



AKADEMISKA
SJUKHUSET

Medicinsk Överviktsbehandling

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Akademiska Sjukhuset i
Uppsala

Jävsdeklaration

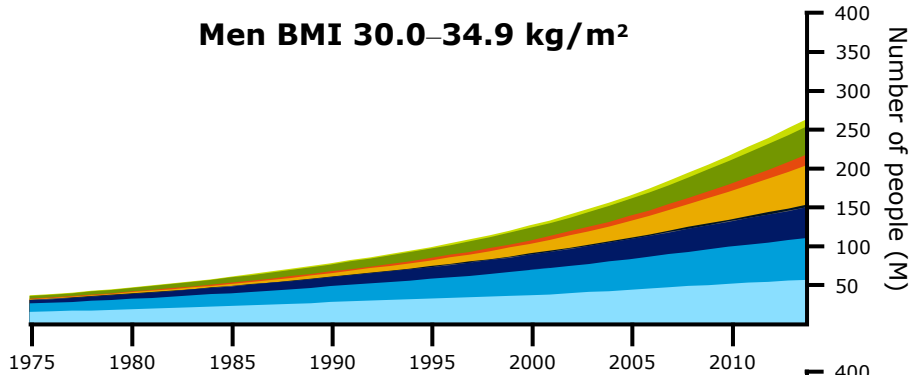
Senaste 5 åren:

- Ordförande NPO-Endokrina Sjukdomar 2022-
- Styrelseledamot Svensk Förening för Obesitasforskning 2016-2020
- Styrelseledamot Svensk förening för Diabetologi 2017-2020
- Kassör Svensk Förening för Endokrinologi 2016-2023
- Lunchföreläsning sept 2022 1h rörande socialstyrelsens obesitasriktlinjer, arvoderad av NovoNordisk.
- Principal and Coordinating Investigator Sweden BI 1404-0036 A Phase II, randomized. double blind, parallel group, 46 weeks dose-finding study of BI 456906 administered once weekly subcutaneously compared with placebo in patients with obesity or overweight" 2021-2023
- Principal and Coordinating Investigator Sweden STEP-4, "En forskningsstudie för att undersöka effekt och säkerhet av läkemedlet semaglutid vid behandling av personer med övervikt eller fetma." 2018-2020
- Principal and Coordinating investigator" A Multinational Observational Study to Evaluate the Safety of Repatha in Pregnancy" 2016-2020
- Subinvestigator" Observational Serial Chart Review of Repatha Use in European Subjects with Hyperlipidaemia" 2016-2020

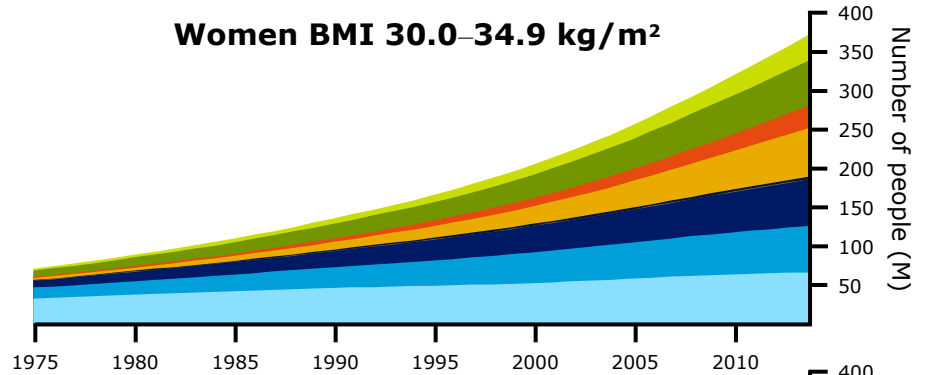


Obesitas ökar

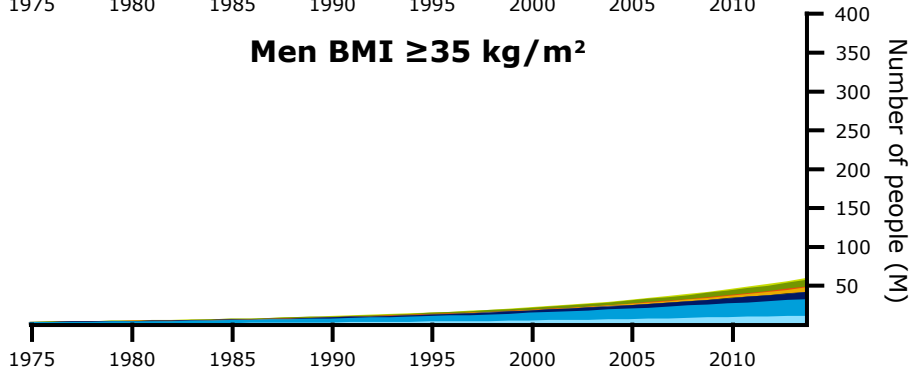
Men BMI 30.0–34.9 kg/m²



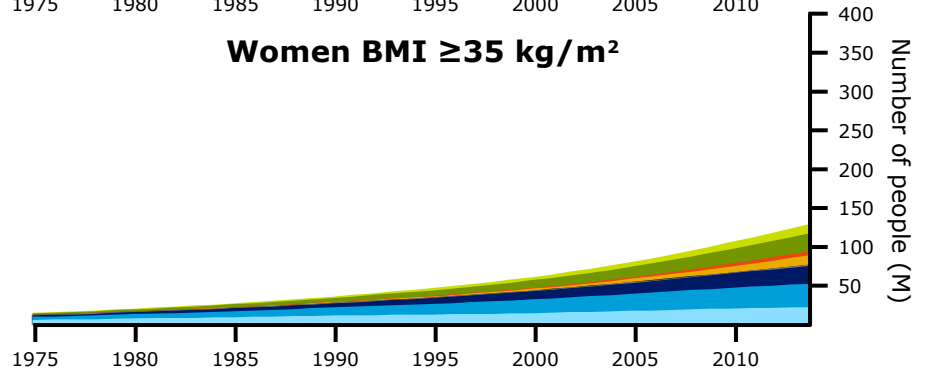
Women BMI 30.0–34.9 kg/m²



Men BMI ≥35 kg/m²



Women BMI ≥35 kg/m²

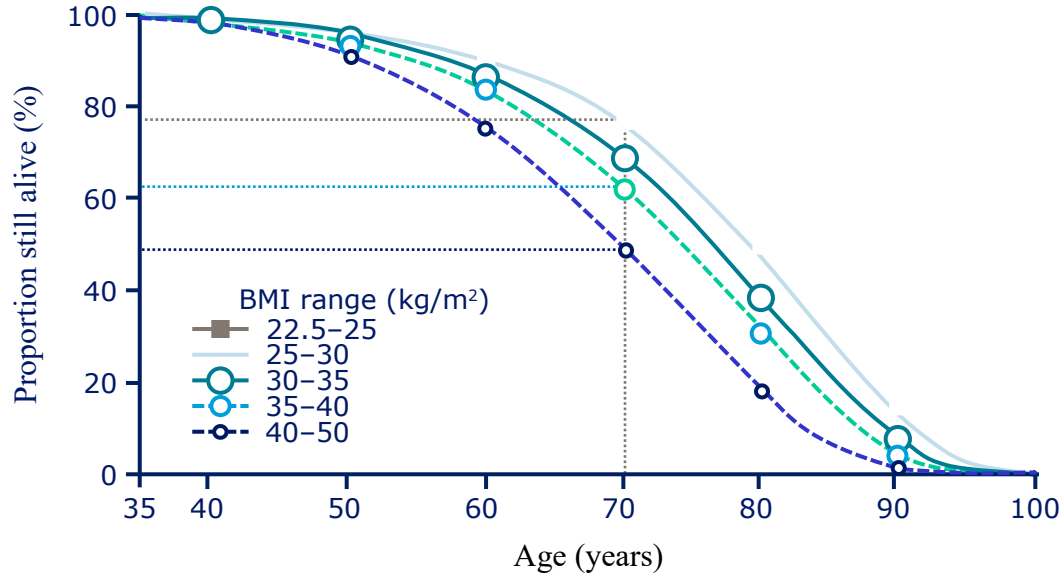


- Sub-Saharan Africa
 - Central Asia, Middle East and North Africa
 - South Asia
- East and South East Asia
 - High-income Asia Pacific
 - Oceania
- Latin America and Caribbean
 - High-income English speaking countries and Western Europe
 - Central and Eastern Europe

M, million



Life expectancy decreases as BMI increases



BMI 35–40 =
~60% chance of reaching age 70

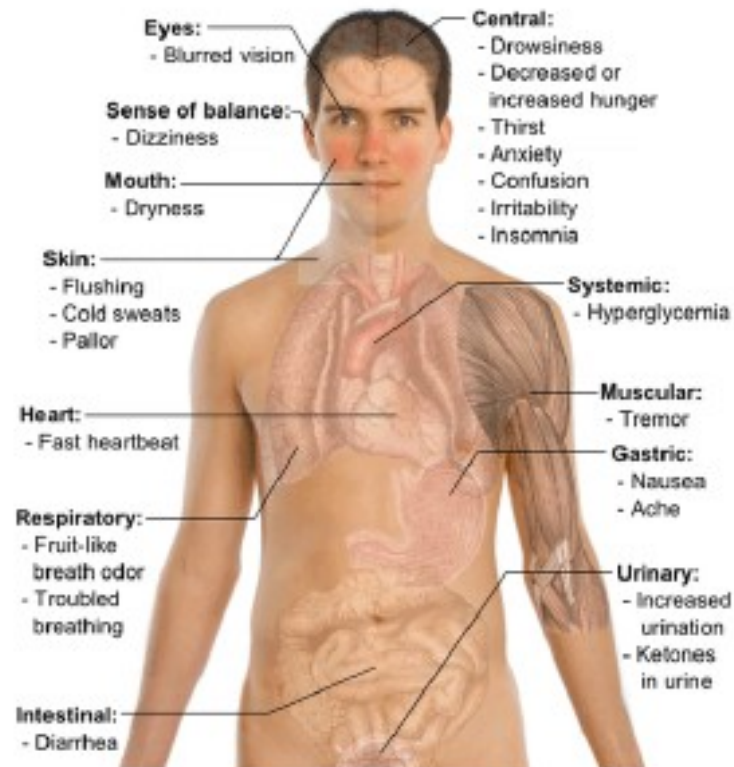
BMI 40–50 =
~50% chance of reaching age 70

BMI 50 = röka 1 pack om dagen



Varför är det svårt att gå ned i vikt?

