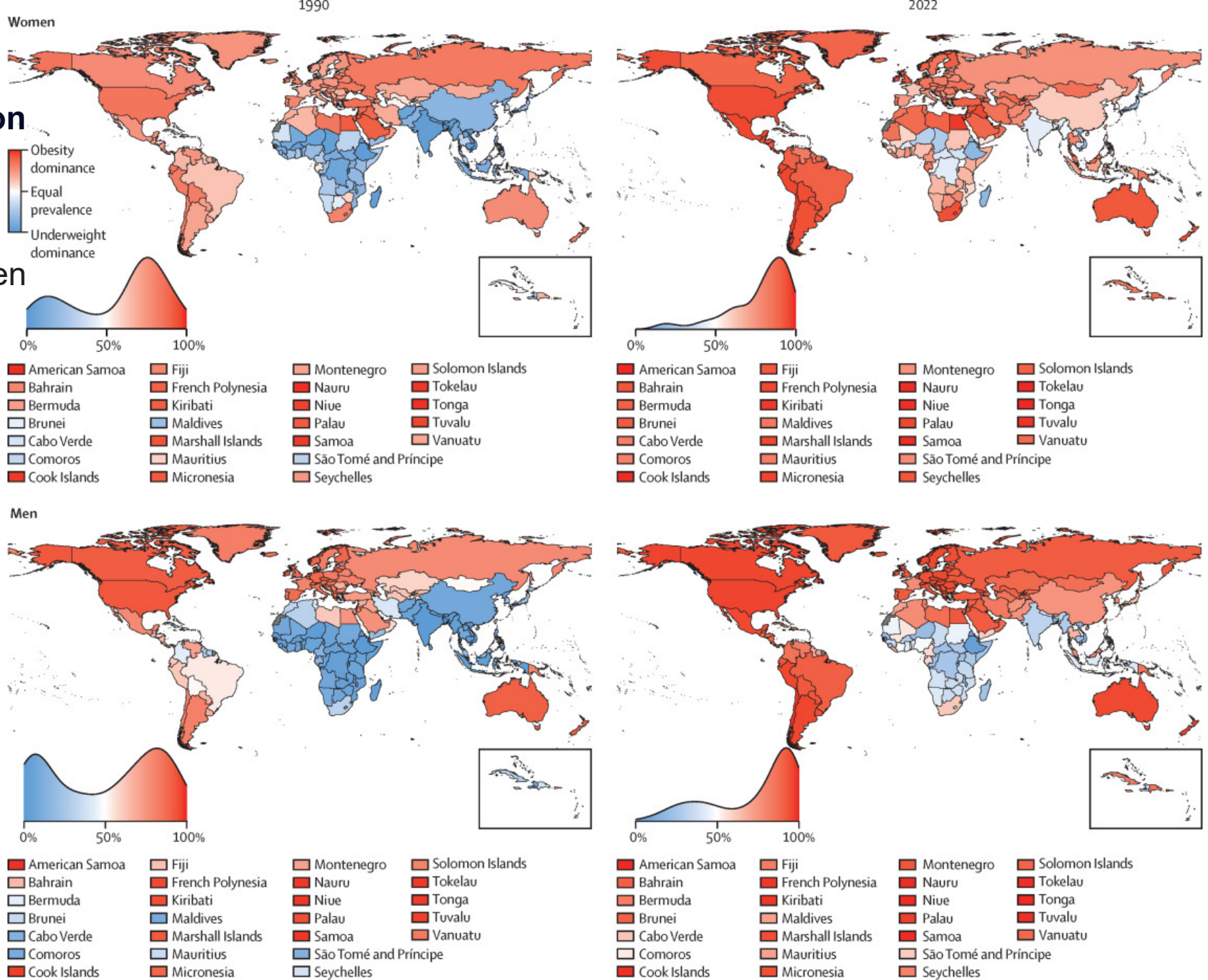
CONFLICT OF INTEREST

Consulting fees from Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Medtronic, Fractyl Inc, and Recor Inc.

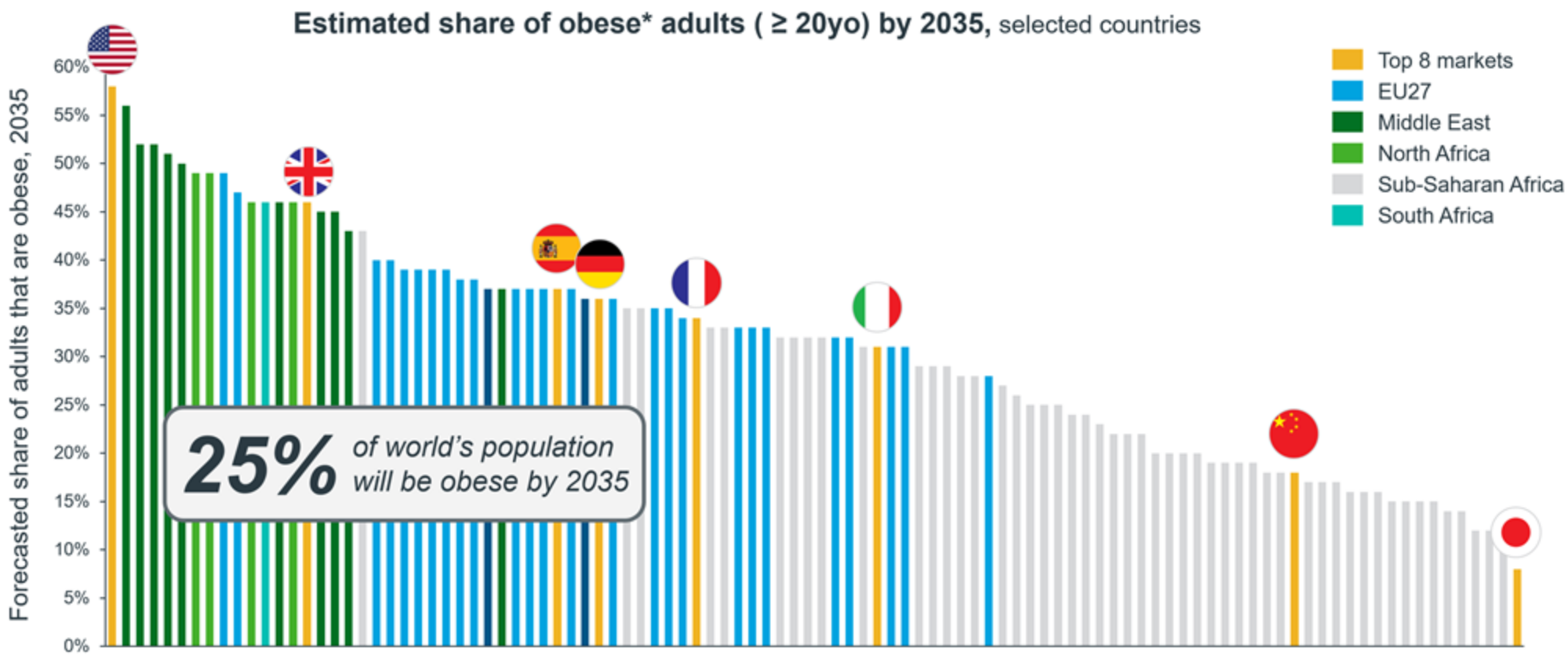
Scientific advisor of Metadeq Inc., Keyron Ltd, GHP Scientific Ltd, and Jemyll Ltd.

Grants from Fractyl Inc.,Metadeq Inc., Keyron Ltd, GHP Scientific Ltd, and Jemyll Ltd.

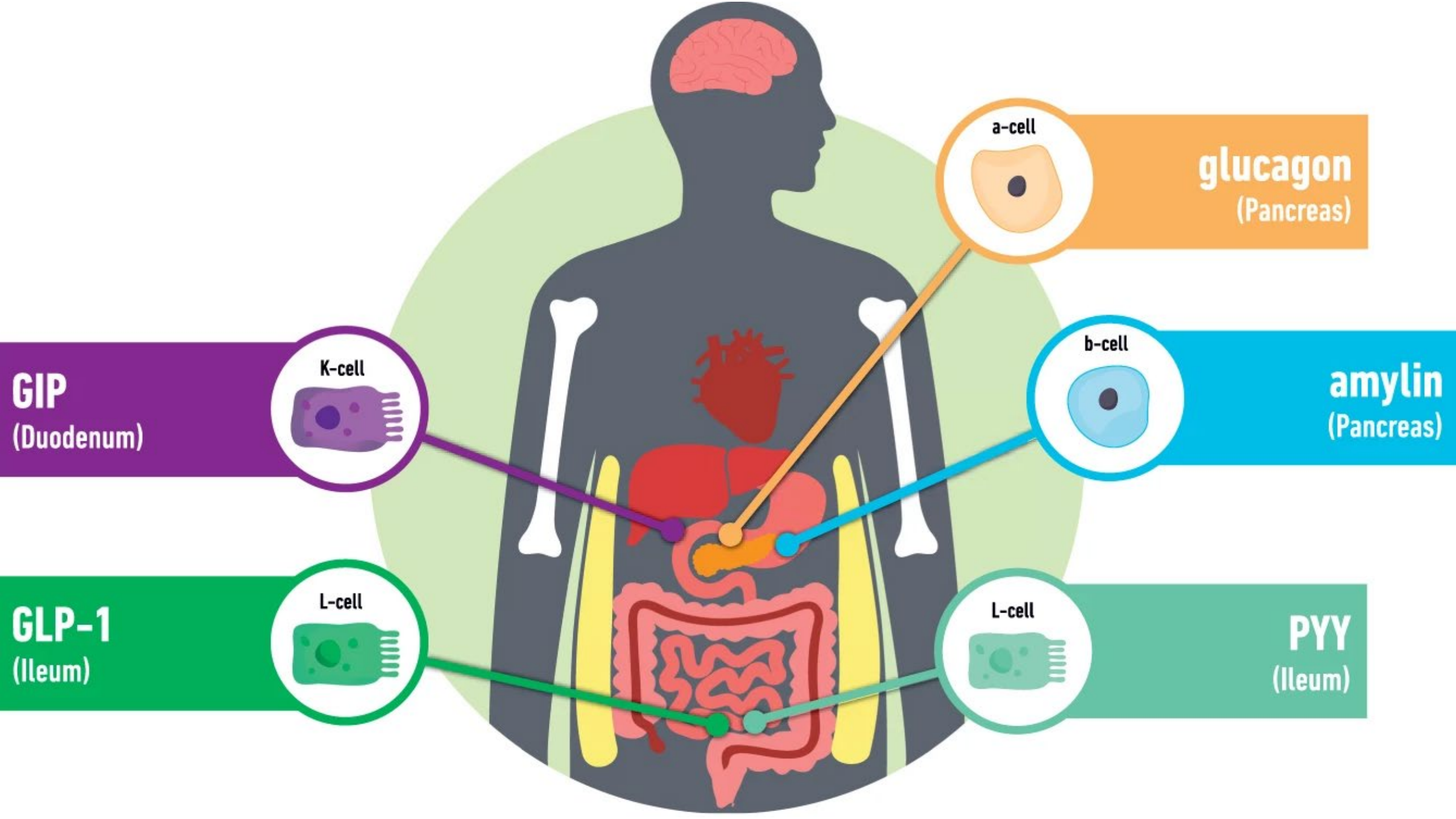
More than **1 billion** people living with obesity:
880 million adults
159 million children



