What is the role of medication in patients with bariatric surgery?

Carel le Roux

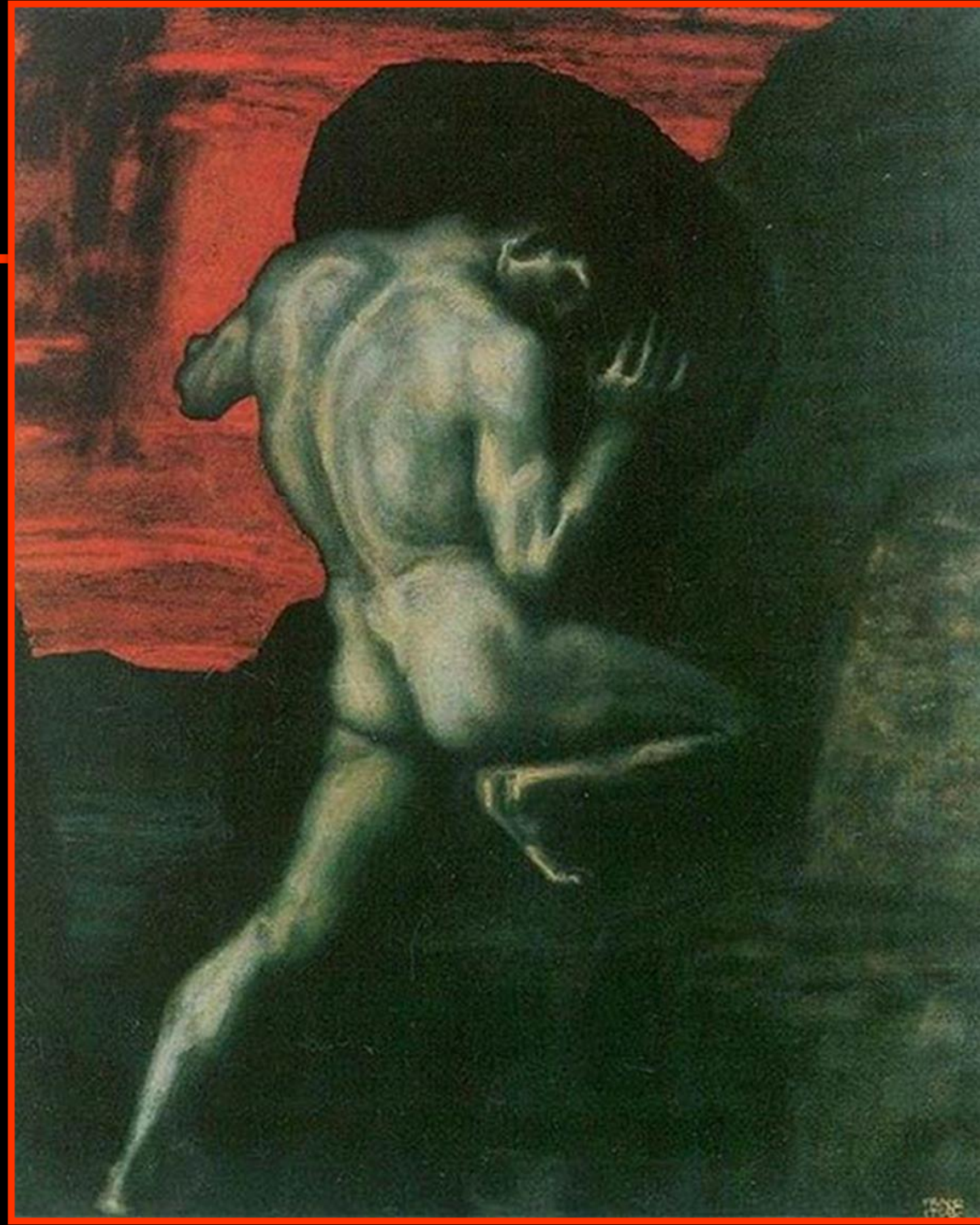
University College Dublin
Ulster University
University of Pretoria

The Bathers, 1919,
Pierre-Auguste Renoir.
Musée d'Orsay, France.

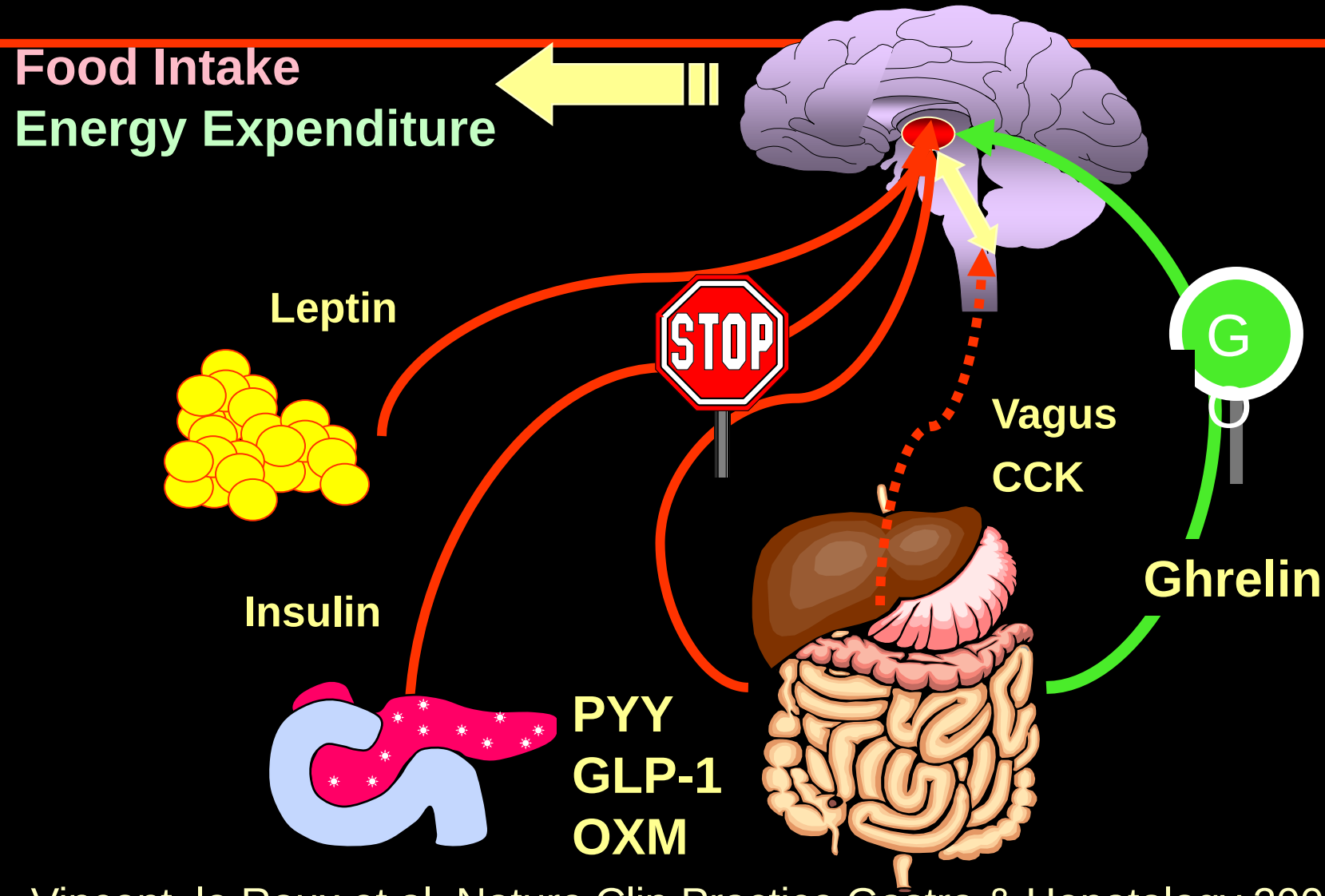
Conflicts of interest

- Consilient Health
- Novo Nordisk
- Herbalife
- Johnson & Johnson
- Covidien
- Fractyl
- GI Dynamics
- Lilly
- Boehringer Ingelheim
- Keyron

My presentation reflects only my point of view, not Lilly's.