- Ökad aptit
- Irritation
- Trötthet
- Ångest
- Sömnproblem
- Depression
- GastroIntestinala besvär
- Fryser
- Koncentrationsproblem
- Sociala problem
- Illamående
- etc



Hunger

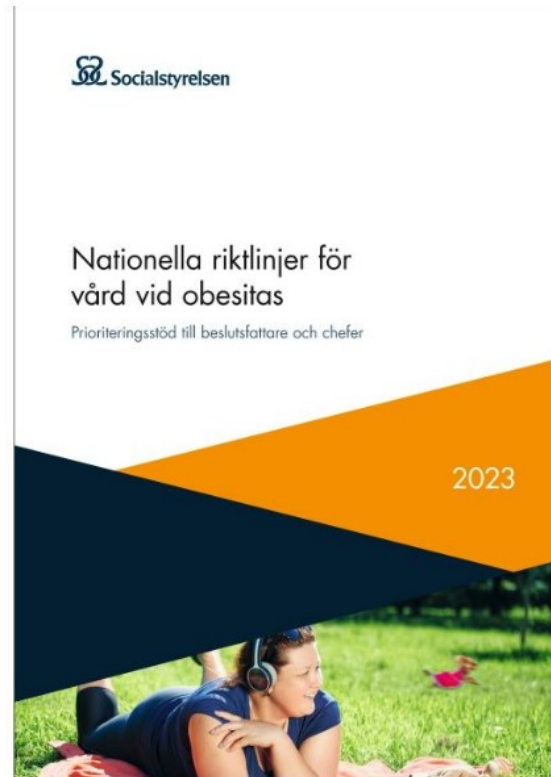
- Hunger de facto en starkare känsla än rädsla, törst, ångest, eller social isolering
- Styrts av AgRP (Agouti-related Peptide)neuron i hypothalamus.
- Knockas de ut slutar möss äta och dör.



Nationella riktlinjer för vård vid obesitas

Stöd för styrning och ledning
2022

Huvudbudskap: Utbilda personal och erbjud mer vård



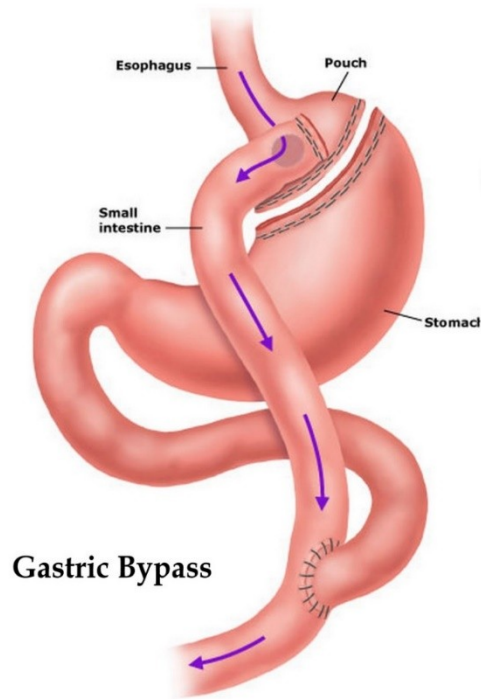
Nationella riktlinjer för vård vid obesitas

Stöd för styrning och ledning
2022

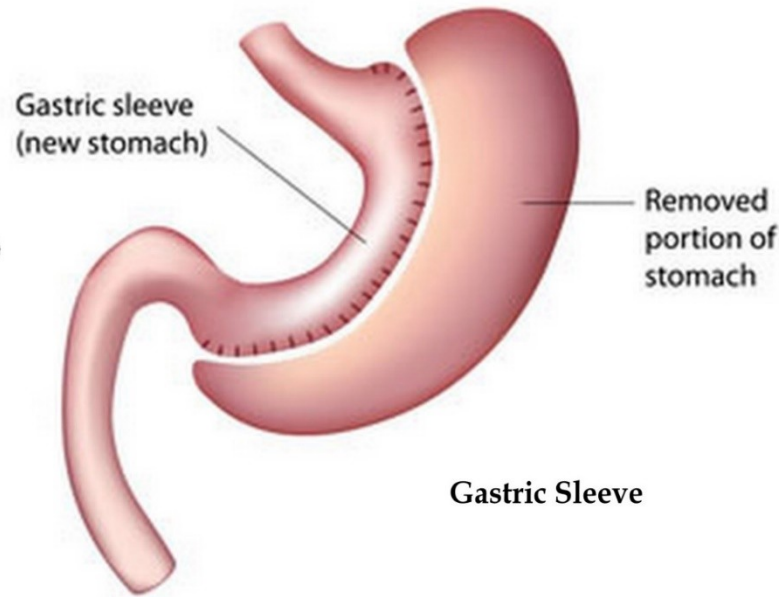
Rekommendationer till hälso- och sjukvården: Kirurgi

Id	Erbjud operationen ...	fyll personer med obesitas som är aktuella för operationen och ...	Prioritet
18	gastric bypass	<ul style="list-style-type: none">• är vuxna• har BMI \geq 35	2
14		<ul style="list-style-type: none">• är barn i åldern 15–17 år• har BMI \geq 35	3
16		<ul style="list-style-type: none">• är vuxna• har BMI 30–35	3
19	sleeve-gastrektomi	<ul style="list-style-type: none">• är vuxna• har BMI \geq 35	3
20	BPD/DS (biliopankreatisk diversion med duodenal switch)	<ul style="list-style-type: none">• är vuxna• har BMI \geq 50	5
Id	Endast inom ramen för forskning och utveckling: Erbjud operationen ...	fyll personer med obesitas som ...	Prioritet
15	sleeve-gastrektomi	<ul style="list-style-type: none">• är barn i åldern 15–17 år• har BMI \geq 35	FoU
17		<ul style="list-style-type: none">• är vuxna• har BMI 30–35	FoU



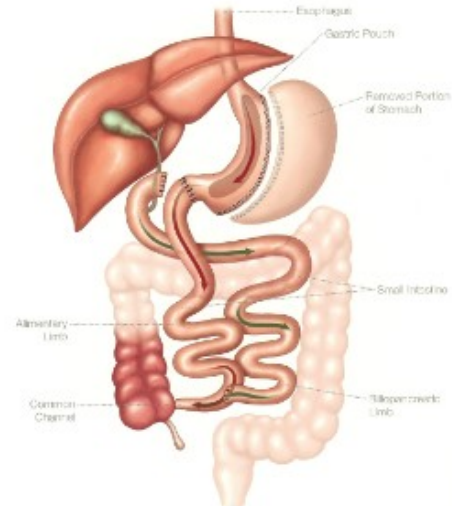


Gastric Bypass

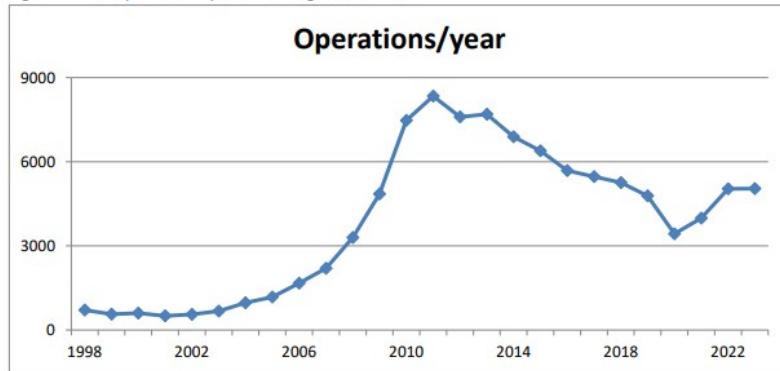


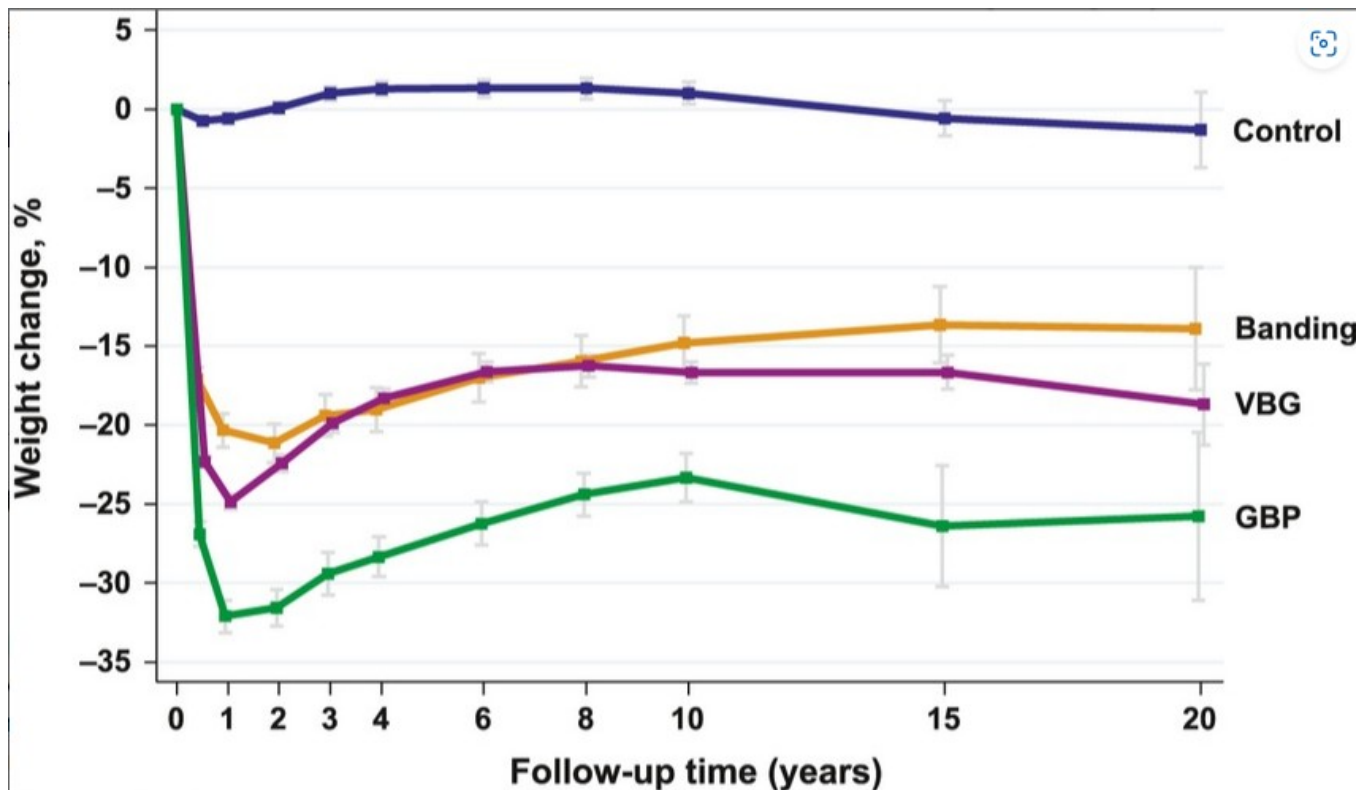
Gastric Sleeve

Duodenal Switch



Figur 1: Antal operationer per år i Sverige 1998 – 2023





No. examined

Control	2037	1490	1242	1267	556	176
Banding	376	333	284	284	150	50
VBG	1369	1086	987	1007	489	82
GBP	265	209	184	180	37	13

SOS-study,
Sjöström et al, NEJM
2007;357:741-52.



