ANTI OBESITY DRUGS IN BARIATRIC PATIENTS

FARMACI DI NUOVA GENERAZIONE

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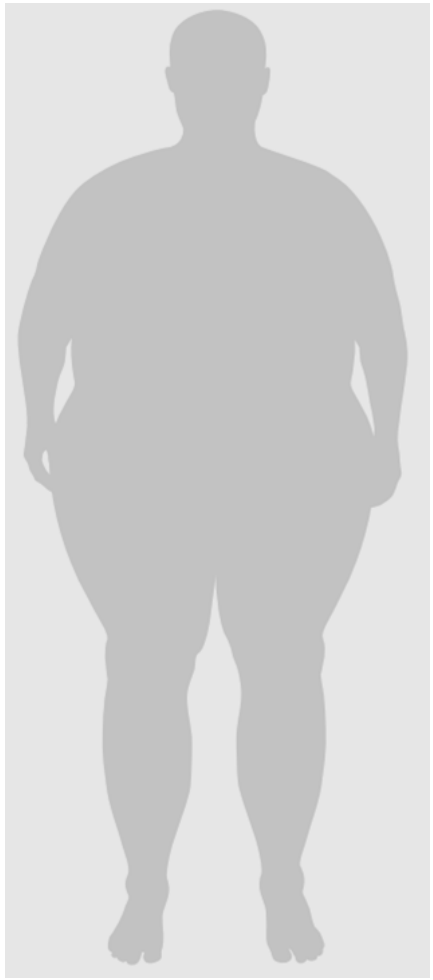
UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

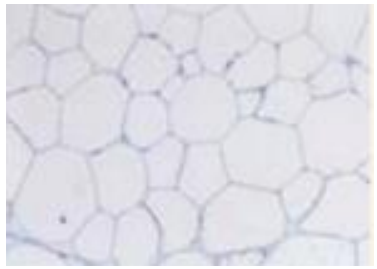
Mechanism linking obesity to type 2 diabetes, dyslipidemia and cardiovascular diseases

- Type 2 diabetes
- NAFLD
- Hypertension
- Dyslipidemia
- CVD
- OSAS
- Obesity hypoventilation syndrome (OHS)
- Hypogonadism

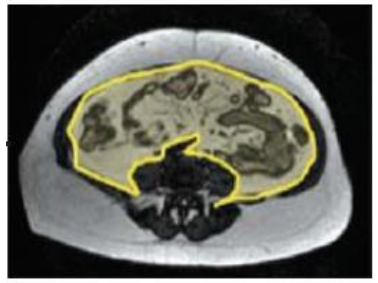
Adverse Signals:
- Adipokines
- Metabolites
- Immune cells



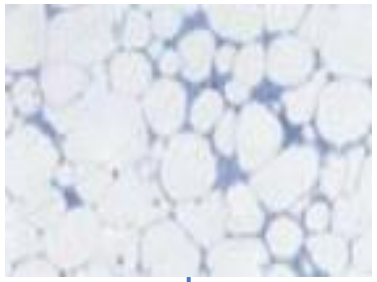
- ↓ Fitness
- Chronic positive energy balance
- Genetic factors



- ↑ Adipocyte size



- Ectopic fat ↑ (e.g. liver) ↓ leg fat

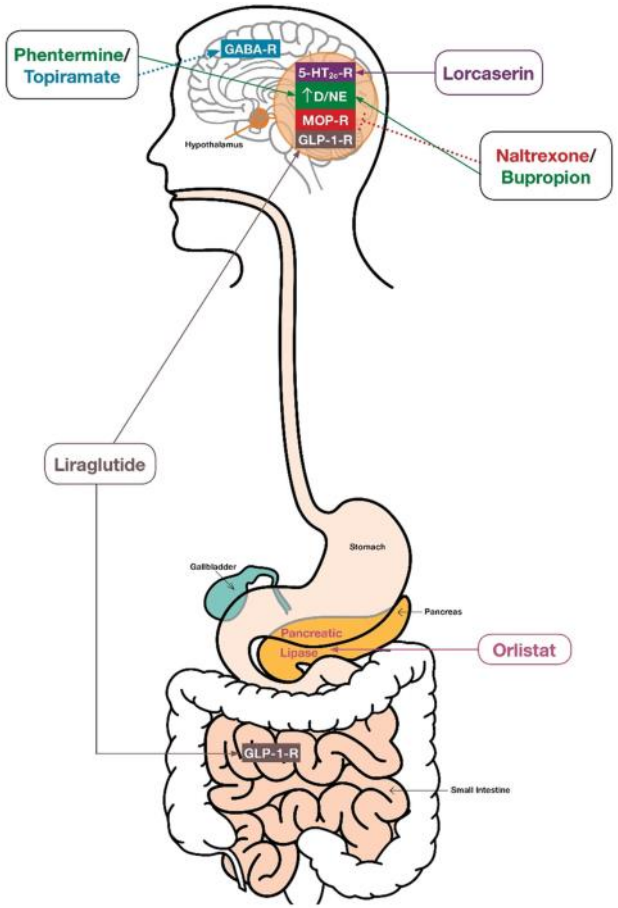


- Adipose tissue inflammation

Blüher M. Endocr Rev. 2020

Palma G & Perrini S et al., Int. J. Mol. Sci. 2022,

Anti-obesity drugs approved by the US FDA and/or EMA

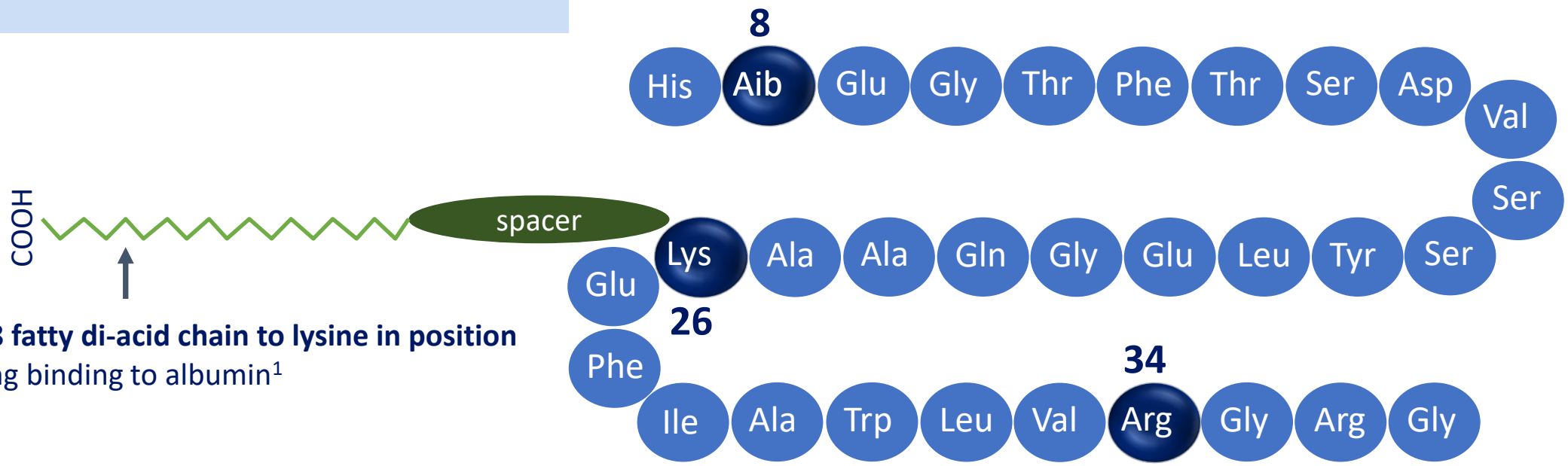


- Orlistat
- Lorcaserin
- Phentermine + Topiramate
- Naltrexone + Buproprione
- Liraglutide 3.0 mg
- Semaglutide
- Tirzepatide
- Cotadutide

Semaglutide is a human GLP-1 analogue

- **94%** homology to human GLP-1[1]
- $t_{½}$ of approximately **1 week**[2,3]

Amino acid substitution at position 8
(alanine to alpha-aminoisobutyric acid)
protects against DPP-4 degradation[1]



Spacer and C-18 fatty di-acid chain to lysine in position 26 provide strong binding to albumin[1]

Amino acid substitution at position 34
(lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site[1]

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; t½, half-life.

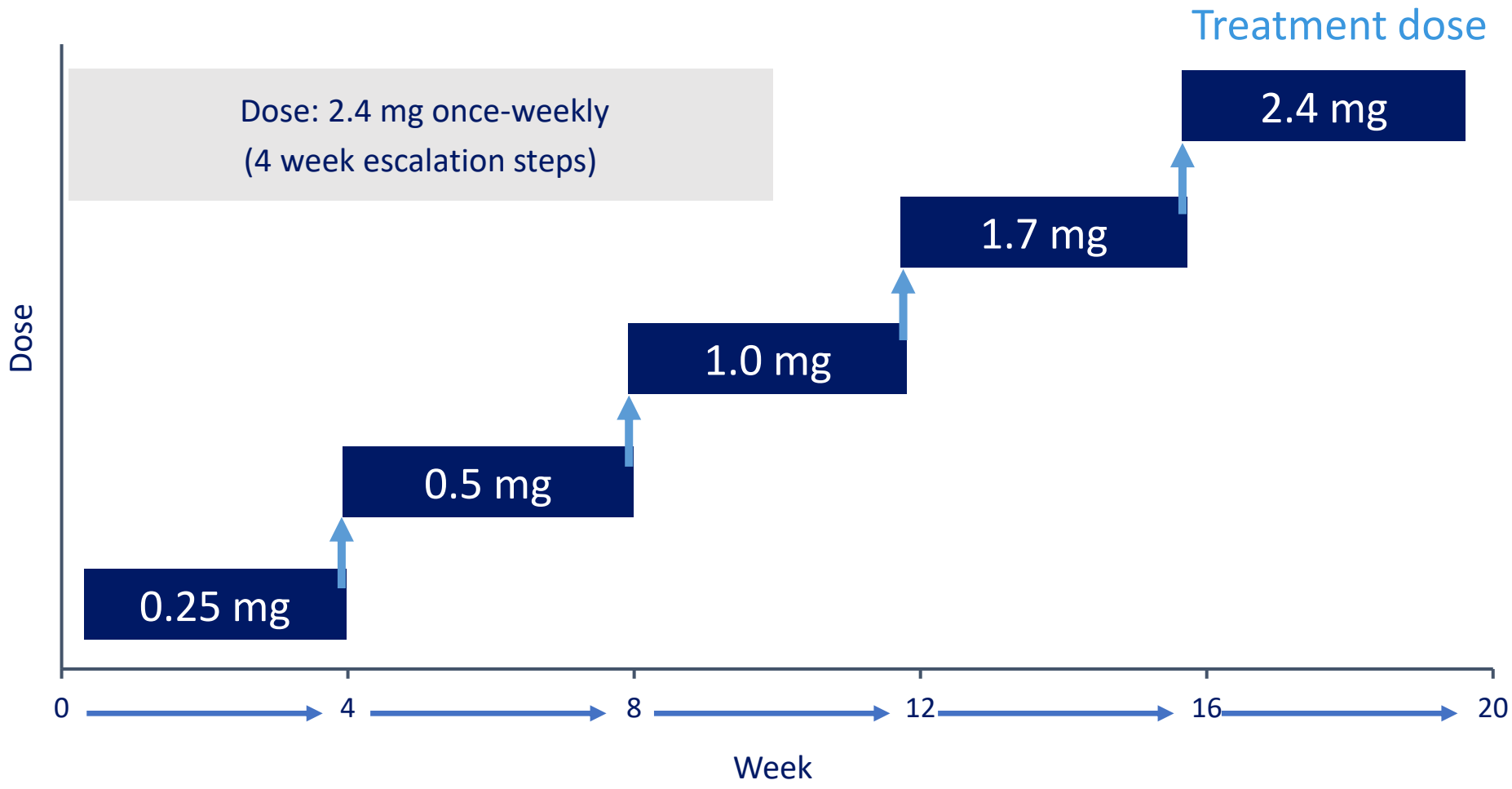
1. Lau J et al. J Med Chem 2015;58:7370–80; 2. Kapitza C et al. J Clin Pharmacol 2015;55:497–504; 3. Marbury TC et al. Clin Pharmacokinet 2017;56:1381–90.

Once-Weekly Semaglutide in Adults with Overweight or Obesity

Characteristic	Semaglutide (N=1306)	Placebo (N=655)
Age — yr	46±13	47±12
Female sex — no. (%)	955 (73.1)	498 (76.0)
Race or ethnic group — no. (%)†		
White	973 (74.5)	499 (76.2)
Asian	181 (13.9)	80 (12.2)
Black or African American	72 (5.5)	39 (6.0)
Other	80 (6.1)	37 (5.6)
Hispanic or Latino ethnic group — no. (%)†	150 (11.5)	86 (13.1)
Body weight — kg	105.4±22.1	105.2±21.5
Body-mass index‡		
Mean	37.8±6.7	38.0±6.5
Distribution — no. (%)		
<30	81 (6.2)	36 (5.5)
≥30 to <35	436 (33.4)	207 (31.6)
≥35 to <40	406 (31.1)	208 (31.8)
≥40	383 (29.3)	204 (31.1)
Waist circumference — cm	114.6±14.8	114.8±14.4
Glycated hemoglobin — %	5.7±0.3	5.7±0.3
Prediabetes — no. (%)§	593 (45.4)	263 (40.2)
Blood pressure — mm Hg		
Systolic	126±14	127±14
Diastolic	80±10	80±10

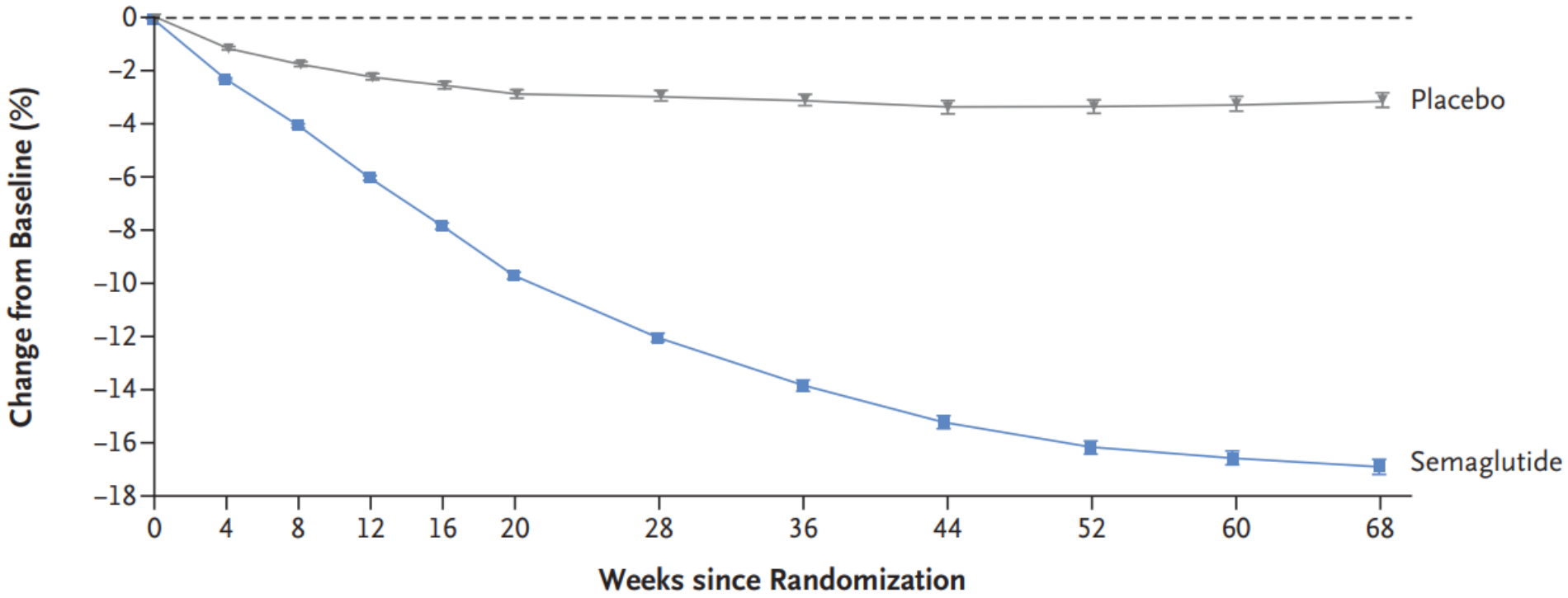
Wilding JPH et al., NEJM 2021

Semaglutide obesity dose escalation



Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183. Online ahead of print.