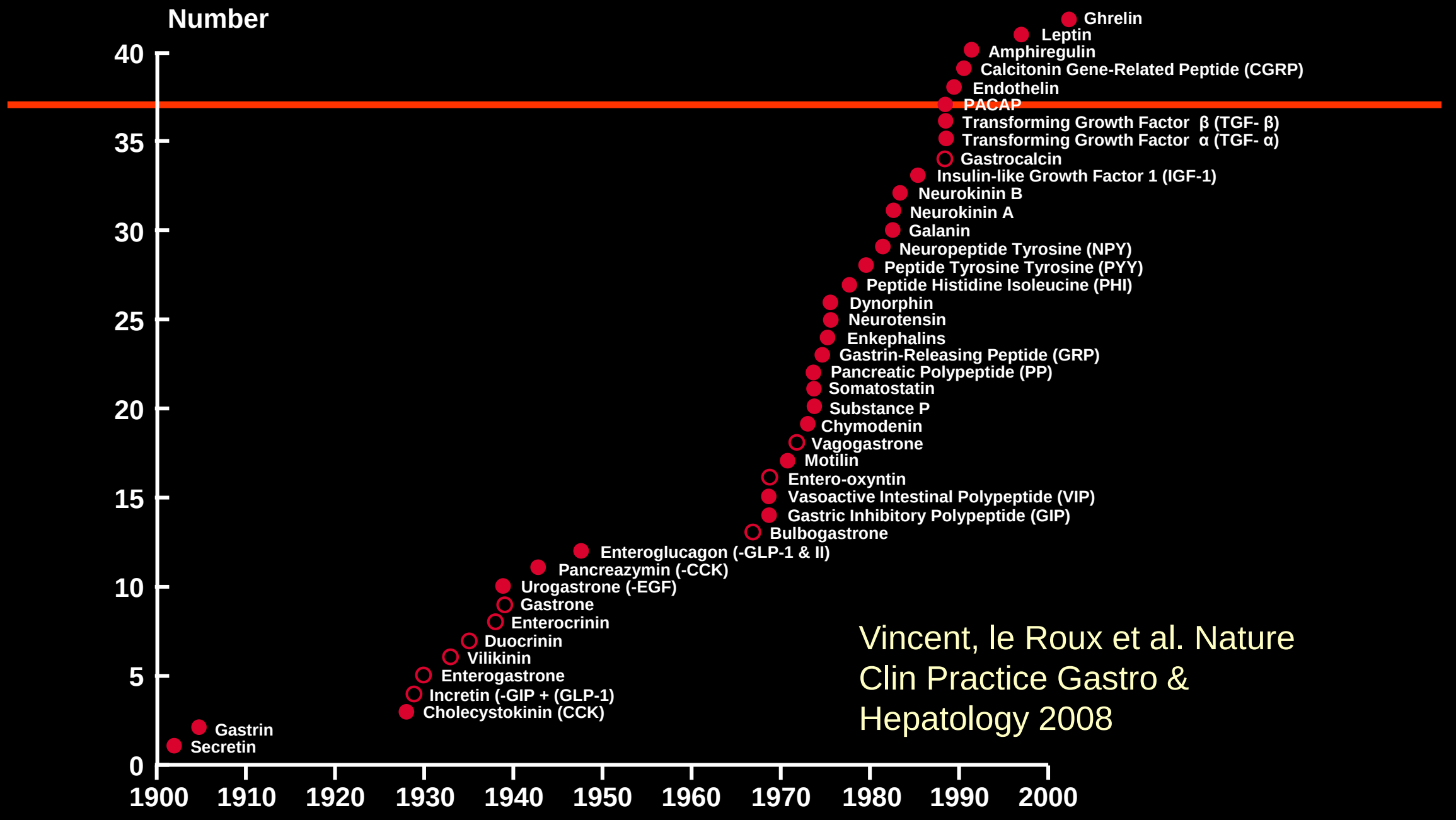


Afferent factors in appetite regulation



Vincent, le Roux et al. Nature Clin Practice Gastro & Hepatology 2008

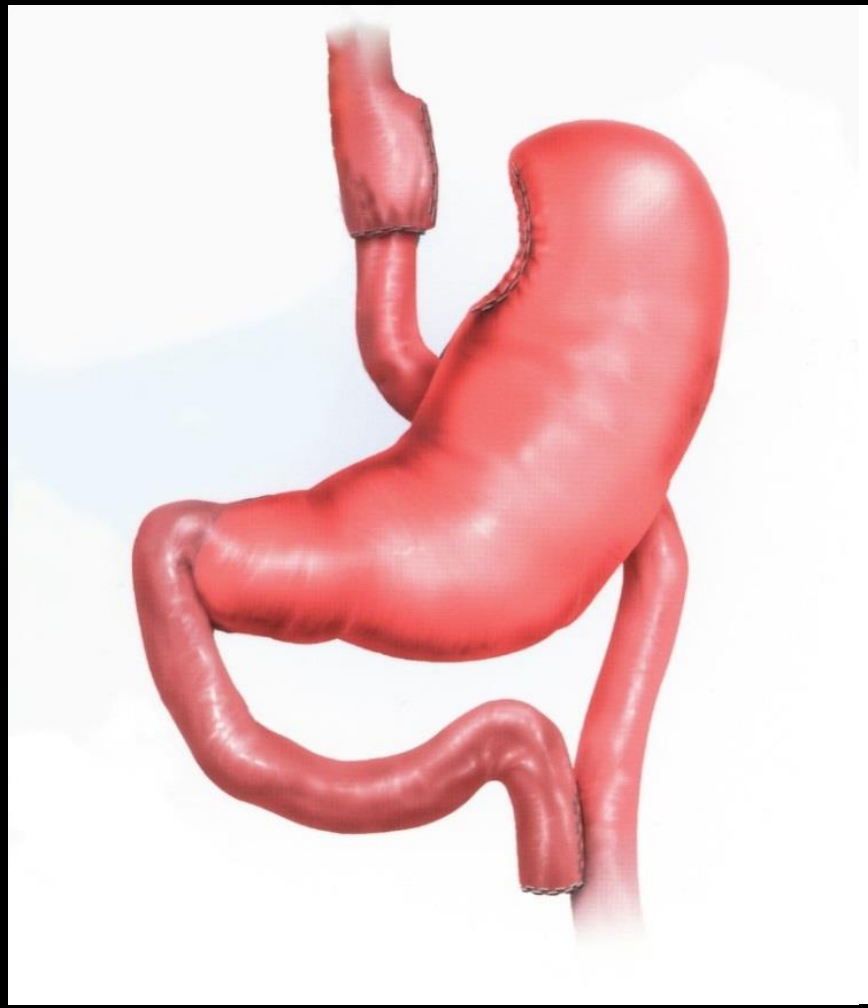
Discovery of gastrointestinal hormones



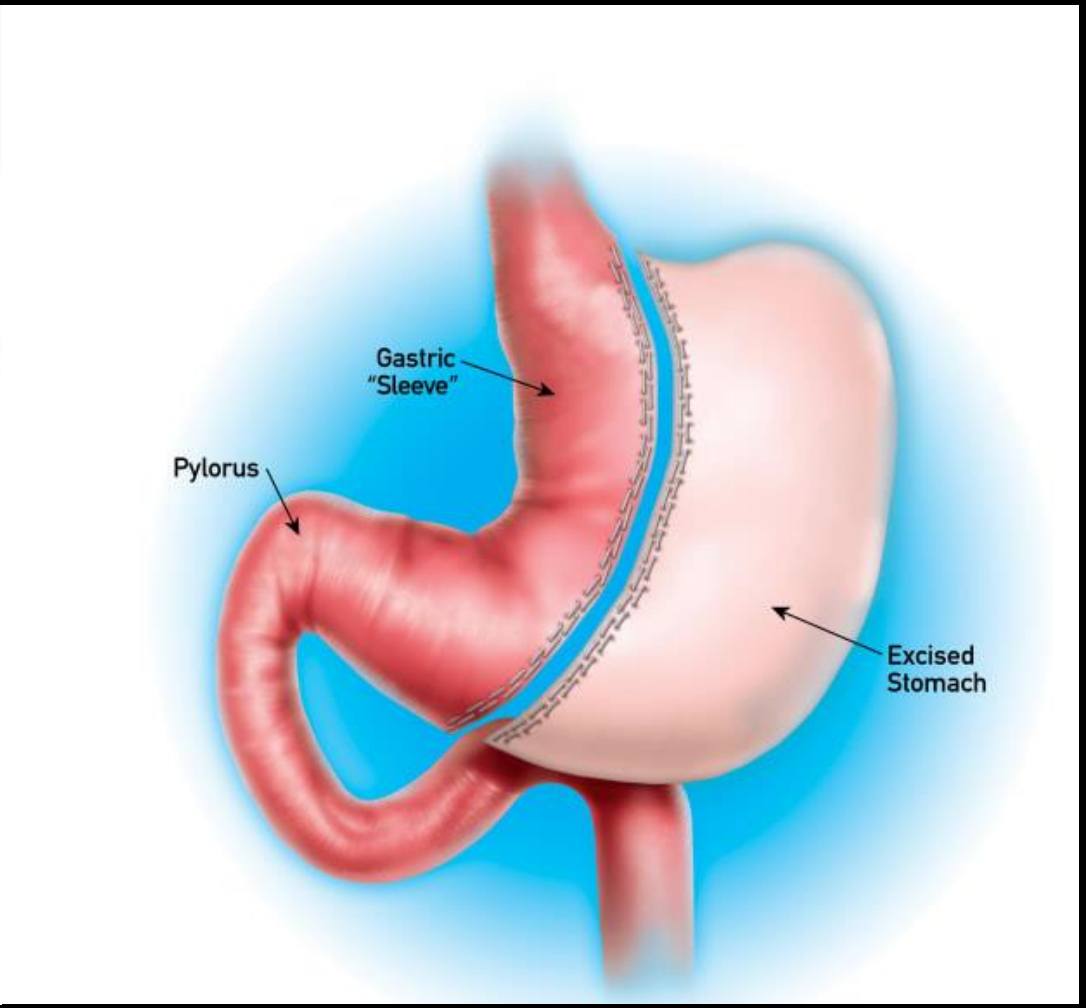
Vincent, le Roux et al. Nature Clin Practice Gastro & Hepatology 2008

Surgical principles

Tadross, le Roux et al. Int J Obes 2009

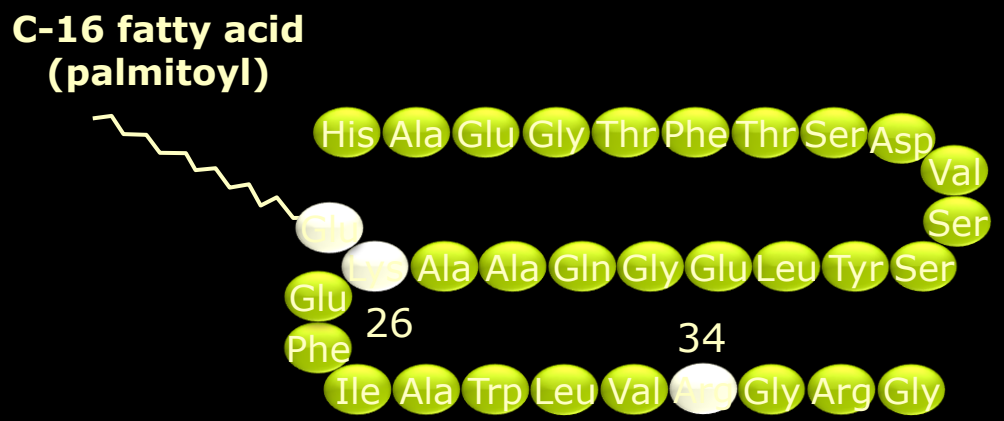


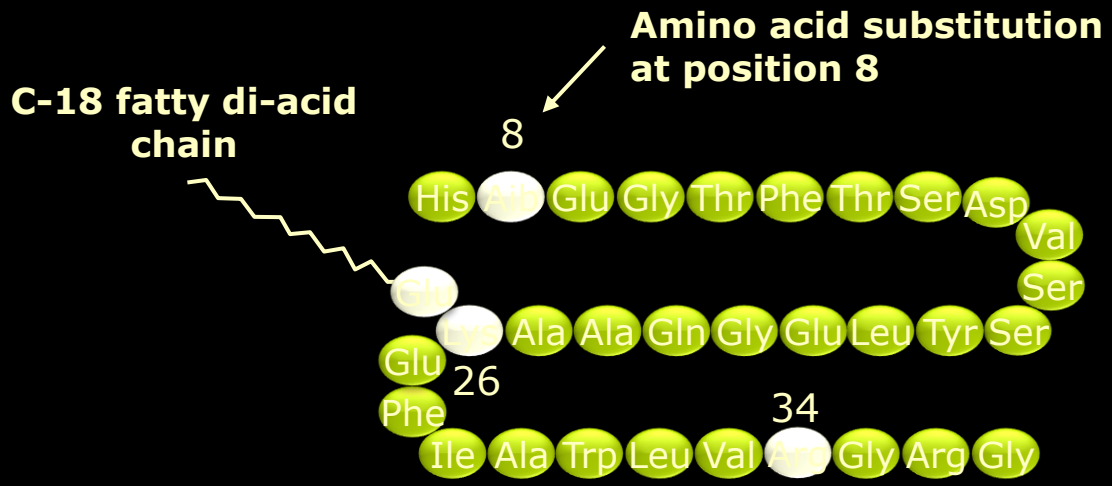
Bypass



Sleeve

Liraglutide and semaglutide





Liraglutide

- 97% amino acid homology to native GLP-1[1,2]
- $t_{½}$ 12 hours, allowing once-daily dosing[2]

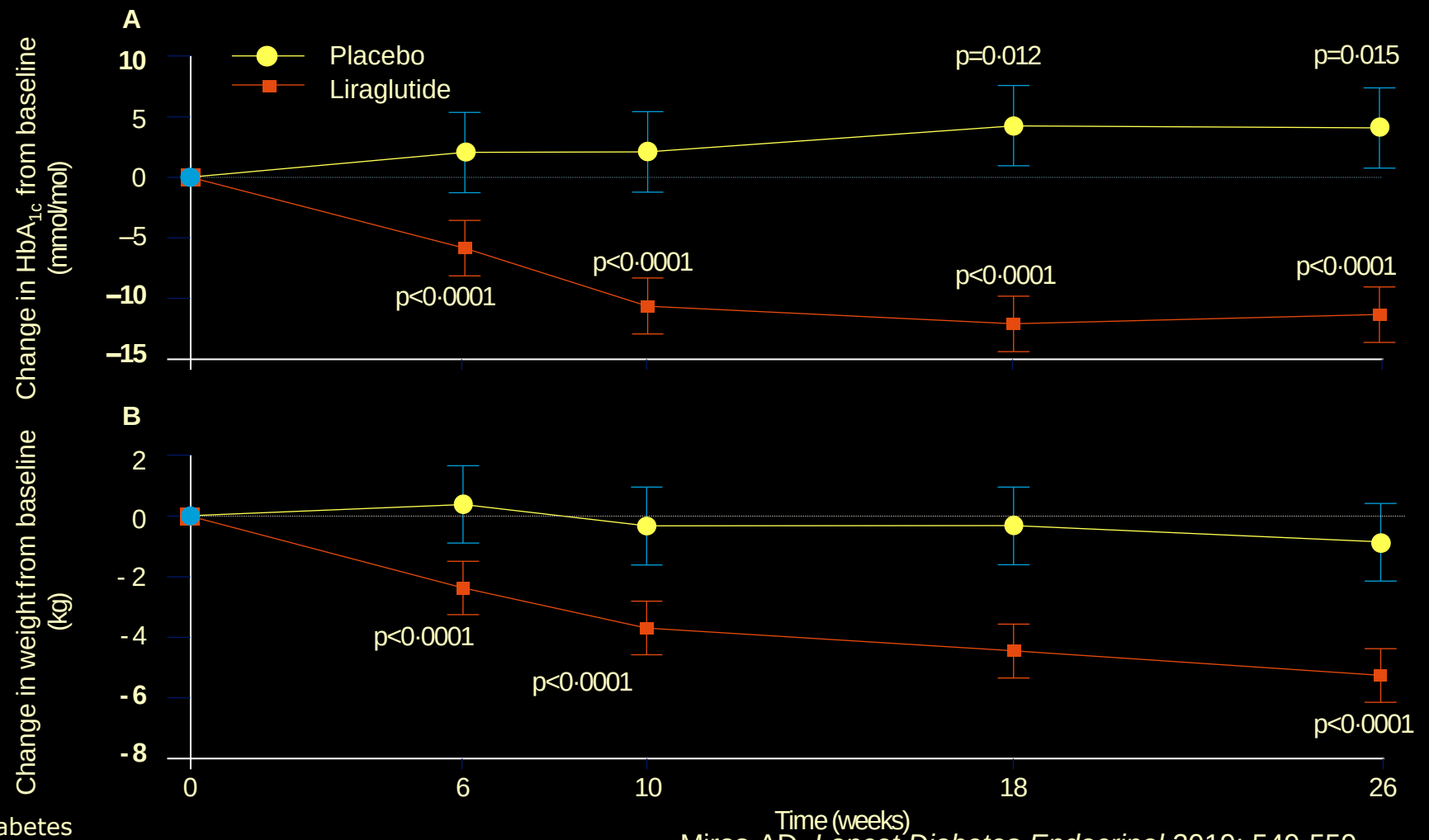
Semaglutide

- 94% amino acid homology to native GLP-1[3]
- $t_{½}$ ~1 week, allowing once-weekly dosing[4,5]

GLP-1, glucagon-like peptide-1; $t_{½}$, plasma half-life.