The global prevalence of obesity




Science
AAAS
2023
BREAKTHROUGH
OF THE YEAR


a-cell
glucagon
(Pancreas)
b-cell
amylin
(Pancreas)
K-cell
GIP
(Duodenum)
L-cell
GLP-1
(Ileum)
L-cell
PYY
(Ileum)

GLP-1

- ↓ appetite, ↓ food intake; ↑ nausea
- ↑ insulin, ↓ glucagon
- ↓ gastric emptying
- ↑ lipolysis
- ↑ cardioprotection; ↑ heart rate

GIP

- ↓ appetite*; ↓ nausea
- ↑ insulin; ↑ glucagon
- ↓ gastric acid secretion
- ↑ lipid deposition; ↑ lipogenesis
- ↓ bone resoption

Amylin

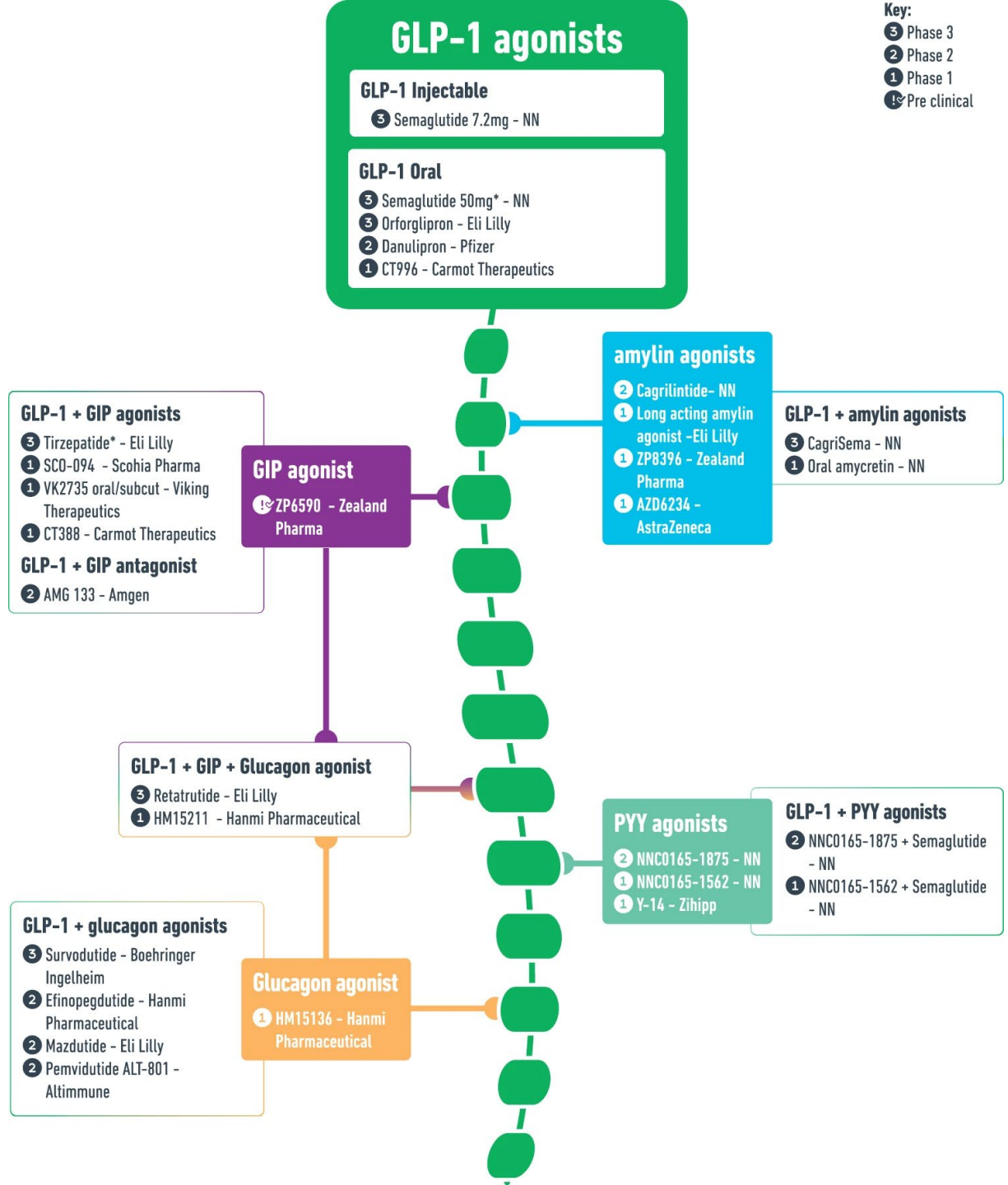
- ↓ appetite; ↓ food intake
- ↓ glucagon
- ↑ energy expenditure*
- ↓ gastric emptying
- ↓ osteoclast activity; ↑ osteoblast activity

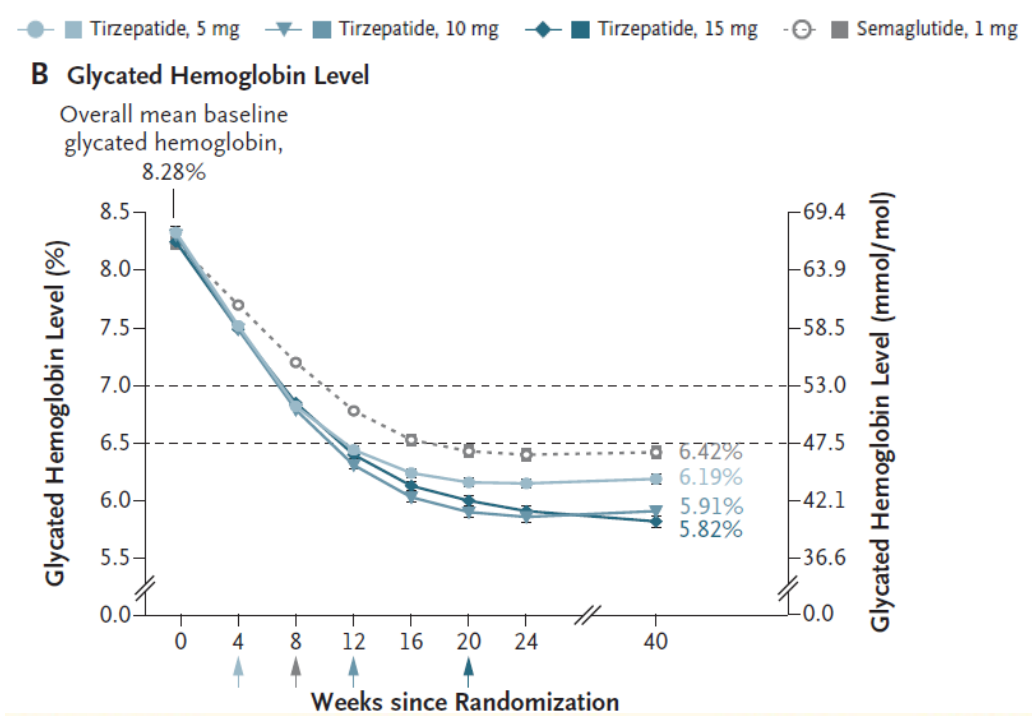
Glucagon

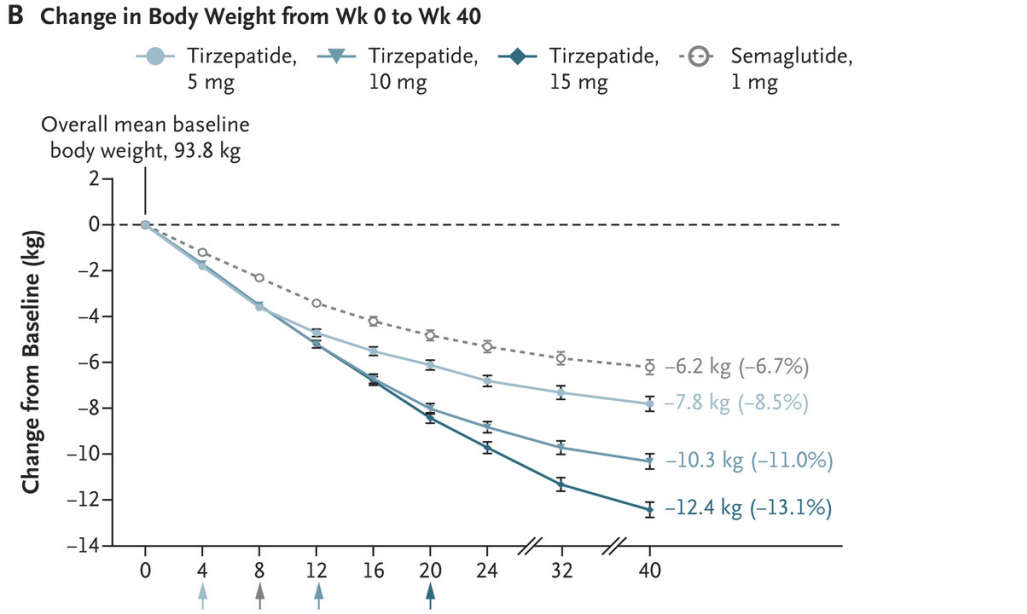
- ↓ appetite, ↓ food intake; ↑ nausea
- ↑ insulin
- ↑ hepatic glucose production; ↑ lipid oxidation, ↓ hepatic lipid synthesis
- ↓ gastric emptying
- ↑ energy expenditure
- ↑ heart rate