Once-Weekly Semaglutide in Adults with Overweight or Obesity

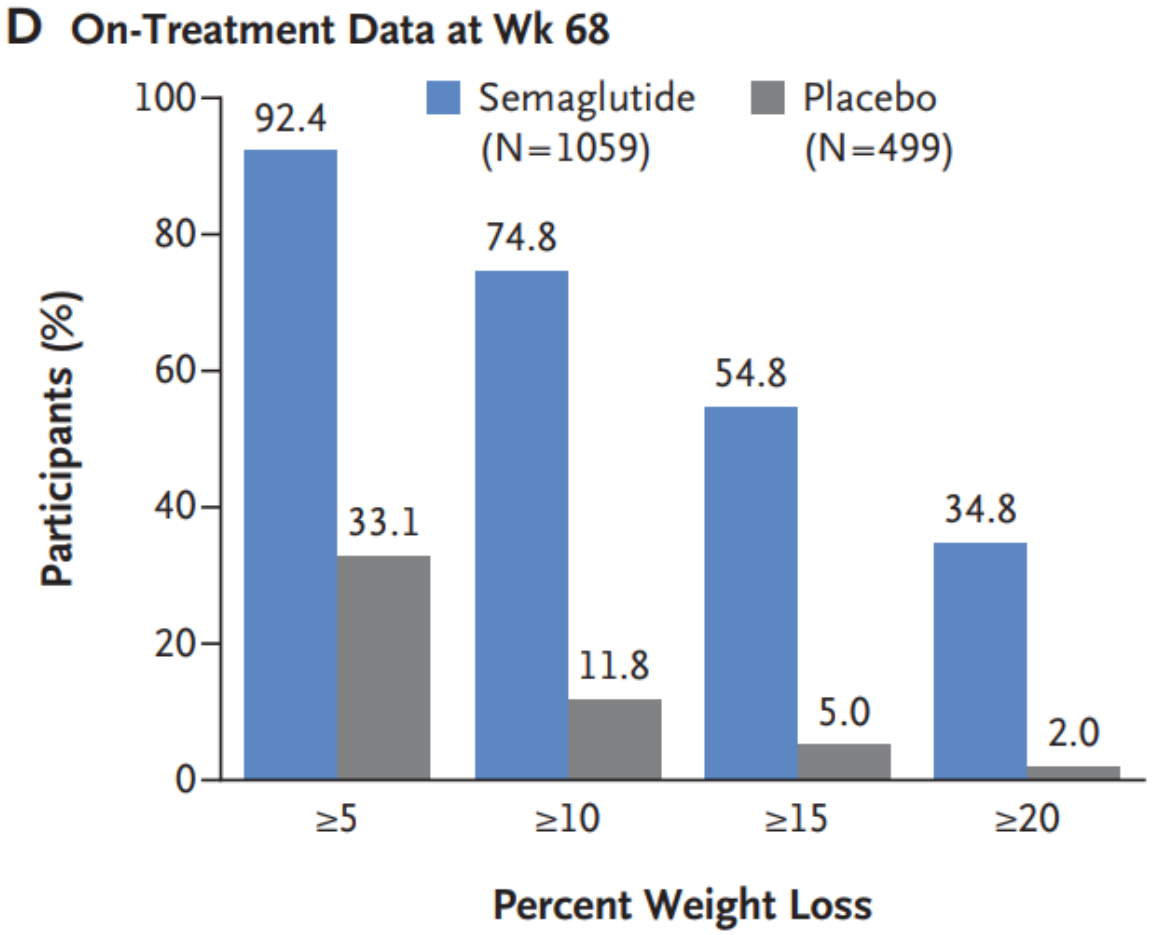


No. at Risk

Placebo	655	647	637	613	607	593	576	555	529	520	514	499
Semaglutide	1306	1283	1259	1225	1206	1193	1176	1166	1135	1115	1100	1059

Wilding JPH et al., NEJM 2021

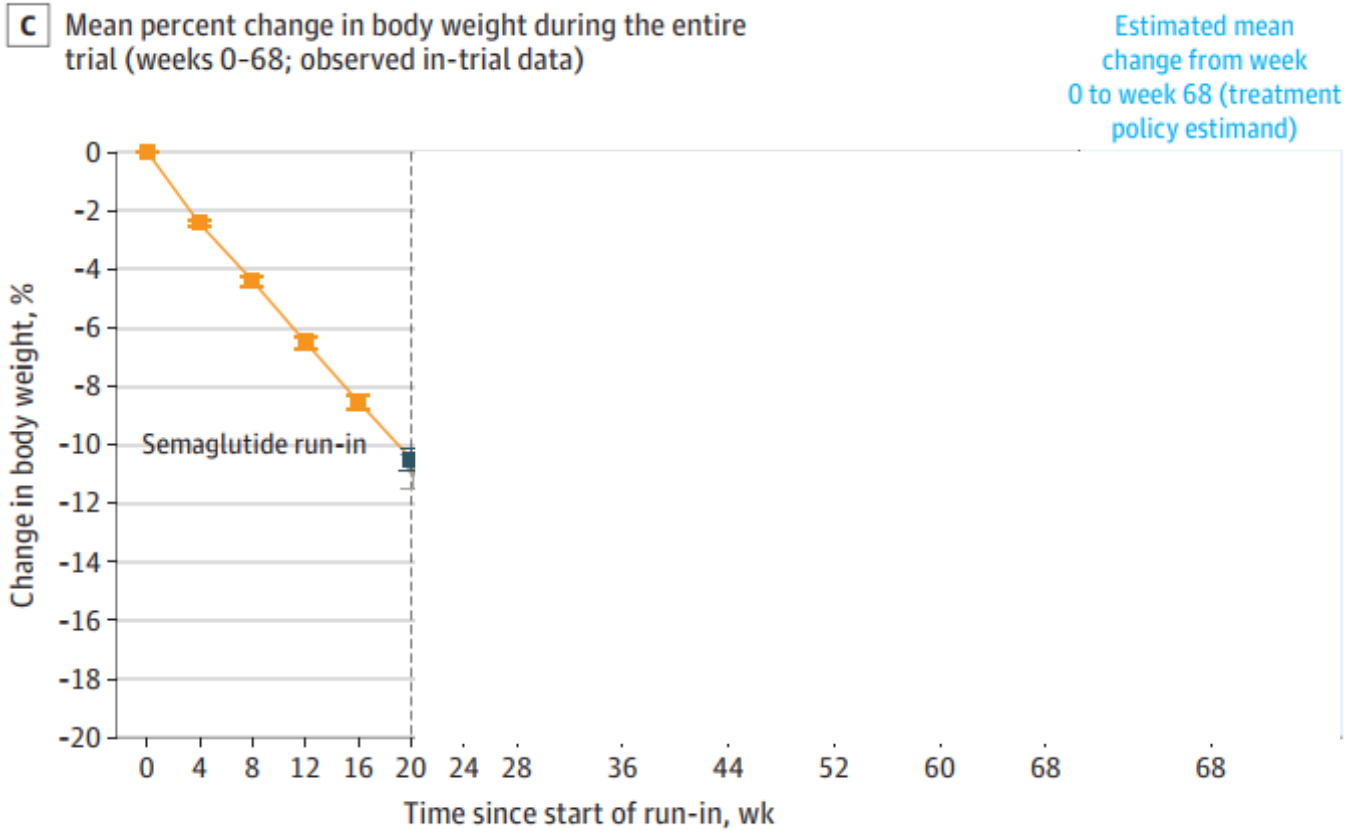
Once-Weekly Semaglutide in Adults with Overweight or Obesity

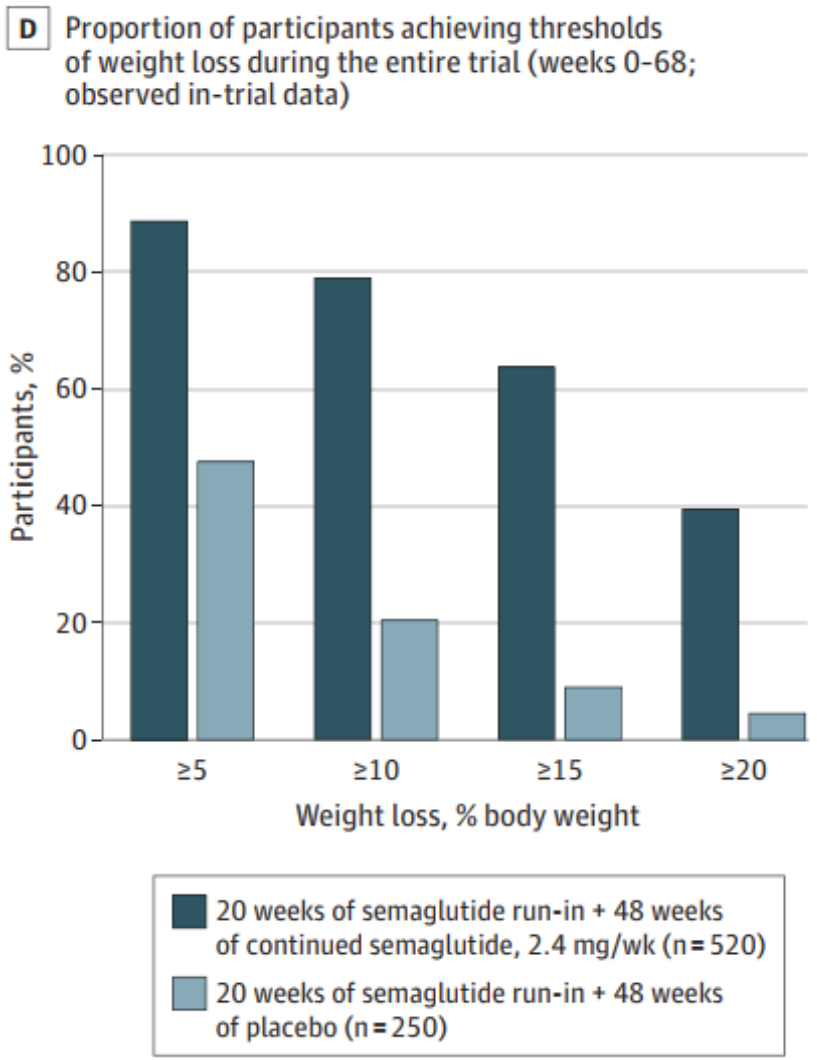


This trial showed that among adults with overweight or obesity (without diabetes), once weekly subcutaneous semaglutide **plus lifestyle intervention** was associated with substantial, sustained, clinically relevant mean weight loss of 14.9%, with 86% of participants attaining at least 5% weight loss.

Wilding JPH et al., NEJM 2021

Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity



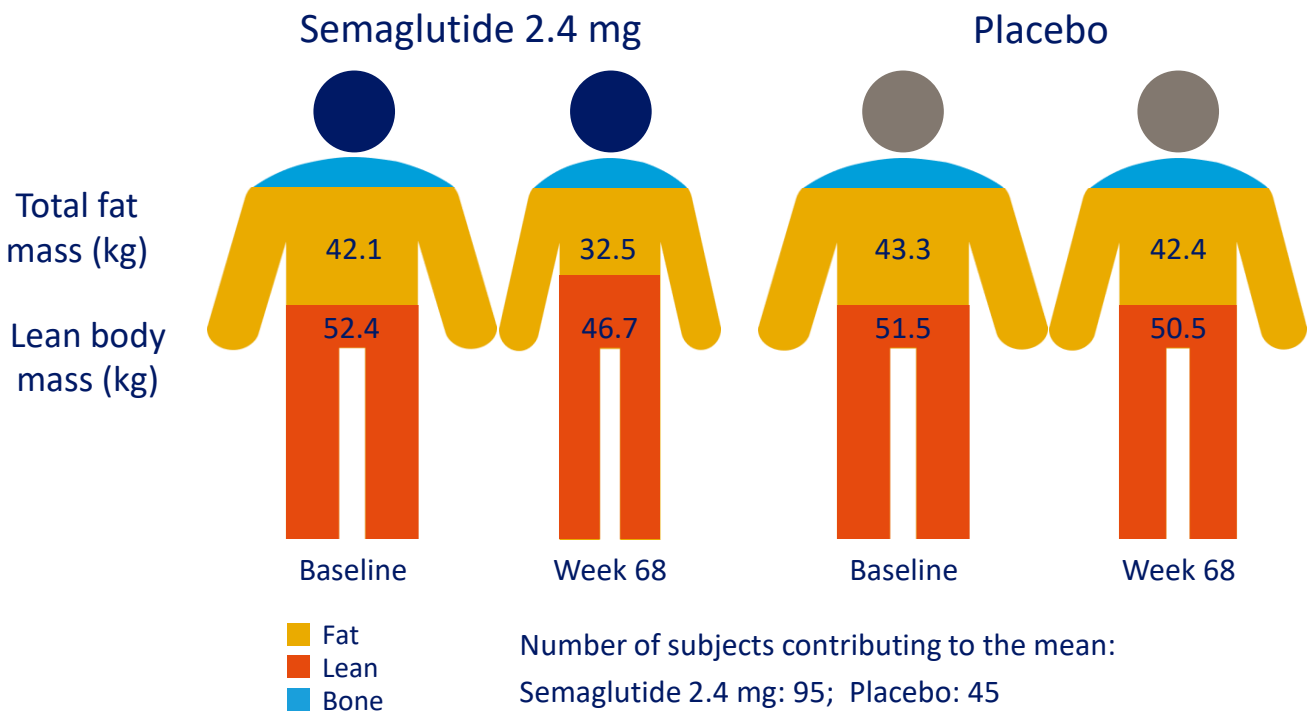


Rubino D. et al., JAMA. 2021

Once-Weekly Semaglutide in Adults with Overweight or Obesity

Change in body composition (DEXA)