1. Knudsen *et al. J Med Chem* 2000;43:1664–9; 2. Degn *et al. Diabetes* 2004;53:1187–94; 3. Lau *et al. J Med Chem* 2015;58:7370–80;
4. Kapitza *et al. J Clin Pharmacol* 2015;55:497–504; 5. Marbury *et al. Diabetologia* 2014;57(Suppl. 1):S358

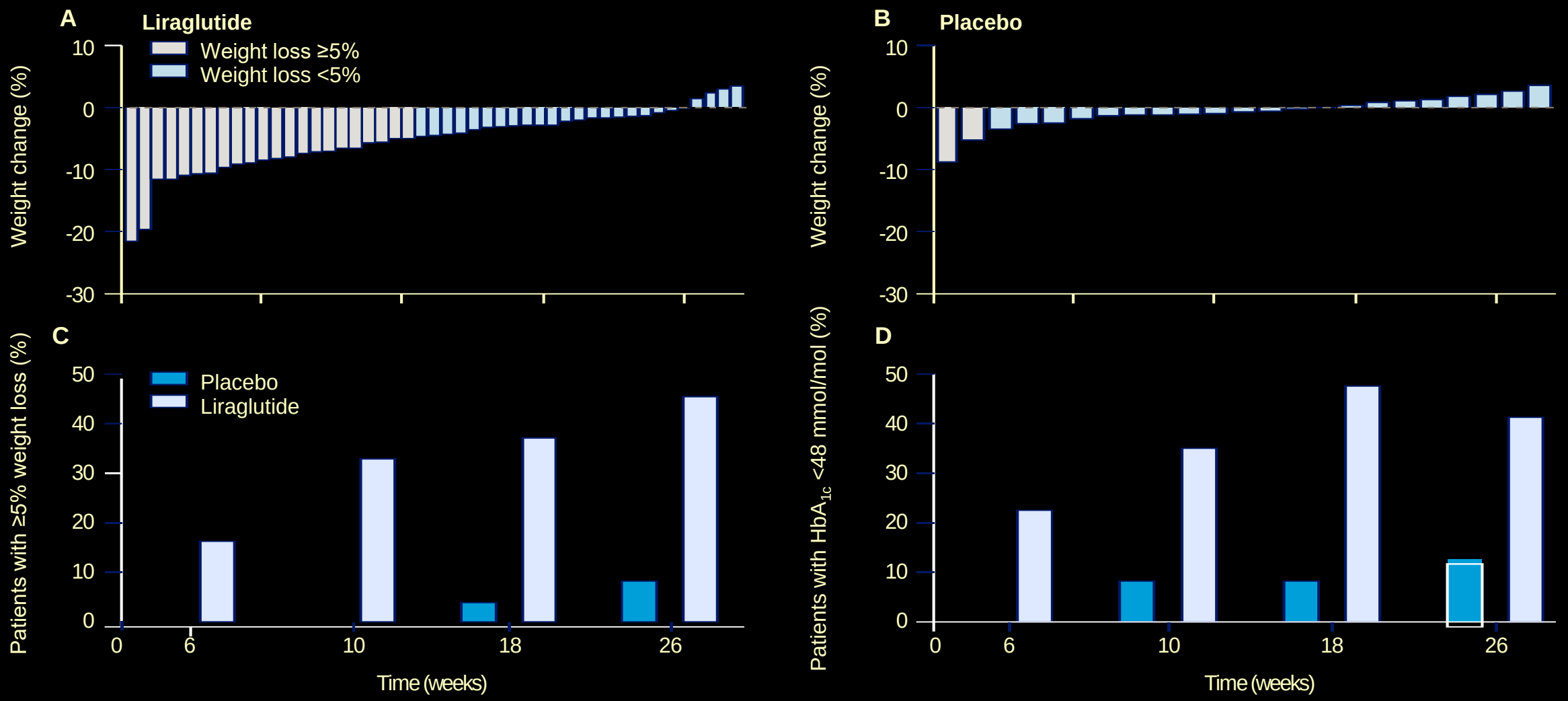
Adjunctive liraglutide treatment in patients with persistent or recurrent T2D after metabolic surgery



T2D, type 2 diabetes

Miras AD, *Lancet Diabetes Endocrinol* 2019; 549-559

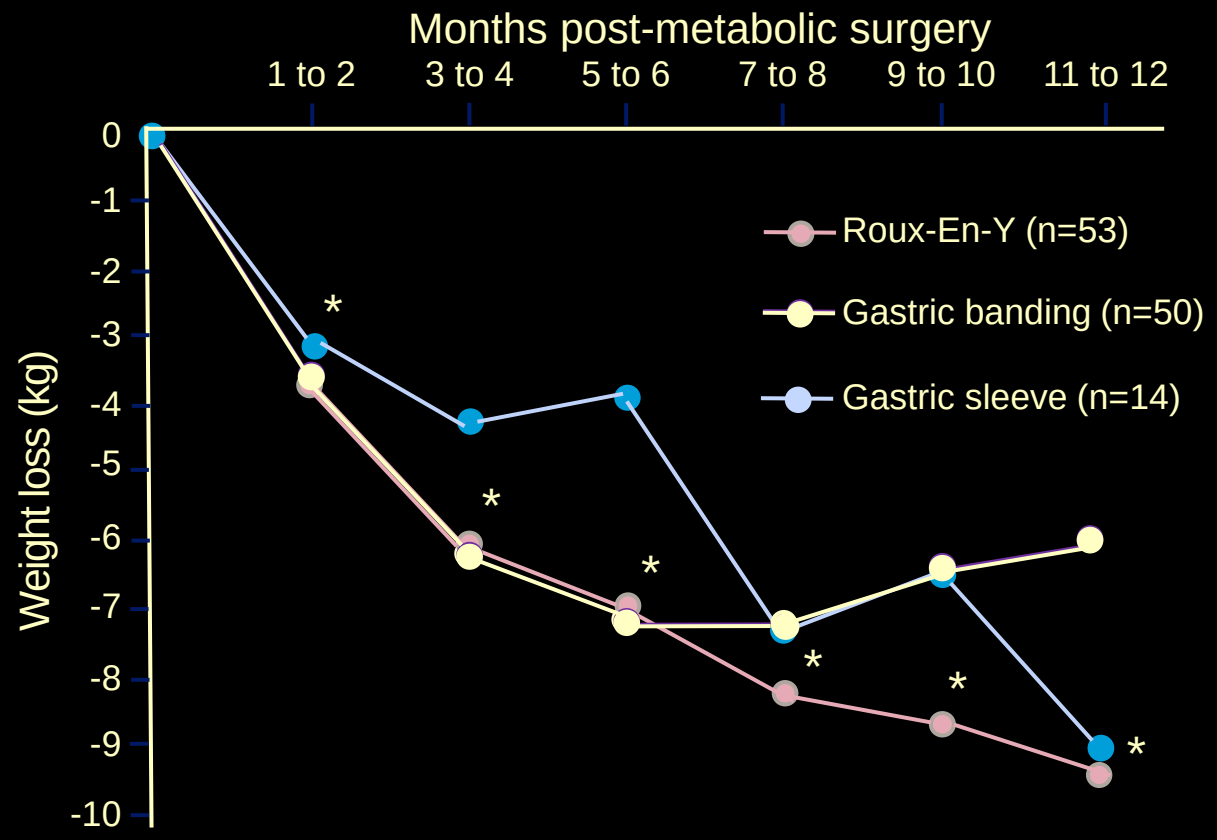
Weight loss and glycaemic improvement responses in participants who completed the trial



Miras AD, *Lancet Diabetes Endocrinol* 2019; 549-559

Liraglutide in combination with metabolic surgery

Weight loss post-surgery with liraglutide 3.0 mg by type of metabolic surgery (n=117)



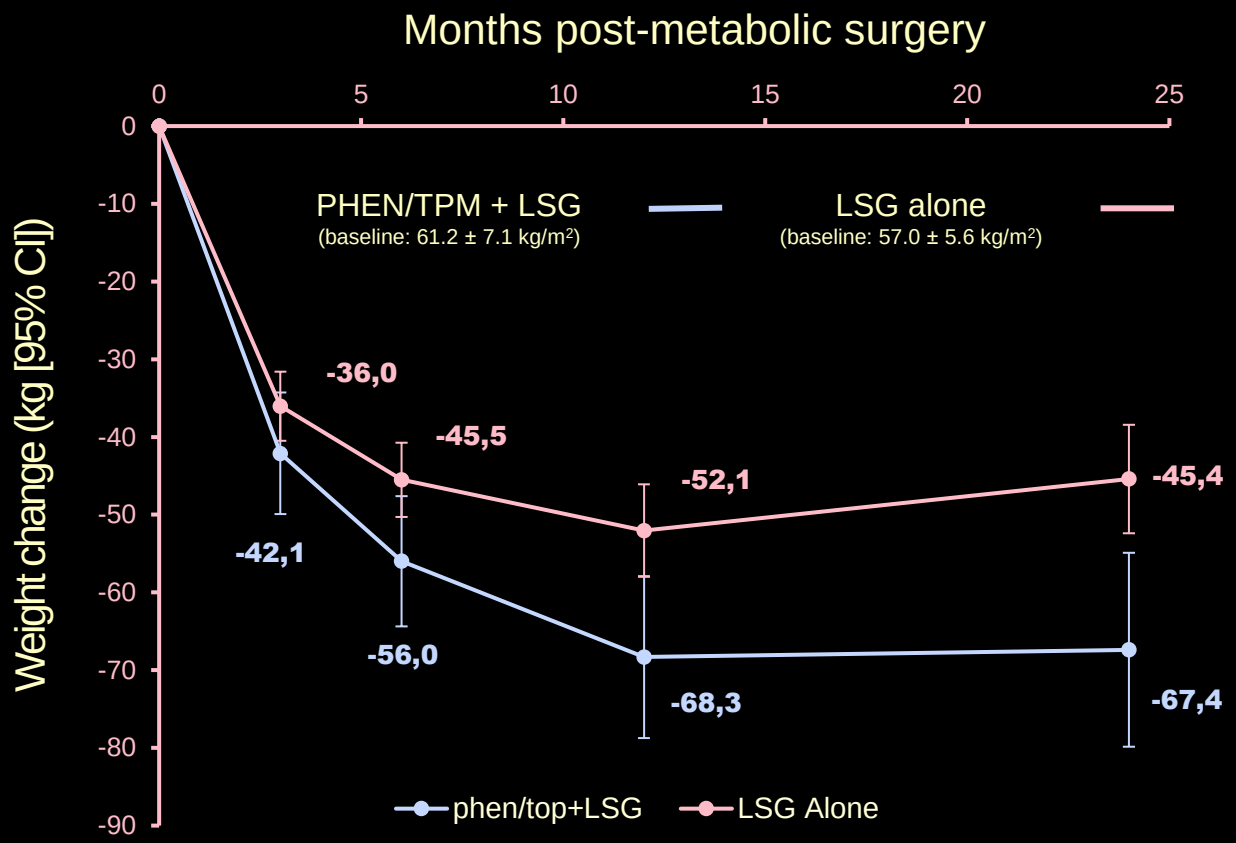
Mean BMI (SD) pre-liraglutide	Mean weight loss (SD) after 7.6 (± 7.1) months of liraglutide
42.5 (± 9.6) kg/m^2	5.5 (± 6.2) %

*Significantly different from baseline regardless of surgical group (p<0.05). SD, standard deviation

1. Wharton *et al. Clin Obes* 2019;9:e12323

PHEN/TPM + LSG in people with BMI ≥50 kg/m^2

Single-centre open-label study of 25 people with pre- and post-operative PHEN/TPM use



Visit (months)	Difference between LSG alone and LSG + PHEN/TPM % [95% CI]	*P*-value
3	–3.77 [–8.27, 0.72]	0.098
6	–5.54 [–10.52, –0.56]	0.030
12	–7.91 [–14.43, –1.39]	0.018
24	–11.16 [–19.07, –3.24]	0.007

Visit-specific estimates and comparisons are from a mixed model approach
CI, confidence interval; LSG, laparoscopic sleeve gastrectomy; PHEN/TPM, phentermine/topiramate

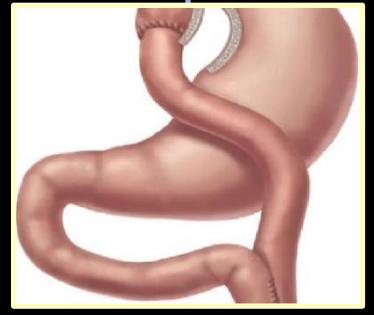
Ard *et al. Surg Obes Relat Dis* 2019;15:1039–43