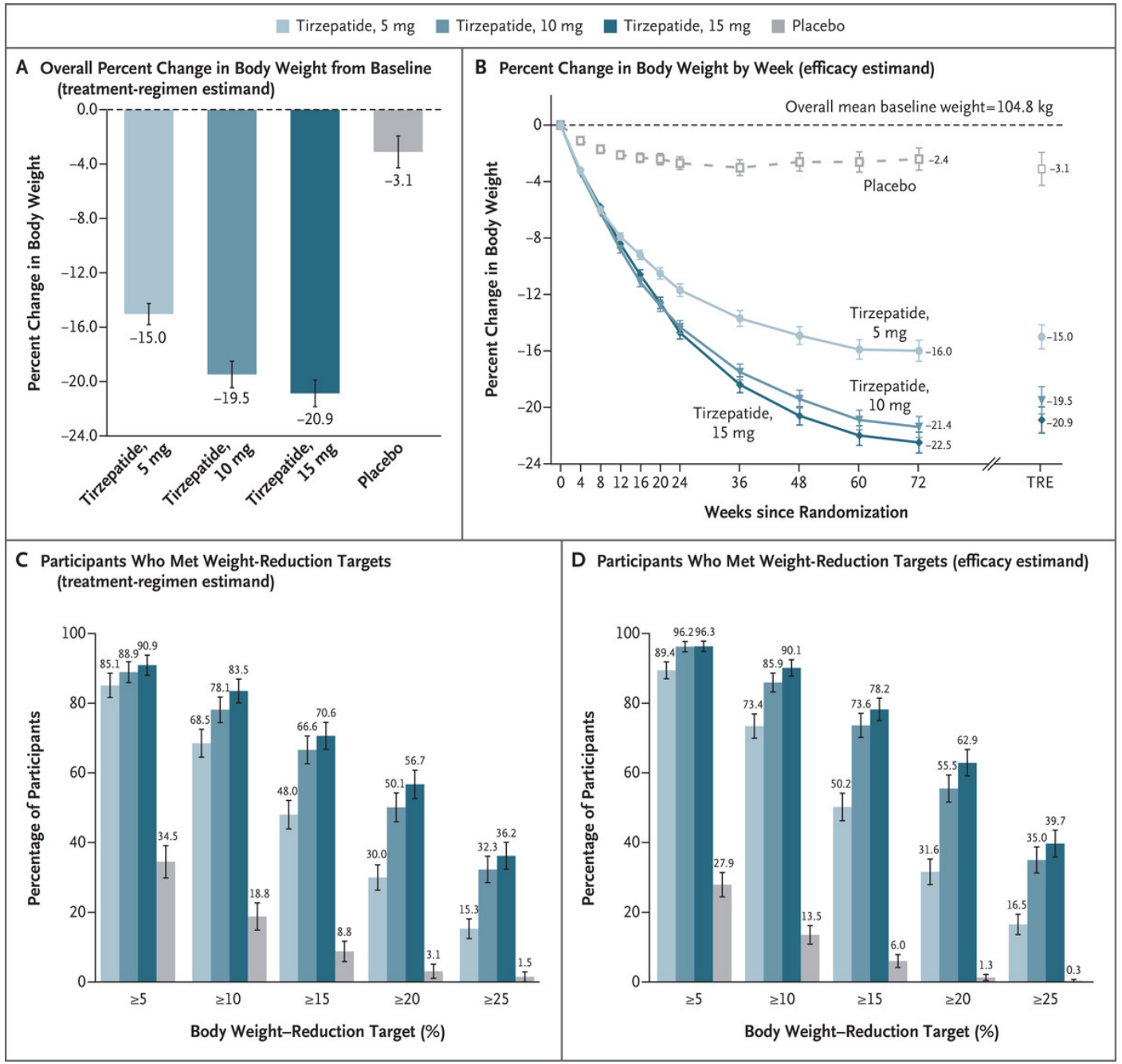
PYY

- ↓ appetite, ↓ food intake; ↑ nausea
- ↓ gastric emptying
- ↑ energy expenditure*


Key:
3 Phase 3
2 Phase 2
1 Phase 1
1c Pre clinical
GLP-1 agonists
GLP-1 Injectable
3 Semaglutide 7.2mg - NN
GLP-1 Oral
3 Semaglutide 50mg* - NN
3 Orforglipron - Eli Lilly
2 Danulipron - Pfizer
1 CT996 - Carmot Therapeutics
amylin agonists
2 Cagrilintide- NN
1 Long acting amylin agonist -Eli Lilly
1 ZP8396 - Zealand Pharma
1 AZD6234 - AstraZeneca
GLP-1 + amylin agonists
3 CagriSema - NN
1 Oral amycretin - NN
GLP-1 + GIP agonists
3 Tirzepatide* - Eli Lilly
1 SCO-094 - Scohia Pharma
1 VK2735 oral/subcut - Viking Therapeutics
1 CT388 - Carmot Therapeutics
GLP-1 + GIP antagonist
2 AMG 133 - Amgen
GIP agonist
1c ZP6590 - Zealand Pharma
GLP-1 + GIP + Glucagon agonist
3 Retatrutide - Eli Lilly
1 HM15211 - Hanmi Pharmaceutical
PYY agonists
2 NNC0165-1875 - NN
1 NNC0165-1562 - NN
1 Y-14 - Zihipp
GLP-1 + PYY agonists
2 NNC0165-1875 + Semaglutide - NN
1 NNC0165-1562 + Semaglutide - NN
GLP-1 + glucagon agonists
3 Survodutide - Boehringer Ingelheim
2 Efinopegdutide - Hanmi Pharmaceutical
2 Mazdutide - Eli Lilly
2 Pemvidutide ALT-801 - Altimmune
Glucagon agonist
1 HM15136 - Hanmi Pharmaceutical

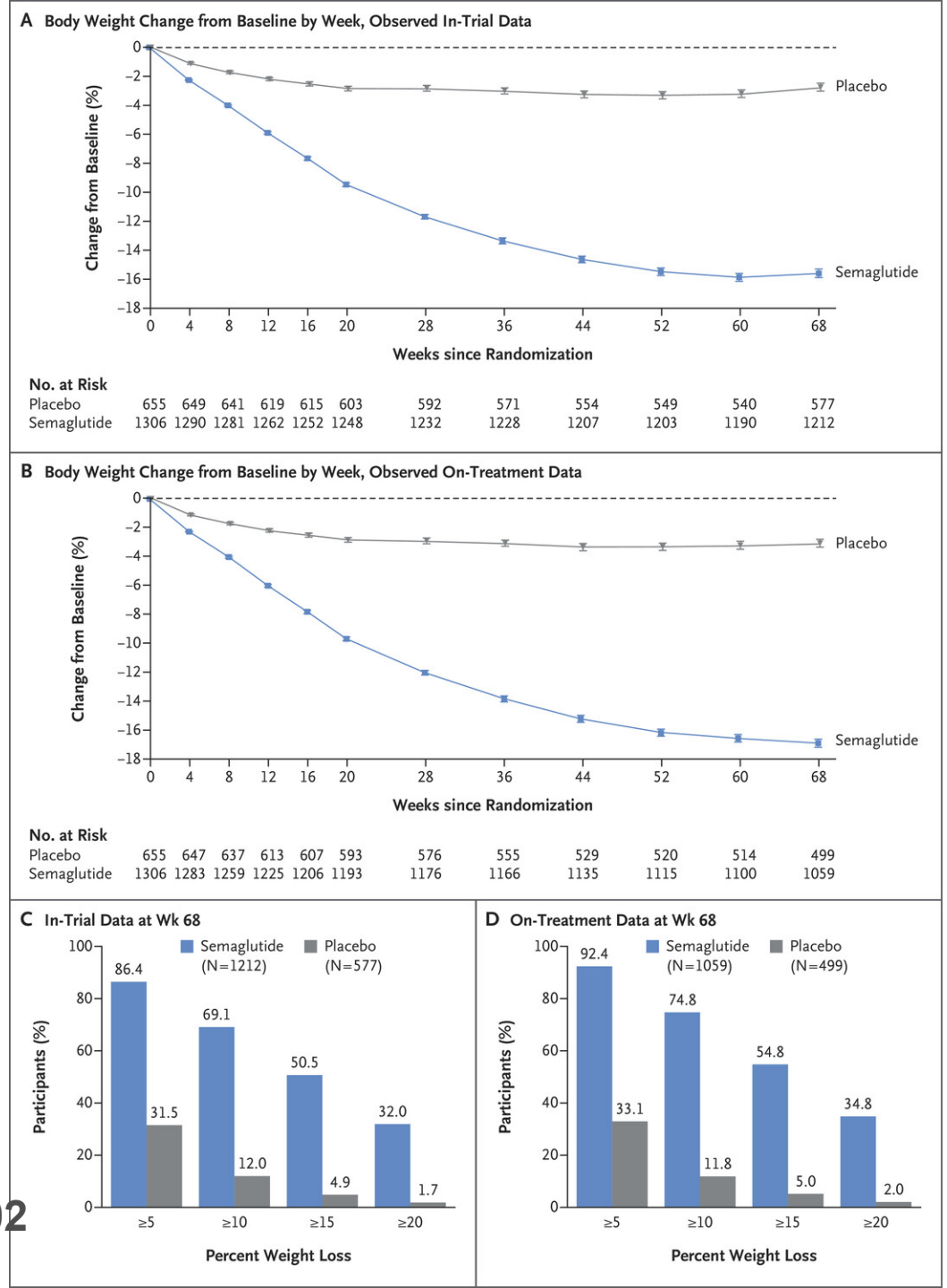






Frias JP et al N Engl J Med 2021; 385:503-515

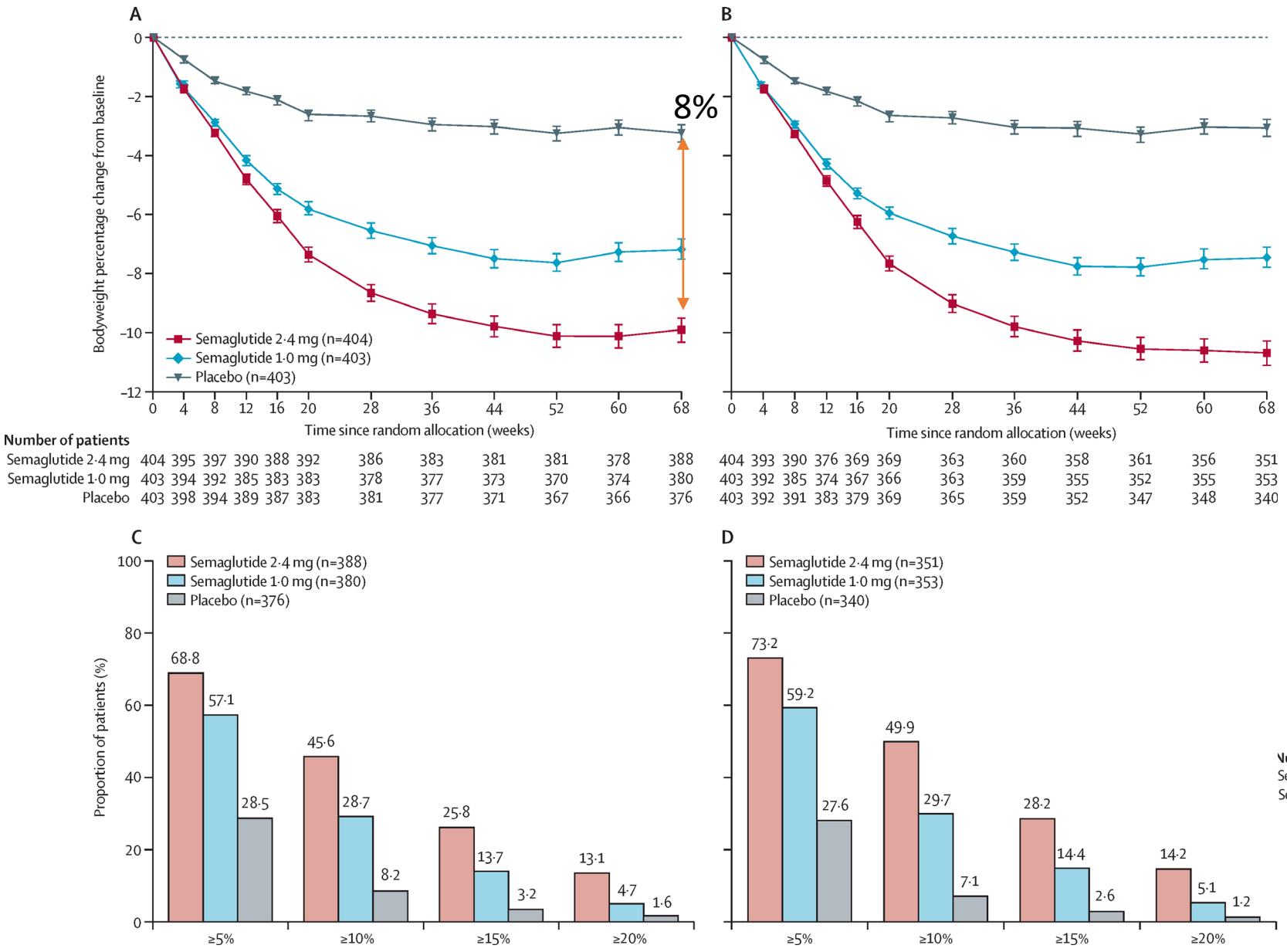
AM Jastreboff et al. 397, P293-304, JANUARY 23, 2021 N Engl J Med 2022.