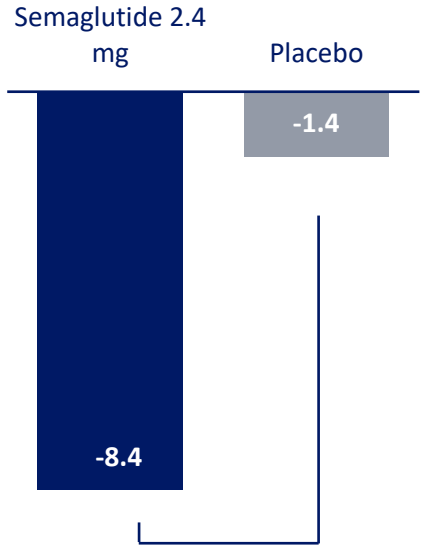
In-trial§



Number of subjects contributing to the mean:
Semaglutide 2.4 mg: 95; Placebo: 45

Total fat mass (kg)#

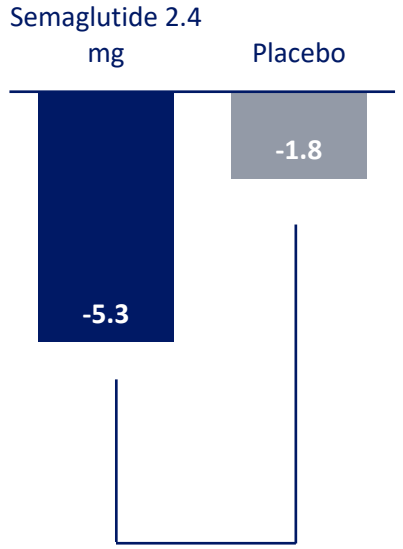
Mean baseline: 42.5 kg



ETD: -7.0 kg
95% CI: [-9.79;-4.19]; p<0.0001

Lean body mass (kg)#

Mean baseline: 52.1 kg

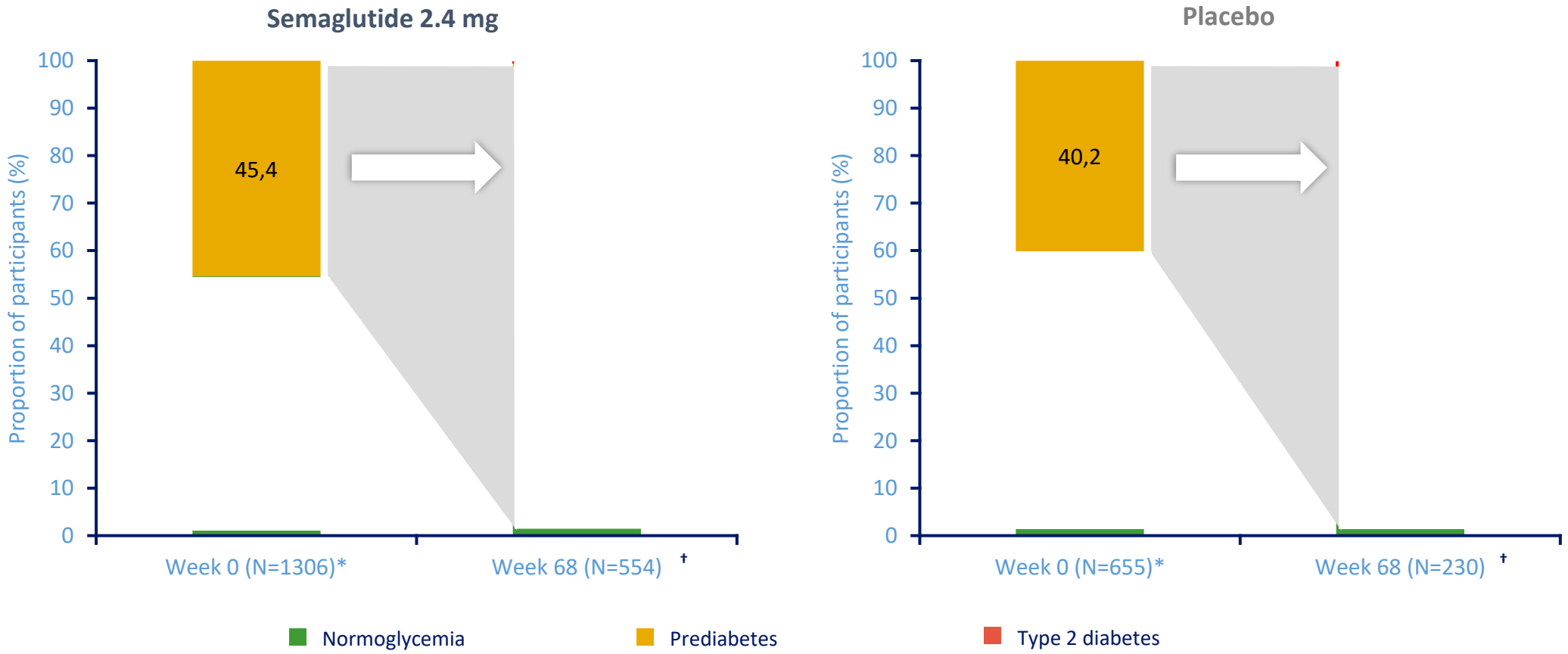


ETD: -3.4 kg
95% CI: [-4.74;-2.13]; p<0.0001

§ Observed data for the in-trial period; # Estimated data for the treatment policy estimand.
CI, confidence interval; DEXA, dual energy x-ray absorptiometry; ETD, estimated treatment difference.
Wilding JPH, et al. presented at the Endocrine Society (ENDO) virtual meeting, March 20-23, 2021.

Once-Weekly Semaglutide in Adults with Overweight or Obesity

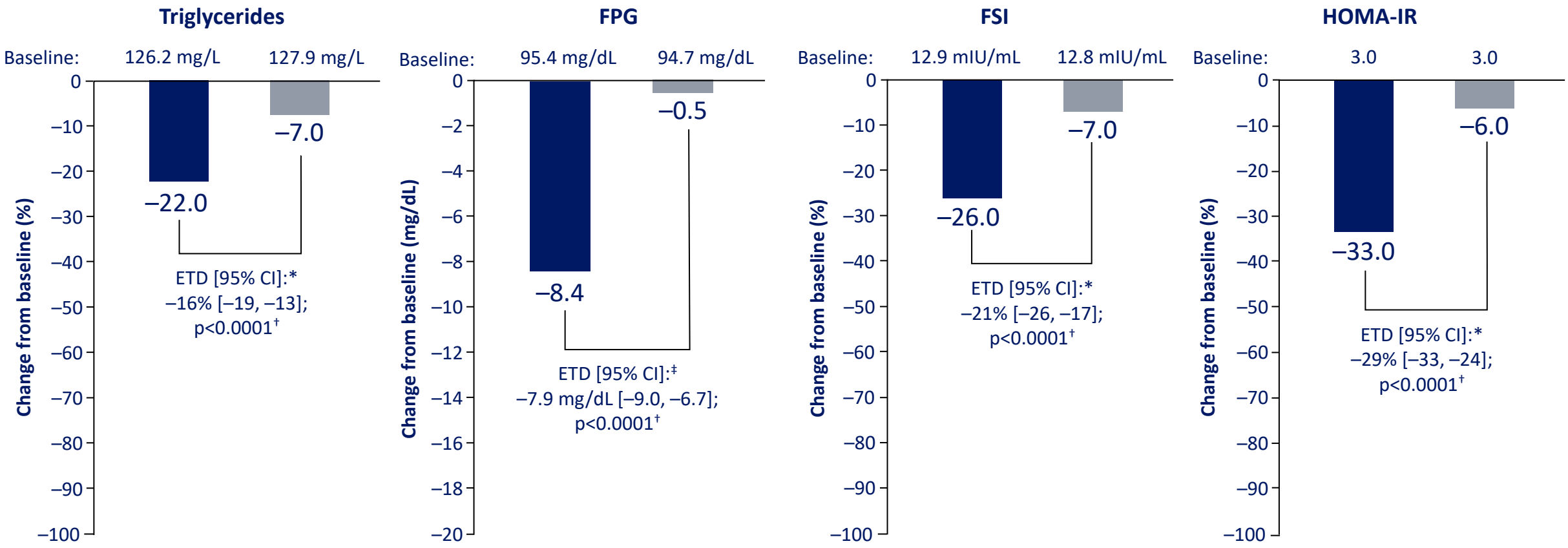
Shift from baseline to week 68 in glycaemic status Participants with prediabetes at baseline



Data are observed data during the in-trial period (regardless of treatment discontinuation or rescue intervention).
glycaemic category was evaluated by the investigator based on all available relevant information (e.g. concomitant medication, medical records and blood glucose parameters) in accordance with American Diabetes Association definitions.
Perreault et al. Presented at the American Diabetes Association (ADA) virtual meeting. June 25–29, 2021.

Once-Weekly Semaglutide in Adults with Overweight or Obesity

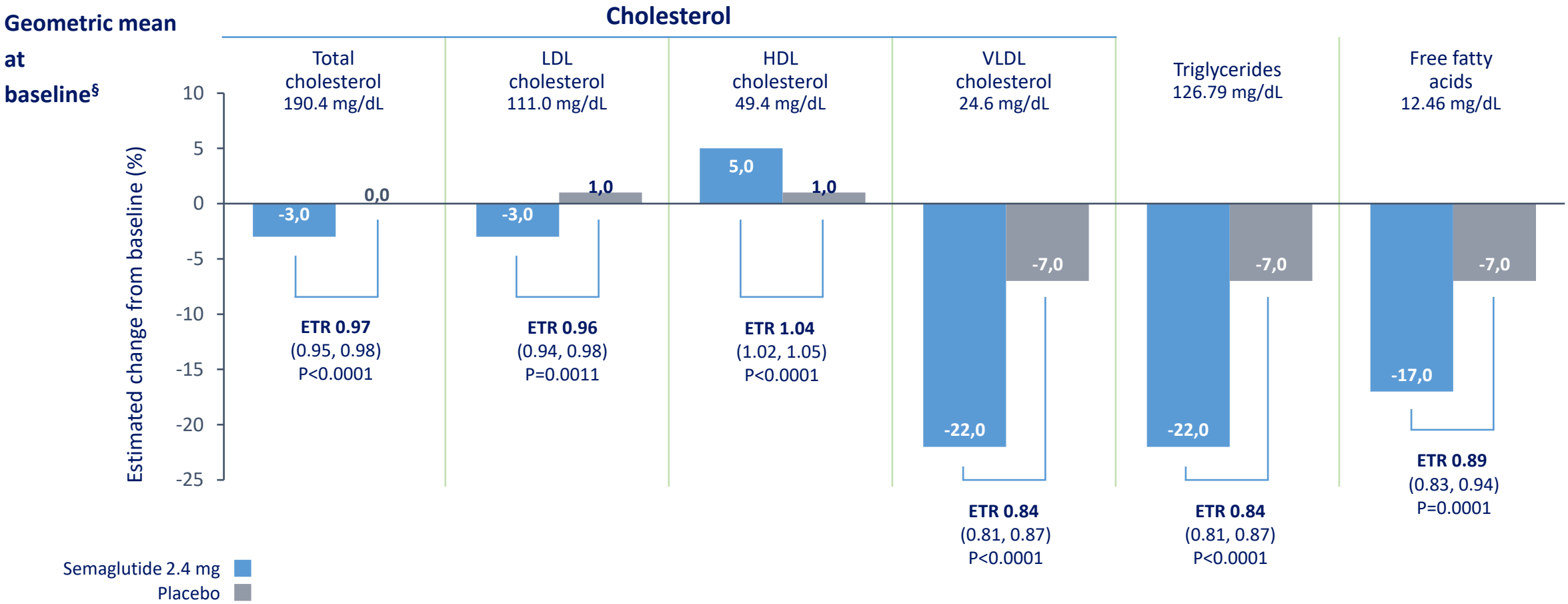
Changes in metabolic risk parameters from baseline to week 68



**Expressed as estimated relative percentage difference between groups. †Not adjusted for multiplicity. ‡Expressed as estimated absolute difference between groups.*
Data are for the in-trial period and the treatment policy estimand.
CI, confidence interval; ETD, estimated treatment difference; FPG, fasting plasma glucose; FSI, fasting serum insulin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance.
Garvey et al. Presented at the European and International Congress on Obesity (ECO) virtual meeting. May 10–13, 2021.

Once-Weekly Semaglutide in Adults with Overweight or Obesity

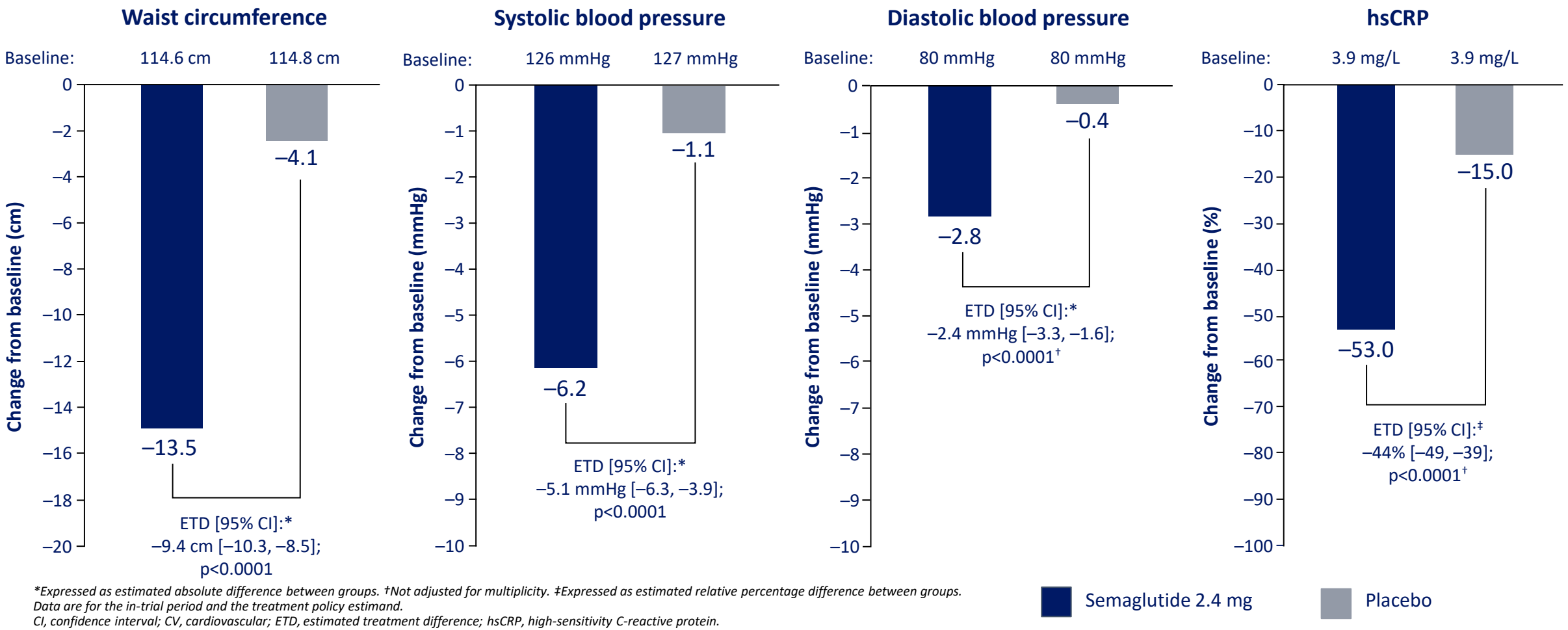
Change in fasting lipids



Estimated change from baseline for treatment policy estimand. § geometric mean at baseline for both treatment groups.
ETR, estimated treatment ratio.
Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183. Online ahead of print.