Microvascular Outcomes after Metabolic Surgery

MOMS Trial Cohen et al EClinMed 2022

100 pts

n=49



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n=51

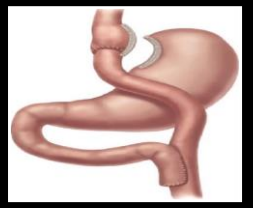
T2D, uACR>30 mg/g, BMI 30-35 kg/m^2, Early stage kidney disease

MOMS trial design

Cohen et al EClinMed 2022

Best Medical Treatment

- ✓ Metformin
- ✓ **GLP1 RA**
- ✓ **SGLT-2 i**
- ✓ **Insulin**
- ✓ Glitazones
- ✓ DPP4 i
- ✓ ACEi/ARB
- ✓ Statins
- ✓ Diuretics



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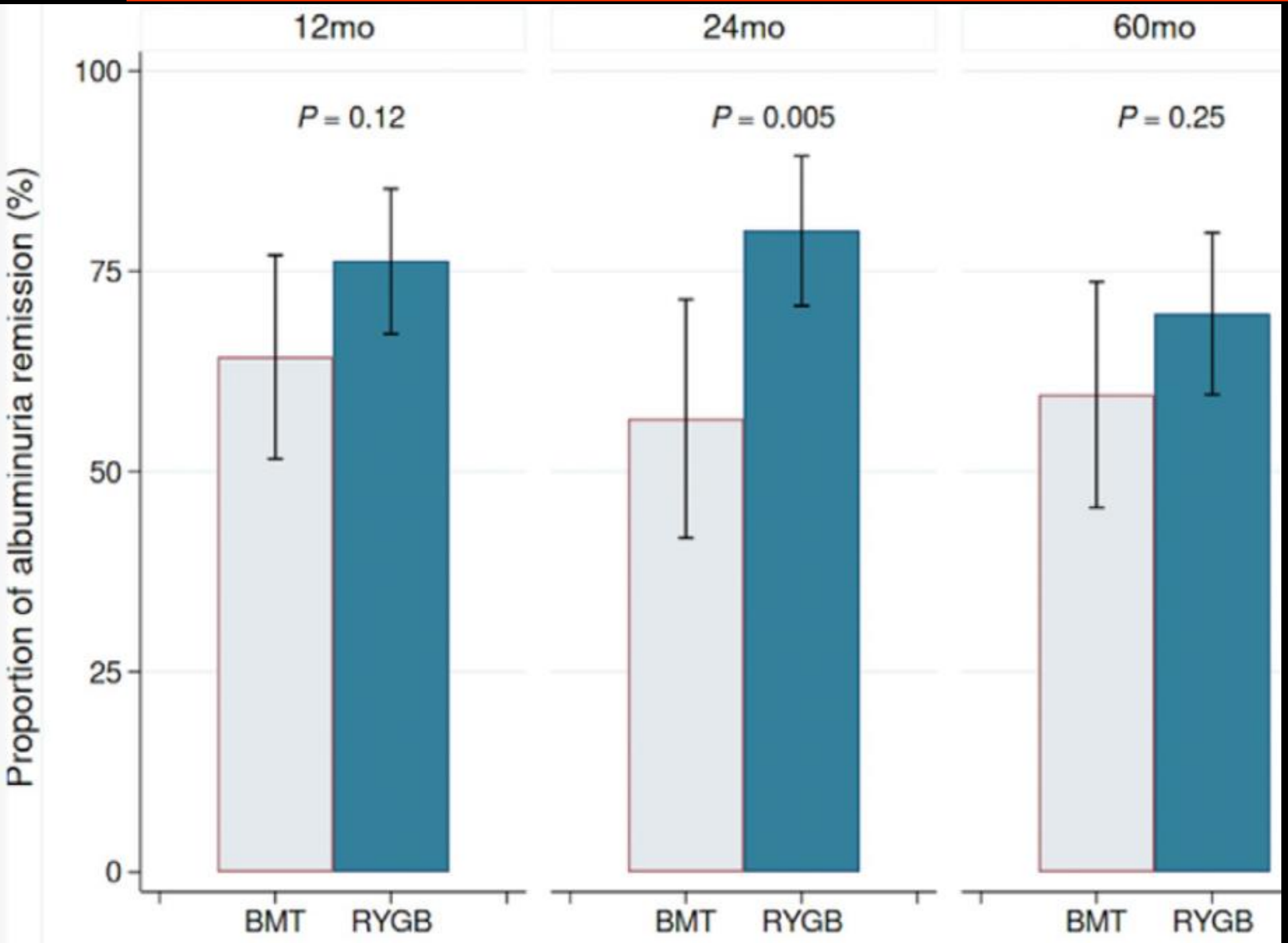
RYGB + BMT

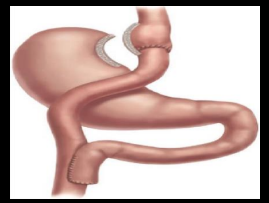
- ✓ACE/ARB
- ✓Statins
- ✓Metformin
- ✓Multivitamins

MOMS trial – 5 years outcomes

Dichotomous primary outcome uACR <30 mg/g



vs



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60%

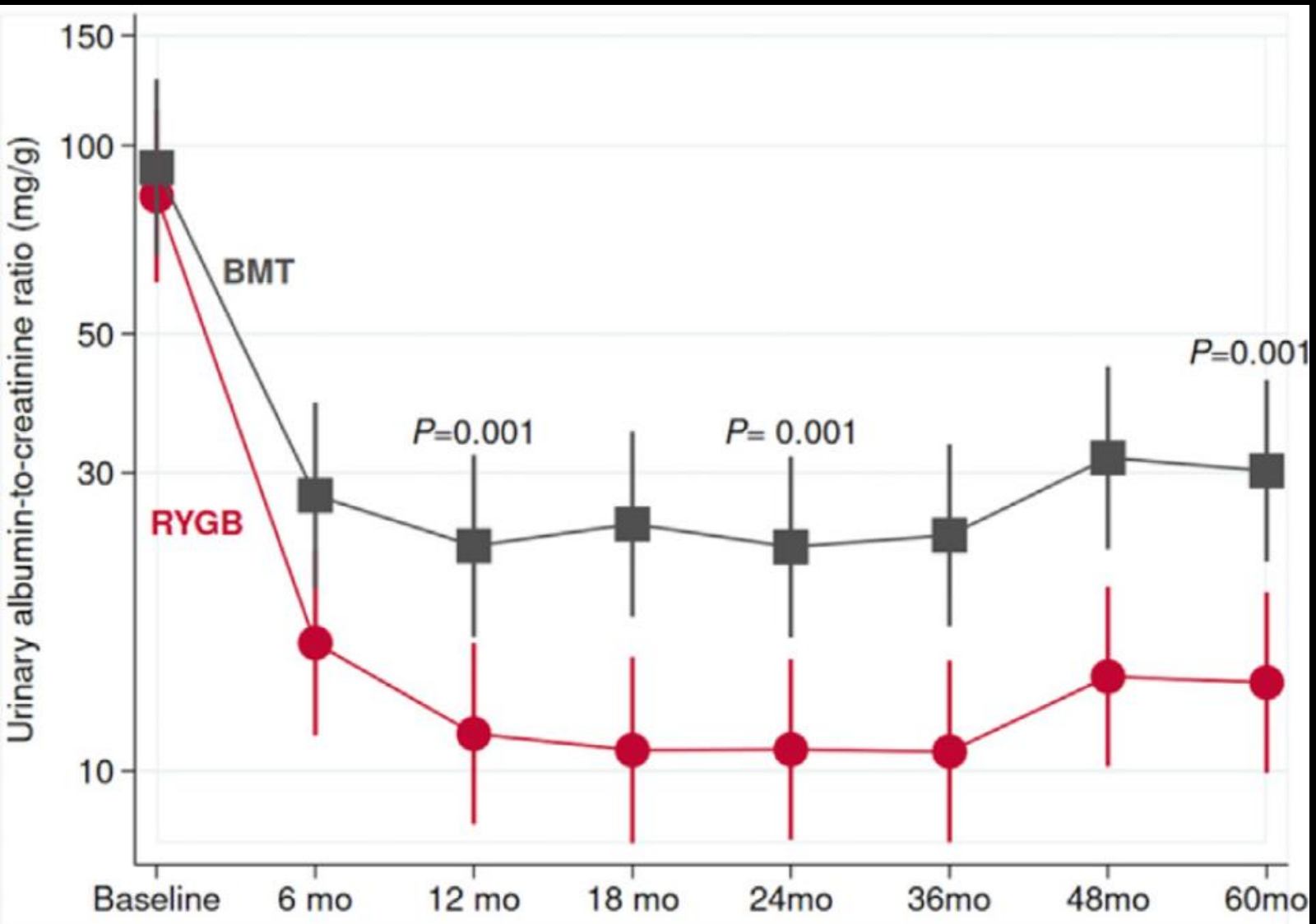
70%

***p= 0.32**

MOMS trial – 5 years outcomes

uACR- continuous variable

Cohen et al EClinMed 2022



The geometric mean for albuminuria levels was 46% lower after RYGB (P = 0.001)