Spelar viktnedgång roll? #1

105/2500 pat med viktnedgång <15% 1 år postop

Table 2 Weight loss outcomes, $N = 105$

Variable	Baseline at time of operation (mean, SD)	Result at 1 year postoperatively (mean, SD)	<i>p</i> value
Weight, kg	133.0 ± 29.3	119.0 ± 25.0	<0.01
BMI, kg/m ²	46.8 ± 8.8	41.9 ± 7.9	<0.01
Excess weight, kg	62.0 ± 25.6	48.0 ± 22.1	<0.01
BMI lost, kg/m ²	N/A	4.8 ± 2.3	N/A
% Excess weight loss	N/A	24.4 ± 15.6	N/A
% Total weight loss	N/A	10.2 ± 4.8	N/A



Spelar viktnedgång roll? #2

Variable	Baseline at time of operation (mean, SD)	Result at 1 year postoperatively (mean, SD)	<i>p</i> value
Number of anti-hypertensives used	1.7 ± 1.0	1.3 ± 1.3	<0.01
HDL cholesterol, mg/dL	46.3 ± 11.6	54.1 ± 12.7	<0.01
LDL cholesterol, mg/dL	103.6 ± 35.8	89.2 ± 30.0	<0.01
Triglyceride, mg/dL	177.3 ± 139.1	117.6 ± 59.3	<0.01
Number of oral hypoglycemic agents used	1.8 ± 1.1	0.5 ± 0.8	<0.01
Fasting blood glucose level, mg/dL	128.9 ± 55.3	102.7 ± 27.3	<0.01
Hemoglobin A ₁ C, %	7.3 ± 1.9	6.1 ± 1.0	<0.01
Metabolic Score	3.0 ± 1.0	2.1 ± 1.1	<0.01

Metabolic Score (central fetma, hyperlipidemi, hypertension, bukumfång, hyperglykemi)



Mediciner

- Orlistat (Xenical, Alli)
- Naltrexon/Bupropion (Mysimba)
- **GLP-1-analoger** (Semaglutide)
- **GLP-1/GIP-analoger** (Tirzepatide)
- Pipeline



Nationella riktlinjer för vård vid obesitas

Stöd för styrning och ledning
2022

Rekommendation till hälso- och sjukvården: Läkemedelsbehandling

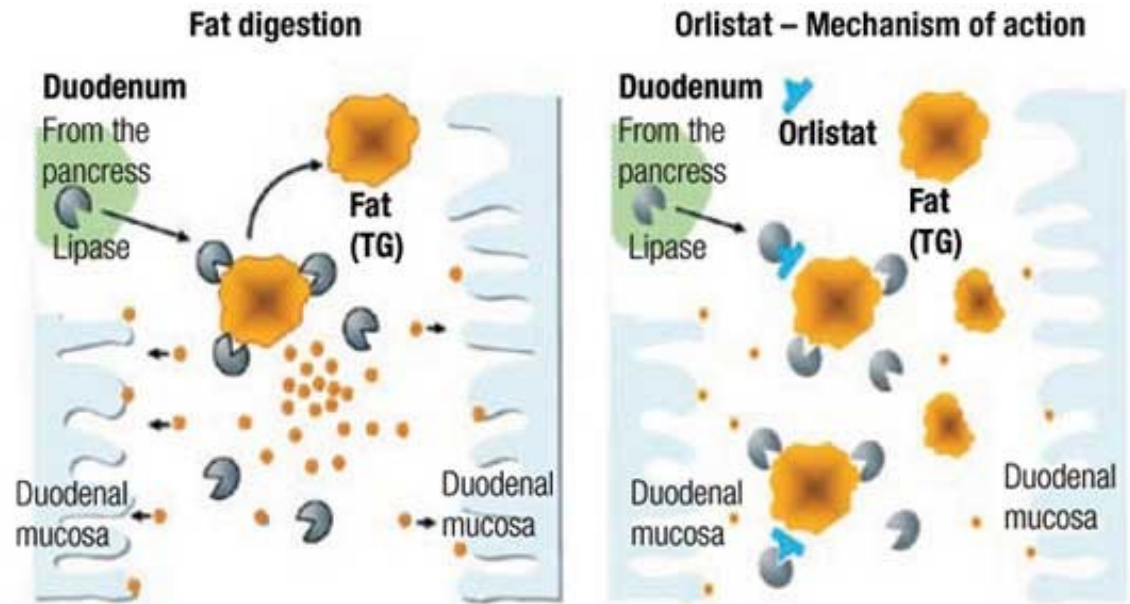
Id	Rekommendation	Prioritet
13	Erbjud läkemedlet orlistat som tillägg till levnadsvanebehandling, till vuxna med obesitas som är aktuella för läkemedelsbehandling.	4



Orlistat(Xenical/Alli)

Hämmar pankreatiskt lipas och
därmed fettupptag, c:a 30% ut
icke nedbrytet i feces

Effekt och bieffekt – fettiga diarrer



Orlistat - mechanism of action.



Orlistat (Xenical/Alli)

- Vid obesitas hos vuxna ger behandling med Orlistat i varierande dos (180-360 mg/dag), som tillägg till levnadsvanebehandling jämfört med placebo:
- Viktnedgång **-2,63kg**
- 6kr/dag, 180kr/mån



Naltrexon/Bupropion (Mysimba)

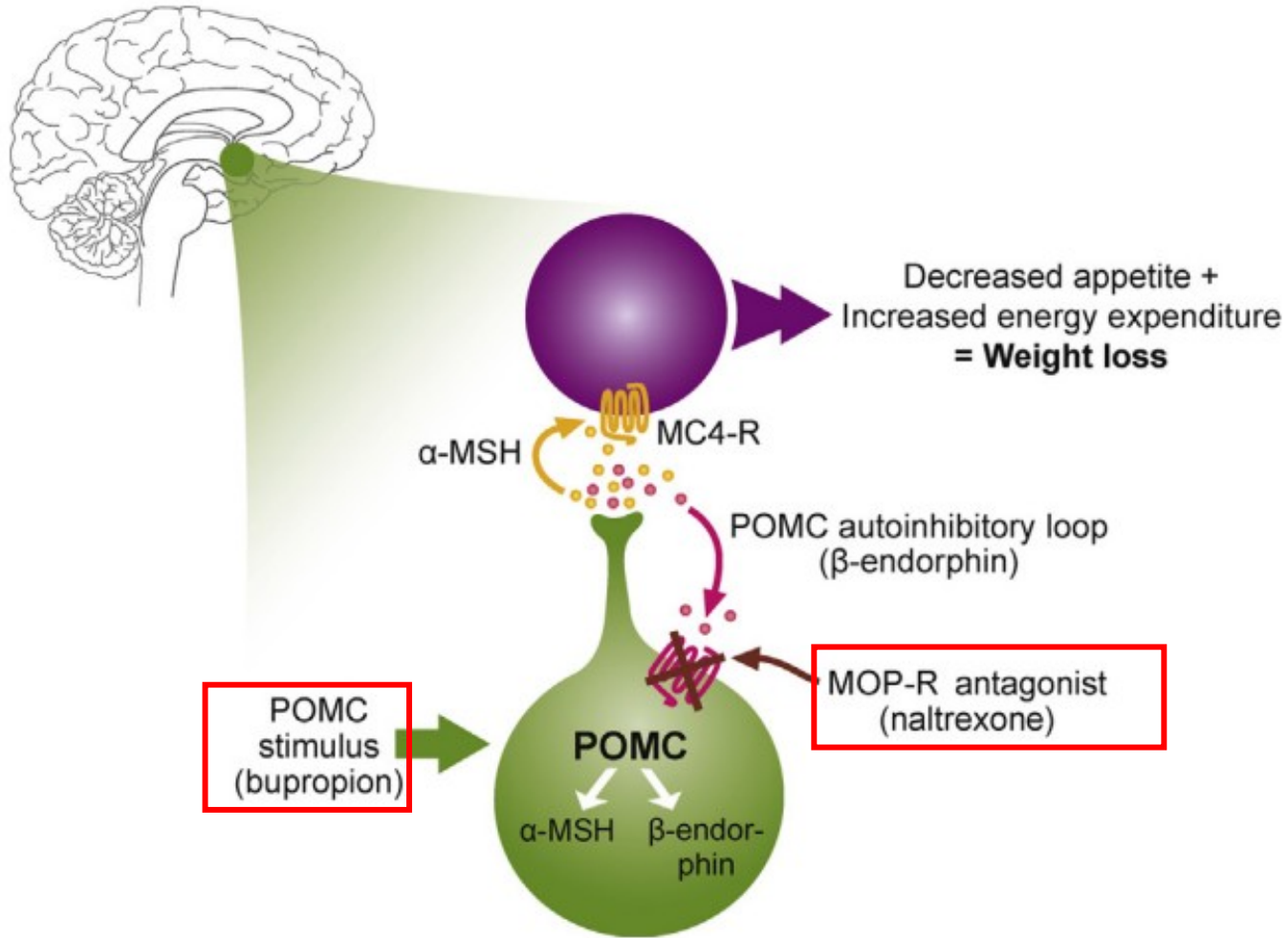


Fig. 3. Mechanism for naltrexone/bupropion action in the hypothalamic melanocortin system. The hypothalamus contains cells that produce pro-opiomelanocortin (POMC). In these cells, POMC is cleaved into peptides including α -melanocyte stimulating hormone (α -MSH) and β -endorphin, which are co-released from POMC cells. α -MSH stimulates the melanocortin-4 receptor (MC4R), which leads to decreased food intake, increased energy expenditure and weight loss. β -Endorphin binds to the inhibitory μ -opioid receptor (MOP-R) on POMC cells and acts like a brake to reduce activity of POMC cells. Bupropion stimulates activity of POMC cells, increasing POMC production and release of α -MSH and β -endorphin. Naltrexone blocks the MOP-R and prevents the β -endorphin-mediated feedback autoinhibition of POMC cells. Together, the naltrexone/bupropion combination produces a greater increase in POMC activity than either drug alone. This increased POMC activity is thought to contribute to weight loss in humans.

Pharmacological Research 84 (2014) 1–11

Naltrexone/bupropion for obesity: An investigational combination pharmacotherapy for weight loss

Sonja K. Billes^a, Puspha Sinnayah^b, Michael A. Cowley^{c,*}



Naltrexon/Bupropion (Mysimba)

Vid Obesitas hos vuxna ger behandling med kombinationstabletten Naltrexon/bupropion i doserna 16 alt 32 mg Naltrexon med fast dos Bupropion, som tillägg till levnadsvanebehandling:



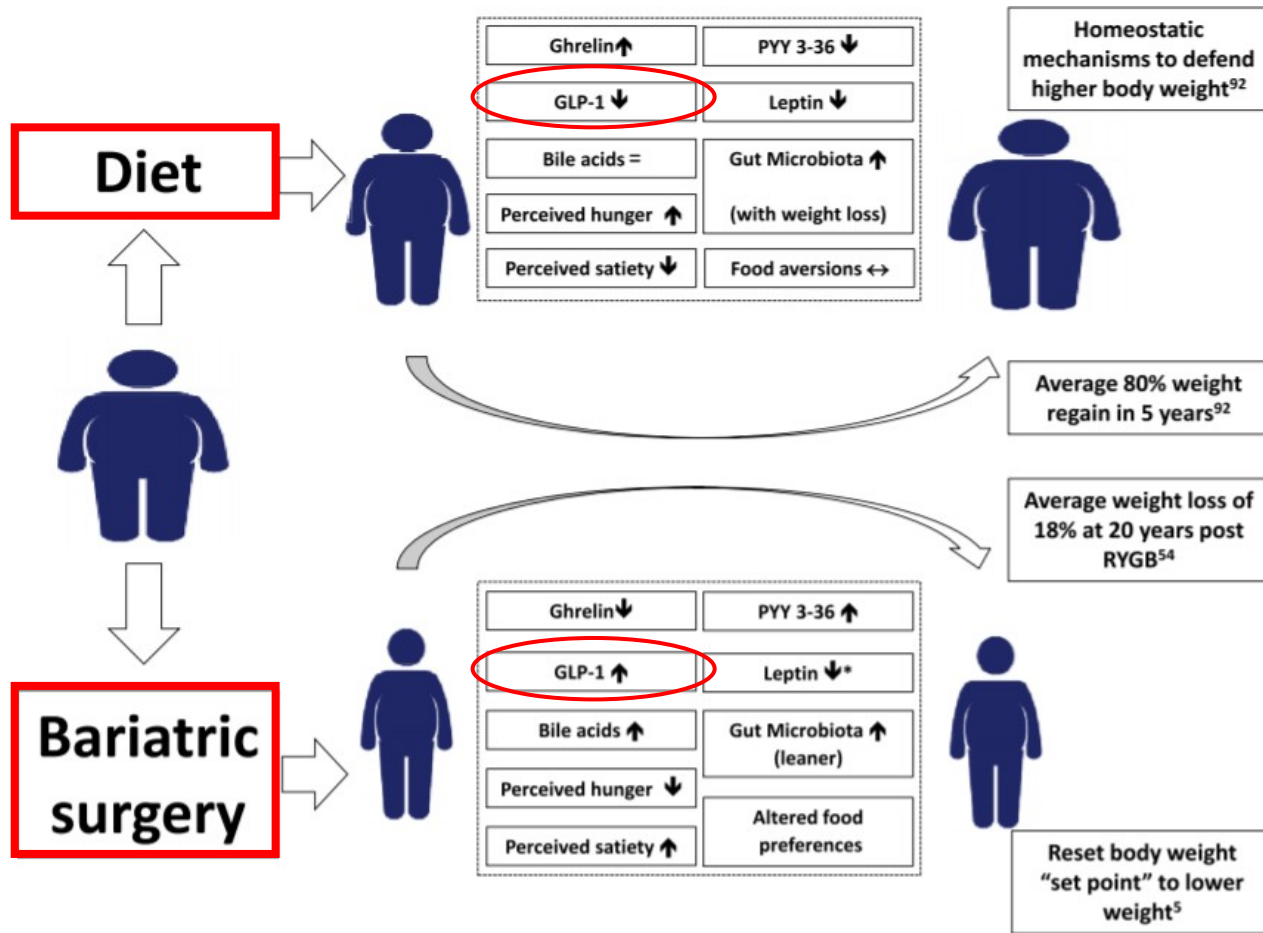
Viktning jmf med placebo. 5,0 % (32mg) och 3,7 % (16mg)

Utan subvention, 36kr/dag, **1100kr/mån**

Biv: ångest, sömnproblem, huvudvärk, yrsel, pulsökning,
illamående

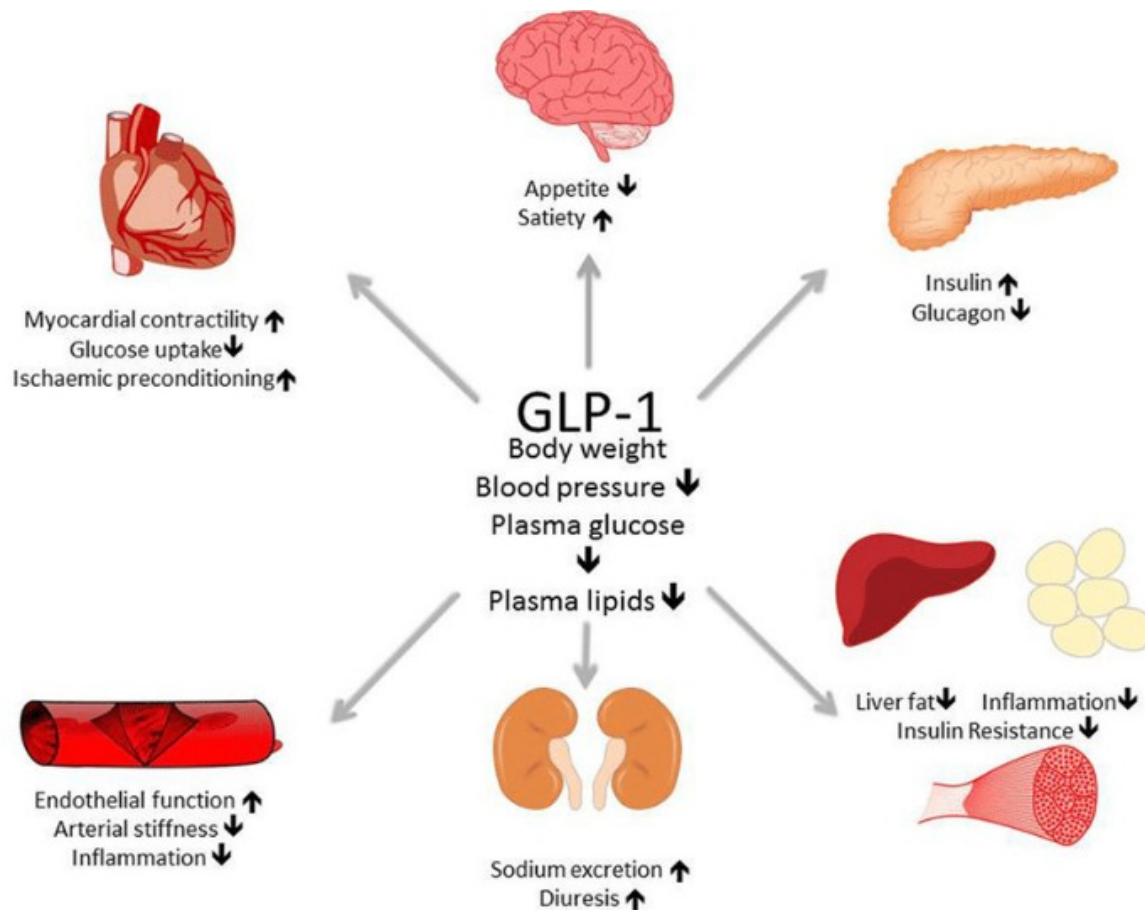


Operation vs. Medicinsk behandling – mekanismer/Skillnader



GLP-1-analoger

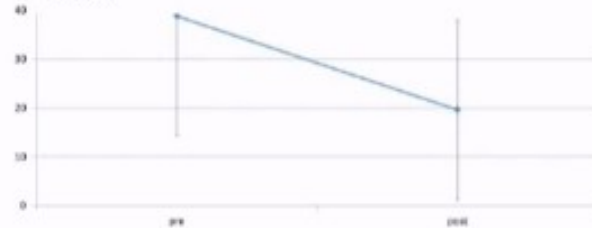
- Sänker aptit
- Förlångsammnar magsäckstömning



Effect of GLP-1 liraglutide on eating behaviour

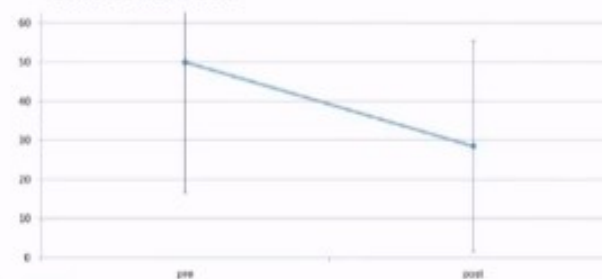
Uncontrolled eating

uncontrolled eating = tendency to eat more than usual due to a loss of control over intake