Once-Weekly Semaglutide in Adults with Overweight or Obesity

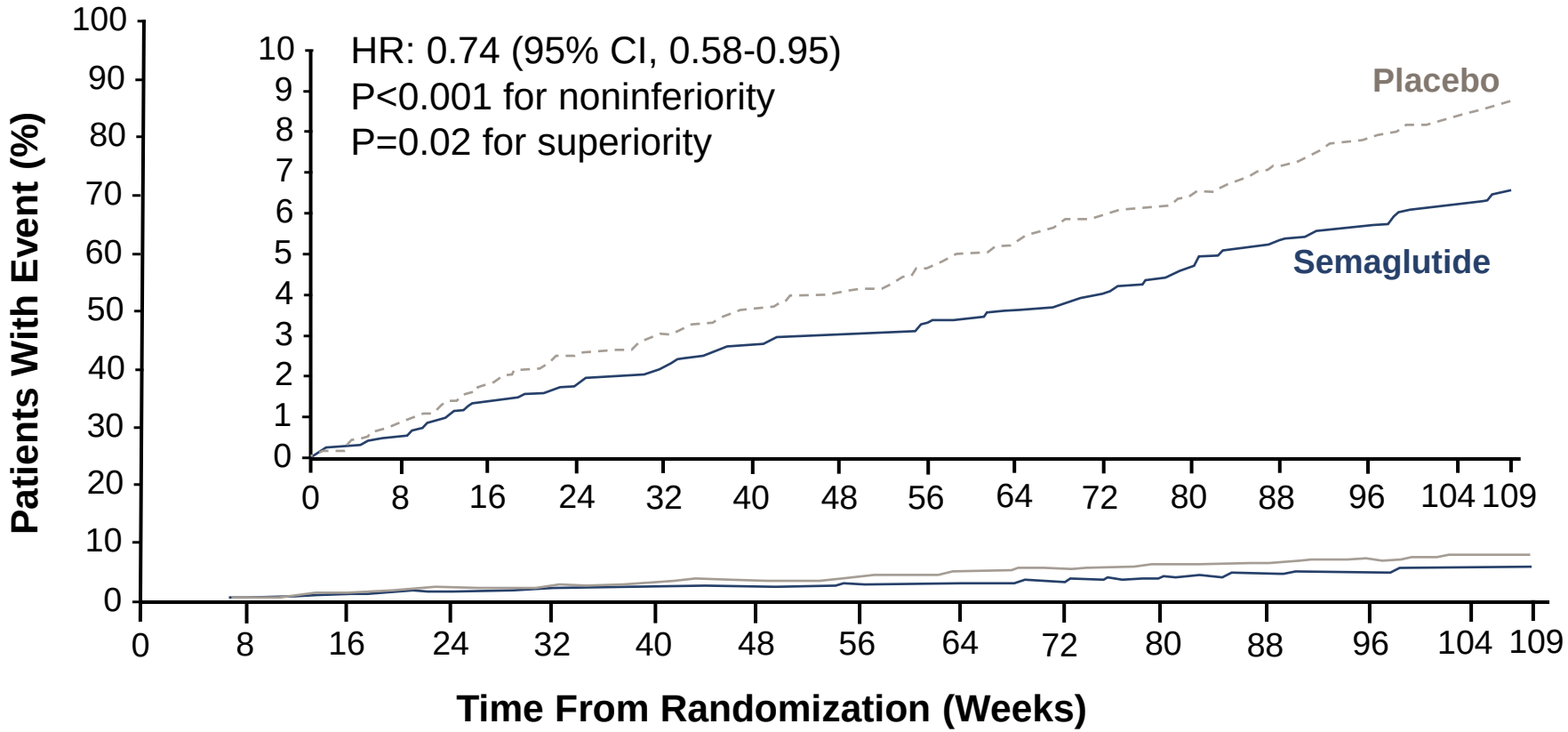
Changes in CV risk parameters from baseline to week 68



**Expressed as estimated absolute difference between groups. †Not adjusted for multiplicity. ‡Expressed as estimated relative percentage difference between groups.*
Data are for the in-trial period and the treatment policy estimand.
CI, confidence interval; CV, cardiovascular; ETD, estimated treatment difference; hsCRP, high-sensitivity C-reactive protein.
Garvey et al. Presented at the European and International Congress on Obesity (ECO) virtual meeting. May 10–13, 2021.

SUSTAIN 6: Primary Outcome

CV Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke



No. at risk							
Semaglutide	1648	1619	1601	1584	1568	1543	1524
Placebo	1649	1616	1586	1567	1534	1508	1479

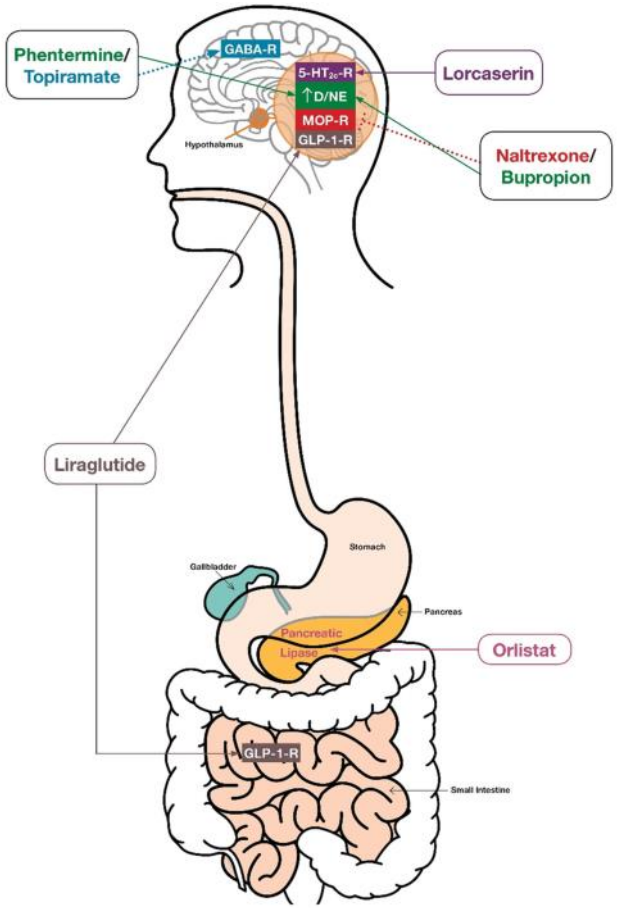
Marso SP et al. N Engl J Med 2016

Once-Weekly Semaglutide in Adults with Overweight or Obesity

Adverse Event	Semaglutide (N=1306)			Placebo (N=655)		
	No. of participants (%)	No. of events	Events/100 person-yr	No. of participants (%)	No. of events	Events/100 person-yr
Any adverse event	1171 (89.7)	9658	566.1	566 (86.4)	3302	398.0
Serious adverse events	128 (9.8)	164	9.6	42 (6.4)	53	6.4
Adverse events leading to discontinuation of drug or placebo	92 (7.0)	123	7.2	20 (3.1)	23	2.8
Gastrointestinal disorders	59 (4.5)	78	4.6	5 (0.8)	5	0.6
Fatal events†‡	1 (0.1)	1	0.1	1 (0.2)	3	0.3
Adverse events reported in ≥10% of participants§						
Nausea	577 (44.2)	1068	62.6	114 (17.4)	146	17.6
Diarrhea	412 (31.5)	766	44.9	104 (15.9)	138	16.6
Vomiting	324 (24.8)	636	37.3	43 (6.6)	52	6.3
Constipation	306 (23.4)	390	22.9	62 (9.5)	73	8.8
Nasopharyngitis	281 (21.5)	480	28.1	133 (20.3)	216	26.0
Headache	198 (15.2)	387	22.7	80 (12.2)	104	12.5
Dyspepsia	135 (10.3)	179	10.5	23 (3.5)	30	3.6
Abdominal pain	130 (10.0)	175	10.3	36 (5.5)	41	4.9
Upper respiratory tract infection	114 (8.7)	158	9.3	80 (12.2)	116	14.0
Safety focus areas¶						
Gastrointestinal disorders‖	969 (74.2)	4309	252.6	314 (47.9)	739	89.1
Gallbladder-related disorders	34 (2.6)	42	2.5	8 (1.2)	8	1.0
Hepatobiliary disorders‖	33 (2.5)	40	2.3	5 (0.8)	5	0.6

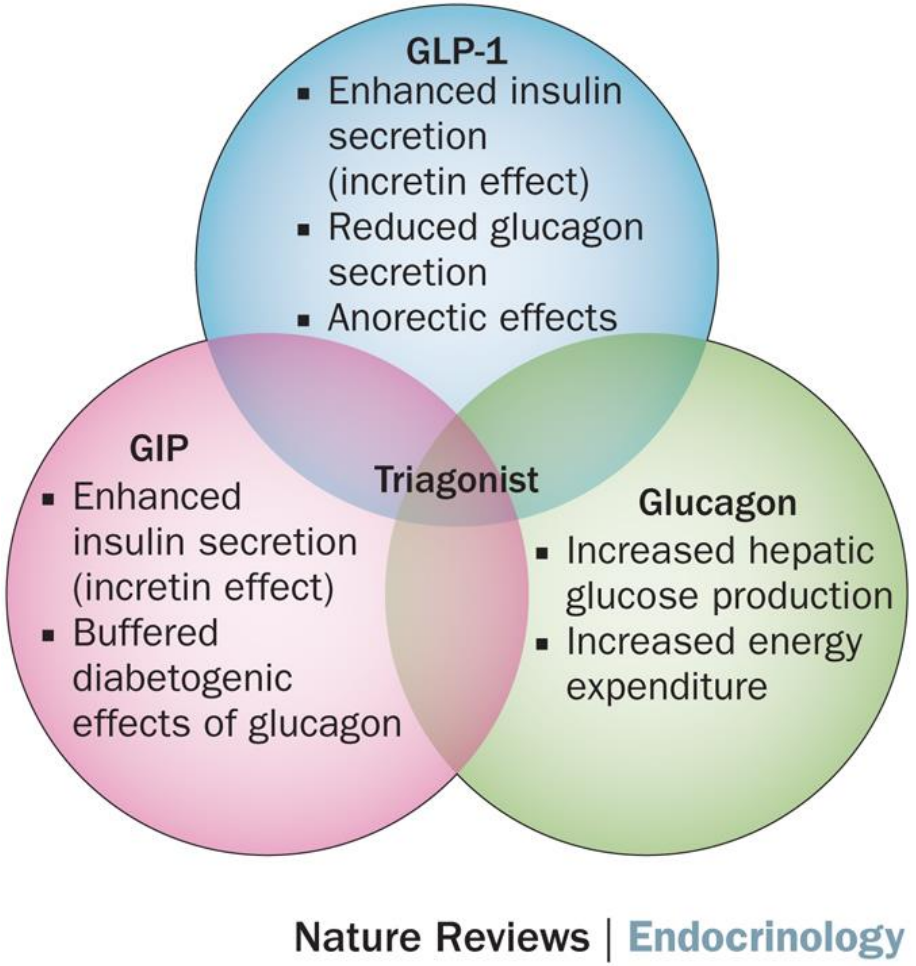
Wilding JPH et al., NEJM 2021

Anti-obesity drugs approved by the US FDA and/or EMA



- Orlistat
- Lorcaserin
- Phentermine + Topiramate
- Naltrexone + Buproprione
- Liraglutide 3.0 mg
- Semaglutide
- Tirzepatide

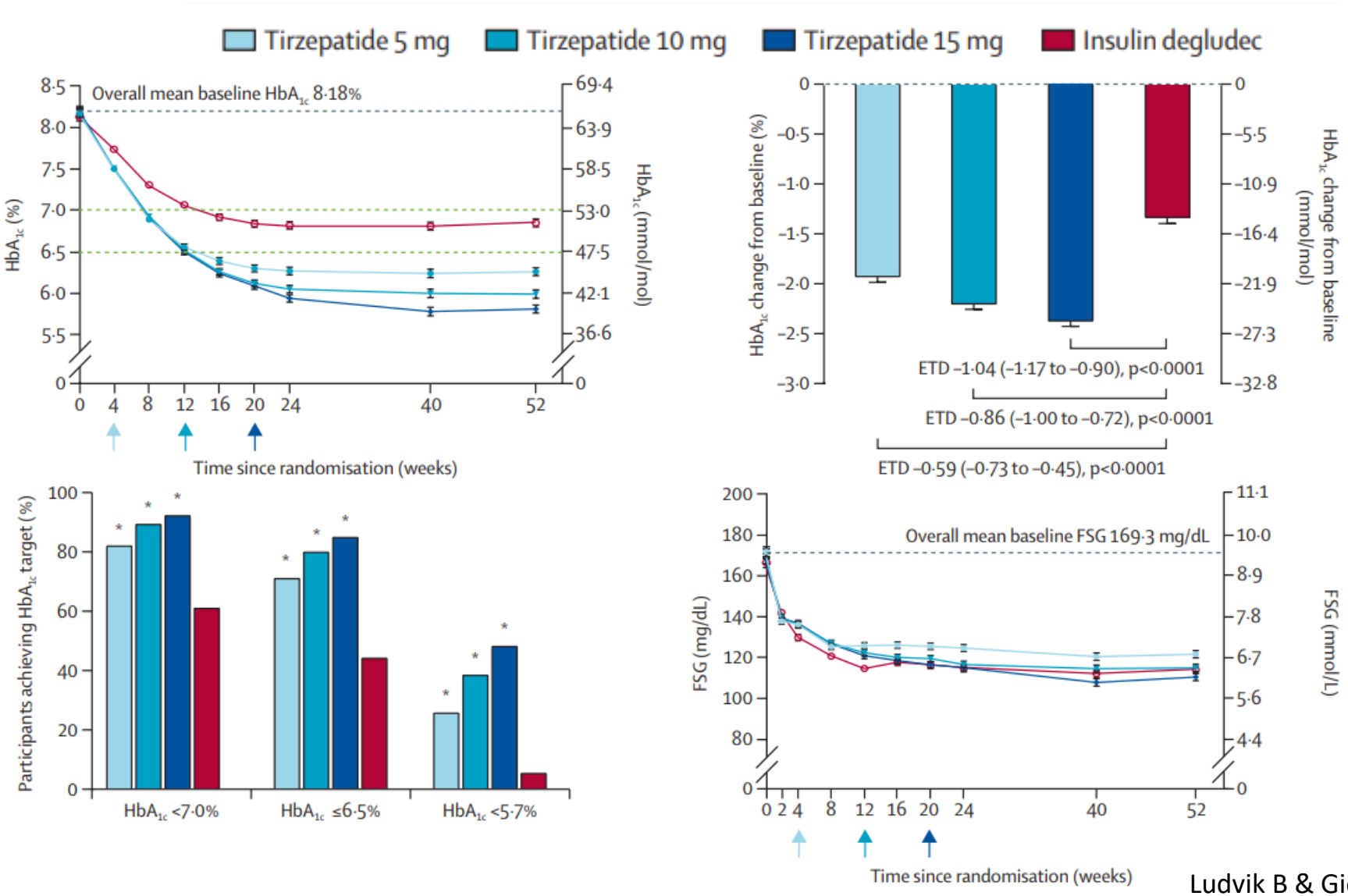
Unimolecular Polypharmacy for Treatment of Diabetes and Obesity



Complementary (but also opposing) effects of the individual components of a peptide triagonist targeting GLP-1, GIP and glucagon receptors that could be used to treat obesity and type 2 diabetes mellitus

Once-weekly Tirzepatide versus once-daily Insulin Degludec in Patients with Type 2 Diabetes