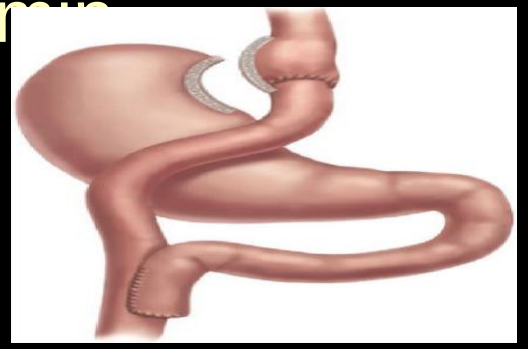
MOMS trial – 5 years outcomes

Cohen et al EClinMed 2022

Early-stage CKD remission

Remission of albuminuria with eGFR
> 60 ml/min

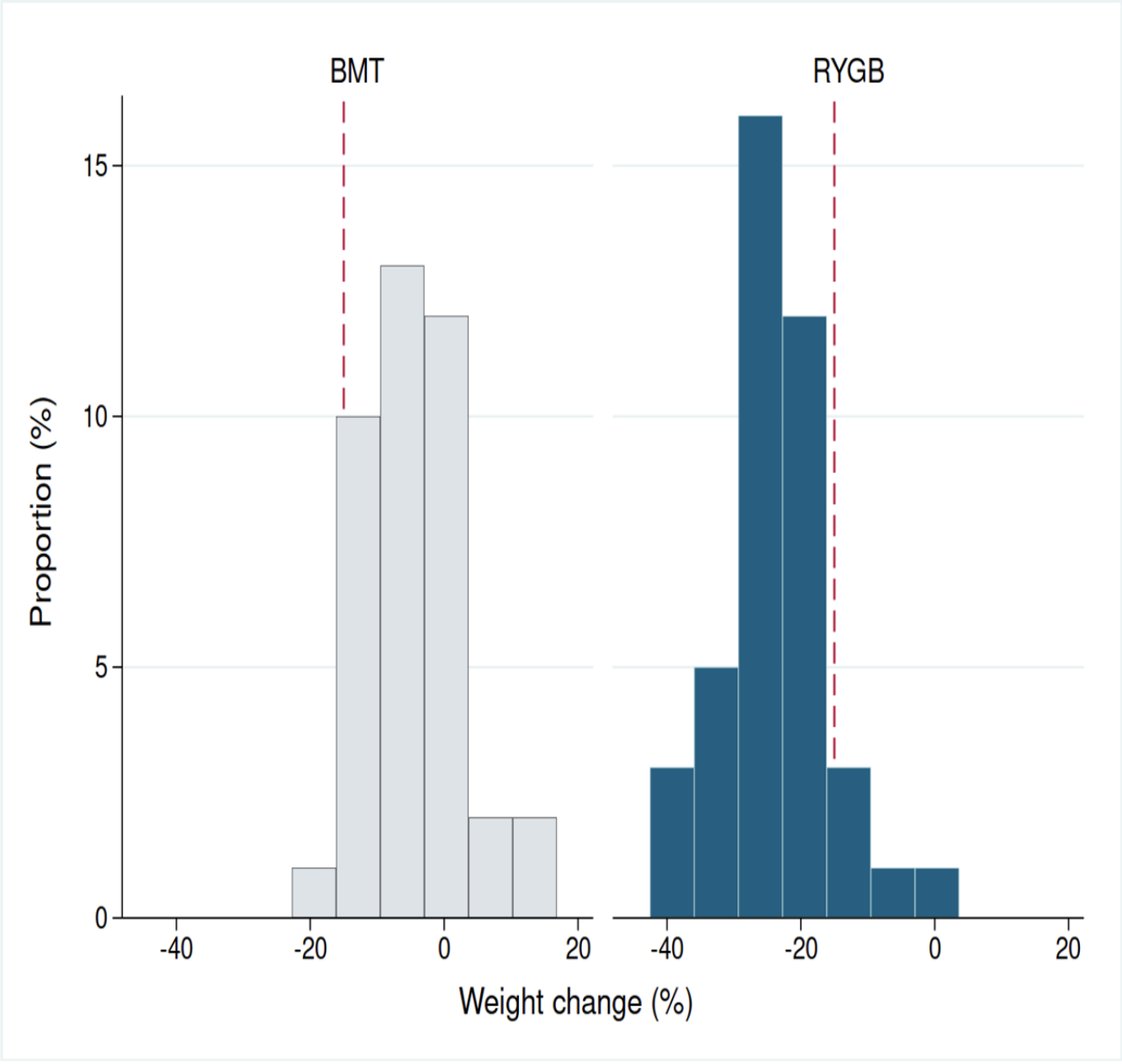
52.8%



+

63.1%

***p= 0.32**



Weight loss

Cohen et al EClinMed 2022

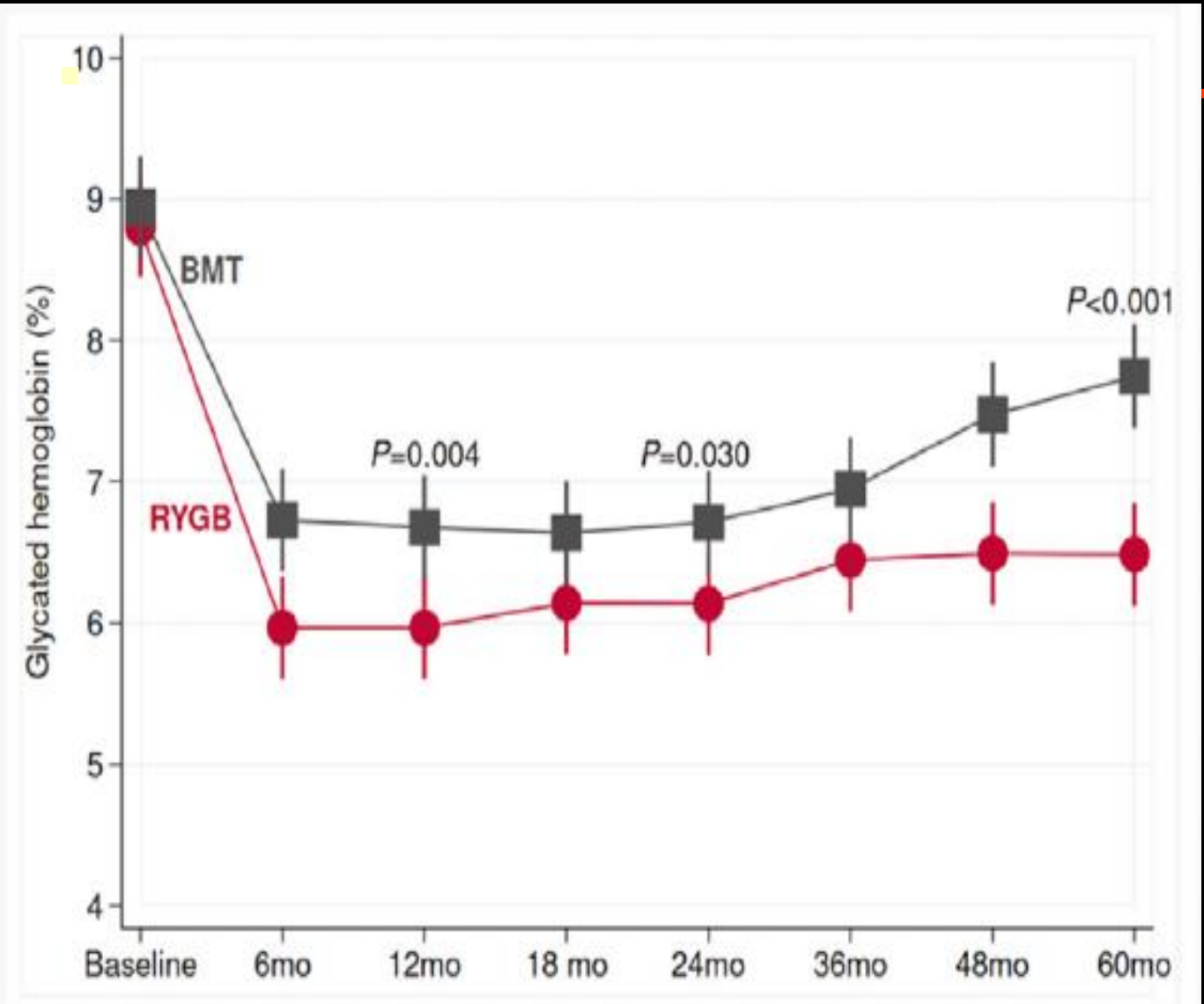
22.5% BMT >15% TBWL
90% RYGB >15% TBWL

No BMT patient reached BMI <25 kg/m²

After RYGB 53% of patients BMI <25 kg/m²

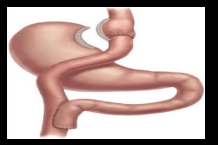
(P < 0.001)

Glycaemic control



Cohen et al EClinMed 2022

The ADA target of HbA1c ≤ 6.5%

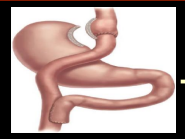


25.4% **60.2%**

P < 0.001

Blood pressure

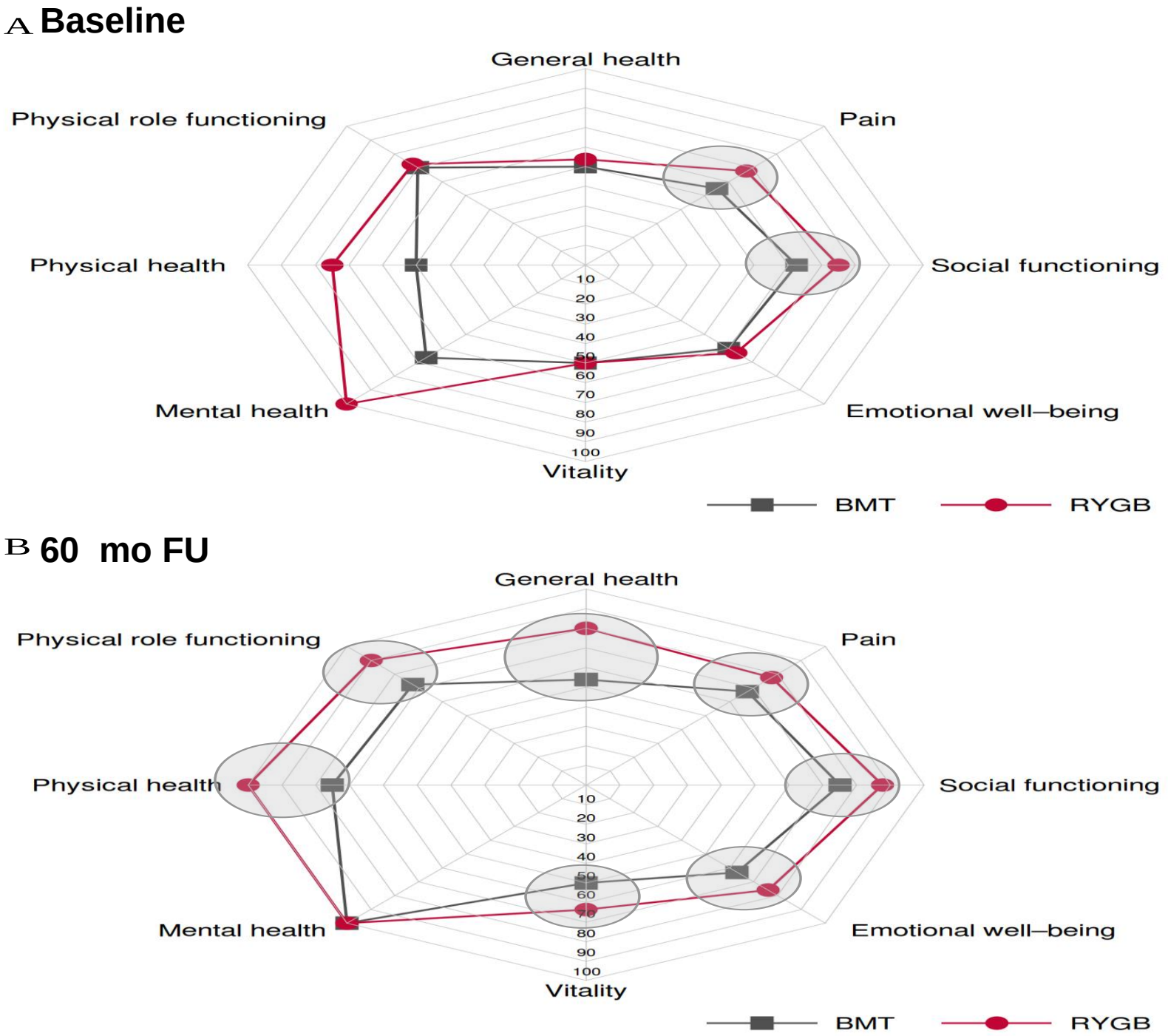
@ baseline, 78% had hypertension

		 + 	Difference	
SBP - mmHg	135.9 (130.9-141.0)	131.1 (126.2-136.1)	-4.81 (-11.9 to 2.25)	0.18
DBP - mmHg	86.0 (82.9-89.1)	78.9 (75.8- 82.0)	-7.12 (-11.5 to -2.7)	0.001
Estimated proportion (%) - SBP <130 mmHg	16.6 (4.8-28.3)	38.8 (23.8-53.8)	22.3 (3.2-41.3)	0.03
Estimated proportion (%) - DBP <80 mmHg	8.5 (0.01-17.5)	38.7 (23.6-53.8)	30.3 (12.6 to 47.7)	0.003

No difference in Systolic BP, but RYGB decreased Diastolic BP

Quality of Life (QOL)

Cohen et al EClinMed 2022



MOMS trial: Adverse events & Safety

Safety outcomes	RYGB (n = 46)	BMT (n = 46)	OR (95% CI)	P
Serious adverse events	11 (24)	7 (15)	1.74 (0.55-5.92)	0.80
Grade I	46 (100)	45 (98)	1.00 (0.03, +inf)	>0.99
Grade II	28 (61)	36 (78)	0.44 (0.15-1.18)	0.11
Grade III	5 (11)	2 (4.3)	2.66 (0.41-29.3)	0.43
Grade IV	2 (4.3)	2 (4.3)	1.00 (0.07, 14.4)	>0.99

Summary of treatment-emergent adverse events (safety population, 46 participants per treatment group) after 5 years of follow-up. BMT - best medical treatment; RYGB -Roux-en-Y gastric bypass.; OR - odds ratio. 95% CI denotes a 95% confidence interval. P values refer to two-sided tests based on exact logistic regression models. Grades I to IV refers to Clavien-Dindo for grading adverse events. +inf denotes that the upper bound cannot be computed (+infinity).

Table 3: Safety outcomes (safety population, n = 92).