Emotional eating

emotional eating = inability to resist emotional cues



Restrained eating

cognitive restraint = conscious restriction of food intake

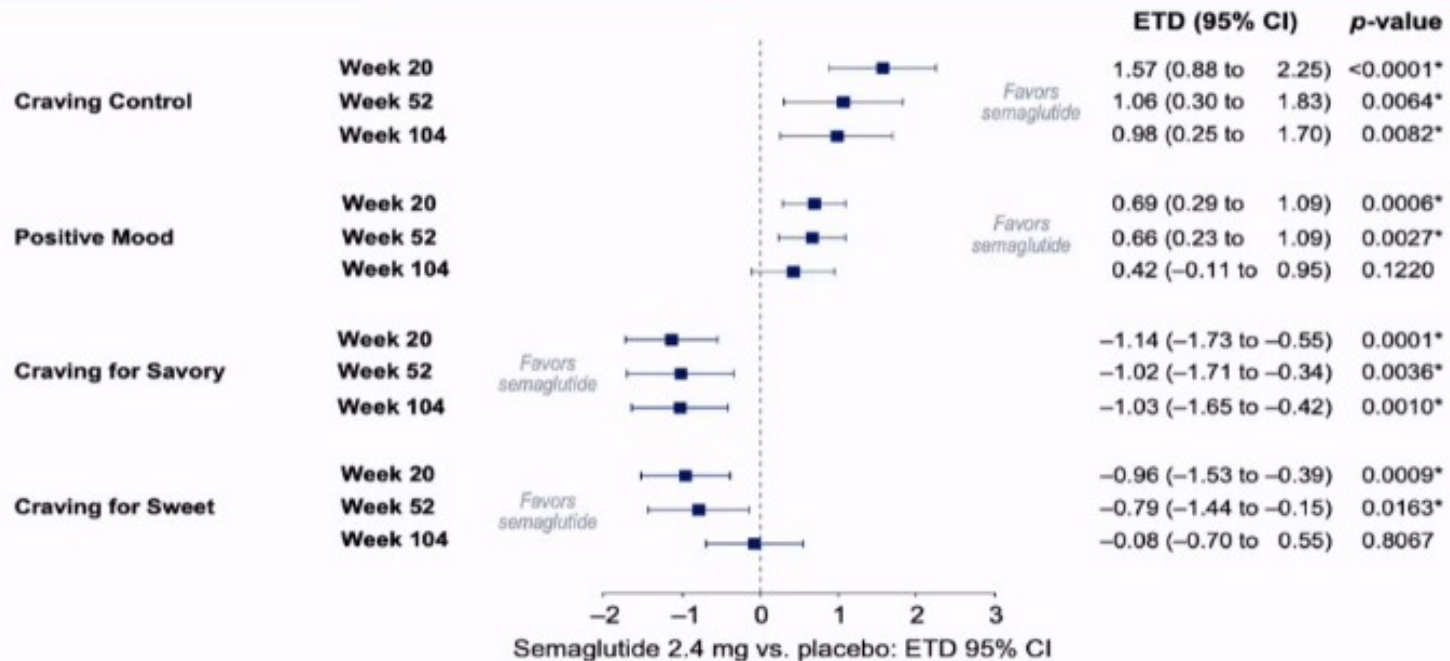


Jensterle, Janez A. Endocrine Research 2016



The effect of semaglutide 2.4 mg on control of eating and taste preference

Change in Control of Eating Questionnaire domain scores



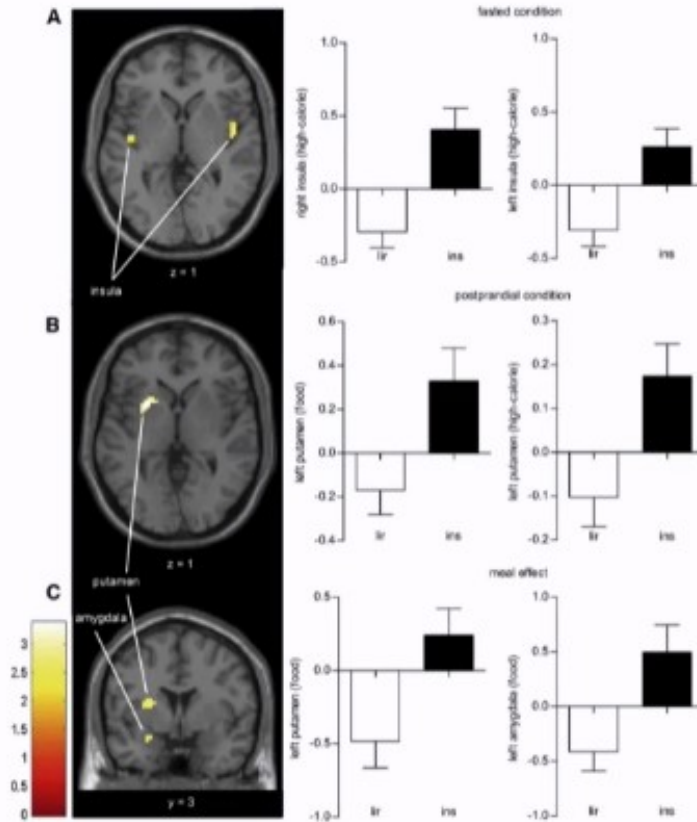
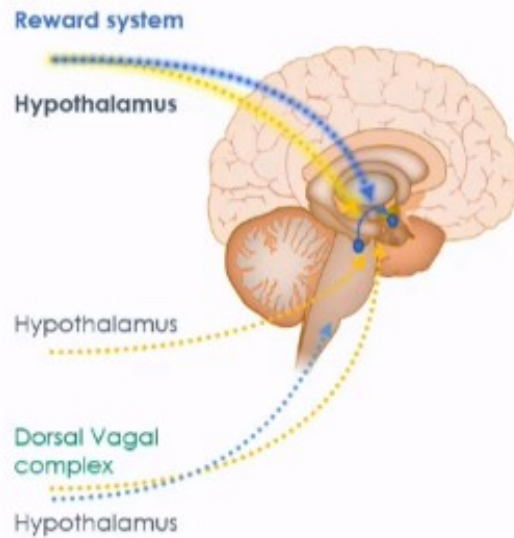
Garvey, W.T., Batterham, R.L., Bhatta, M. *et al.* Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. *Nat Med* 28, 2083–2091 (2022).



Liraglutide Reduces CNS Activation in Response to Visual Food Cues Only After Short-term Treatment in Patients With Type 2 Diabetes

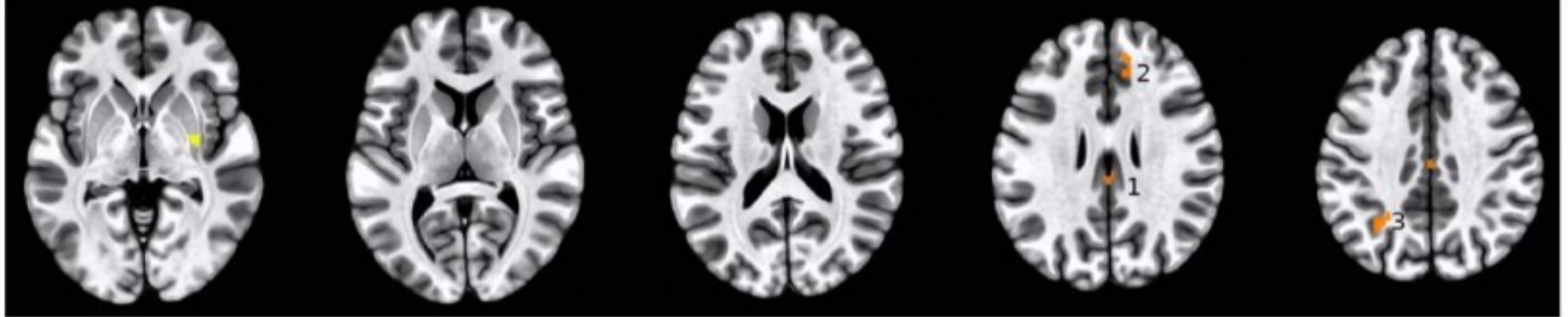
Diabetes Care 2016;39:214–221 | DOI: 10.2337/dci15-0772

Jennifer S. ten Kulve,¹ Dick J. Veltman,²
 Liselotte van Bloemendaal,¹
 Frederik Barkhof,³ Madeleine L. Drent,⁴
 Michaela Diamant,^{1,2} and
 Richard G. Utzerman¹



Results: functional MRI scan

Visual cue task

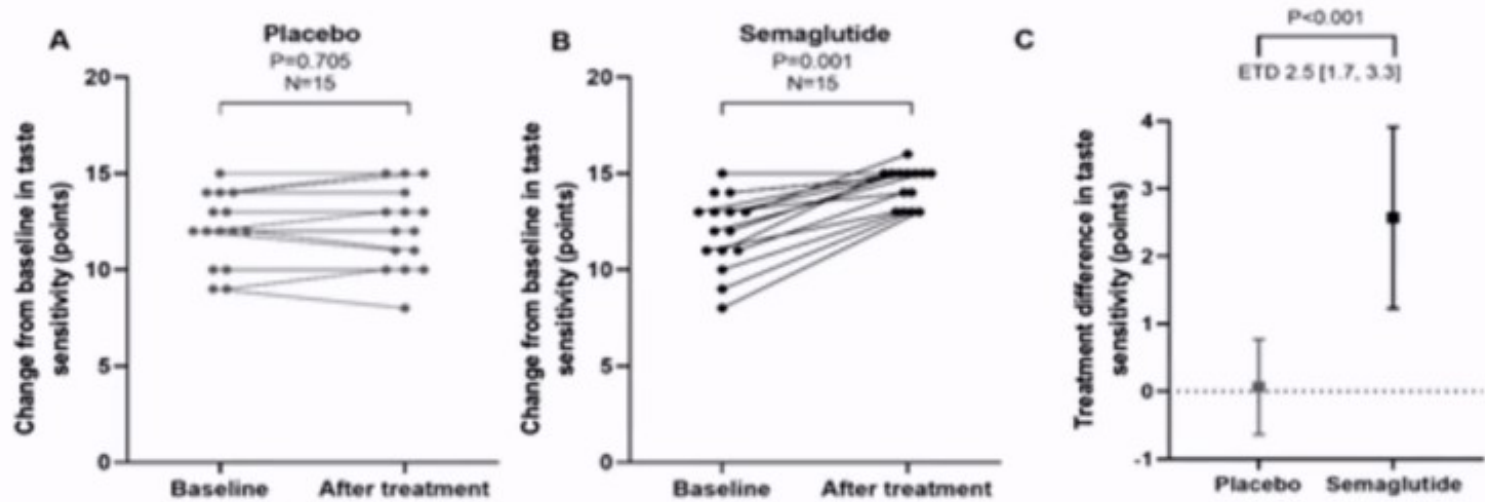


Semaglutide decreased activation in the putamen in response to calorie dense food cues- area involved in the reward system.



Smaksensitivitet

Results: chemical gustometry

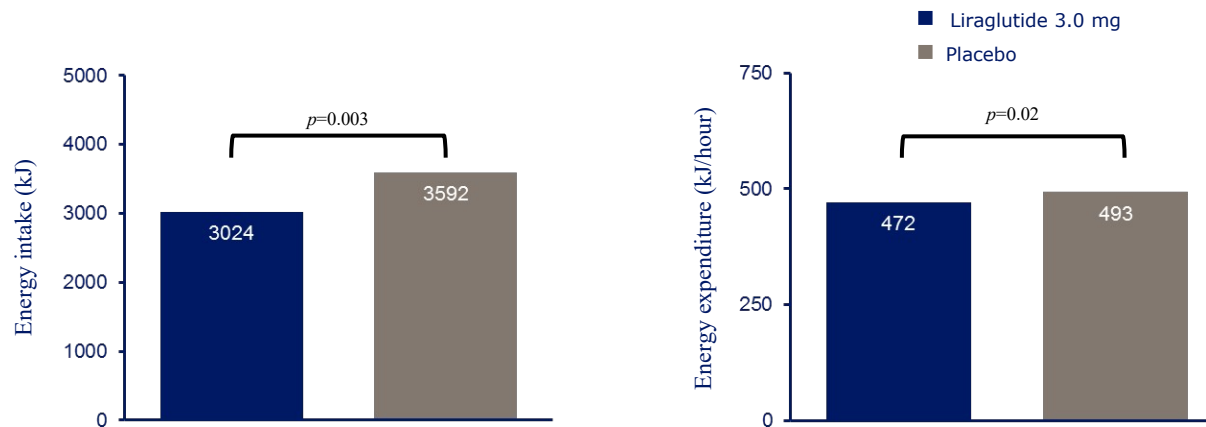


Unpublished data in review

Ökad aktivitet på PET i gyrus angularis om beh med semaglutide



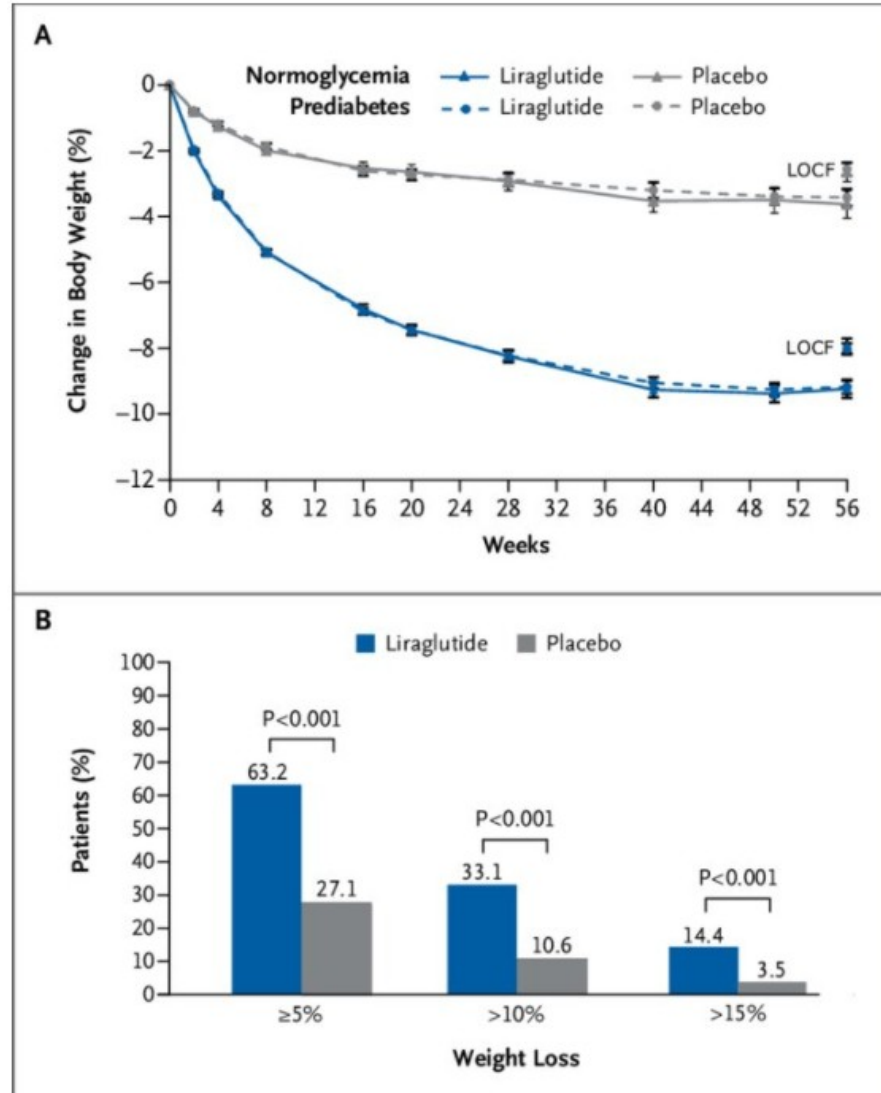
Liraglutide 3.0 mg reducerar energiintag – men ingen effekt på energiförbrukning