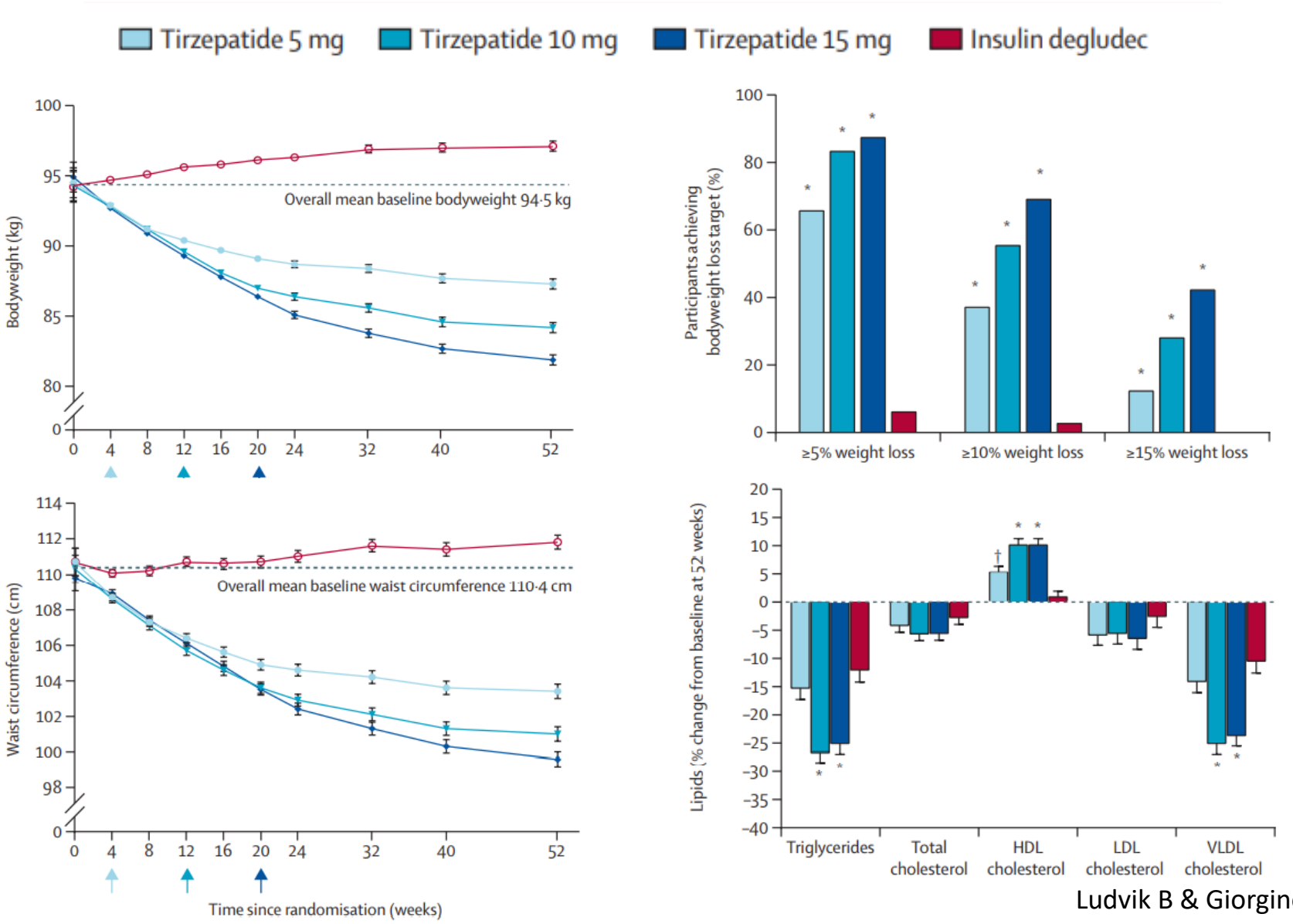
Tirzepatide: dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist



Ludvik B & Giorgino F et al., Lancet, 2021

Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes

Tirzepatide: dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist



Ludvik B & Giorgino F et al., Lancet, 2021

Tirzepatide Once Weekly for the Treatment of Obesity

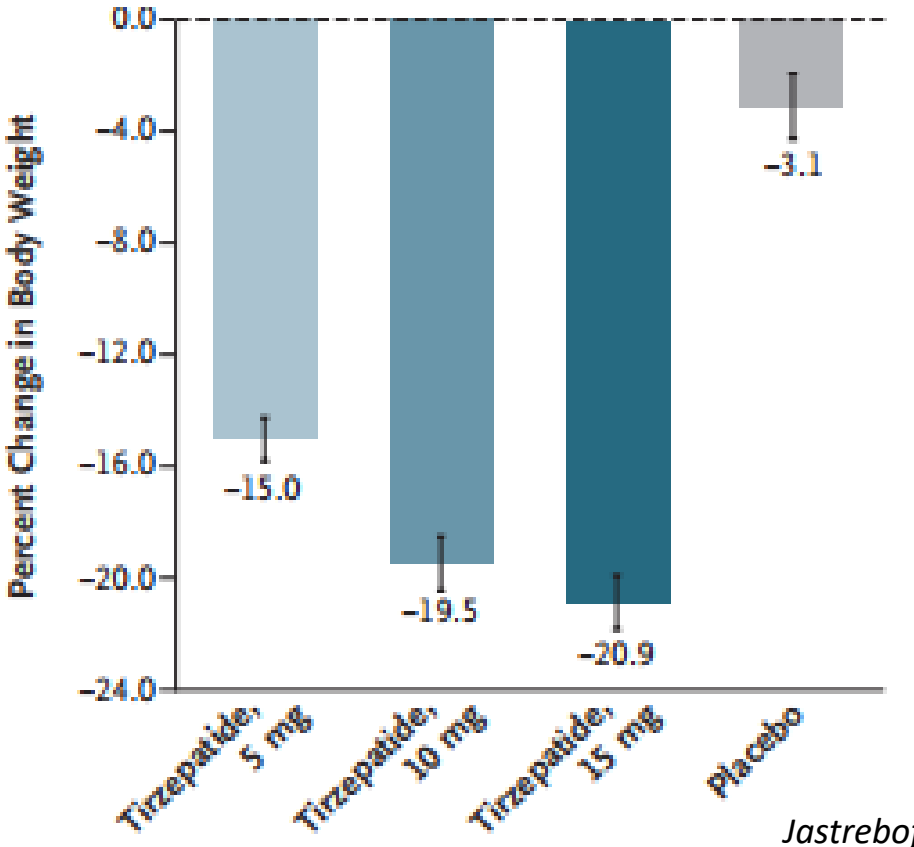
Characteristic	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)	Total (N=2539)
Age — yr	45.6±12.7	44.7±12.4	44.9±12.3	44.4±12.5	44.9±12.5
Female sex — no. (%)	426 (67.6)	427 (67.1)	425 (67.5)	436 (67.8)	1714 (67.5)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	56 (8.9)	58 (9.1)	59 (9.4)	58 (9.0)	231 (9.1)
Asian	68 (10.8)	71 (11.2)	66 (10.5)	71 (11.0)	276 (10.9)
Black or African American	48 (7.6)	47 (7.4)	51 (8.1)	55 (8.6)	201 (7.9)
White	447 (71.0)	452 (71.1)	443 (70.3)	450 (70.0)	1792 (70.6)
Native Hawaiian or other Pacific Islander	2 (0.3)	2 (0.3)	3 (0.5)	2 (0.3)	9 (0.4)
Multiple	9 (1.4)	6 (0.9)	8 (1.3)	7 (1.1)	30 (1.2)
Hispanic or Latino — no. (%)	308 (48.9)	297 (46.7)	299 (47.5)	310 (48.2)	1214 (47.8)
Duration of obesity — yr	14.0±10.81	14.7±11.05	14.8±10.75	14.0±10.71	14.4±10.83
Body weight — kg	102.9±20.71	105.8±23.32	105.6±22.92	104.8±21.37	104.8±22.12
Mean body-mass index	37.4±6.63	38.2±7.01	38.1±6.69	38.2±6.89	38.0±6.81
Body-mass index category — no. (%)					
<30	38 (6.0)	38 (6.0)	40 (6.3)	24 (3.7)	140 (5.5)
≥30 to <35	241 (38.3)	209 (32.9)	199 (31.6)	227 (35.3)	876 (34.5)
≥35 to <40	174 (27.6)	187 (29.4)	179 (28.4)	180 (28.0)	720 (28.4)
≥40	177 (28.1)	202 (31.8)	212 (33.7)	212 (33.0)	803 (31.6)
Waist circumference — cm	113.2±14.25	114.8±15.80	114.4±15.59	114.0±14.92	114.1±15.16
Blood pressure — mm Hg					
Systolic	123.6±12.45	123.8±12.77	123.0±12.94	122.9±12.77	123.3±12.73
Diastolic	79.3±8.14	79.9±8.32	79.3±8.23	79.6±7.95	79.5±8.16
Pulse — beats per min	72.3±9.60	71.8±9.57	72.5±9.95	72.9±9.27	72.4±9.60

Jastreboff AM. Et al., NEJM, 2022,

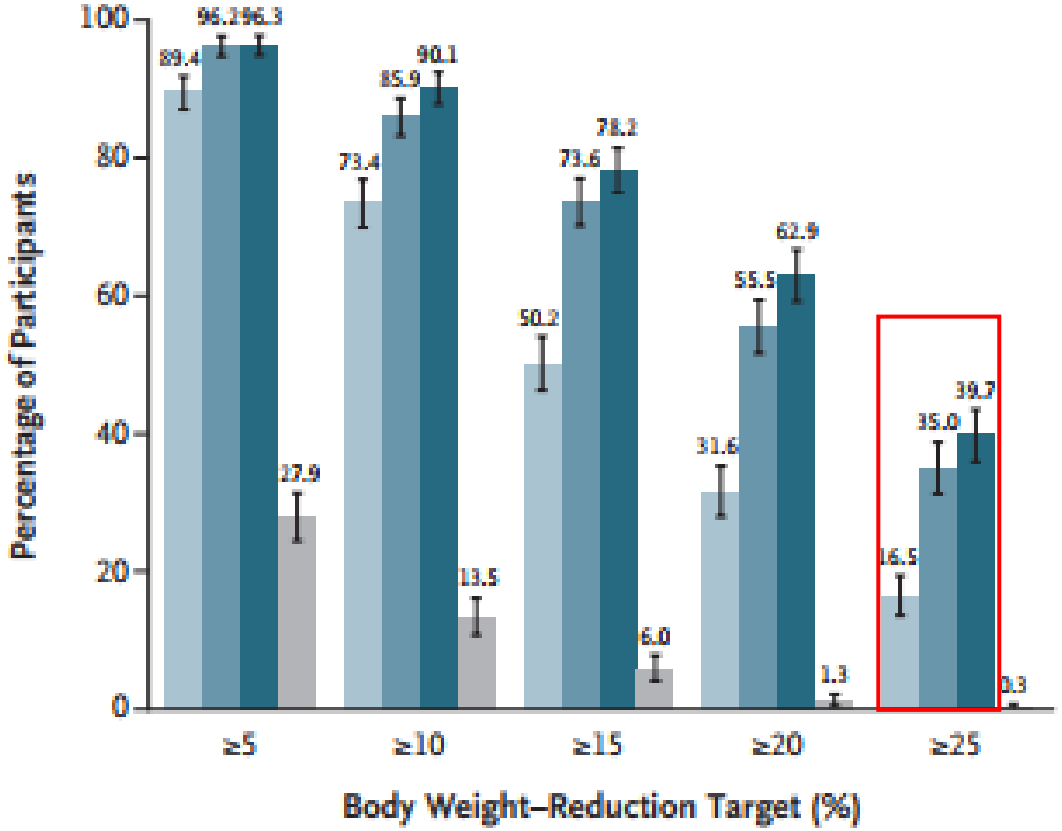
Tirzepatide Once Weekly for the Treatment of Obesity

Tirzepatide, 5 mg Tirzepatide, 10 mg Tirzepatide, 15 mg Placebo

Overall Percent Change in Body Weight from Baseline (treatment-regimen estimand



Percent Change in Body Weight by Week (efficacy estimand)



Jastreboff AM. Et al., NEJM, 2022,

Tirzepatide Once Weekly for the Treatment of Obesity

End Points	Pooled Tirzepatide Groups†	Placebo (N = 643)	Estimated Treatment Difference from Placebo (95% CI)
	least-squares mean (95% CI)		
Key secondary end points‡			
Change from baseline to week 20 in body weight — kg§	−12.8 (−13.1 to −12.5)	−2.7 (−3.2 to −2.2)	−10.1 (−10.7 to −9.6)
Change in measure			
SF-36 physical function score§¶	3.6 (3.2 to 4.0)	1.7 (0.8 to 2.6)	1.9 (1.0 to 2. 9)
Systolic blood pressure — mm Hg	−7.2 (−7.8 to −6.7)	−1.0 (−2.3 to −0.3)	−6.2 (−7.7 to −4.8)
Percentage change in level‖			
Triglycerides — mg/dl	−24.8 (−26.3 to −23.1)	−5.6 (−10.0 to −1.2)	−20.3 (−24.3 to −16.1)
Non-HDL cholesterol — mg/dl	−9.7 (−10.7 to −8.6)	−2.3 (−4.9 to −0.2)	−7.5 (−10.1 to −4.9)
HDL cholesterol — mg/dl	8.0 (6.9 to 9.1)	−0.7 (−2.9 to 1.5)	8.8 (6.1 to 11.5)
Fasting insulin — mIU/liter**	−42.9 (−44.9 to −40.9)	−6.6 (−15.3 to 2.2)	−38.9 (−44.8 to −32.4)
Additional secondary end points††			
Change in diastolic blood pressure — mm Hg	−4.8 (−5.2 to −4.4)	−0.8 (−1.6 to 0.0)	−4.0 (−4.9 to −3.1)
Percentage change in level‖			
Total cholesterol — mg/dl	−4.8 (−5.6 to −4.0)	−1.8 (−3.7 to 0.1)	−3.1 (−5.2 to −1.0)
LDL cholesterol — mg/dl	−5.8 (−6.9 to −4.6)	−1.7 (−4.6 to 1.3)	−4.2 (−7.2 to −1.0)
VLDL cholesterol — mg/dl	−24.4 (−25.9 to −22.9)	−4.8 (−9.2 to −0.4)	−20.6 (−24.6 to −16.4)
Free fatty acids — mmol/liter	−7.5 (−10.7 to −4.3)	9.5 (3.8 to 15.3)	−15.6 (−20.8 to −9.9)