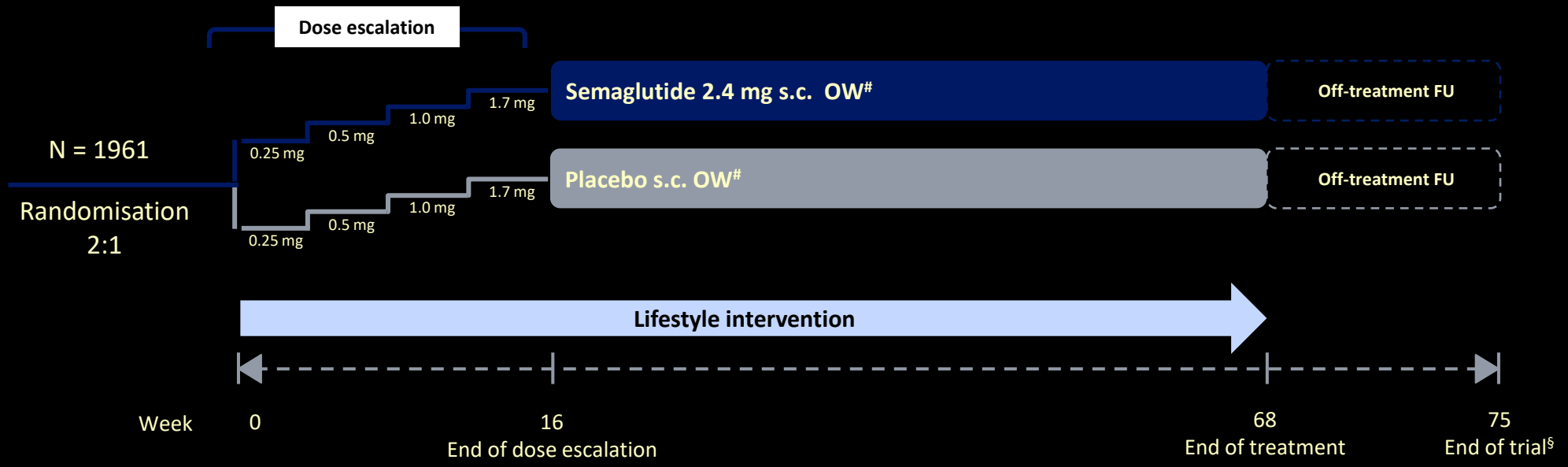
- ✓ **1 surgical complication managed by endoscopy**
- ✓ **No serious hypoglycemia**
- ✓ **No malnutrition**
- ✓ **No excessive weight-loss**

STEP 1: Trial design

Randomised, double-blind, multicentre, placebo-controlled trial

1961 subjects
with overweight or obesity

- Male or female ≥18 years
- BMI: ≥30 kg/m^2 or ≥27 kg/m^2 and ≥1 comorbidity
- Stable body weight ≥90 days
- HbA_{1c} ≤ 6.5%



Trial objectives

- To compare the effect of semaglutide 2.4 mg versus placebo# on body weight, cardiovascular risk factors, COAs, glucose metabolism, and other factors related to body weight
- To compare the safety and tolerability of semaglutide 2.4 mg versus placebo#

Primary endpoints

- %-weight loss
- 5%-responders

Confirmatory secondary endpoints

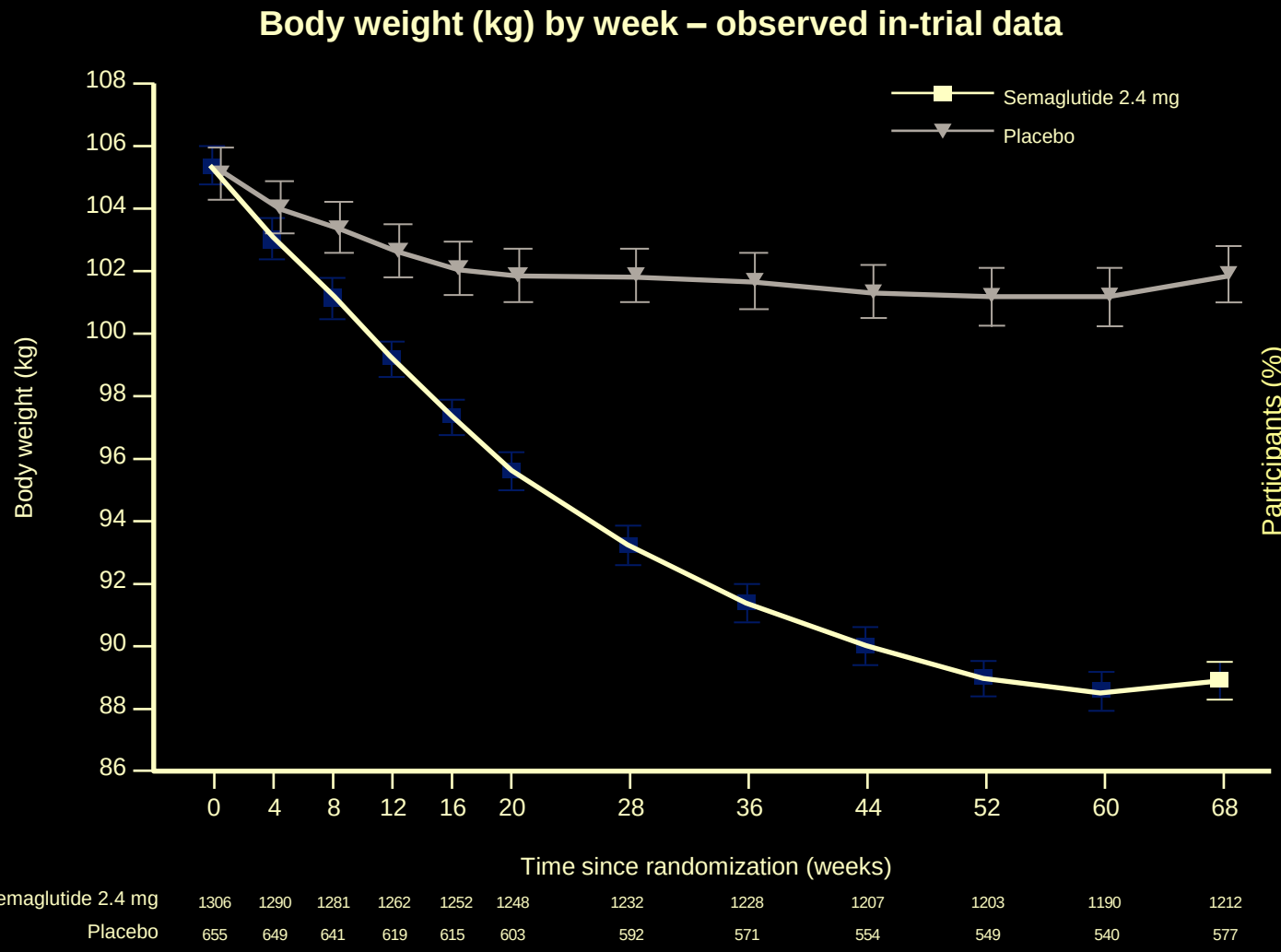
- 10%- and 15%-responders
- Waist circumference, systolic blood pressure, SF-36 physical functioning, IWQOL-Lite-CT physical function

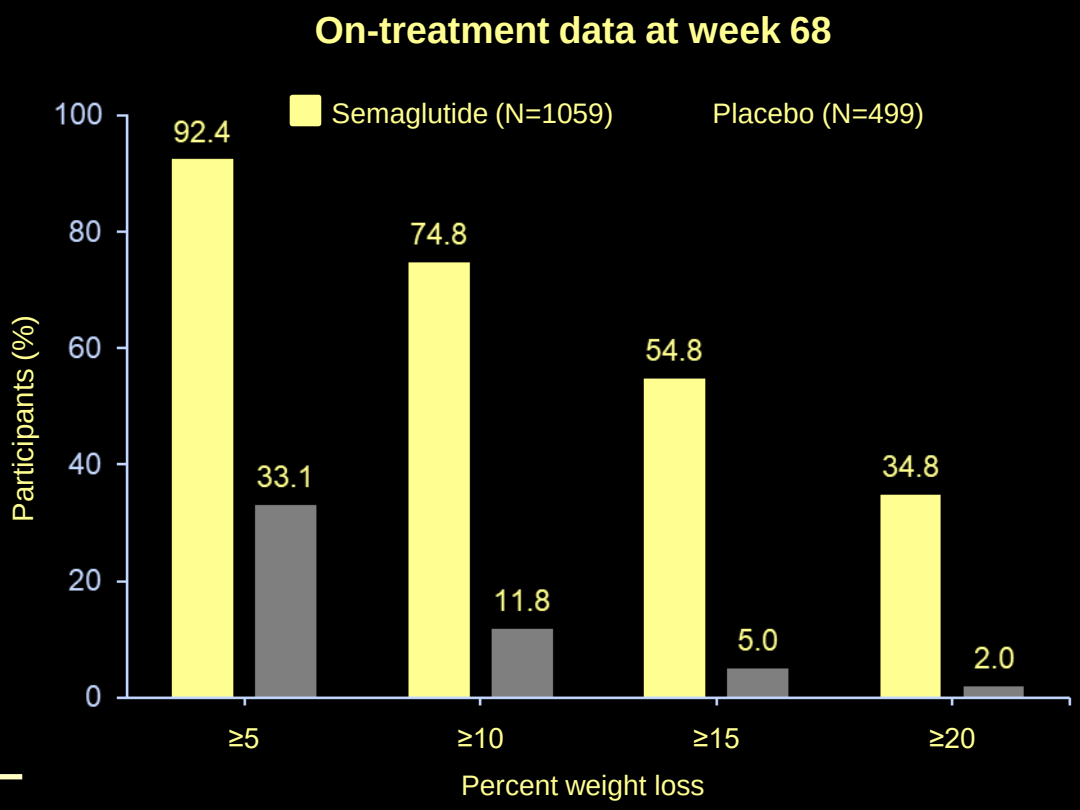
 # As an adjunct to lifestyle intervention (-500 kcal/day diet + 150 min/week physical activity). § End of trial for the main phase.

BMI, body mass index; COAs, clinical outcome assessments; FU, follow-up; HbA_{1c}, glycated haemoglobin; IWQOL-Lite-CT, Impact of Weight on Quality of Life-lite; OW, once-weekly; s.c., subcutaneous; SF-36, Short Form 36-item Health Survey.

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

Body weight in kilograms by week





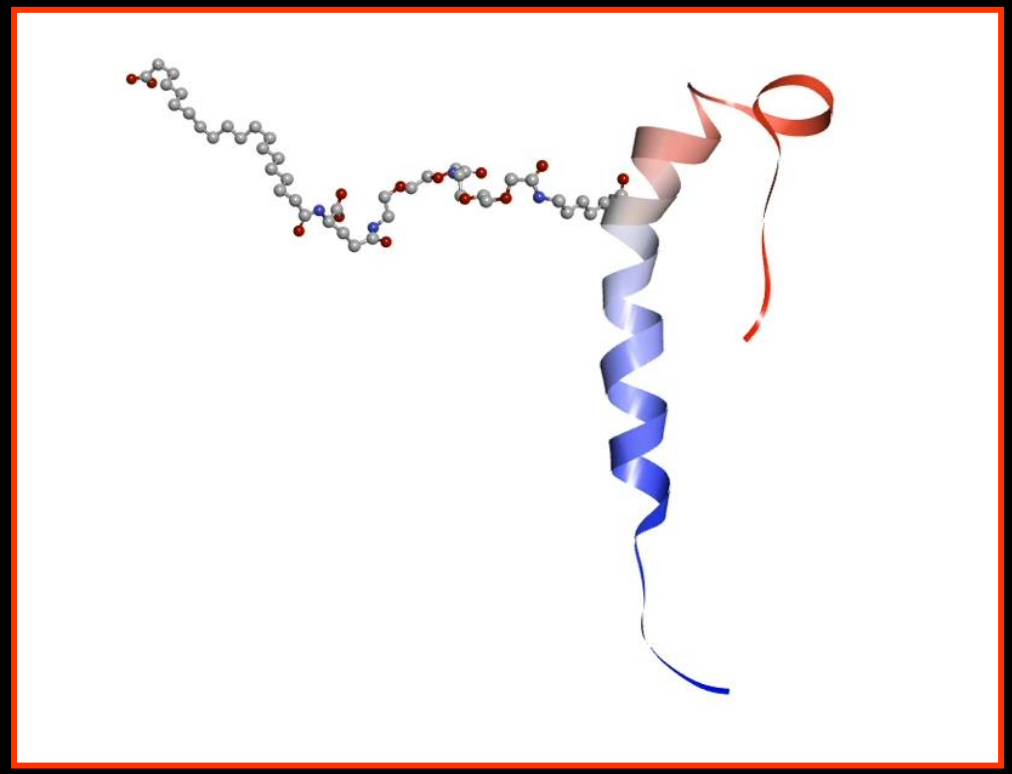
Observed mean body weight (kg) over time for participants in the full analysis set during the in-trial observation period (from randomization to last contact with trial site, regardless of treatment discontinuation or rescue intervention).
Error bars are ± standard error of the mean. N numbers represent the number of participants with available data contributing to the means at each visit.

Adapted from Figure S4. Body weight in kilograms by week

Wilding et al. NEJM 2021; [Full citation to be added once available].

Tirzepatide: GIP/GLP-1 receptor coagonist

- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIP and GLP-1 receptors
- Tirzepatide is a 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- Tirzepatide has a mean half-life of ~5 days (116.7 h), enabling once-weekly dosing



GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1.
Coskun T, et al. *Mol Metab.* 2018;18:3-14.