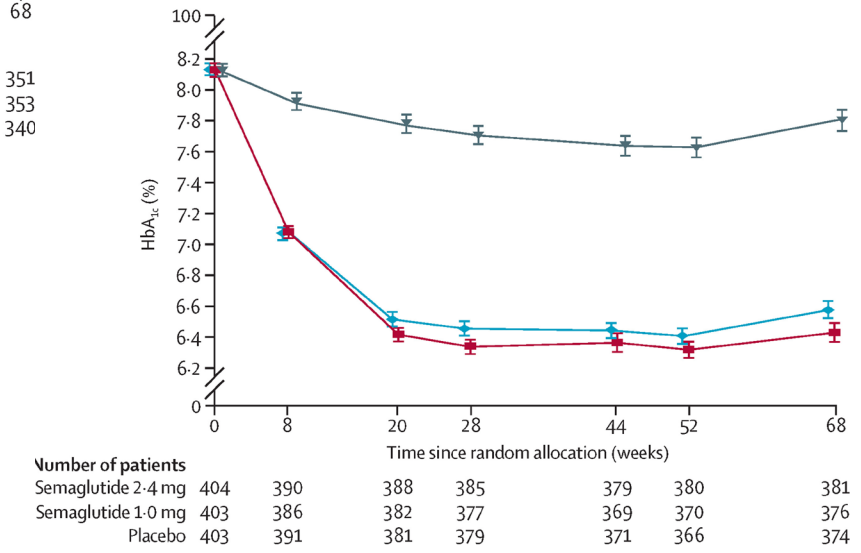
N Engl J Med 2021;384:989-1002

in-trial observation period

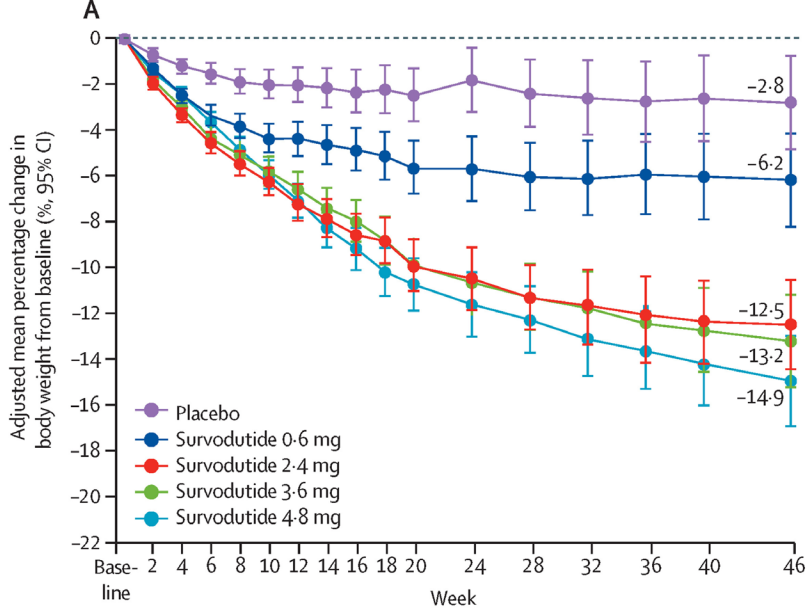
on treatment observation period

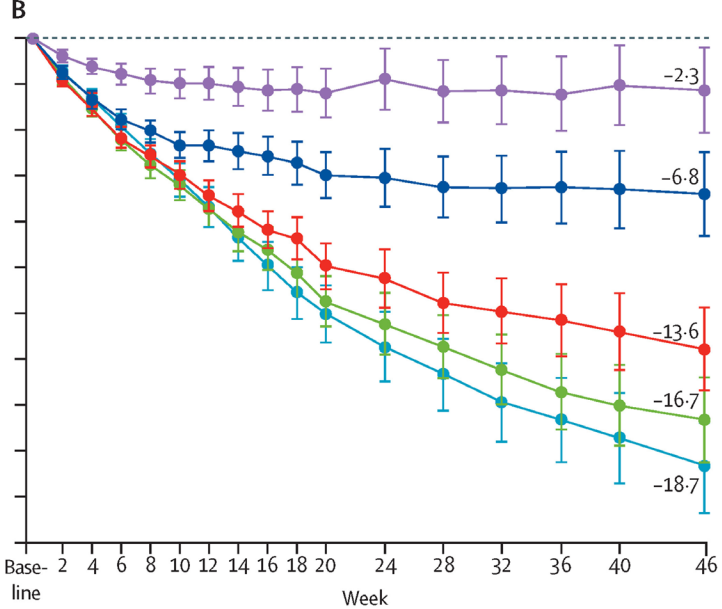


Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial



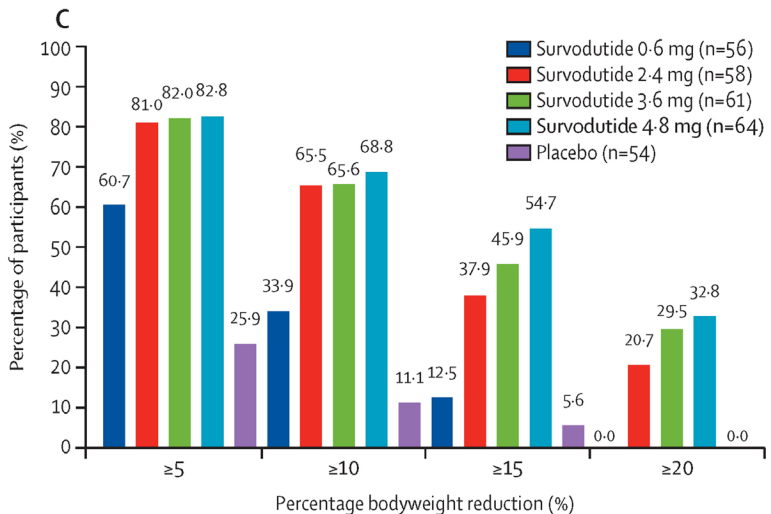
Lancet. 2021 Mar 13;397(10278):971-

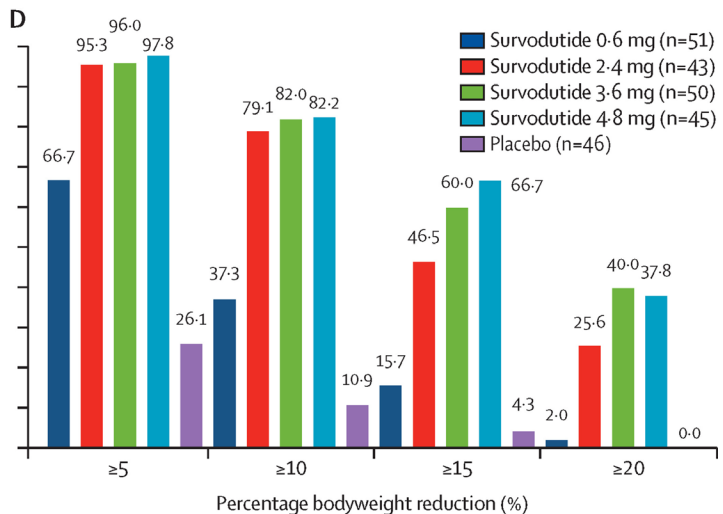




Number of participants																	
Survodutide 0·6 mg once weekly	76	75	73	71	69	65	63	63	60	59	58	55	52	53	50	52	56
Survodutide 2·4 mg once weekly	78	76	76	72	70	71	64	65	56	65	66	64	64	62	60	58	58
Survodutide 3·6 mg once weekly	76	76	73	75	68	67	64	64	59	64	62	64	60	57	59	58	61
Survodutide 4·8 mg once weekly	76	76	75	75	74	74	70	68	65	62	60	63	60	62	60	58	64
Placebo	77	75	72	72	72	70	65	65	63	62	59	59	56	55	55	54	54

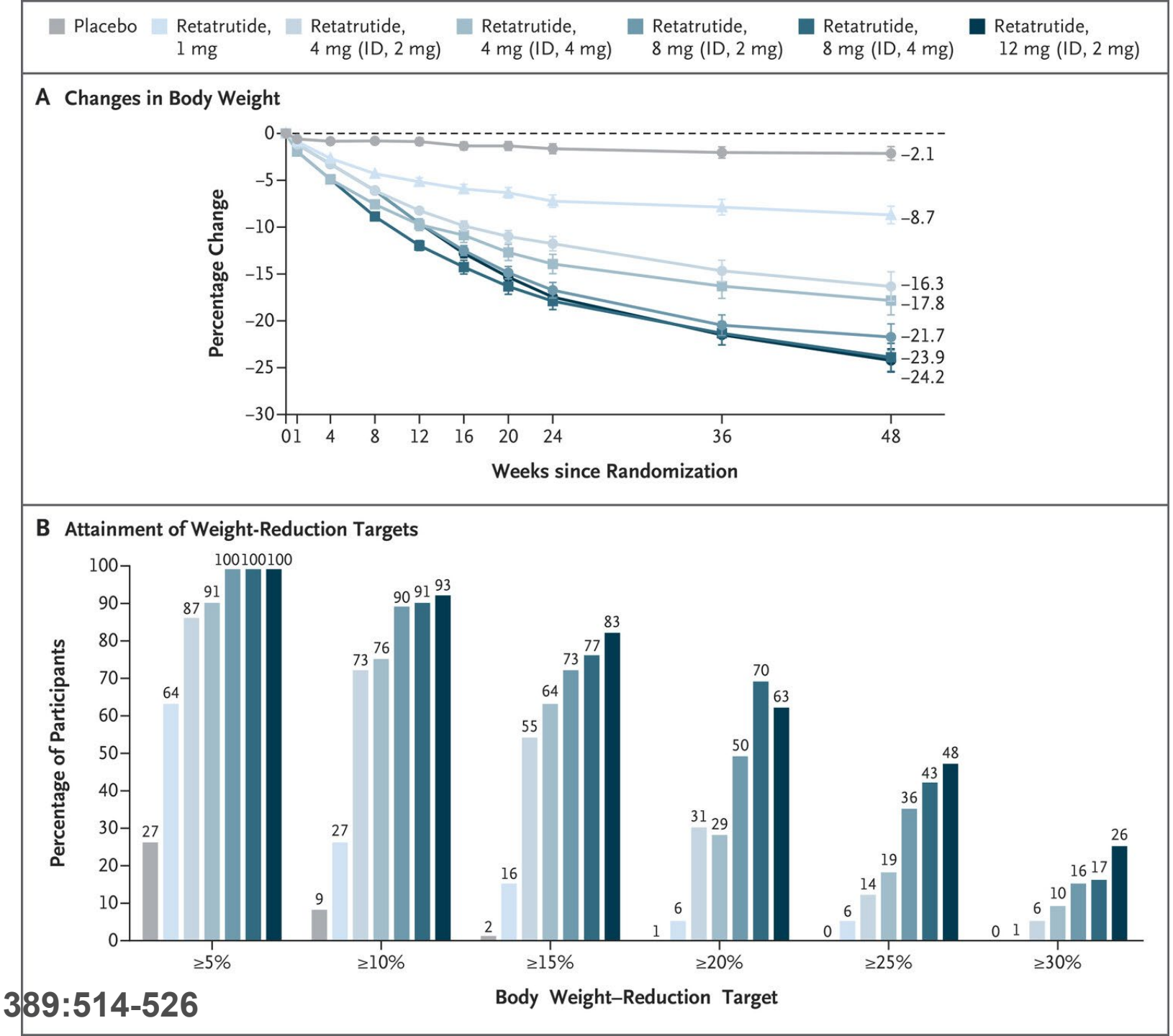
Survodutide 0·6 mg once weekly	88	88	81	79	74	68	67	67	64	63	62	58	54	52	50	50	51
Survodutide 2·4 mg once weekly	92	90	91	88	81	80	68	61	54	57	58	54	53	53	52	47	43
Survodutide 3·6 mg once weekly	71	71	71	71	71	71	70	70	64	64	59	59	57	51	52	50	50
Survodutide 4·8 mg once weekly	54	54	54	54	54	54	53	53	54	53	53	52	50	49	48	47	45
Placebo	76	75	72	72	70	69	64	64	62	60	58	57	53	52	50	48	46





Lancet Diabetes Endocrinol.
2024 Mar;12(3):162-173.