Jastreboff AM. Et al., NEJM, 2022,

Tirzepatide Once Weekly for the Treatment of Obesity

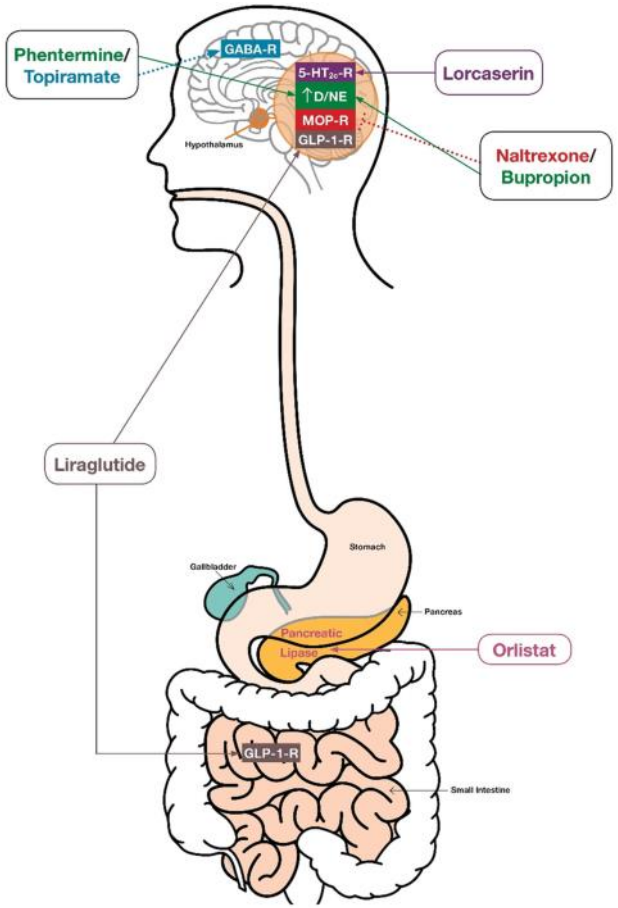
Adverse Events and Safety

Variable	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)
	number (percent)			
Participants with ≥1 adverse event during treatment period	510 (81.0)	520 (81.8)	497 (78.9)	463 (72.0)
Serious adverse events	40 (6.3)	44 (6.9)	32 (5.1)	44 (6.8)
Death*	4 (0.6)	2 (0.3)	1 (0.2)	4 (0.6)
Adverse events leading to discontinuation of trial drug or placebo†	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)
Nausea	6 (1.0)	7 (1.1)	12 (1.9)	2 (0.3)
Diarrhea	2 (0.3)	5 (0.8)	3 (0.5)	0
Abdominal pain	0	2 (0.3)	3 (0.5)	0
Vomiting	0	4 (0.6)	0	0

Jastreboff AM. Et al., NEJM, 2022,

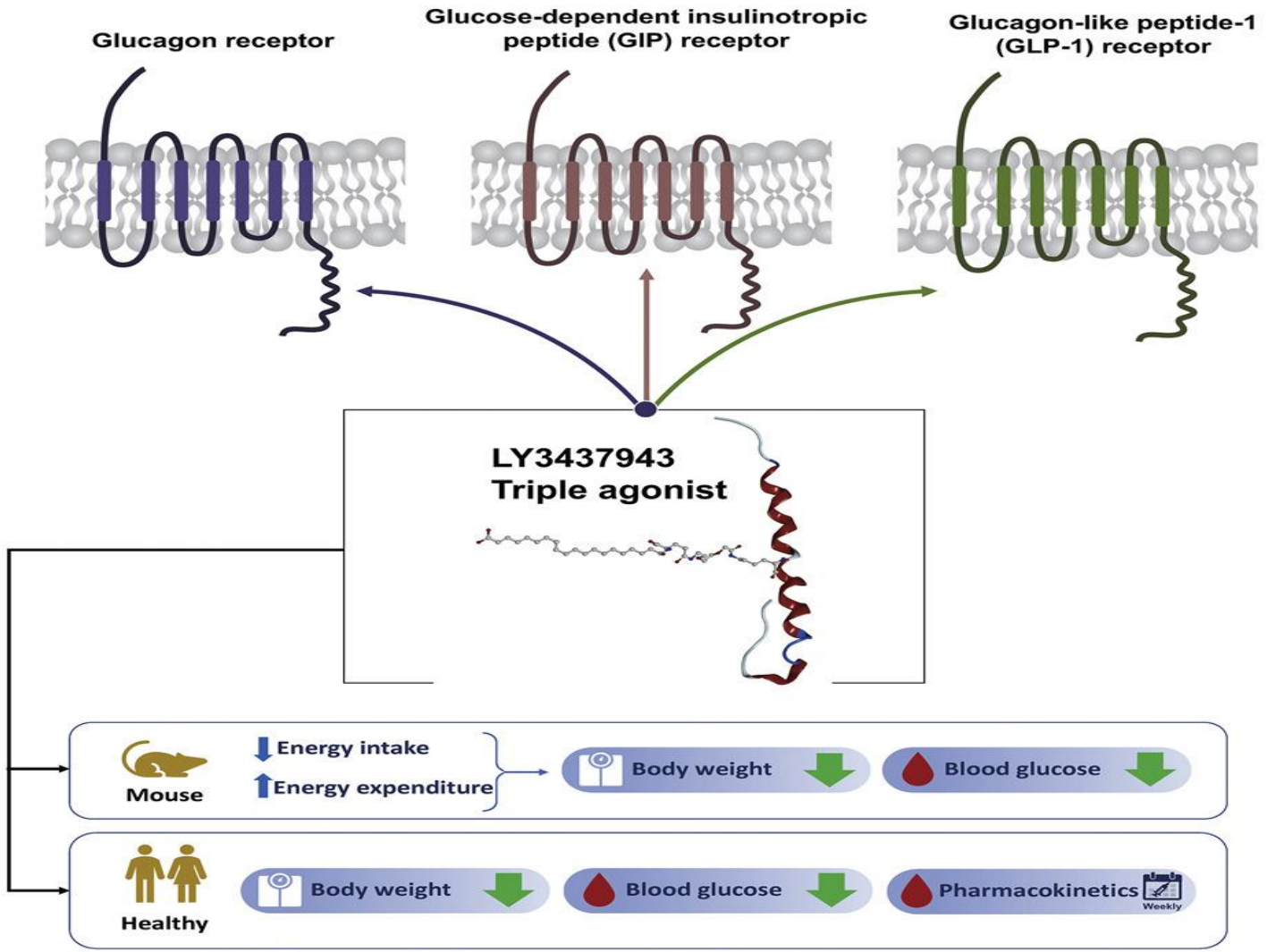

E il futuro?

Anti-obesity drugs approved by the US FDA and/or EMA



- Orlistat
- Lorcaserin
- Phentermine + Topiramate
- Naltrexone + Buproprione
- Liraglutide 3.0 mg
- Semaglutide
- Tirzepatide
- LY3437943
- Cagrilintide

LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss



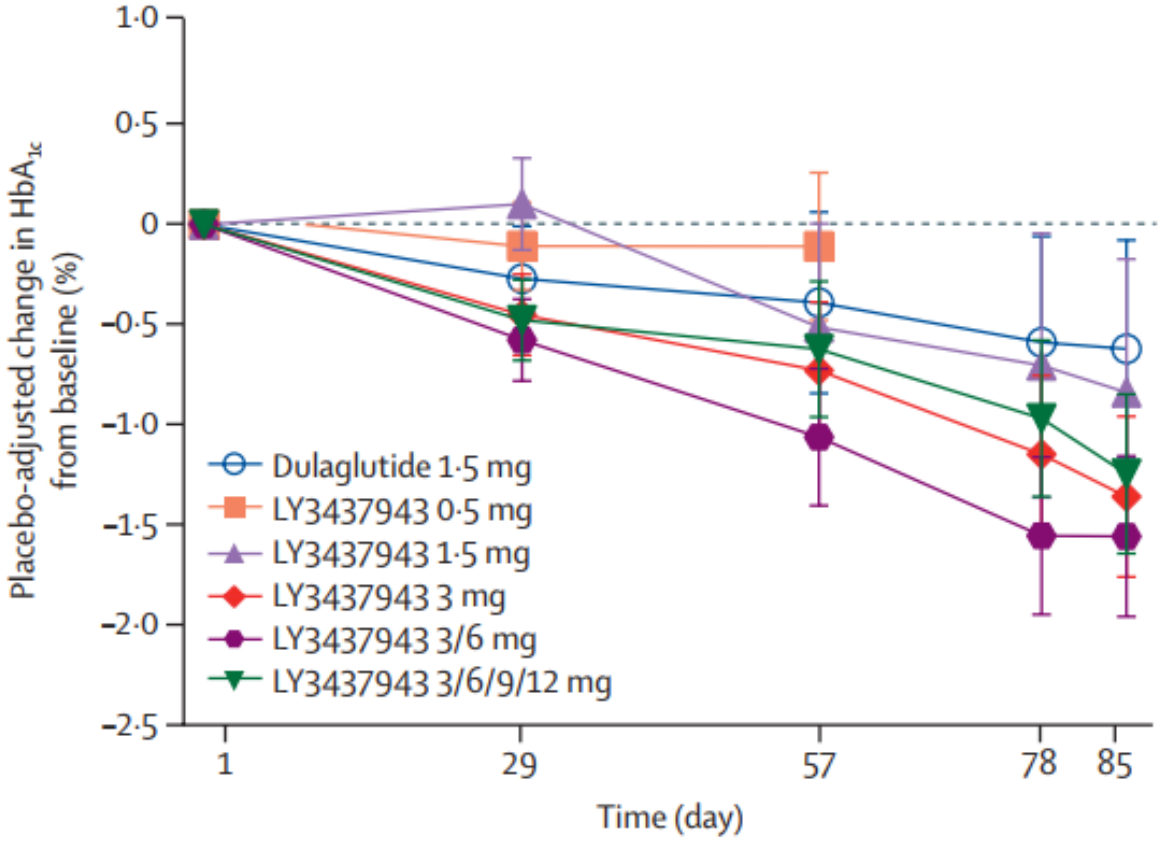
Coskun T., et al., Cell Metabolism, 2022

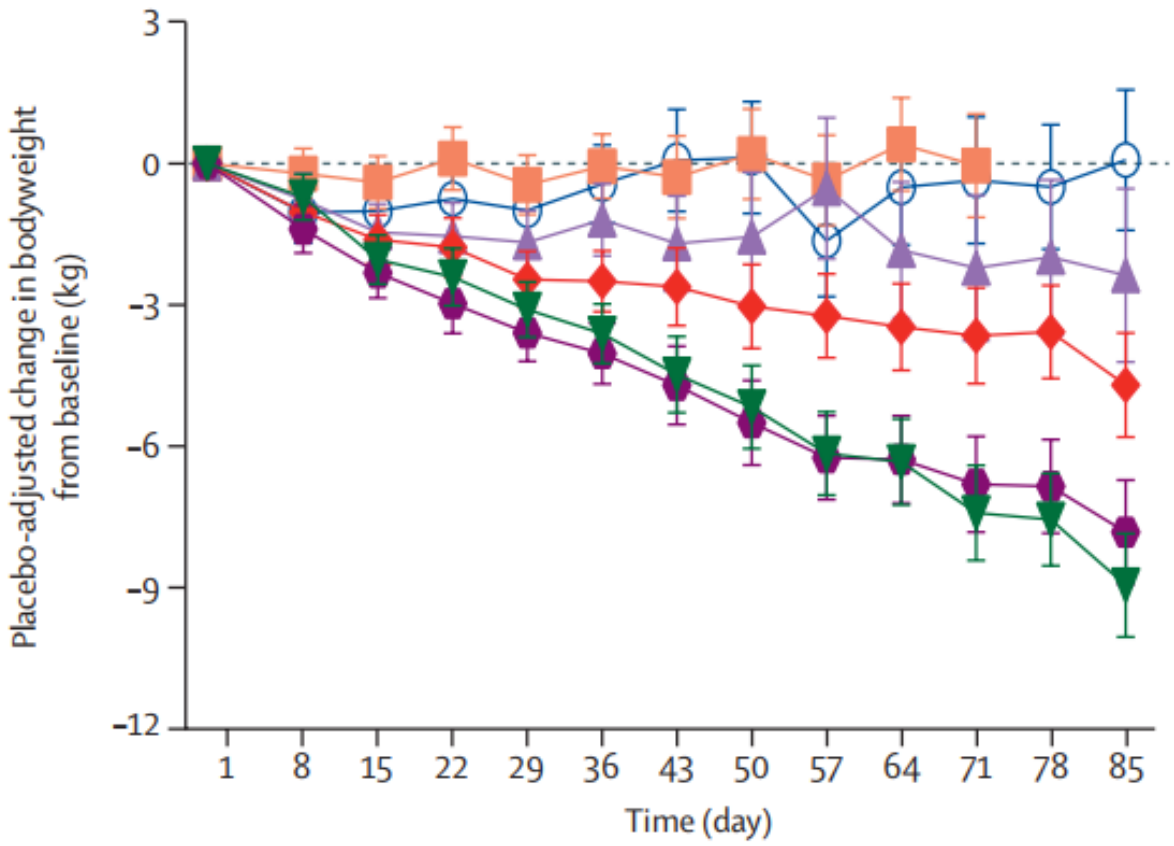
LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes

	Placebo (n=15)	Dulaglutide 1·5 mg (n=5)	LY3437943 0·5 mg (n=9)	LY3437943 1·5 mg (n=9)	LY3437943 3 mg (n=11)	LY3437943 3/6 mg (n=11)	LY3437943 3/6/9/12 mg (n=12)	Total (n=72)
Age, years	58·8 (6·4)	59·8 (7·5)	59·2 (6·6)	56·8 (5·7)	56·8 (8·0)	55·8 (10·7)	61·5 (6·3)	58·4 (7·4)
Sex								
Male	3 (20%)	4 (80%)	4 (44%)	3 (33%)	6 (55%)	7 (64%)	8 (67%)	35 (49%)
Female	12 (80%)	1 (20%)	5 (56%)	6 (67%)	5 (46%)	4 (36%)	4 (33%)	37 (51%)
Ethnicity								
Not Hispanic or Latino	4 (27%)	0	2 (22%)	1 (11%)	4 (36%)	2 (18%)	1 (8%)	14 (19%)
Hispanic or Latino	11 (73%)	5 (100%)	7 (78%)	8 (89%)	7 (64%)	9 (82%)	11 (92%)	58 (81%)
Race								
Asian	0	0	0	0	0	1 (9%)	0	1 (1%)
Black or African American	2 (13%)	0	3 (33%)	1 (11%)	3 (27%)	1 (9%)	1 (8%)	11 (15%)
White	12 (80%)	5 (100%)	6 (67%)	8 (89%)	8 (73%)	9 (82%)	11 (92%)	59 (82%)
Weight, kg	84·1 (19·9)	84·9 (14·1)	86·6 (24·1)	82·5 (17·3)	84·5 (14·4)	92·4 (15·2)	84·7 (14·7)	85·7 (17·1)
BMI, kg/m²	32·3 (6·2)	30·1 (2·0)	33·3 (6·3)	32·4 (6·1)	31·7 (5·1)	33·7 (3·9)	30·5 (3·6)	32·1 (5·1)
Waist circumference, cm	105·8 (17·6)	103·9 (6·5)	108·1 (13·4)	104·1 (12·3)	106·4 (8·9)	109·2 (10·4)	103·7 (10·7)	106·0 (12·2)
Duration of diabetes, years	9·2 (6·0)	14·2 (4·5)	10·7 (5·2)	9·0 (5·8)	10·2 (4·6)	12·9 (7·7)	10·0 (5·4)	10·6 (5·8)
HbA_{1c}, %	8·83 (1·06)	8·50 (0·86)	8·07 (0·74)	8·87 (0·79)	8·65 (0·98)	9·05 (0·81)	8·45 (0·92)	8·66 (0·92)