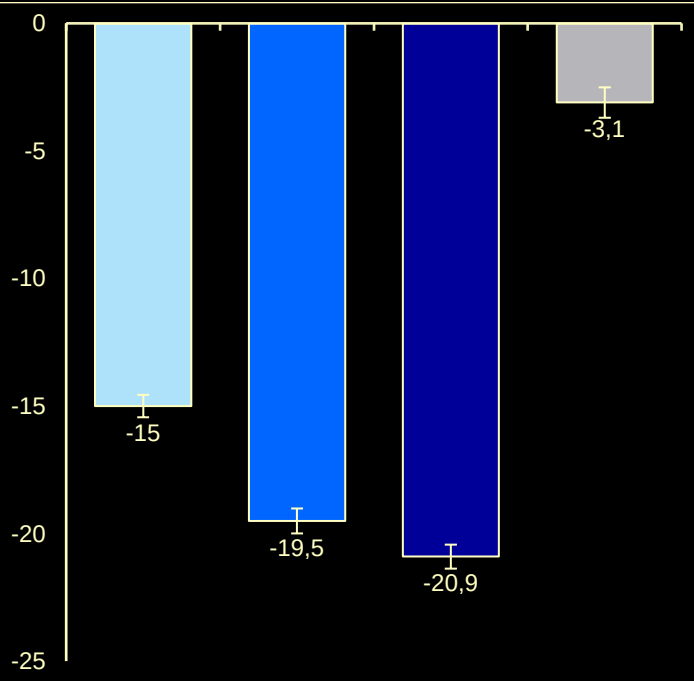
Change in body weight from baseline to 72 weeks

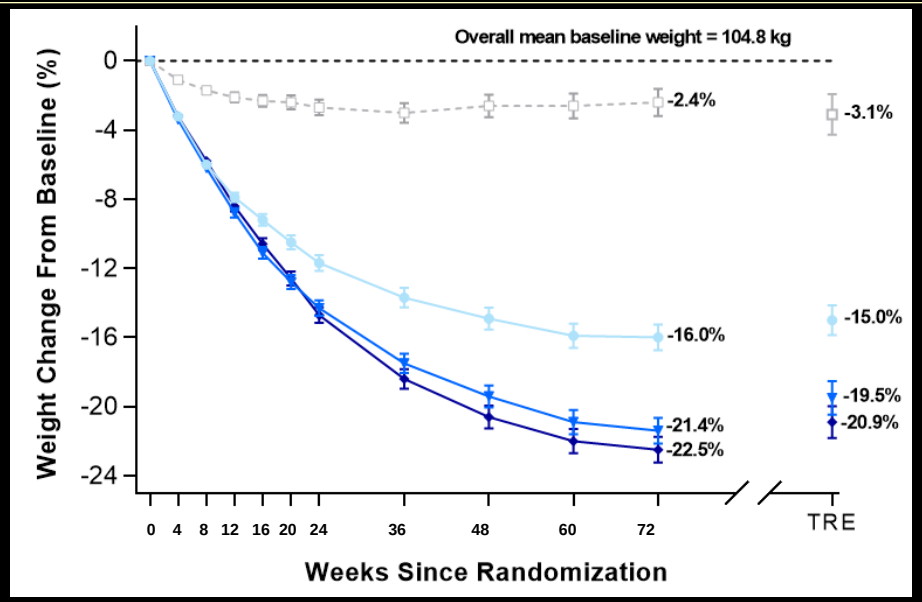
- **Statistically significant difference in weight reduction with all tirzepatide doses compared to placebo**
- **Weight reductions of 19.5% and 20.9% with tirzepatide 10 mg and 15 mg, respectively (treatment regimen estimand)**

Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Placebo

	TZP 5 mg vs PBO	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	-11.9 (-13.4, -10.4)	-16.4 (-17.9, -14.8)	-17.8 (-19.3, -16.3)
P value	<.001		

	TZP 5 mg vs PBO	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	−13.5 (−14.6 to −12.5)	−18.9 (−20.0, −17.8)	−20.1 (−21.2, −19.0)
P value	<.001		





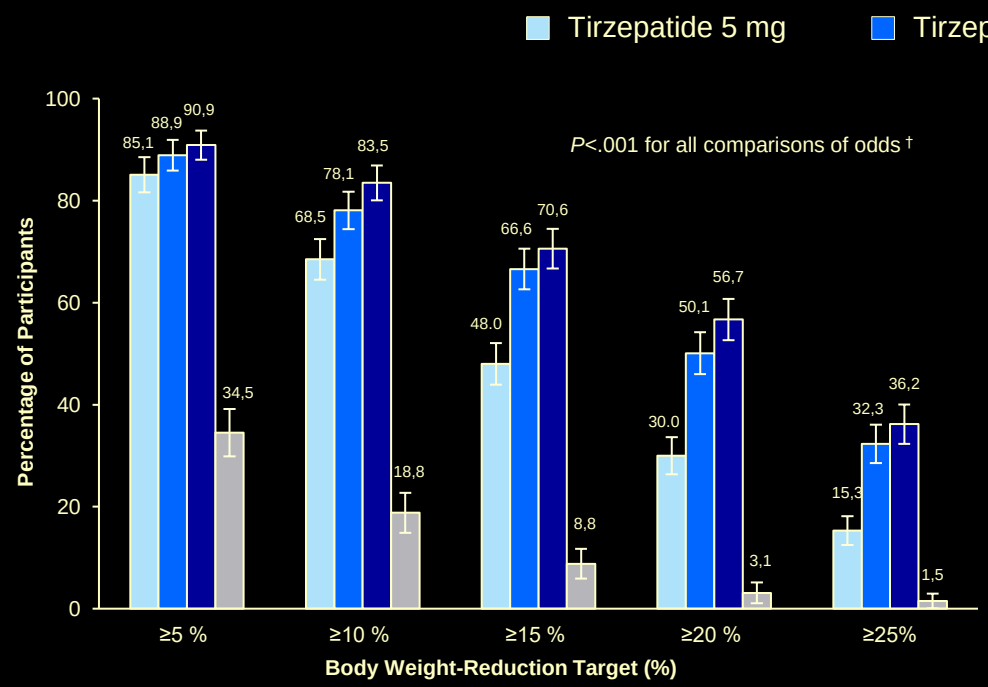
CI = Confidence Interval; ETD = Estimated Treatment Difference; TRE = Treatment Regimen Estimand; TZP = Tirzepatide; PBO = Placebo.

Jastreboff AM, et al. *New Engl. J. Med.* 2022; (Accepted).

% of participants achieving BW reductions targets

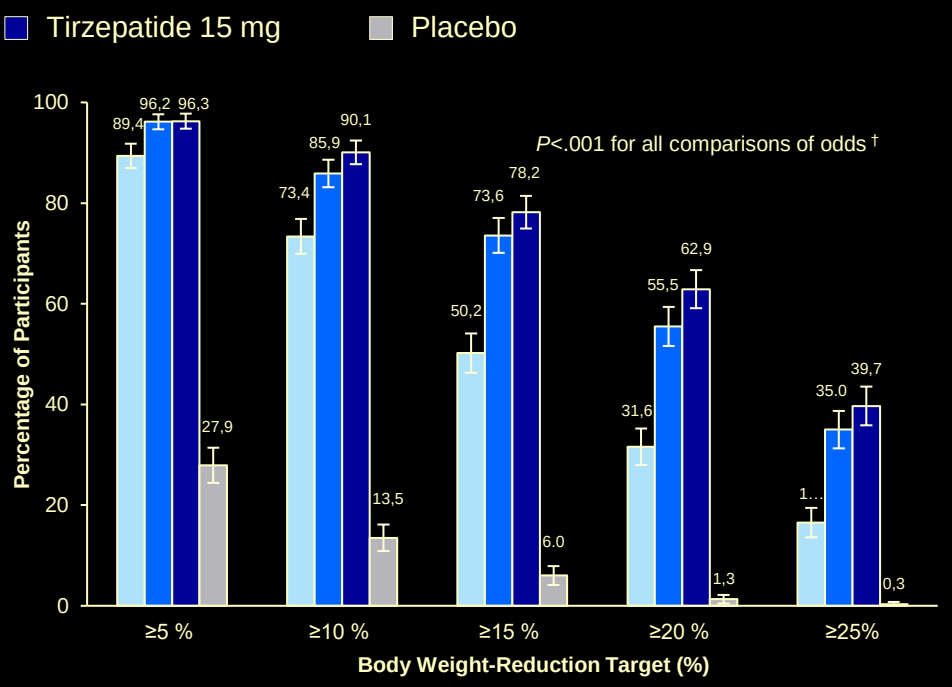
- **Significantly greater proportion of participants on tirzepatide treatment achieved body weight reductions of ≥5%, ≥10%, ≥15%, and ≥20% from baseline than placebo**
- **36.2% of patients achieved pre-specified exploratory endpoint of >25% body weight reduction with TZP 15 mg**

Treatment Regimen Estimand*



Note: The percentage was calculated with the use of Rubin's rules by combining the percentages of patients who met the target in imputed data sets. Missing value at week 72 was imputed using MMRM if missing was solely due to COVID-19 and using multiple imputation if missing was not due to COVID-19

Efficacy Estimand*



Note: The percentage of participants achieving weight loss targets was obtained by dividing the number of participants reaching respective goals at week 72 by the number of participants with baseline value and at least one non-missing postbaseline value. Missing value at week 72 was predicted from MMRM analysis. Logistic regression analysis was used for all comparisons to placebo

*Least-squares means are presented, unless otherwise noted. Error bars indicate the 95% confidence interval

† Participants with weight reduction ≥25% is an exploratory endpoint and hence not controlled for type 1 error; therefore *P*-values are not shown

MMRM = Mixed-model or Repeated-measures.

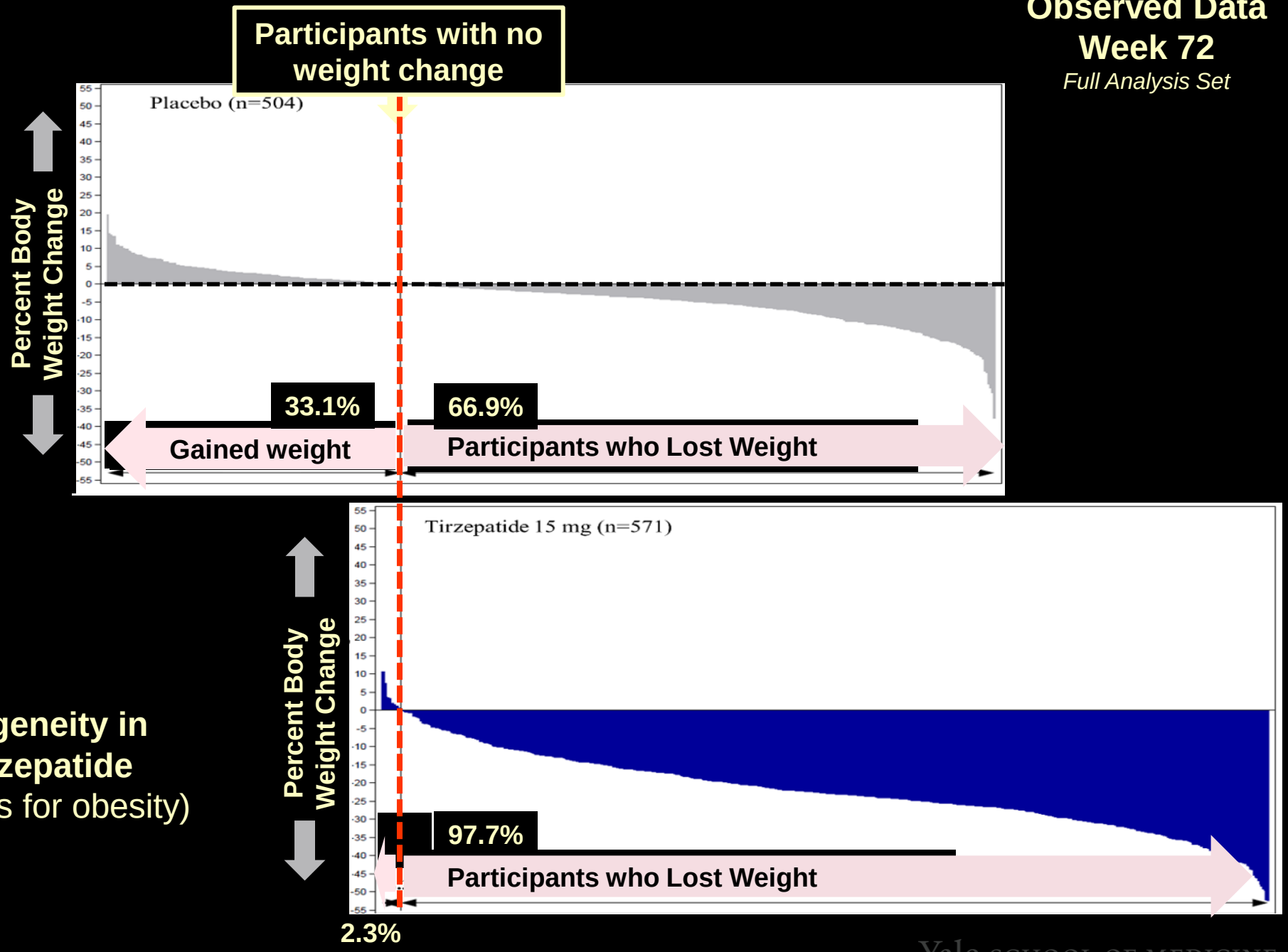
Jastreboff AM, et al. *New Engl. J. Med.* 2022; (Accepted).