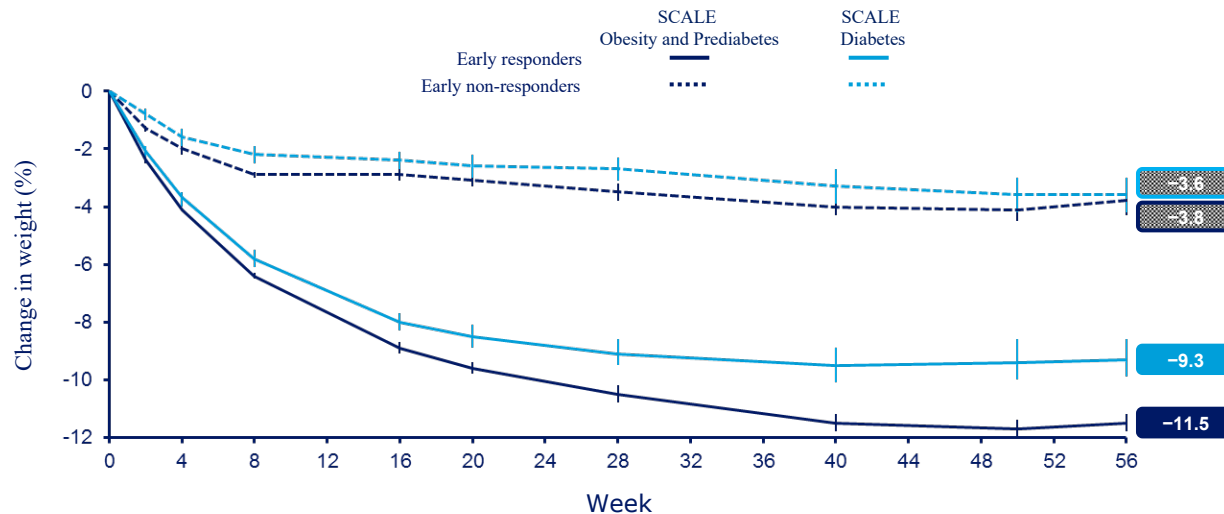
Nu tillgängliga GLP-1-analoger

Liraglutide (Victoza©/Saxenda©)

- 56v
- N3731
- icke-dm
- 3,0mg/dag
- BMI 30+
- Ca 2.500kr/månad



Viktnedgång, uppdelat i responders och non-responders



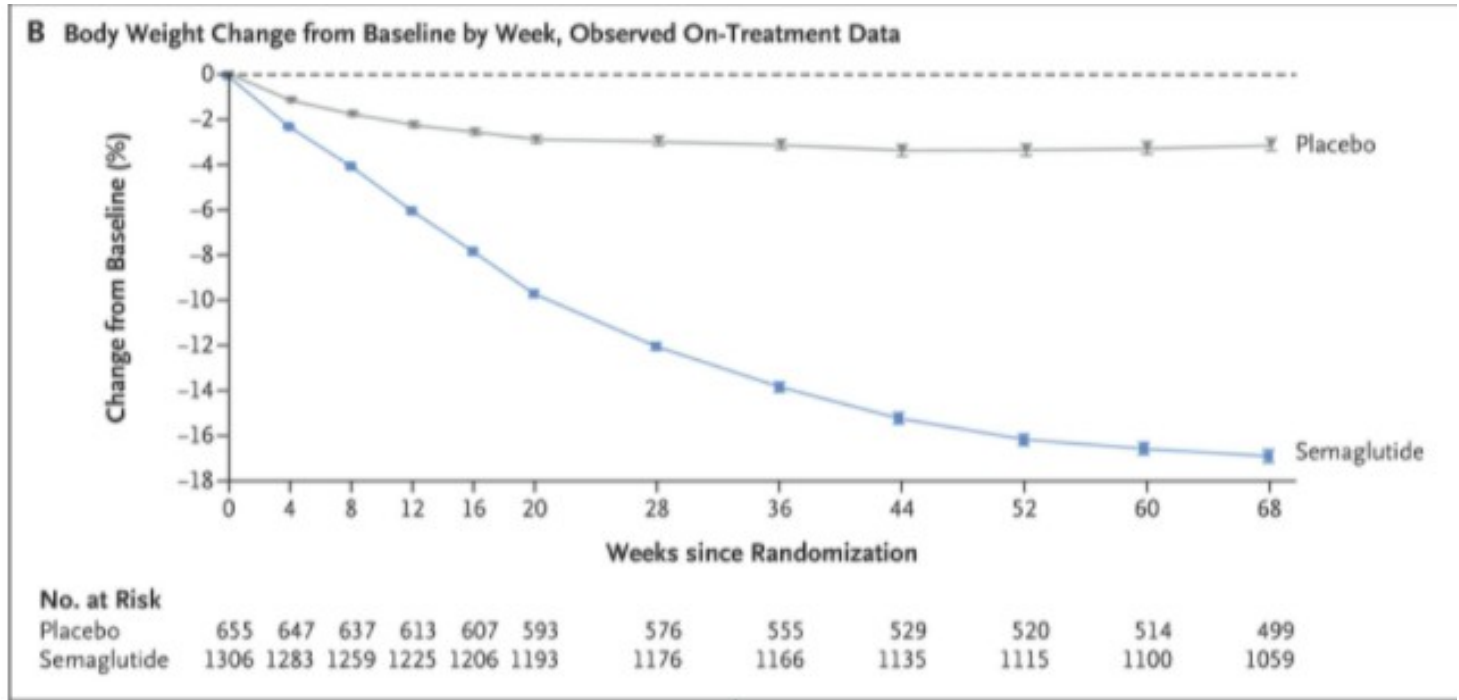
Krav: -5% på 3 mån

Early responders, individuals who achieved $\geq 5\%$ weight loss from baseline at 16 weeks; early non-responders, individuals who achieved $< 5\%$ weight loss from baseline at 16 weeks. Week 56 completers, FAS, fasting visit data only. Line graphs are observed means ($\pm 95\%$ CI). CI, confidence interval; FAS, full analysis set



Under våren kommande GLP-1-analoger Semaglutide(Ozempic©/Wegovy©)

- N1900
- 68v
- 2,4mg/v
(högdosen)

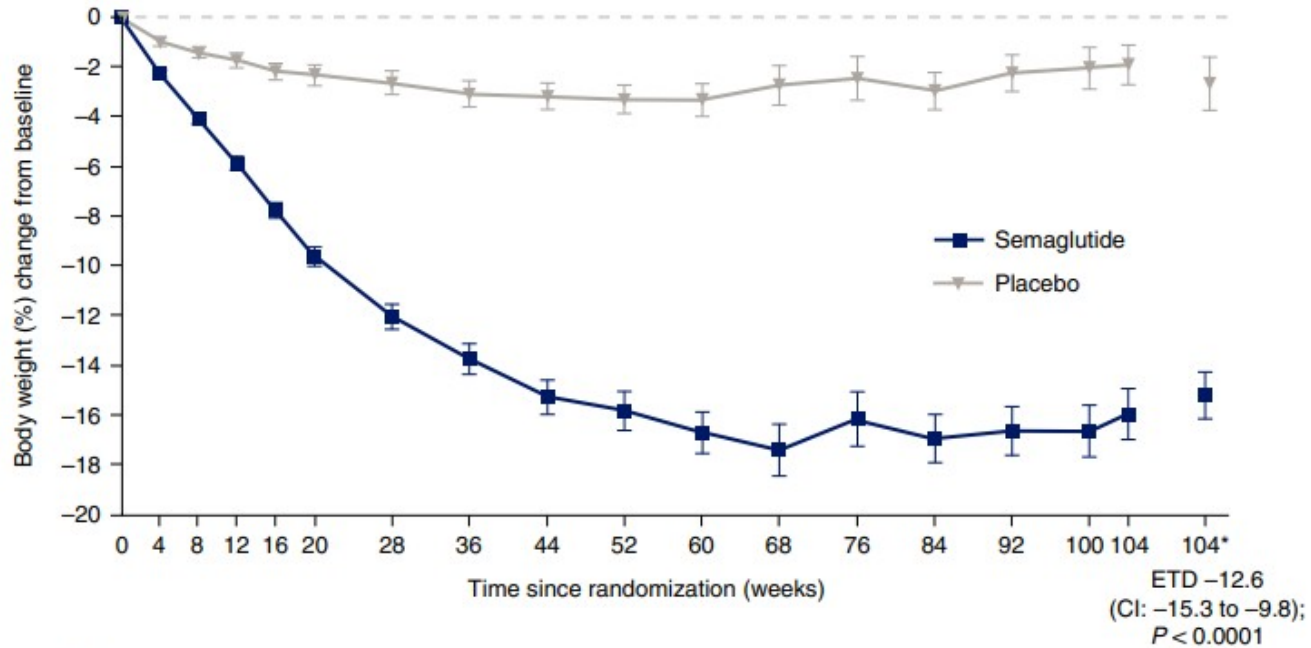


(STEP-1)

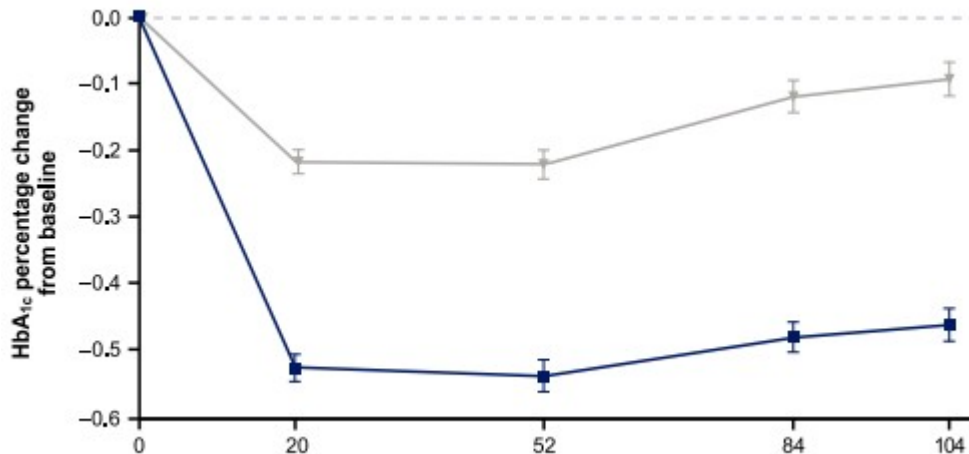
Once-Weekly Semaglutide in Adults with Overweight or Obesity