Phase 2 Trial

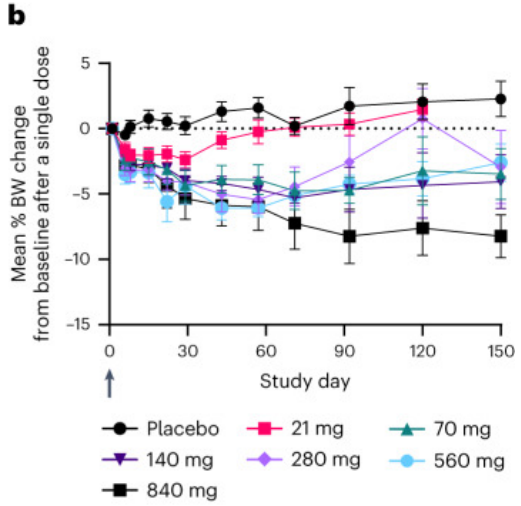


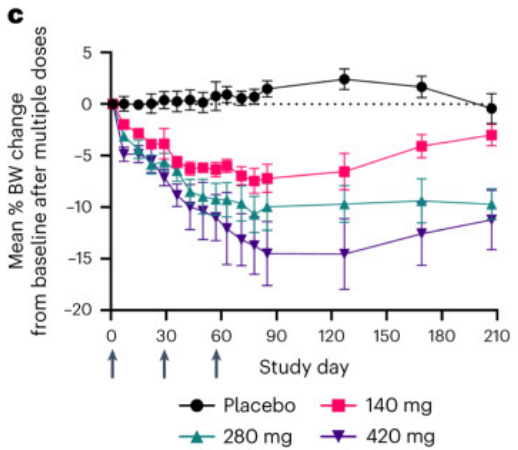
N Engl J Med 2023;389:514-526

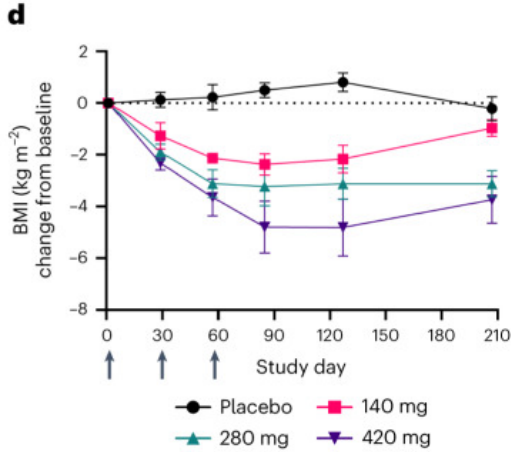
a

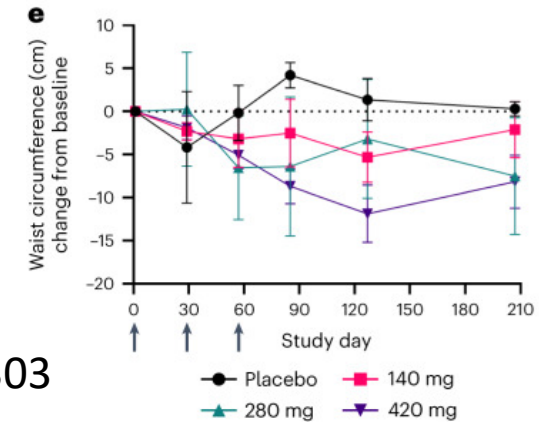
Dose (mg)	N	t_{max} (days) Intact AMG 133	t_{max} (days) Total AMG 133	$t_{1/2}$ (days) Intact AMG 133	$t_{1/2}$ (days) Total AMG 133
21	6	5	5.9	14.3	21
840	6	5.4	5.5	16.5	23.8

Dose (mg)	N	Intact AMG 133 AUC_{0-28} (day-μg ml^{-1})	Total AMG 133 AUC_{0-28} (day-μg ml^{-1})
140	6	214 (8.7%)	297 (9.3%)
280	5	443 (29.7%)	599 (21.1%)
420	3	1,220 (34.3%)	1,610 (37.3%)







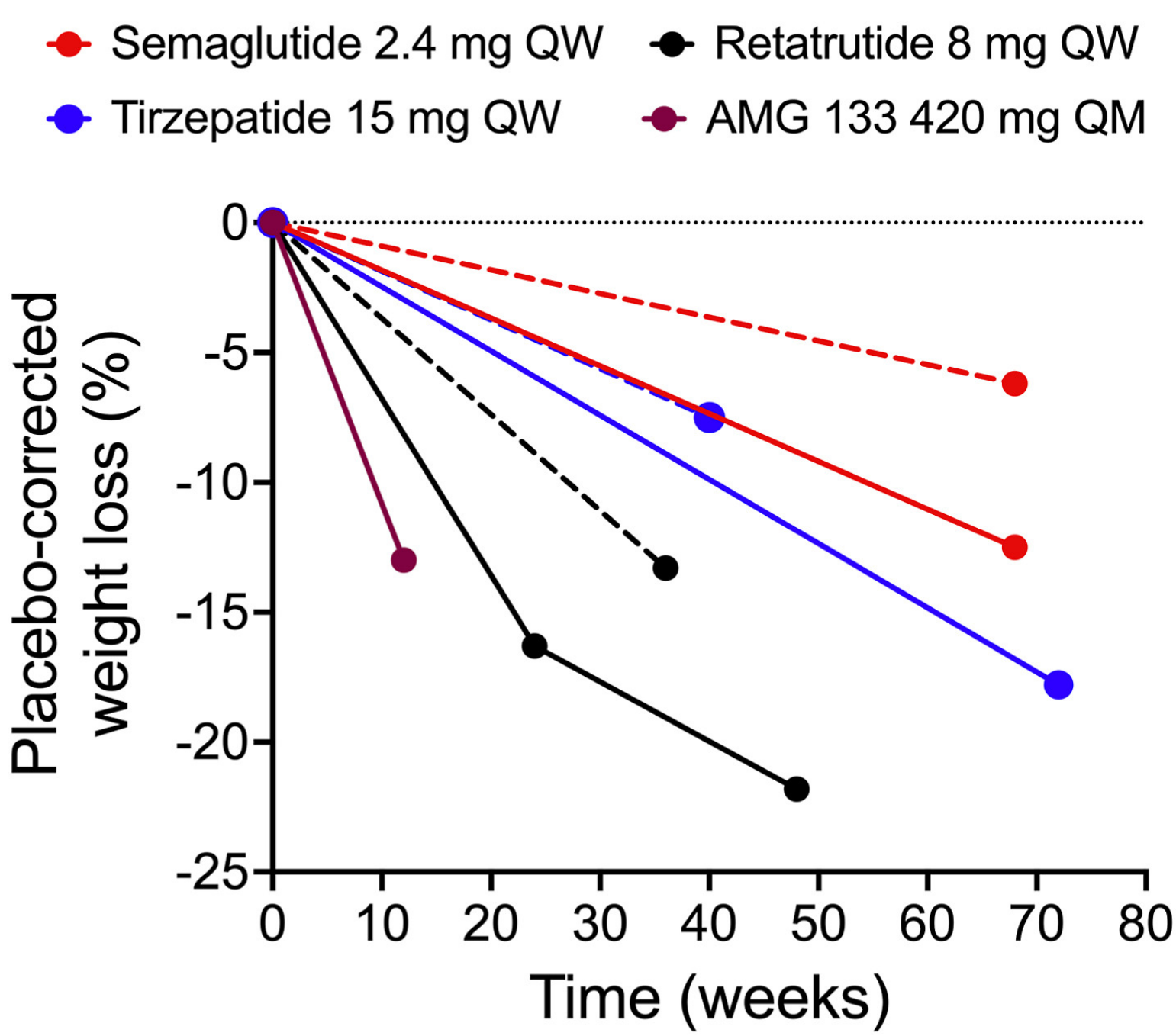


AMG 133 Amgen (maridebart cafraglutide)

is a dual GIPR antagonist and GLP-1R agonist

immunoglobulin G1-kappa, anti-GIPR (gastric inhibitory polypeptide receptor) monoclonal antibody

Nat Metab. 2024 Feb 5;6(2):290–303



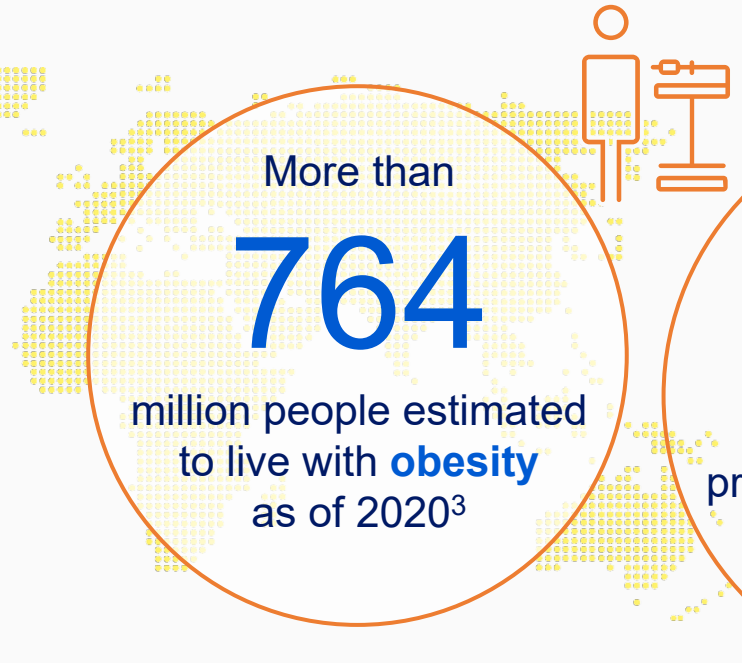
The Lancet Regional Health – Europe 2024 47DOI: (10.1016/j.lanepe.2024.101100)

There is an unmet need for therapies that reduce CV events and support weight management

523 million people had **CVD** in 2019 (globally)[1]

49% of global **CV deaths** are due to **CHD**[1]

32% of all global **deaths** are from **CVD**[2]



More than **764** million people estimated to live with **obesity** as of 2020[3]

1,025 million people predicted to have **obesity** by 2030[4]

Effective interventions that lower CV events & death in this population are greatly needed![5]

Conditions included in CVD definition may vary. CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease.
1. Roth GA et al. J Am Coll Cardiol 2020;76:2982–3021; 2. WHO. Fact sheet – CVDs. Available at: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed January 2023; 3. World Obesity Federation. World obesity atlas 2022. Available at: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022. Accessed March 2023; 4. World Obesity Federation. World obesity atlas 2022. Available at: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022. Accessed January 2023; 5. GBD 2015 Obesity Collaborators. N Engl J Med 2017;377:13–27.