Distribution of percent change in weight for each participant (waterfall plots)

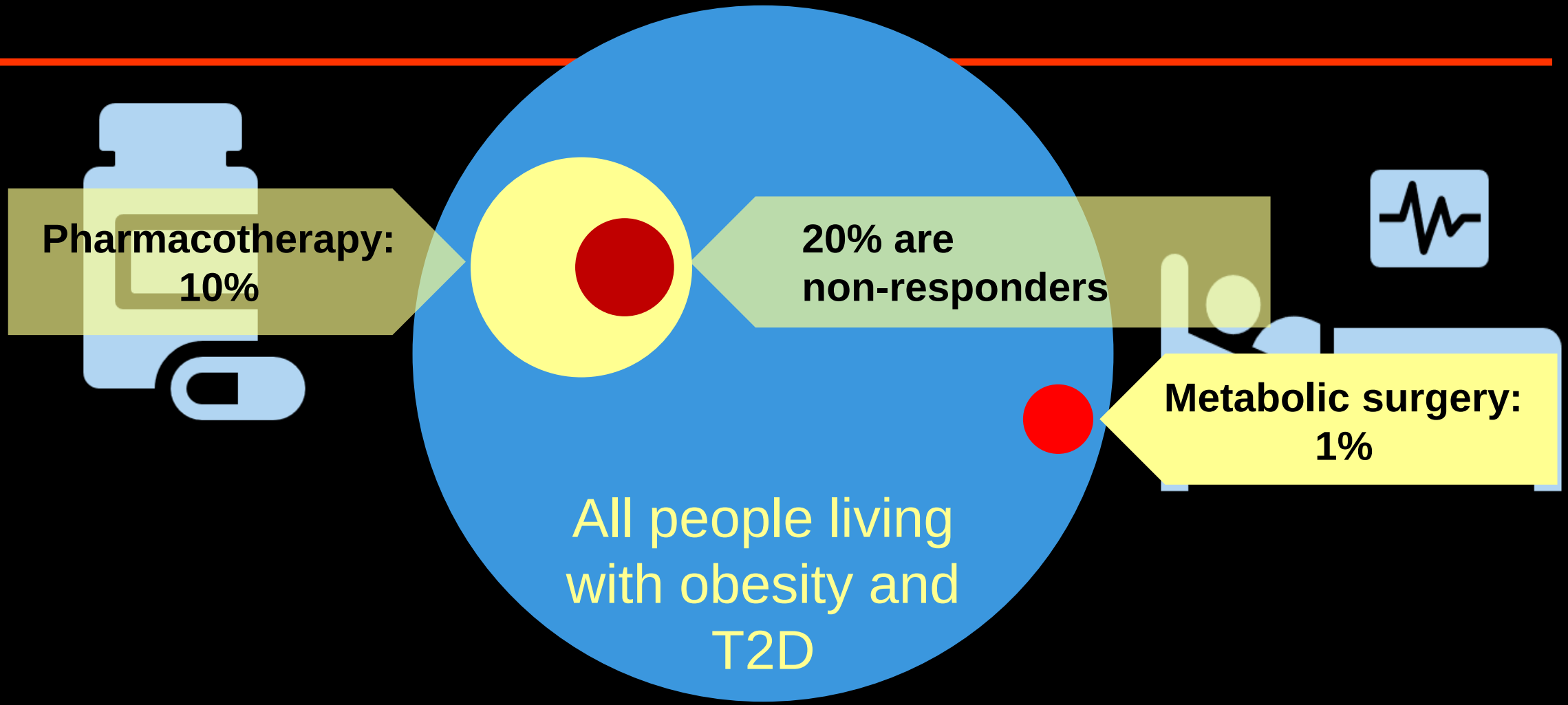
Observed Data
Week 72
Full Analysis Set

Nearly all individuals lost weight with tirzepatide 10 mg and 15 mg

There is heterogeneity in response to tirzepatide
(as with all therapies for obesity)

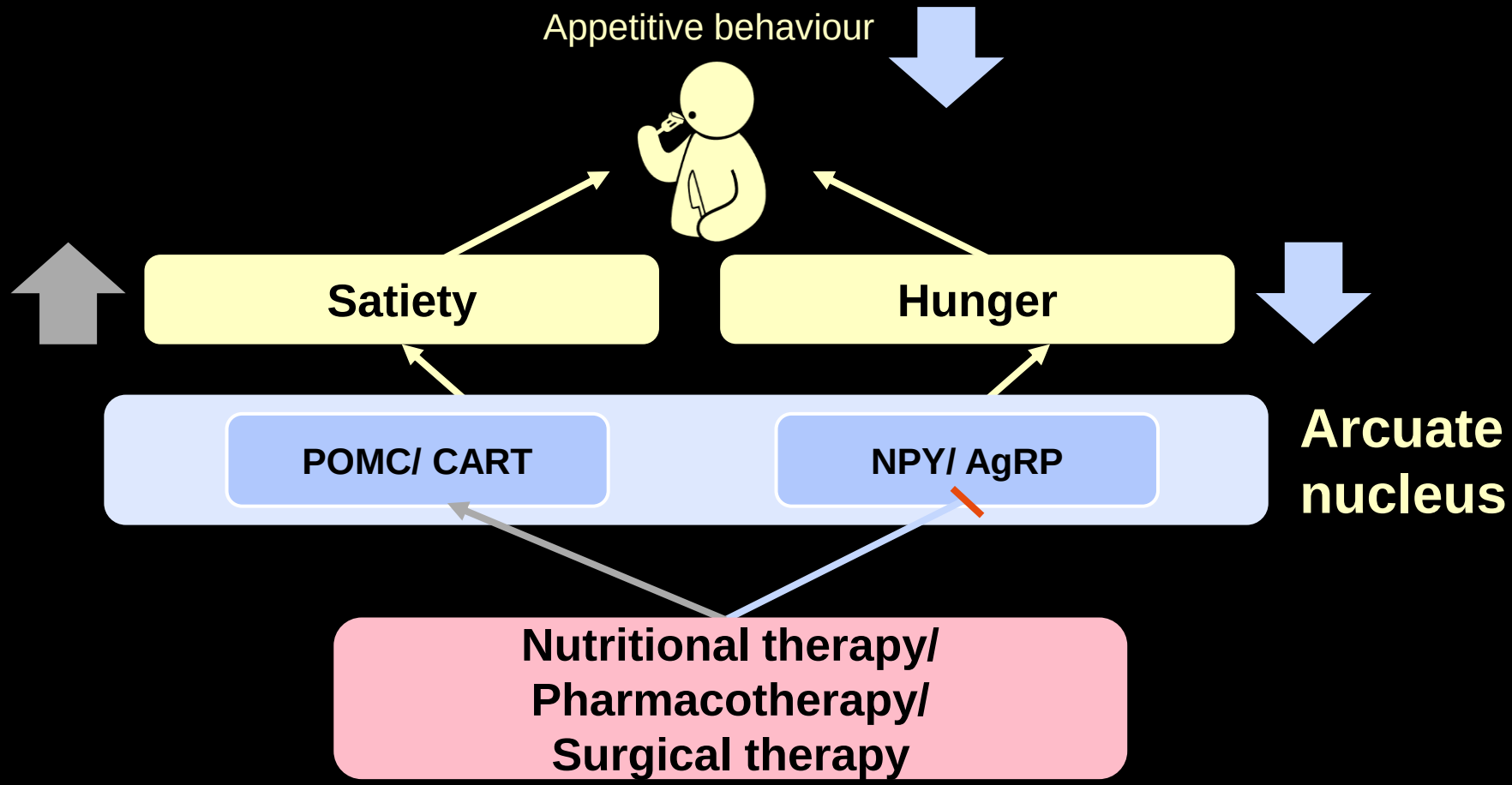


Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S et al. NEJM, 2022


Pharmacotherapy: 10%
20% are non-responders
Metabolic surgery: 1%
All people living with obesity and T2D

Successful weight loss treatments increase satiety and reduce hunger

Via neurons in the arcuate nucleus

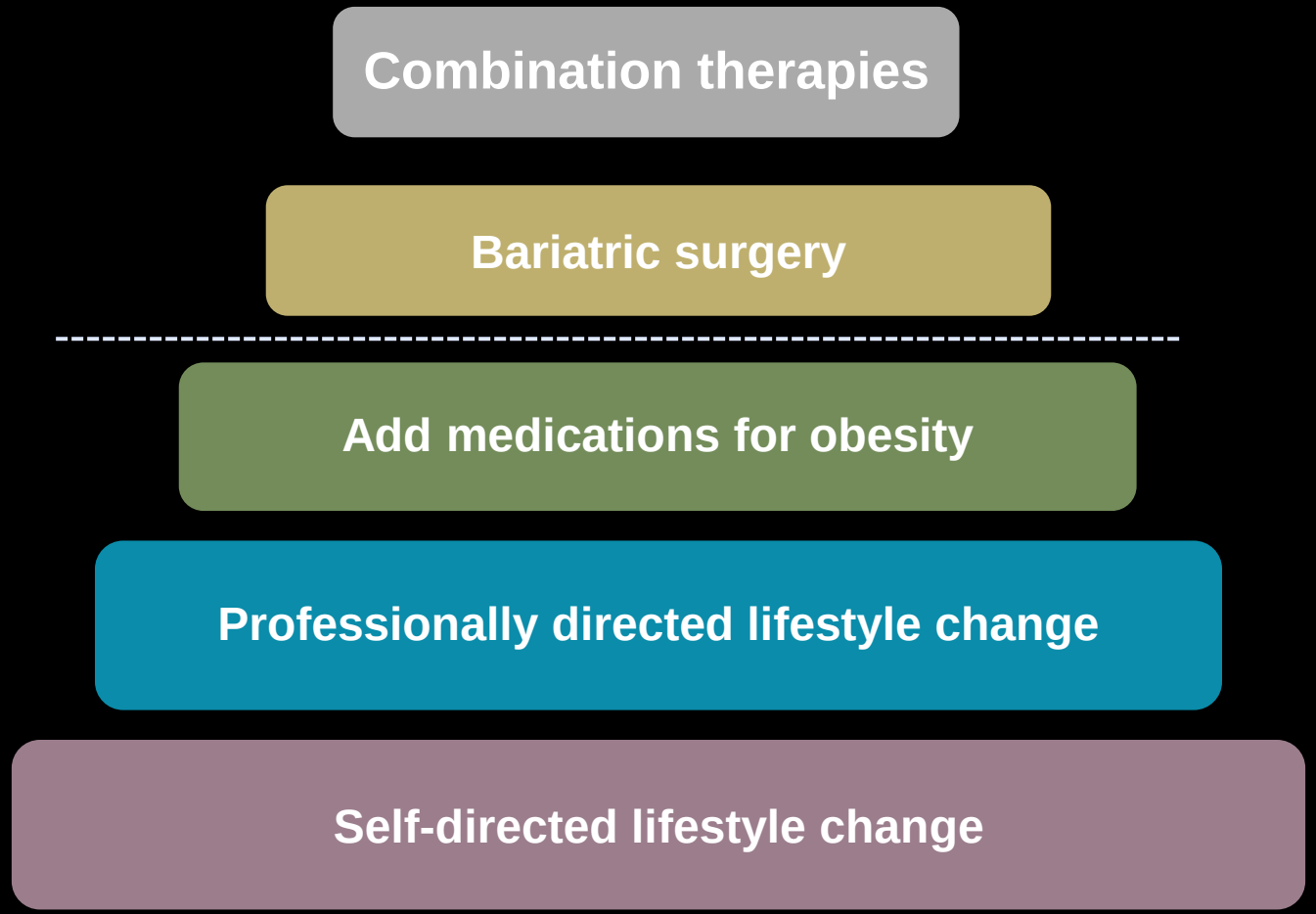


AgRP, Agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; NPY, neuropeptide Y; POMC, pro-opiomelanocortin

Secher, et al. J Clin Invest 2014;124:4473–88; van Can, et al. Int J Obes (Lond) 2014;38:784–93.

Overall treatment strategy

Typical algorithm
(progress through algorithm as clinically required)



Conclusions

- Obesity is
  - a complex and chronic set of diseases
  - characterised by excess adipose tissue causing deterioration in health
  - Multiple and diverse diseases that result in excess adipose tissue
  - Unifying diagnostic criteria may be challenging
  - Not all forms of obesity require treatment, but treatment should always aim to result in health gain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“In the present case it is similarly necessary to renounce a freedom that does not exist and to recognise a dependence of which we are not personally conscious.”