Urva S. et al., Lancet , 2022

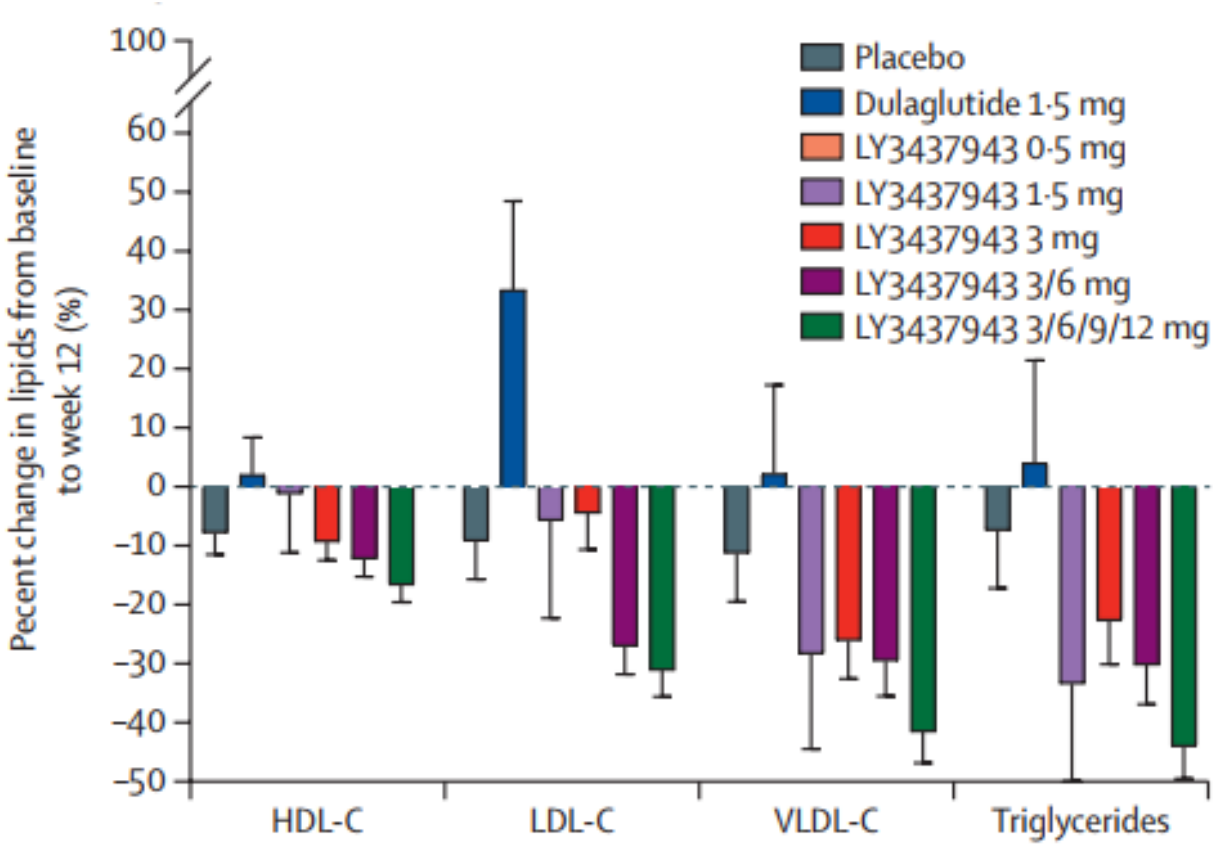
LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes

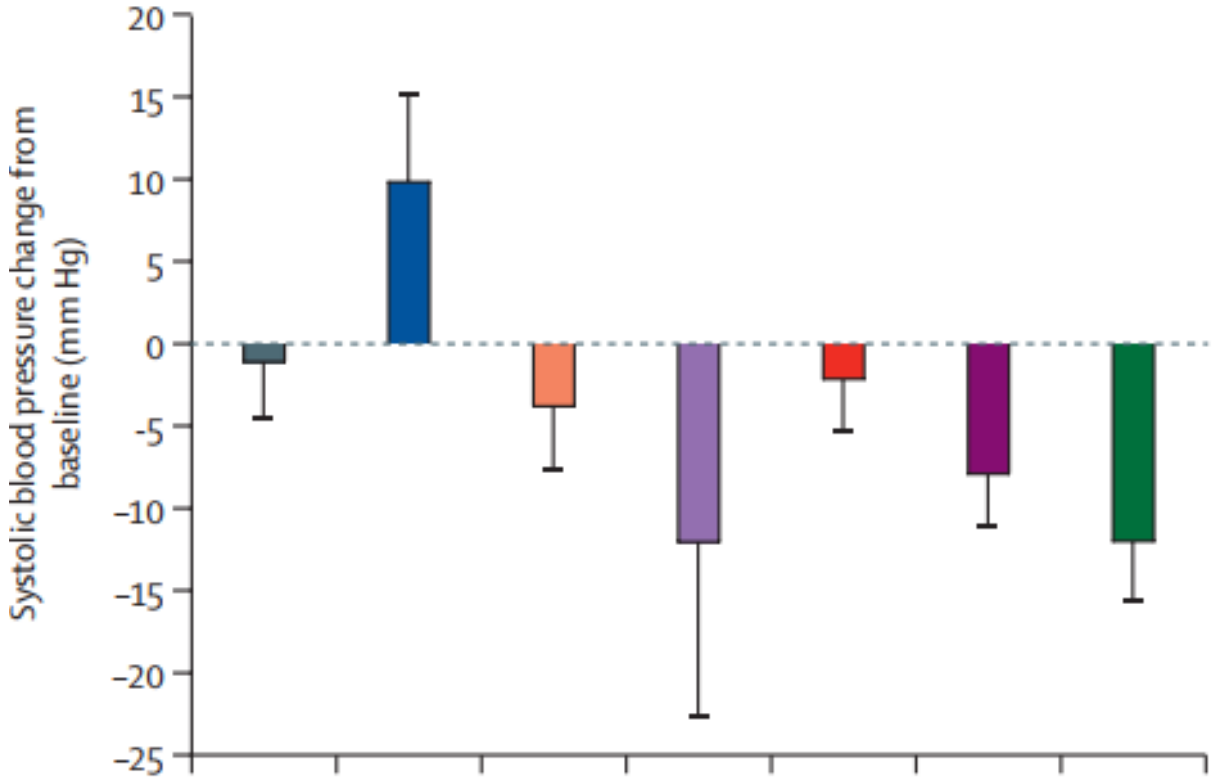




Urva S. et al., Lancet , 2022

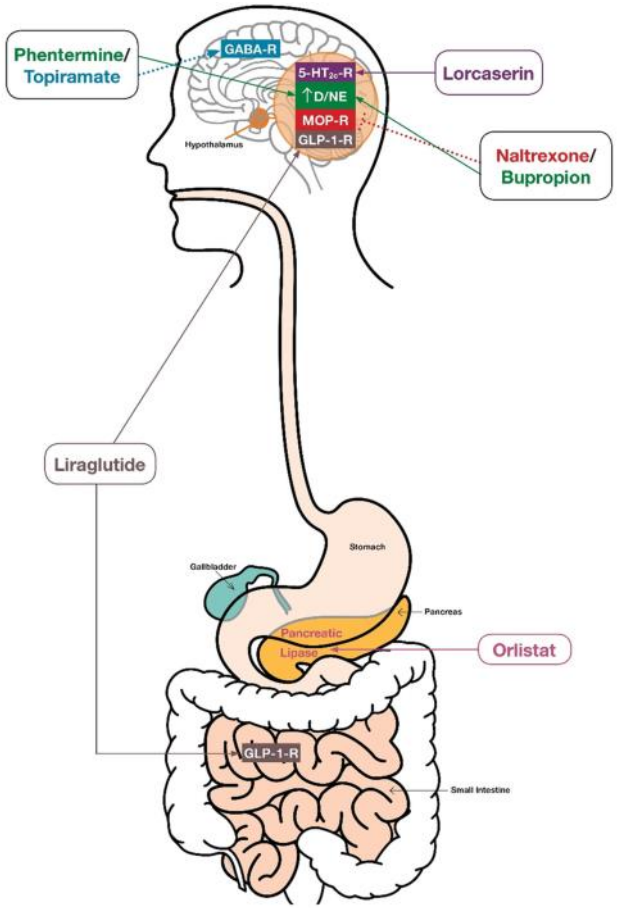
LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes





Urva S. et al., Lancet , 2022

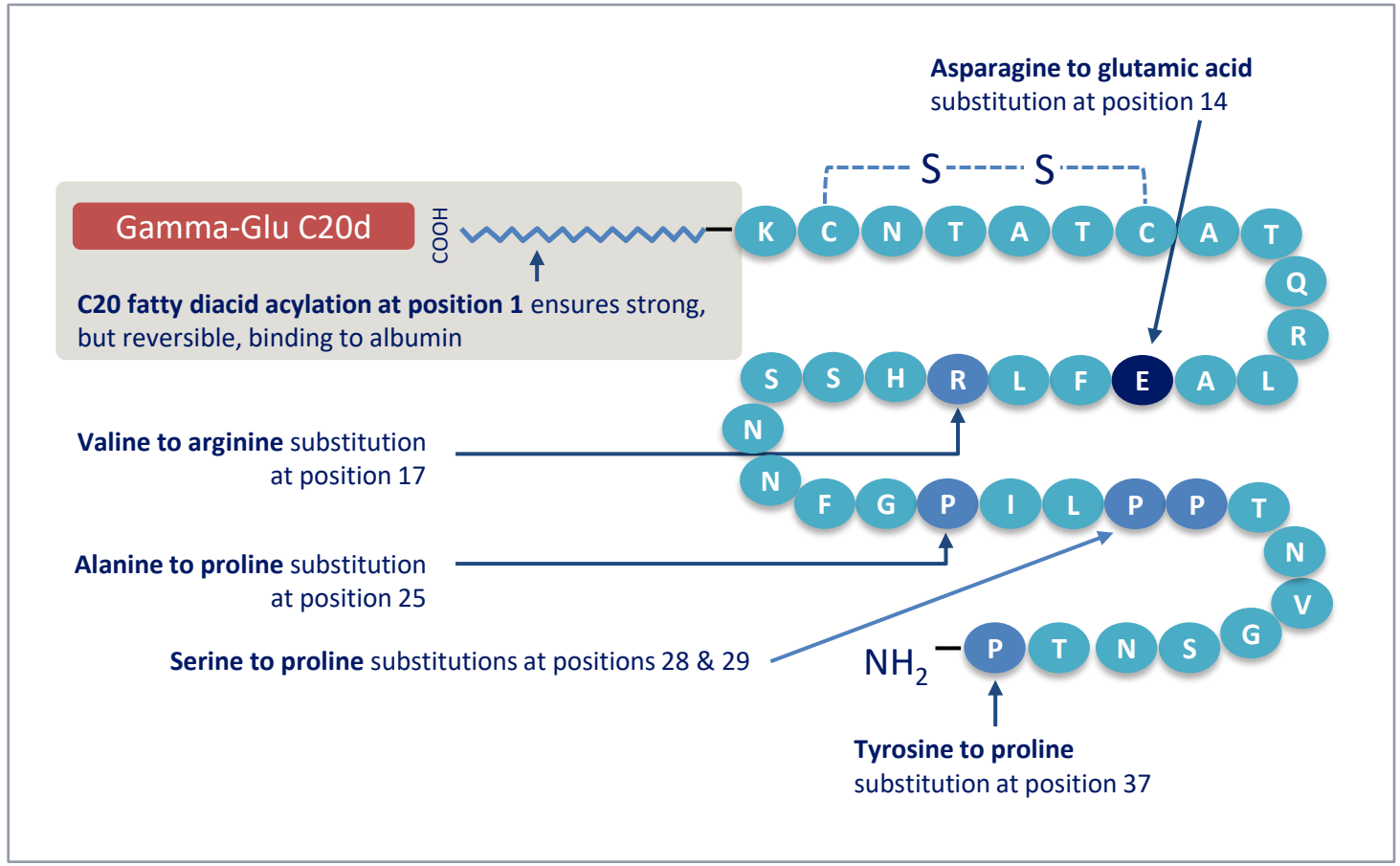
Anti-obesity drugs approved by the US FDA and/or EMA



- Orlistat
- Lorcaserin
- Phentermine + Topiramate
- Naltrexone + Buproprione
- Liraglutide 3.0 mg
- Semaglutide
- Tirzepatide
- Cotadutide
- LY3437943
- Cagrilintide

Cagrilintide is a human long acting amylin analogue

- 84% homology to native human amylin
- The purpose of the amino acid substitutions and acylation were primarily to remove the fibrillating properties of human amylin and ensure stability
- t½ of approximately 180 hours

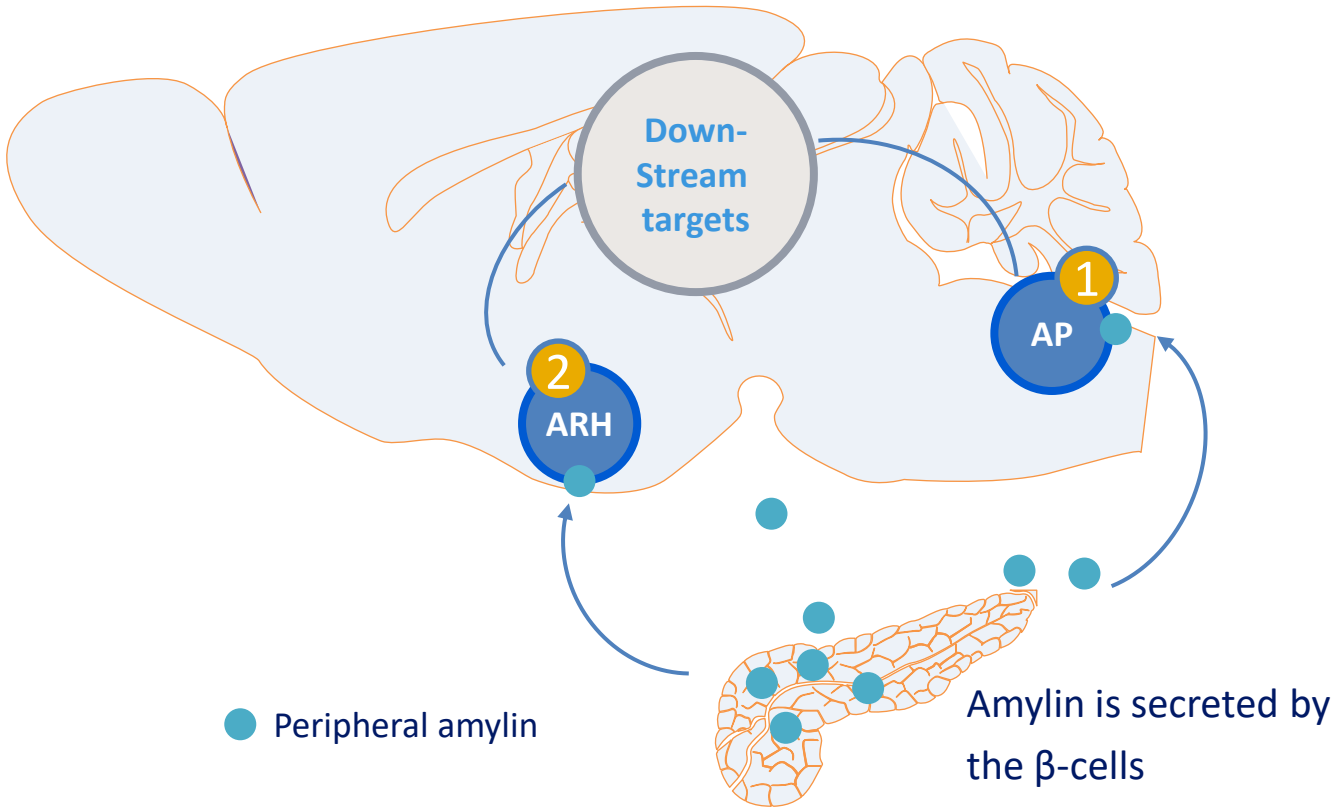


Glu, glutamic acid

1. Kruse et al. Journal of Medicinal Chemistry 2021; 64(15): 11183-11194

Peripheral amylin engages key regions in the brain

- Current evidence indicates that peripheral amylin directly targets neurons in the **area postrema** (AP) and **arcuate nucleus** (ARH)[1,2]
- Several other brain regions are activated by peripheral amylin. These are associated with **hedonic and homeostatic appetite** regulation and are likely downstream signals emerging from the AP and ARH[3]
- AMY1/3 receptor activation in the brain appears to be important for the amylin effects[3]