ESC European Society of Cardiology
European Heart Journal (2024) **00**, 1–36
https://doi.org/10.1093/eurheartj/ehae508

Obesity and cardiovascular disease: an ESC clinical consensus statement

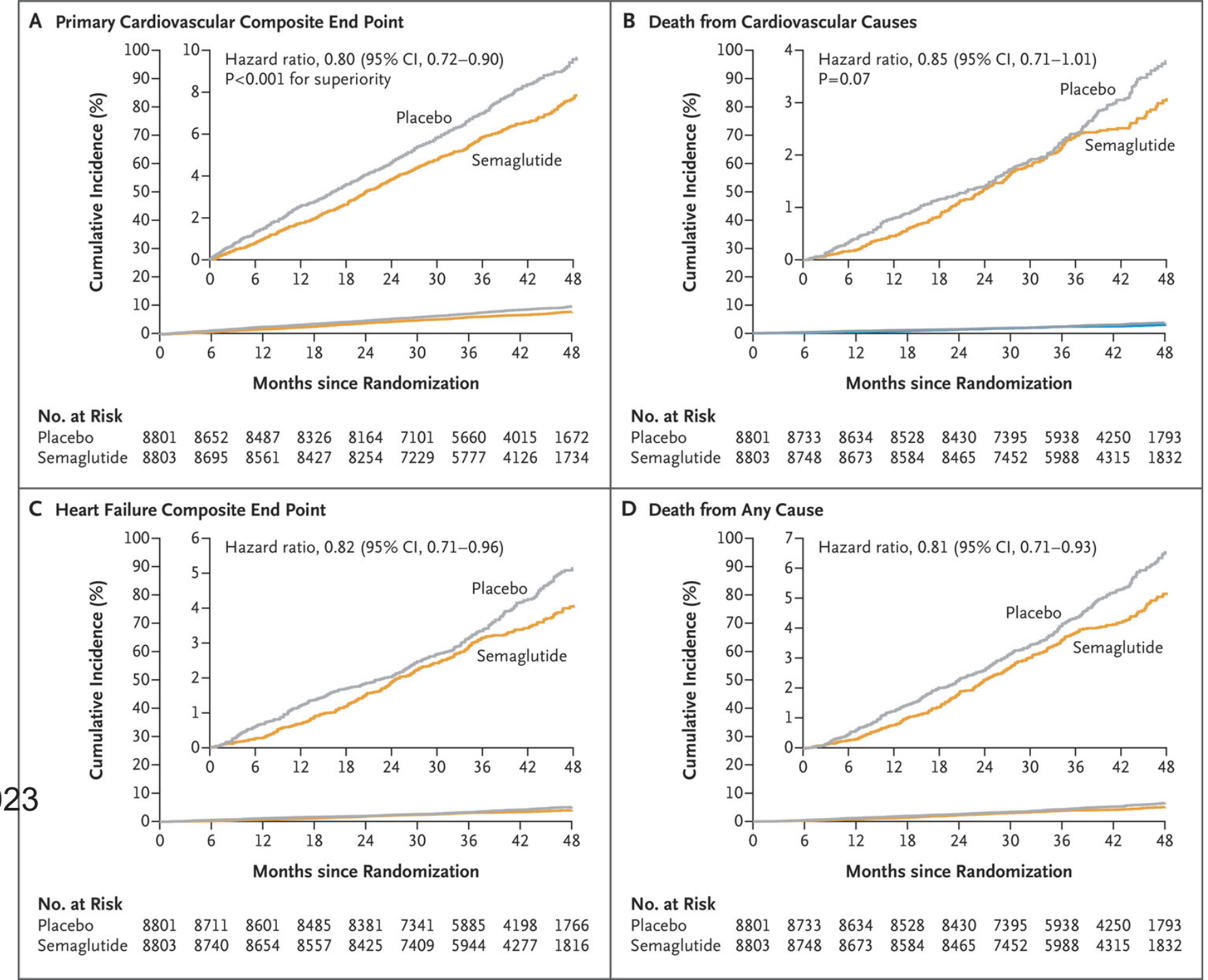
Konstantinos C. Koskinas[1]*†, Emeline M. Van Craenenbroeck[2,3]*†, Charalambos Antoniades[4], Matthias Blüher[5], Thomas M. Gorter[6], Henner Hanssen[7], Nikolaus Marx[8], Theresa A. McDonagh[9,10], Geltrude Mingrone[11,12], Annika Rosengren[13,14], Eva B. Prescott[15]*‡, and the ESC Scientific Document Group

ESC Guidelines recommendations on GLP-1RAs

- Glucose-lowering medications with effects on weight loss (e.g. GLP-1RAs) should be considered in patients with T2DM with overweight or obesity to reduce weight (Class IIa, level of evidence B).[61]
- GLP-1RAs with proven CV benefit (liraglutide, semaglutide s.c., dulaglutide, efpeglenatide) are recommended in patients with T2DM and atherosclerotic CVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication (Class I, level of evidence A).[61]
- The GLP-1 RA semaglutide should be considered in overweight (BMI >27 kg/m^2) or obese chronic coronary syndrome patients without diabetes to reduce CV mortality, MI, or stroke. (Class IIa, level of evidence B).[155]

ESC Guidelines recommendations on bariatric surgery

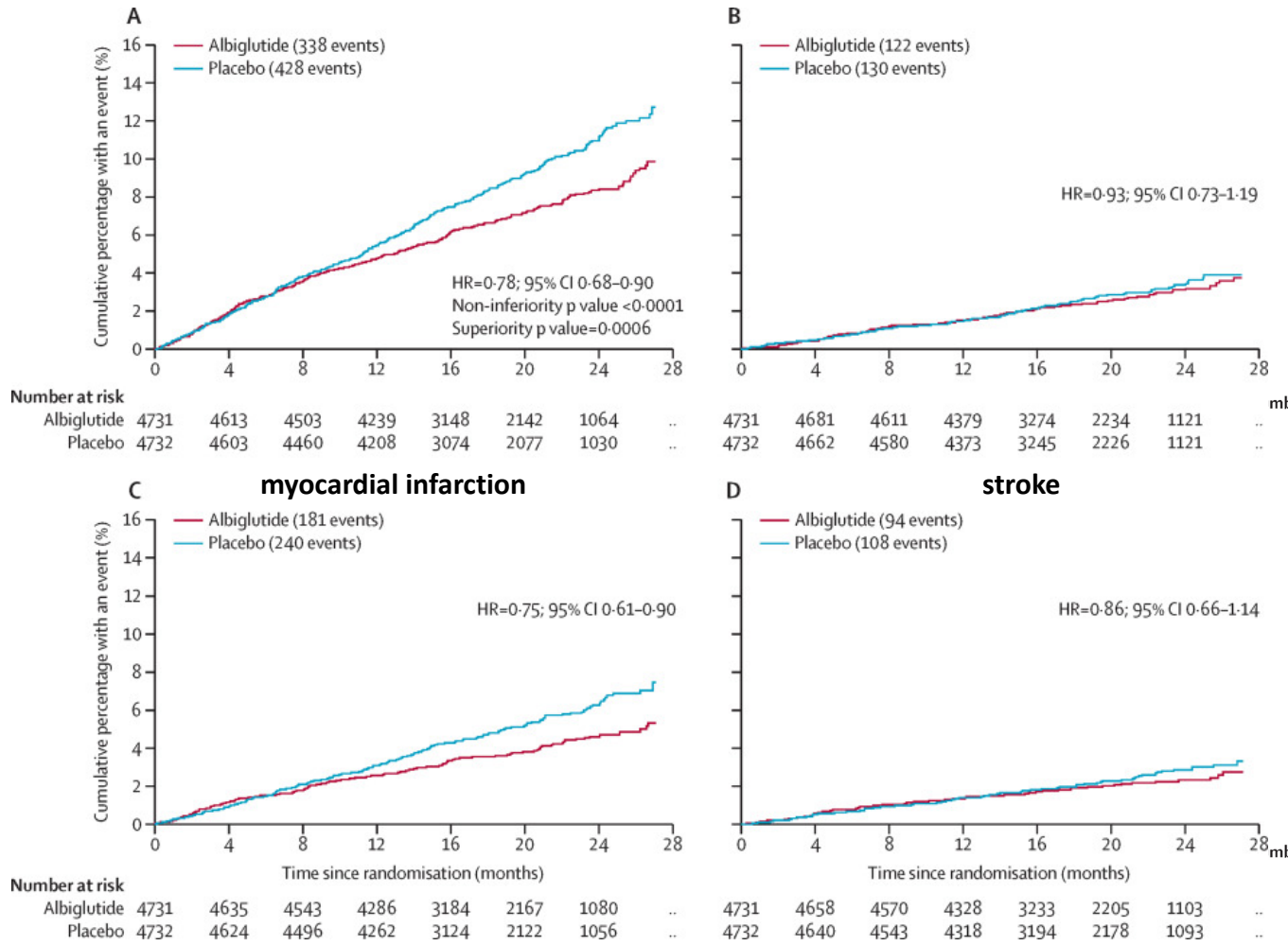
- Bariatric surgery should be considered for obese high-risk individuals when lifestyle change does not result in maintained weight loss (Class IIa, level of evidence B).[42]
- Bariatric surgery should be considered for high and very high risk patients with T2DM and BMI ≥35 kg/m^2 when repetitive and structured efforts of lifestyle changes combined with weight-reducing medications do not result in maintained weight loss (Class IIa, level of evidence B).[61]



N Engl J Med. 2023 Dec 14;389(24): 2221-2232.