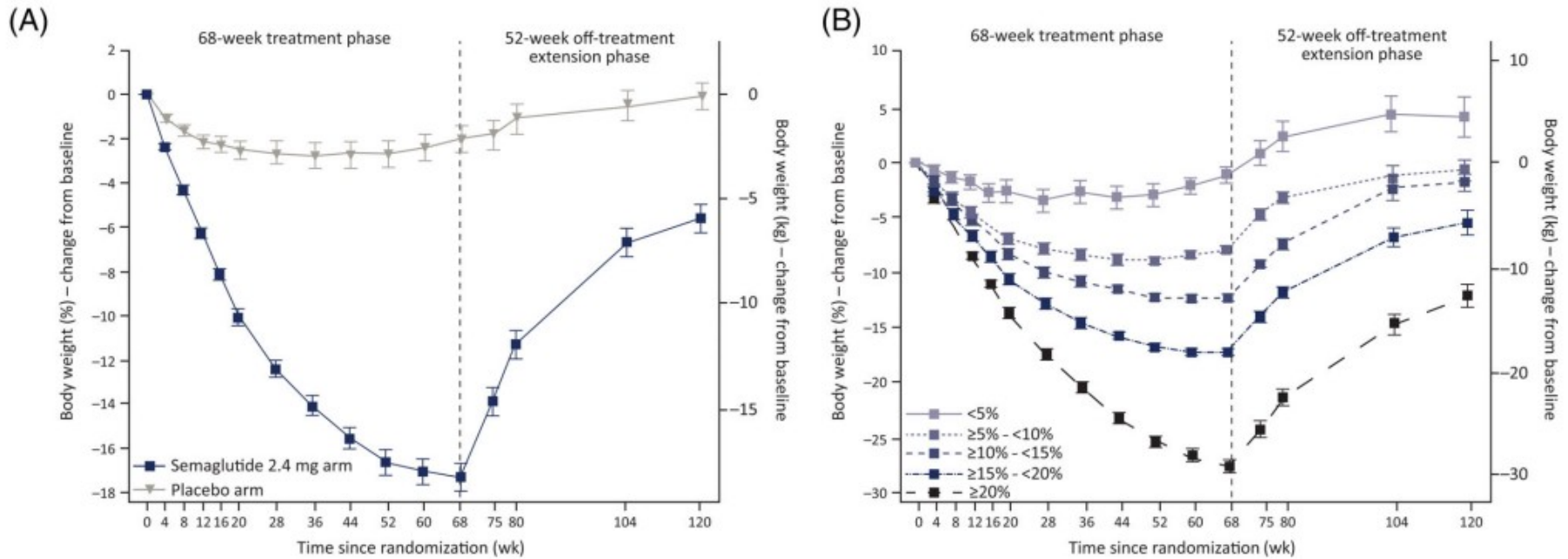
Långtidsdata (2år)



Number of participants



Vad händer efter studien...



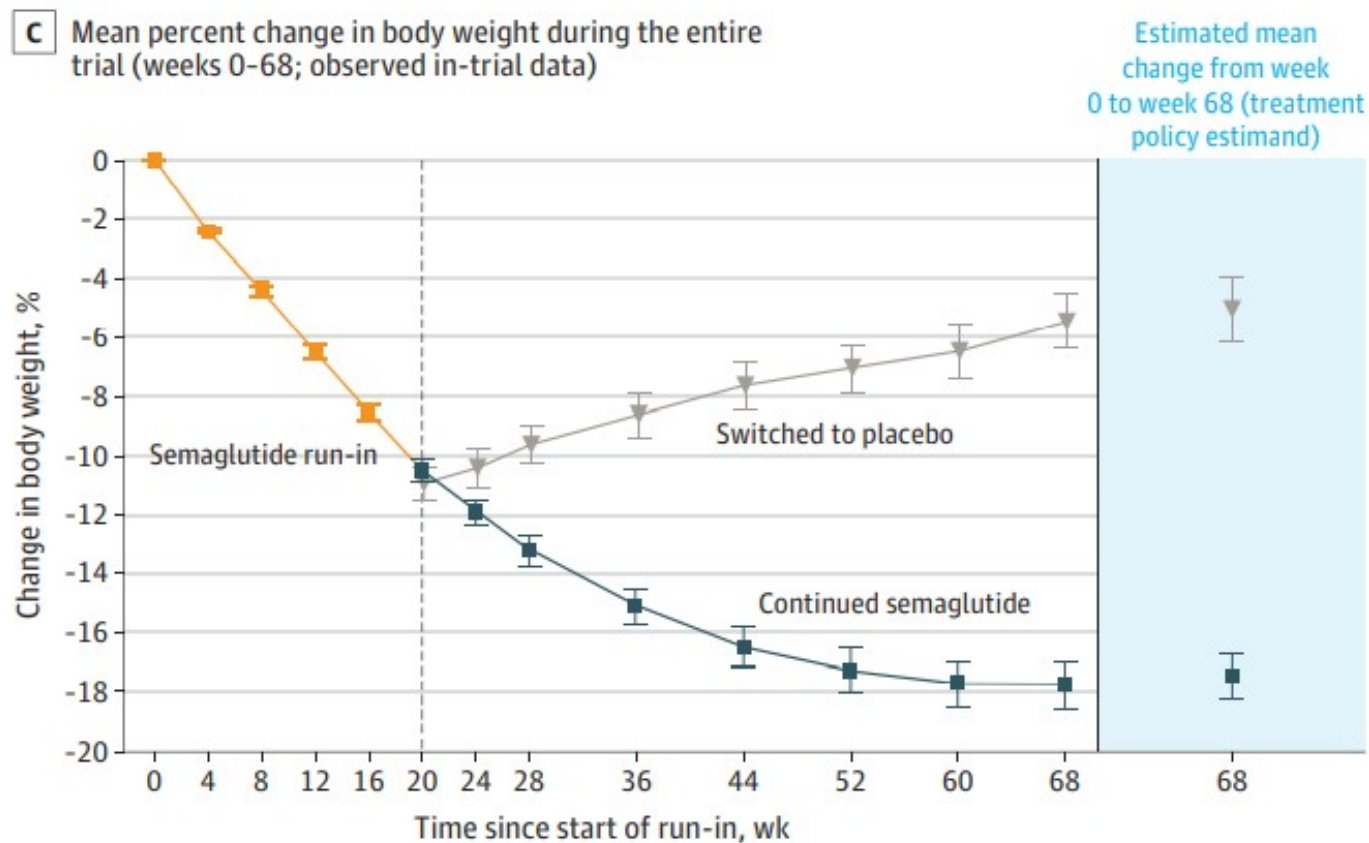
Diabetes Obes Metab. 2022;24:1553-1564.

Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension



Vad händer om man sätter ut GLP-1-analog-behandling, men fortsatt levnadsvanebehandling? (STEP-4)

- N900
- 68v
- alla beh i 20v
- sedan 2,4mg/v vs placebo



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

The STEP 4 Randomized Clinical Trial

Domenica Rubino, MD¹; Niclas Abrahamsson, MD²; Melanie Davies, MD^{3,4}; et al



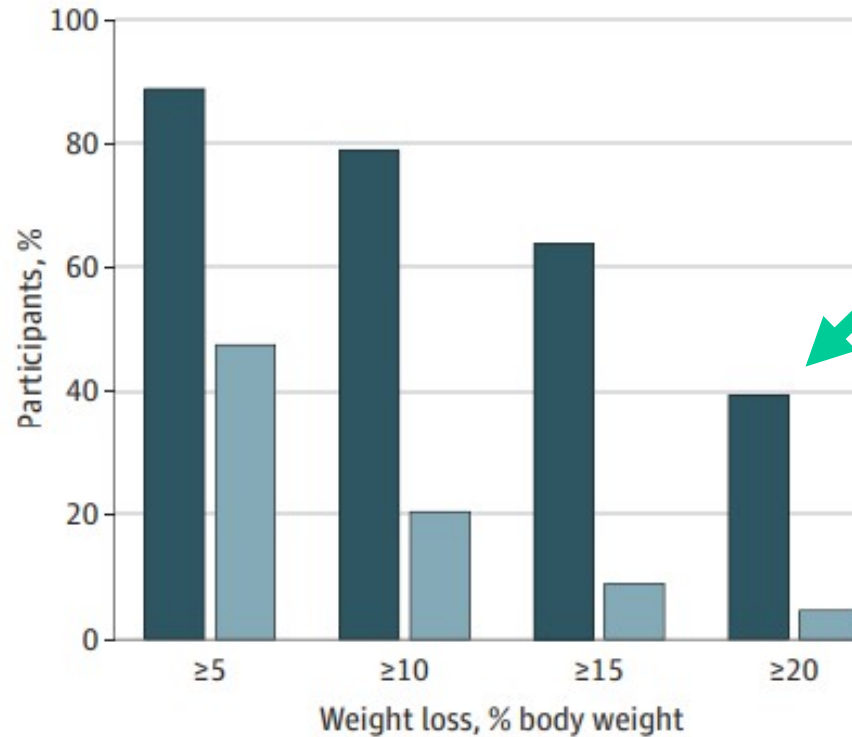
Lägre dos och långsam uttrappning kanske kan hjälpa?

- 64v, BMI 33,2. 49 år. n2200.
- Medeldos 0,77mg (istf 2,4mg semaglutide)
- 15% vikt nedgång
- Digital app som stöd i levnadsvaneförändringar
- Trappade ned långsamt under 9 veckor
- Dock: 26 veckor n1400, 64v n360, 76v n185



Semaglutide - STEP-4

D Proportion of participants achieving thresholds of weight loss during the entire trial (weeks 0-68; observed in-trial data)



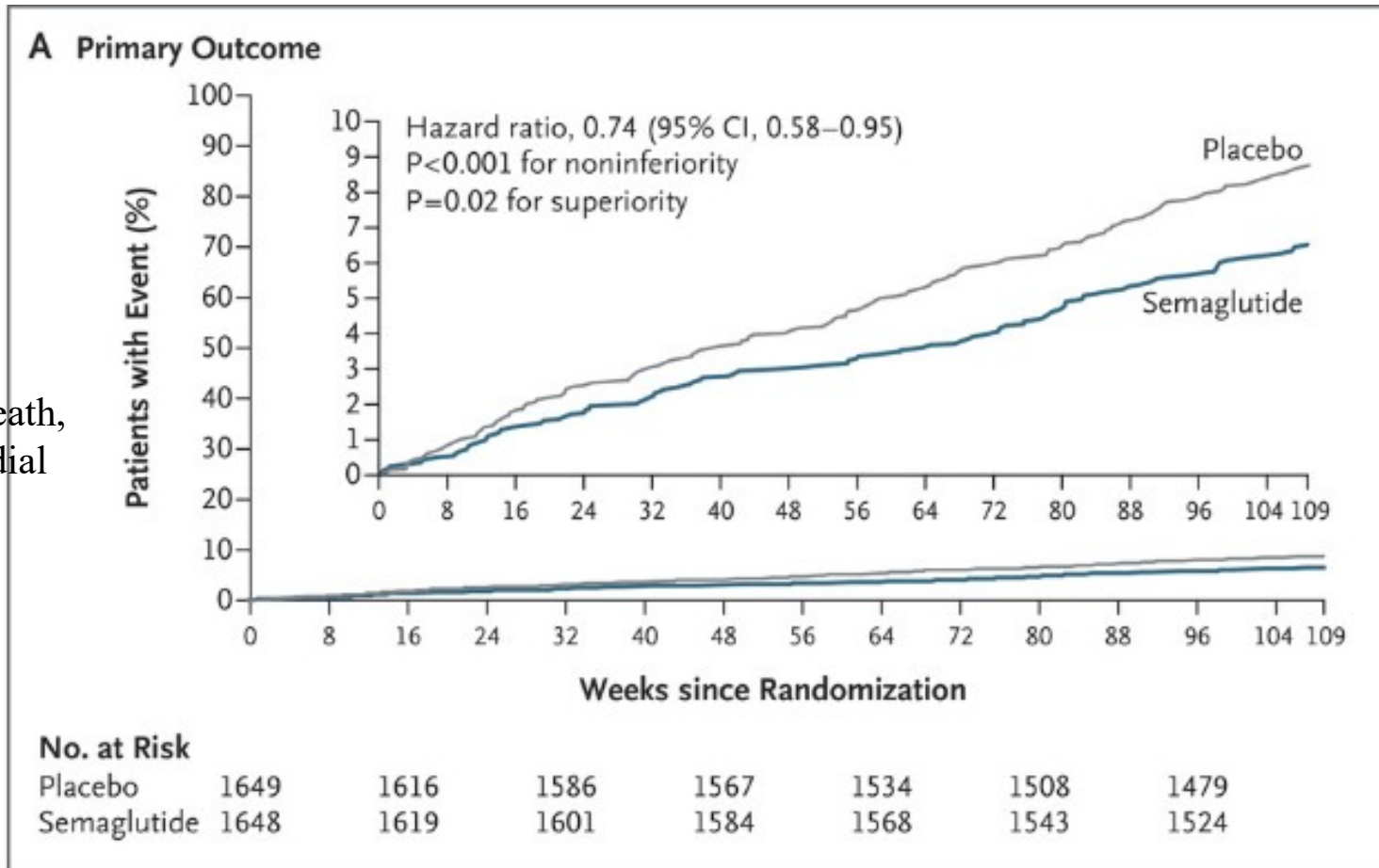
- N900
- 68v
- alla beh i 20v
- sedan 2,4mg/v vs placebo