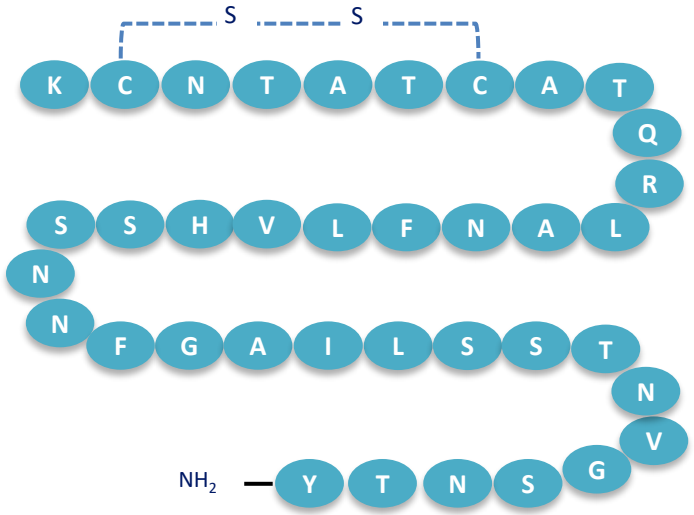


ARH, arcuate nucleus; AP, area postrema; AMY, Amylin

1:Boccia et al. Peptides 2020; 132: 170366; 2: Zakariassen et al. Basic & Clinical Pharmacology & Toxicology 2020; 127(3): 163-177; 3: Skovbjerg et al. Eur J Neurosci 2021; doi:10.1111/ejn.15254

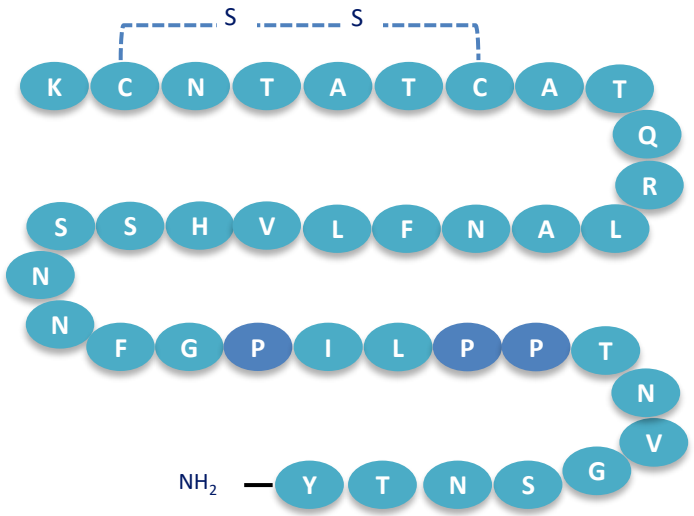
Distinct structural and pharmacokinetic properties

Human amylin, pramlintide and cagrilintide



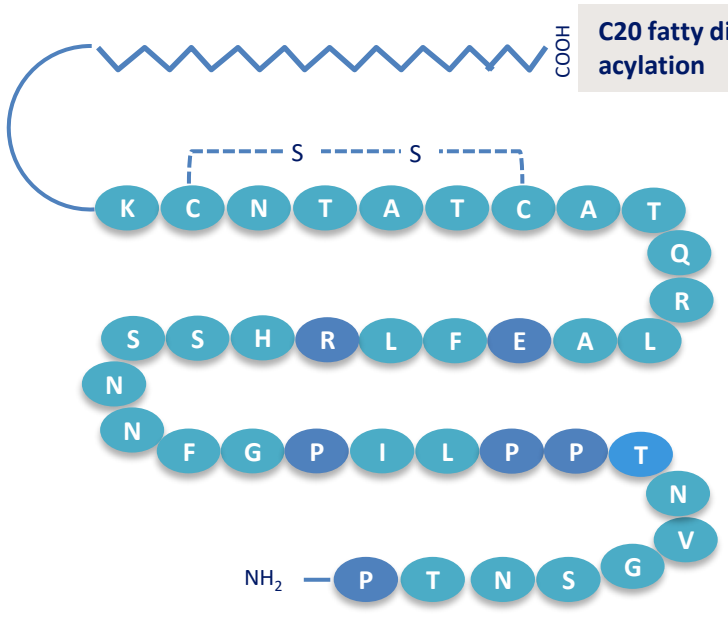
$t_{½}$ 15-20 mins in humans

Human Amylin[1]



$t_{½}$ ~50 mins in humans

Pramlintide[2]



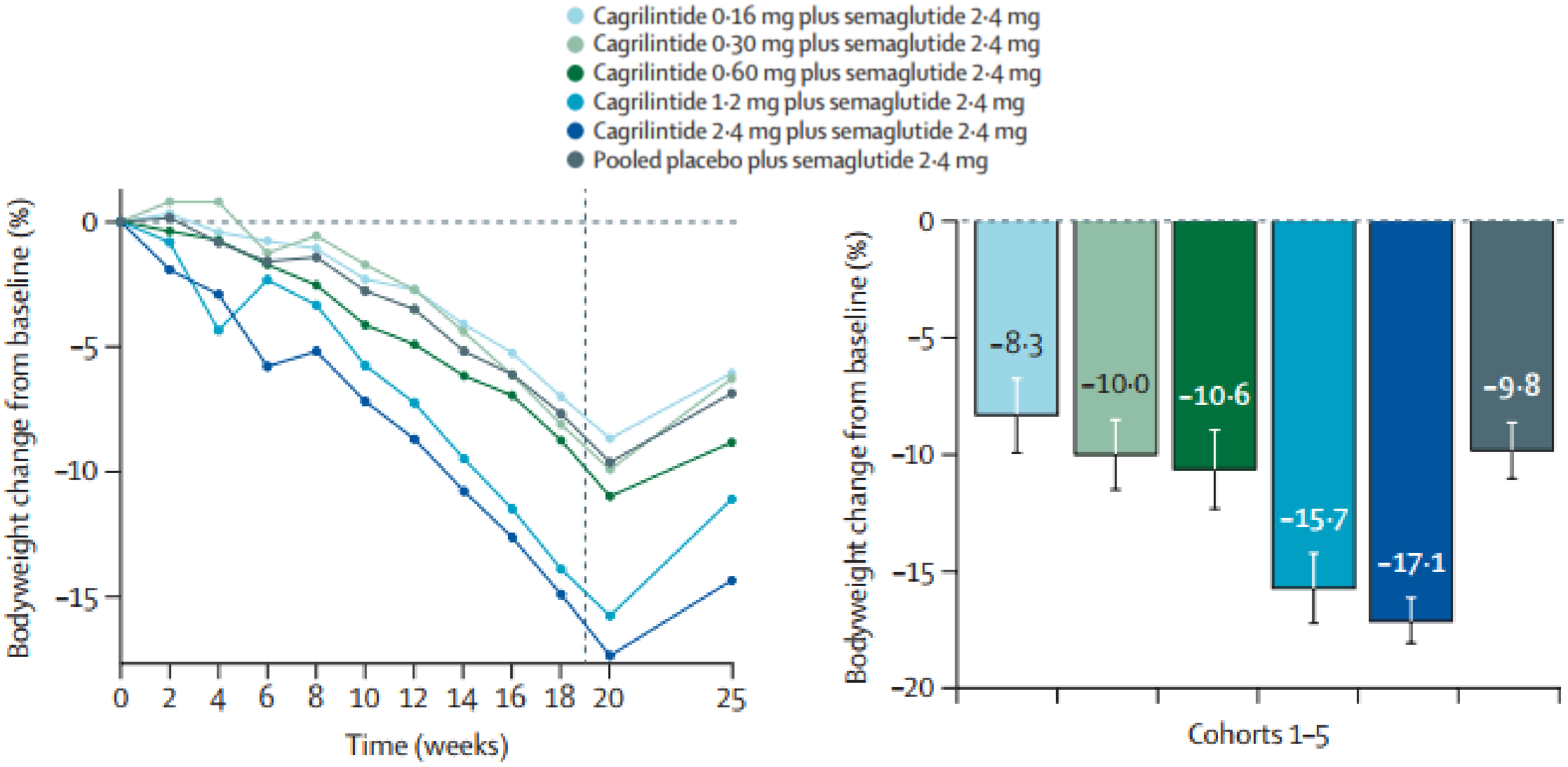
$t_{½}$ ~180 hours in humans

Cagrilintide[3]

Pramlintide is the only approved amylin analogue, for treatment of type 1 and type 2 diabetes)

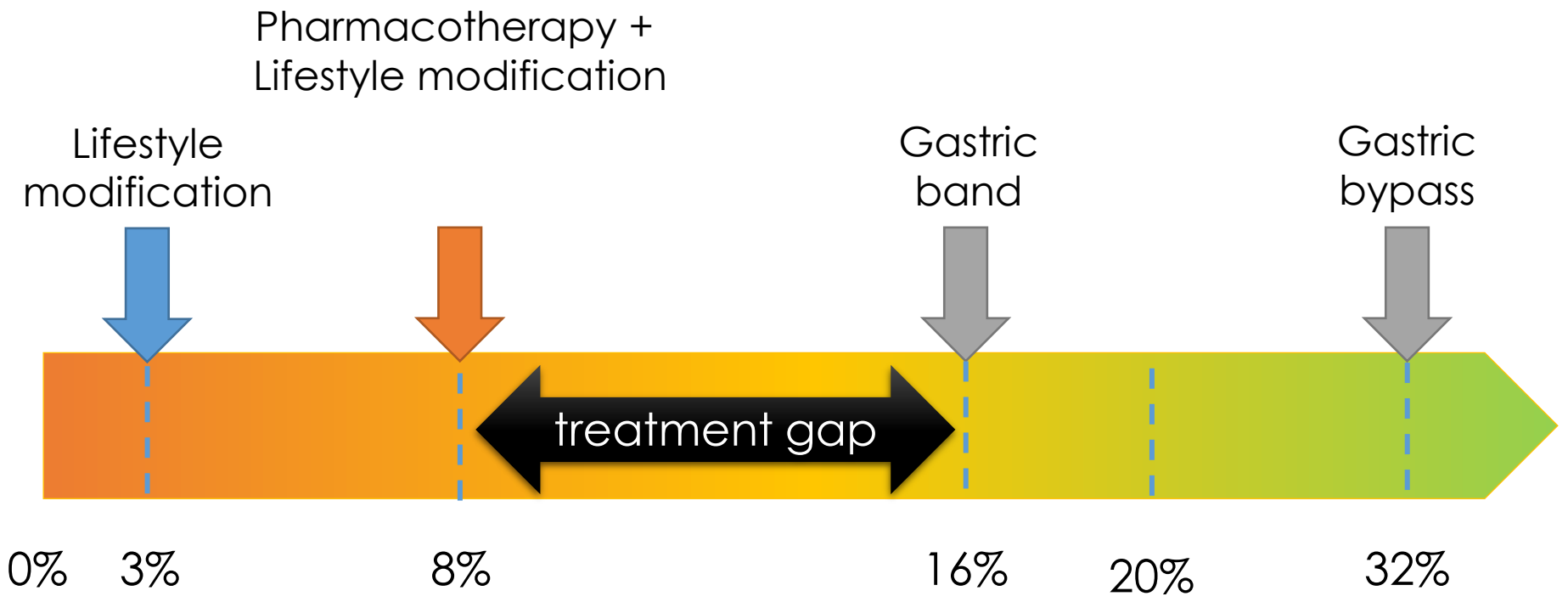
1. Bower et al. Br J Pharmacol 2016; 173(12): 1883-1898;

Safety, tolerability, pharmacokinetics, and pharmacodynamics of Cagrilintide with Semaglutide for weight management



Enebo LB et al., Lancet 2021

Treatment options for people with obesity

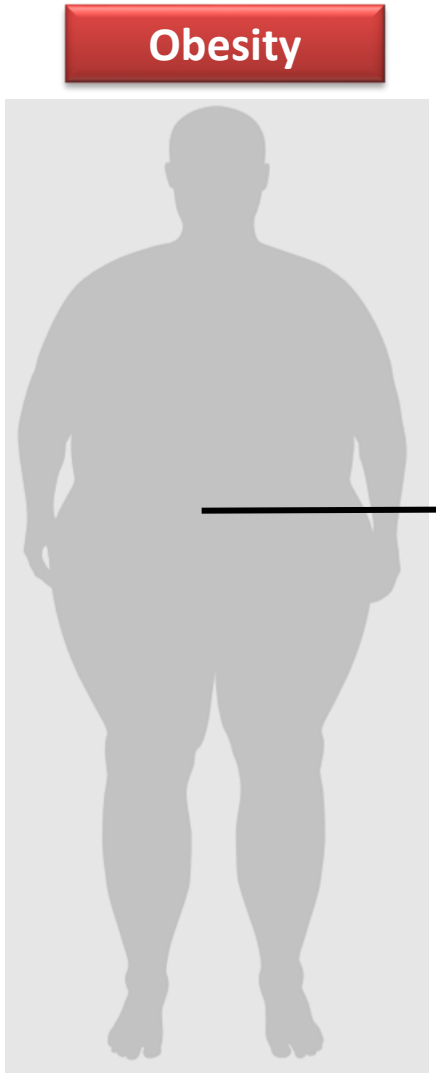


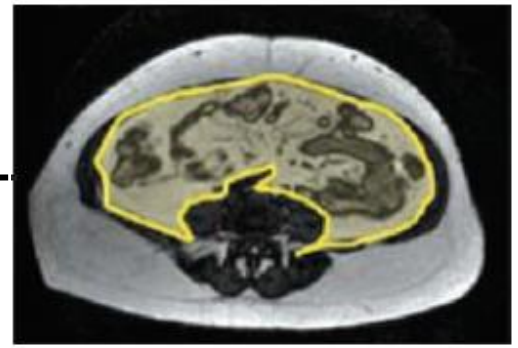
«A treatment gap existes for those patients who do not repond sufficiently to behavioural and lifestyle interventions and who are not viable candidates for, or do not wish to undergo, bariatric surgery. Such patients need additional options for treatment. Used appropriately, effective prescription drugs could potentially help fill that gap»

N Gesundheit, Int J Obes Suppl. 2012 Jul; 2(Suppl 1): S39–S42

Take-home messages

Pharmacological management of obesity-related comorbidities





BMI 31 Kg/m^2
High visceral fat volume 3.9L
High liver fat content
Low amount of leg fat
Higher markers of inflammation
Adipose tissue dysfunction

- Type 2 diabetes
- Dyslipidemia
  NAFLD
- Hypogonadism
- Hypertension
  CVD
- OSAS/OHS

GLP-1RAs ↓ weight

Dual or Triple Agonists ↓ weight
- GIP/GLP-1RAs
- GLP-1/GIP/GlucagonRAs

Blüher M. Endocr Rev. 2020; Frias JP et al., Diabetes Care, 2021; Davies M et al., Lancet 2021, Nahra R et al., Diabetes Care, 2021; Ludvik B., et al., Lancet, 2021; Goldber RB et al., Diabetes Care, 2020; Ballantyne CM et al. *Eur J Prev Cardiol*. 2020; Rader D et al., JCEM, 2021;