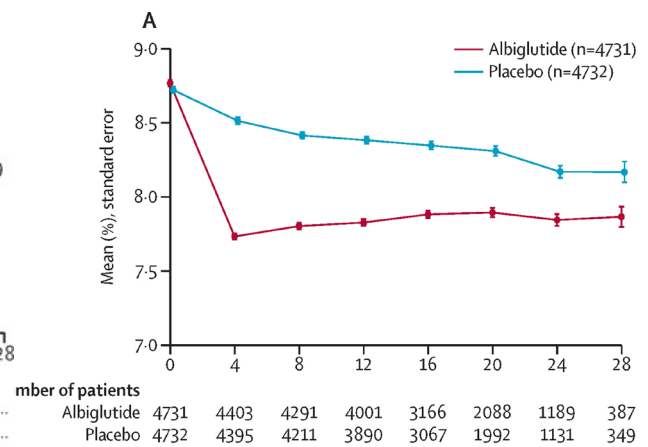
ALBIGLUTIDE

composite of death from cardiovascular causes

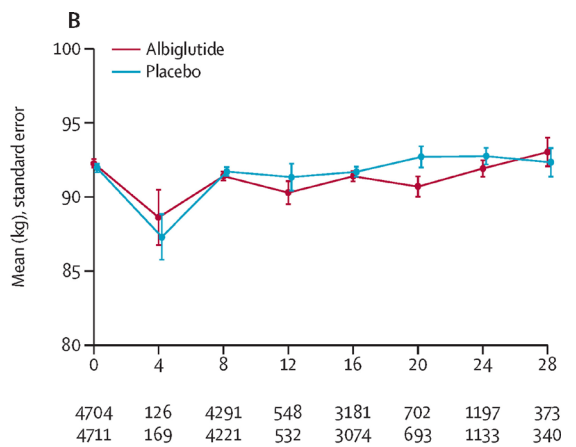


cardiovascular death

HbA1



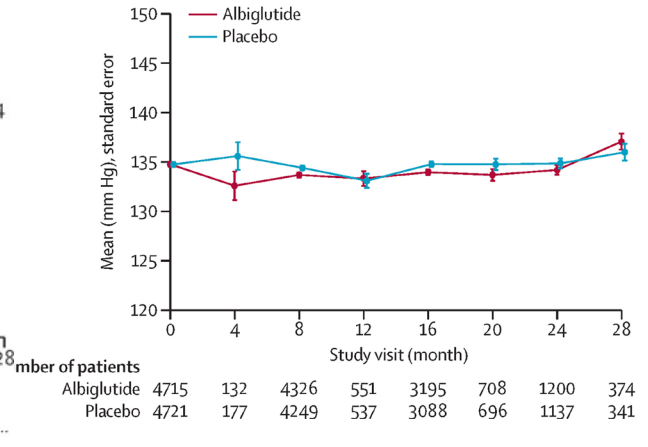
body weight



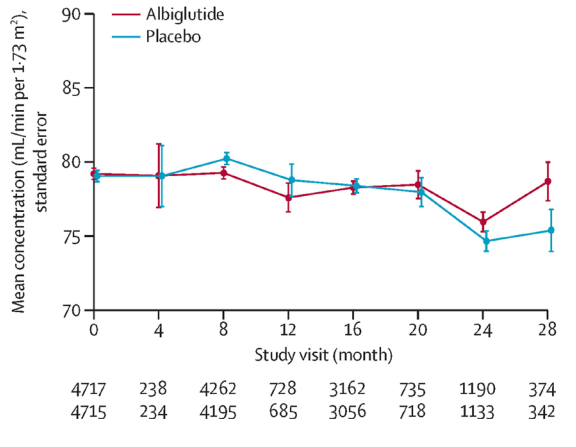
myocardial infarction

stroke

systolic blood pressure



eGFR



Lancet. 2018 Oct 27;392(10157):1519-1529.

Figure S9 Effect of body weight reduction on HR of GLP-1RAs vs. placebo as for reducing MACE **(β = -0.007, P = 0.846)**

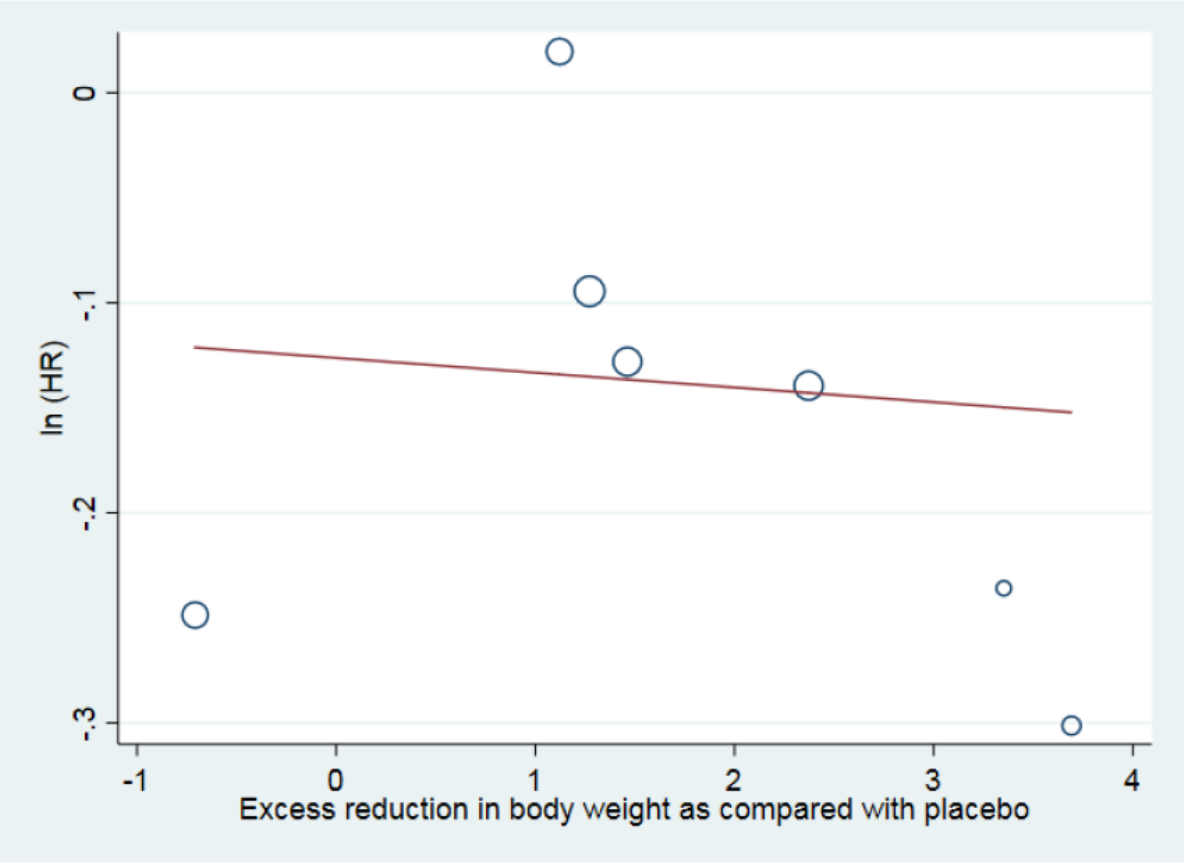
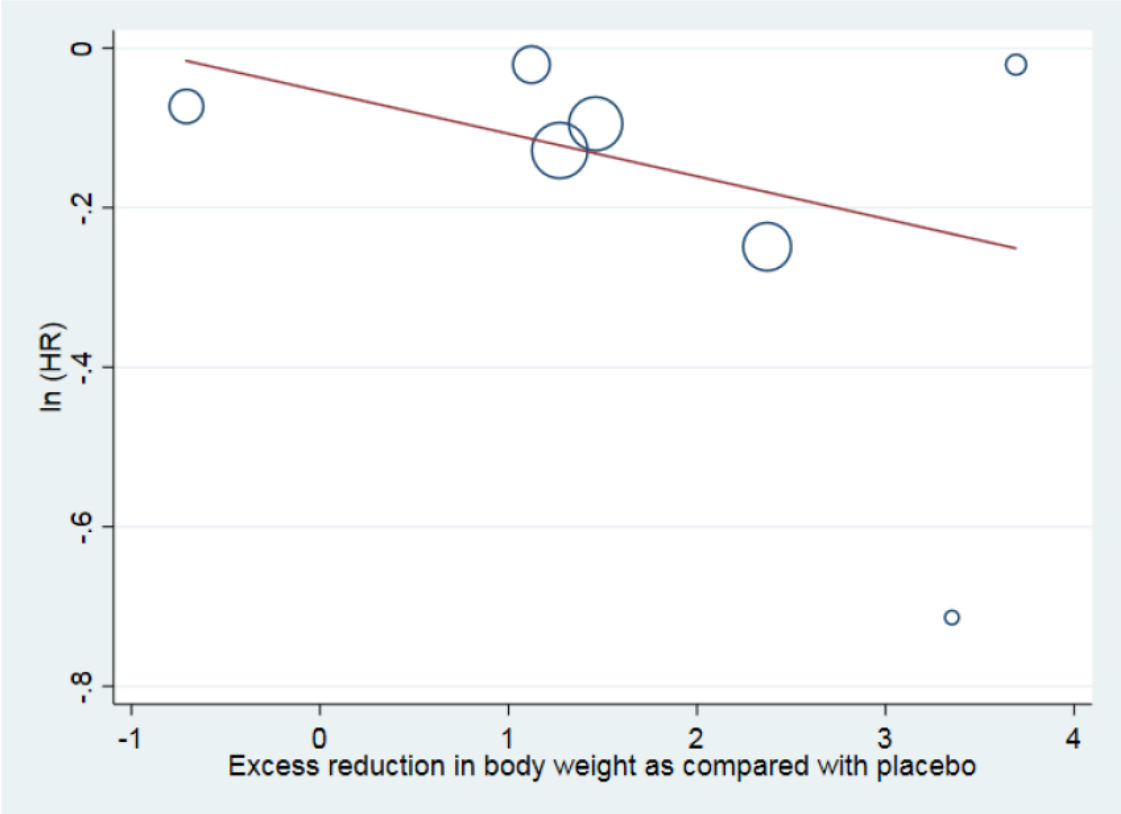


Figure S11 Effect of body weight reduction on HR of GLP-1RAs vs. placebo as for reducing CVD **(β = -0.053, P = 0.268)**



A Meta-Analysis with Meta-Regression. Diabetes Ther. 2020 Oct;11(10):2429-2440.

Of an estimated 687,866 patients at an annual 2435 hospitals, 69.9% underwent **SG** and 30.1% **RYGB**, with median costs of **$10,900** (interquartile range: 8600-14,000) and **$13,600** (10,300-18,000), respectively.

Am Surg. 2023 Oct;89(10):4061-4065.

COST PER YEAR

	UK	US	Germany	Denmark	Italy
Semaglutide 2.4 mg	$ 3693	$ 16234	$ 3918	$ 4380	$ 5105
Tirzepatide 15 mg	$ 2875	$ 12829	$ 3337		$ 8602

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

Table 2. Adverse Events and Safety.*

Event	Tirzepatide						Semaglutide		Total (N=1878)	
	5 mg (N=470)		10 mg (N=469)		15 mg (N=470)		1 mg (N=469)			
	No. of patients (%)	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*
Patients with ≥1 adverse event	299 (63.6)	—	322 (68.7)	—	324 (68.9)	—	301 (64.2)	—	1246 (66.3)	—
Patients with ≥1 serious adverse event	33 (7.0)	—	25 (5.3)	—	27 (5.7)	—	13 (2.8)	—	98 (5.2)	—
Death†	4 (0.9)	—	4 (0.9)	—	4 (0.9)	—	1 (0.2)	—	13 (0.7)	—
Adverse events leading to discontinuation of tirzepatide or semaglutide	28 (6.0)	—	40 (8.5)	—	40 (8.5)	—	19 (4.1)	—	127 (6.8)	—
Adverse events occurring in ≥0.2% of the overall population (i.e., 3 patients) and leading to discontinuation of tirzepatide or semaglutide										
Nausea	6 (1.3)	—	7 (1.5)	—	4 (0.9)	—	4 (0.9)	—	21 (1.1)	—
Vomiting	1 (0.2)	—	4 (0.9)	—	4 (0.9)	—	3 (0.6)	—	12 (0.6)	—
Diarrhea	1 (0.2)	—	3 (0.6)	—	6 (1.3)	—	1 (0.2)	—	11 (0.6)	—
Abdominal pain	2 (0.4)	—	1 (0.2)	—	2 (0.4)	—	4 (0.9)	—	9 (0.5)	—
Dyspepsia	2 (0.4)	—	1 (0.2)	—	2 (0.4)	—	0	—	5 (0.3)	—
Decreased appetite	1 (0.2)	—	2 (0.4)	—	2 (0.4)	—	0	—	5 (0.3)	—
Fatigue	1 (0.2)	—	1 (0.2)	—	1 (0.2)	—	1 (0.2)	—	4 (0.2)	—
Elevated blood calcitonin level	1 (0.2)	—	1 (0.2)	—	1 (0.2)	—	0	—	3 (0.2)	—
Constipation	0	—	2 (0.4)	—	0	—	1 (0.2)	—	3 (0.2)	—
Covid-19–related pneumonia	1 (0.2)	—	1 (0.2)	—	0	—	1 (0.2)	—	3 (0.2)	—
Injection-site reaction	0	—	2 (0.4)	—	1 (0.2)	—	0	—	3 (0.2)	—
Nausea	82 (17.4)	111	90 (19.2)	124	104 (22.1)	136	84 (17.9)	126	360 (19.2)	497
Diarrhea	62 (13.2)	120	77 (16.4)	99	65 (13.8)	102	54 (11.5)	68	258 (13.7)	389
Vomiting	27 (5.7)	35	40 (8.5)	56	46 (9.8)	61	39 (8.3)	53	152 (8.1)	205
Dyspepsia	34 (7.2)	—	29 (6.2)	—	43 (9.1)	—	31 (6.6)	—	137 (7.3)	—
Decreased appetite	35 (7.4)	—	34 (7.2)	—	42 (8.9)	—	25 (5.3)	—	136 (7.2)	—
Constipation	32 (6.8)	—	21 (4.5)	—	21 (4.5)	—	27 (5.8)	—	101 (5.4)	—
Abdominal pain	14 (3.0)	—	21 (4.5)	—	24 (5.1)	—	24 (5.1)	—	83 (4.4)	—
All gastrointestinal adverse events	188 (40.0)	—	216 (46.1)	—	211 (44.9)	—	193 (41.2)	—	808 (43.0)	—
Other adverse events										
Hypoglycemia, blood glucose level <54 mg/dl	3 (0.6)	3	1 (0.2)	2	8 (1.7)	10	2 (0.4)	2	14 (0.7)	17
Severe hypoglycemia	1 (0.2)	1	0	0	1 (0.2)‡	1‡	0	0	2 (0.1)	2
Injection-site reaction	9 (1.9)	—	13 (2.8)	—	21 (4.5)	—	1 (0.2)	—	44 (2.3)	—
Adjudicated pancreatitis	0	—	2 (0.4)	—	2 (0.4)	—	3 (0.6)	—	7 (0.4)	—
Cholelithiasis	4 (0.9)	—	4 (0.9)	—	4 (0.9)	—	2 (0.4)	—	14 (0.7)	—
Hypersensitivity§	9 (1.9)	—	13 (2.8)	—	8 (1.7)	—	11 (2.3)	—	41 (2.2)	—
Diabetic retinopathy¶	0	—	2 (0.4)	—	0	—	0	—	2 (0.1)	—

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Patient Preference and Adherence

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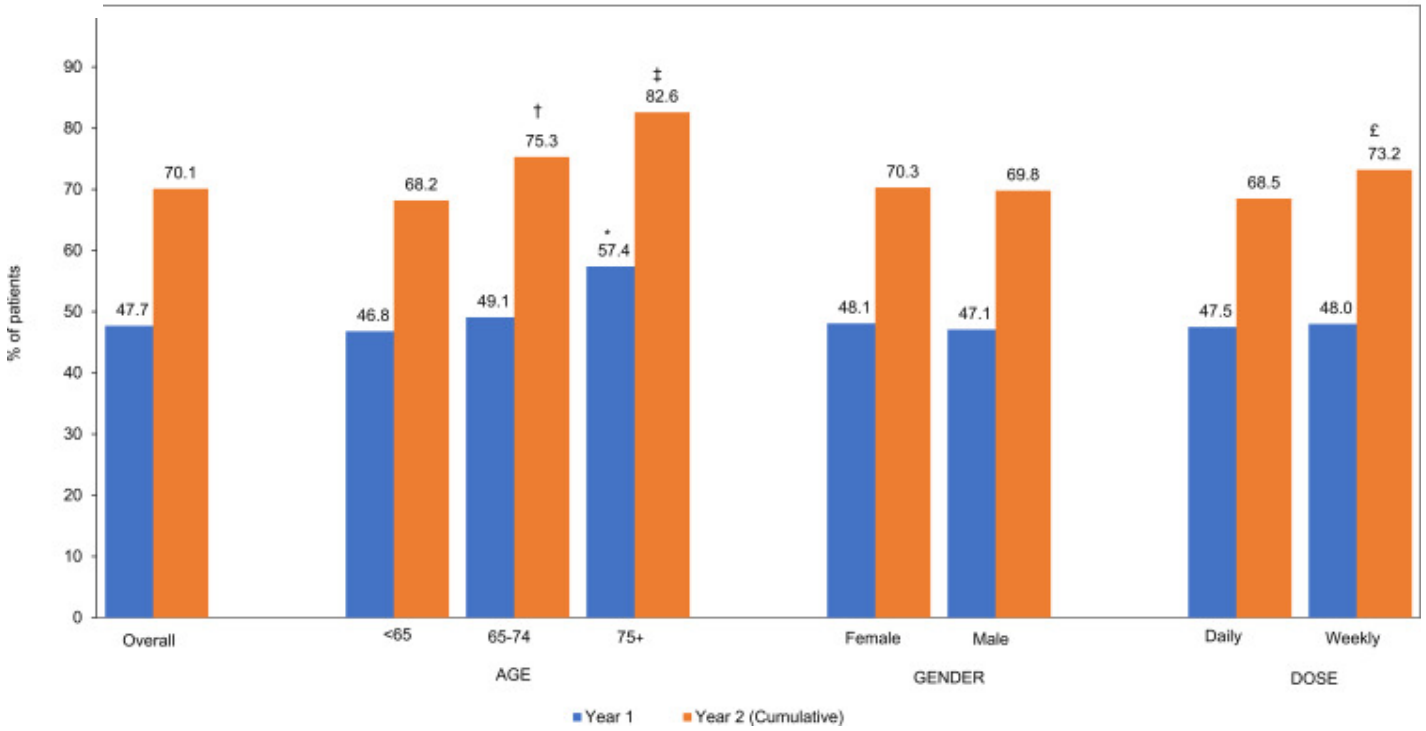
ORIGINAL RESEARCH

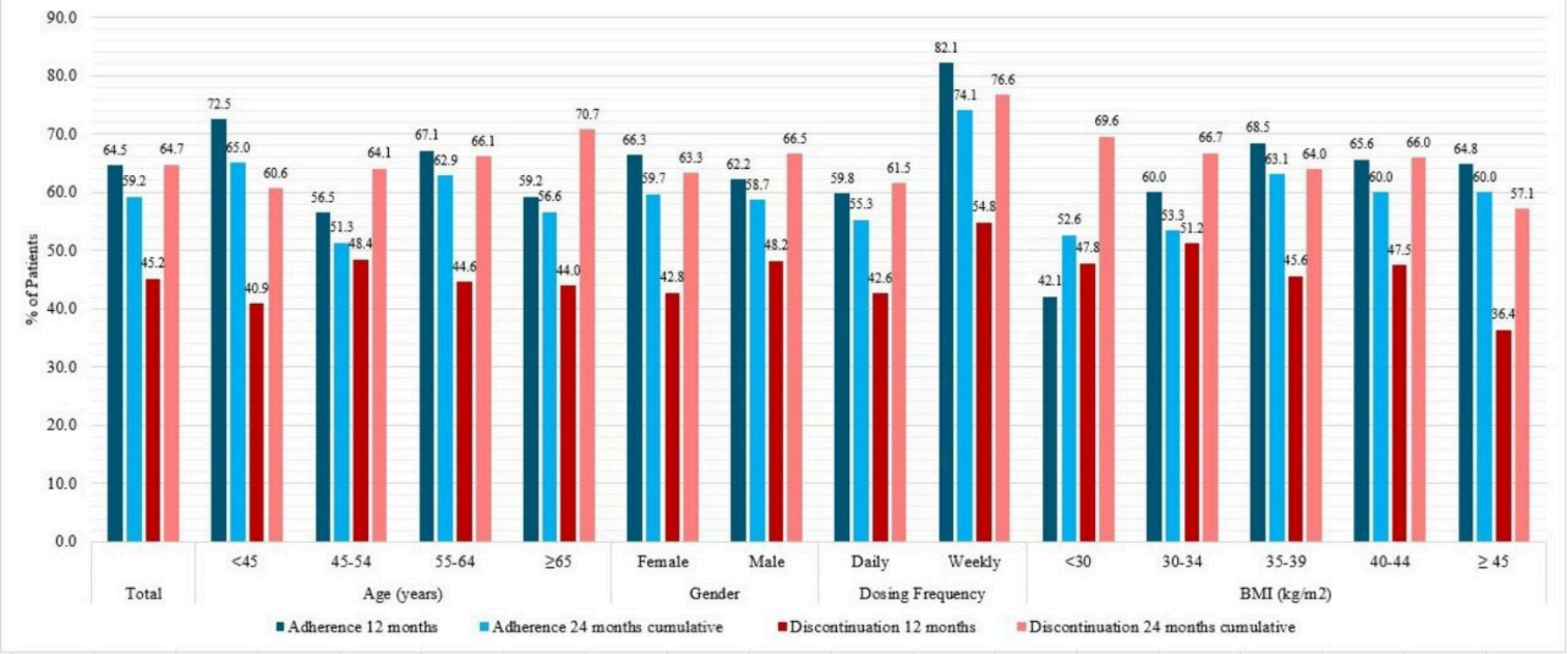
Real-World Adherence and Discontinuation of Glucagon-Like Peptide-1 Receptor Agonists Therapy in Type 2 Diabetes Mellitus Patients in the United States



Proportion of Patients Who Discontinued GLP-1 RA Therapy, n=4791.

A total of 4791 T2DM patients had ≥1 and 3907 had ≥2 GLP-1 RA prescription claims. **50.9% and 47.4% of patients were adherent at 12 and 24 months, respectively.**

Per cent of patients who were adherent to (n=530)† and discontinued (n=589) GLP-1 RA therapy at 12 and 24 months. †Adherence assessed among patients with two or more GLP-1 RA prescriptions. UNITED STATES



"A minority of patients initiating GLP-1 RAs achieved ≥5% weight loss, suggesting the real-world benefit of these agents on weight loss may be lower than that observed in clinical trials. Patients on GLP-1 RAs may benefit from additional support to improve long-term adherence."

Tracey Weiss et al. BMJ Open Diab Res Care 2022;10:e002517

BMJ Open Diabetes Research & Care

CONCLUSIONS

GLP-1 receptor agonists (GLP-1 RAs), along with dual GLP-1 and GIP receptor agonists, and triple agonists targeting GIP, GLP-1, and glucagon receptors, have been shown to significantly reduce appetite and enhance feelings of satiety, resulting in high weight loss.

The weight loss effect is generally more pronounced in individuals with obesity alone compared to those with both obesity and type 2 diabetes. However, despite the difference in weight loss, their impact on glycemic control in individuals with type 2 diabetes appears to be largely independent of weight reduction. Even with less pronounced weight loss, these agents still achieve substantial reductions in glycated hemoglobin (HbA1c), highlighting their potent glucose-lowering effects.

In addition, certain GLP-1 RAs, such as semaglutide (at a dose of 2.4 mg) and albiglutide, demonstrate benefits that extend beyond weight loss. These molecules appear to exert a direct cardioprotective effect, acting on the heart and arteries, further supporting their role in reducing cardiovascular risks in patients with obesity and diabetes. This suggests that the therapeutic advantages of these agents encompass both metabolic and cardiovascular improvements, making them highly valuable in managing these conditions.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