■ 20 weeks of semaglutide run-in + 48 weeks of continued semaglutide, 2.4 mg/wk (n = 520)
■ 20 weeks of semaglutide run-in + 48 weeks of placebo (n = 250)



Semaglutide –mortalitet hos diabetiker

- N3300
- 2 år
- a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)



NEJM 2016

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

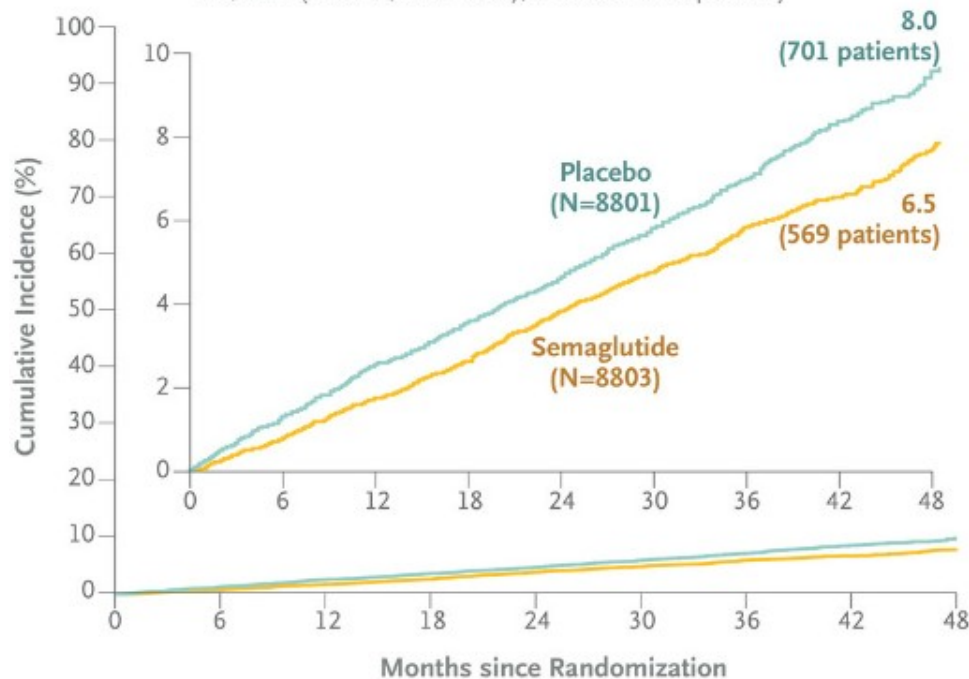
Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D.,



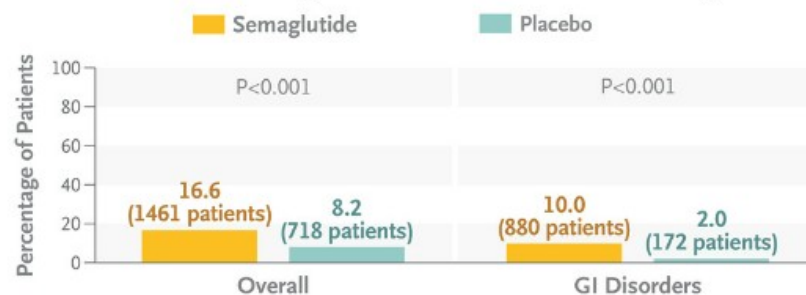
Semaglutides effekt på mortalitet, ickeddiabetiker: -20%

Death from Cardiovascular Causes, Nonfatal MI, or Nonfatal Stroke

HR, 0.80 (95% CI, 0.72–0.90); P<0.001 for superiority

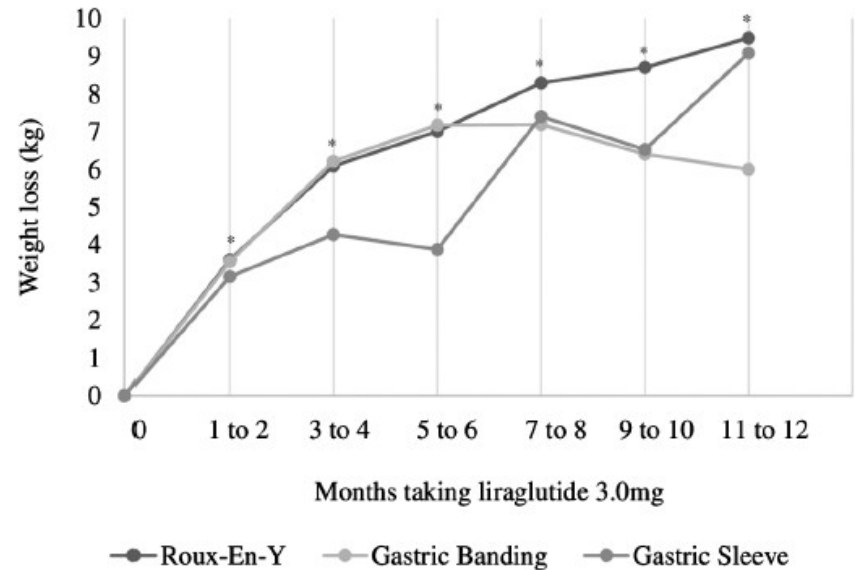


Adverse Events Leading to Permanent Discontinuation of Regimen



Funkar det på opererade patienter?

Liraglutide 3.0 mg for the management of insufficient weight loss or excessive weight regain post-bariatric surgery

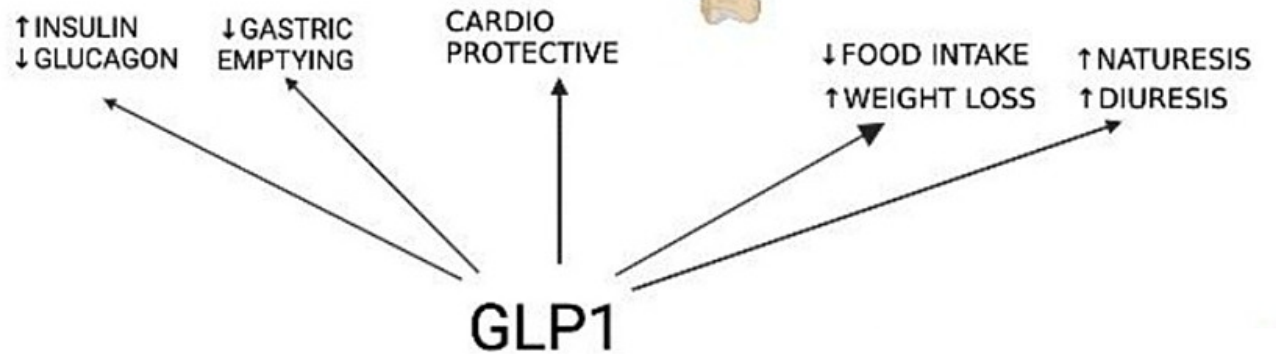
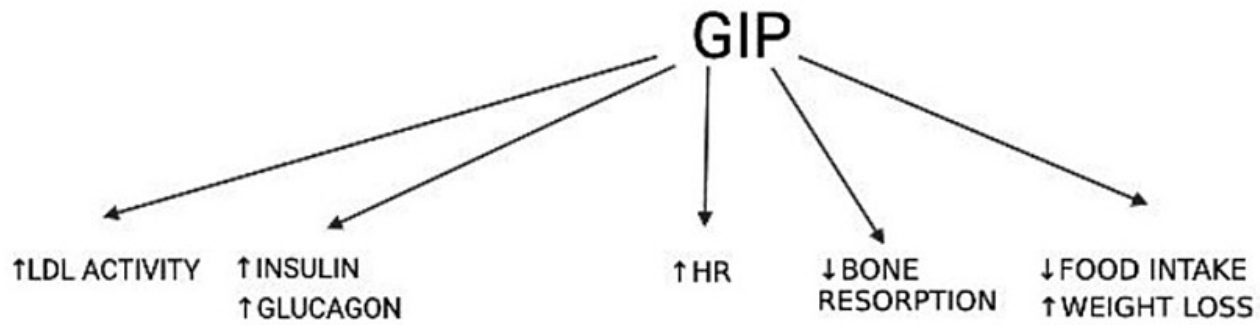


*Significantly different from baseline regardless of surgical group (P<0.05)

FIGURE 1 Weight loss while taking liraglutide 3.0 mg over time by type of bariatric surgery

Variable	Roux-en-Y bypass	Gastric band	Gastric sleeve
Sample size (n)	53	50	14
Age (y)	49.9 ± 9.1	52.5 ± 9.5	51.4 ± 10.3
Men (n, %)	3 (5.7) ^a	8 (16.0)	4 (28.6)
Pre-bariatric surgery BMI (kg/m ²)	50.8 ± 11.2	47.6 ± 13.1 ^e	52.2 ± 11.9
Maximum weight change post-bariatric surgery (kg)	-51.6 ± 23.5 ^{a,b}	-29.8 ± 23.3 ^e	-34.7 ± 19.5
Weight change from lowest post-bariatric surgery weight to initiation of liraglutide 3.0 mg (kg)	19.0 ± 13.5	25.4 ± 20.4 ^e	15.8 ± 14.1
Weight change from lowest post-bariatric surgery weight to initiation of liraglutide 3.0 mg (%) ^c	44.8 ± 54.9 ^a	80.0 ± 79.7 ^f	48.4 ± 31.7 ^g
Preliraglutide BMI (kg/m ²)	39.0 ± 7.0 ^{a,b}	45.4 ± 11.0	45.4 ± 9.6
Weight change on liraglutide 3.0 mg (kg)	-7.1 ± 8.7 ^d	-6.0 ± 7.2 ^d	-4.5 ± 4.5 ^d
Weight change on liraglutide 3.0 mg (%)	-6.6 ± 7.1	-4.9 ± 5.6	-3.6 ± 3.0

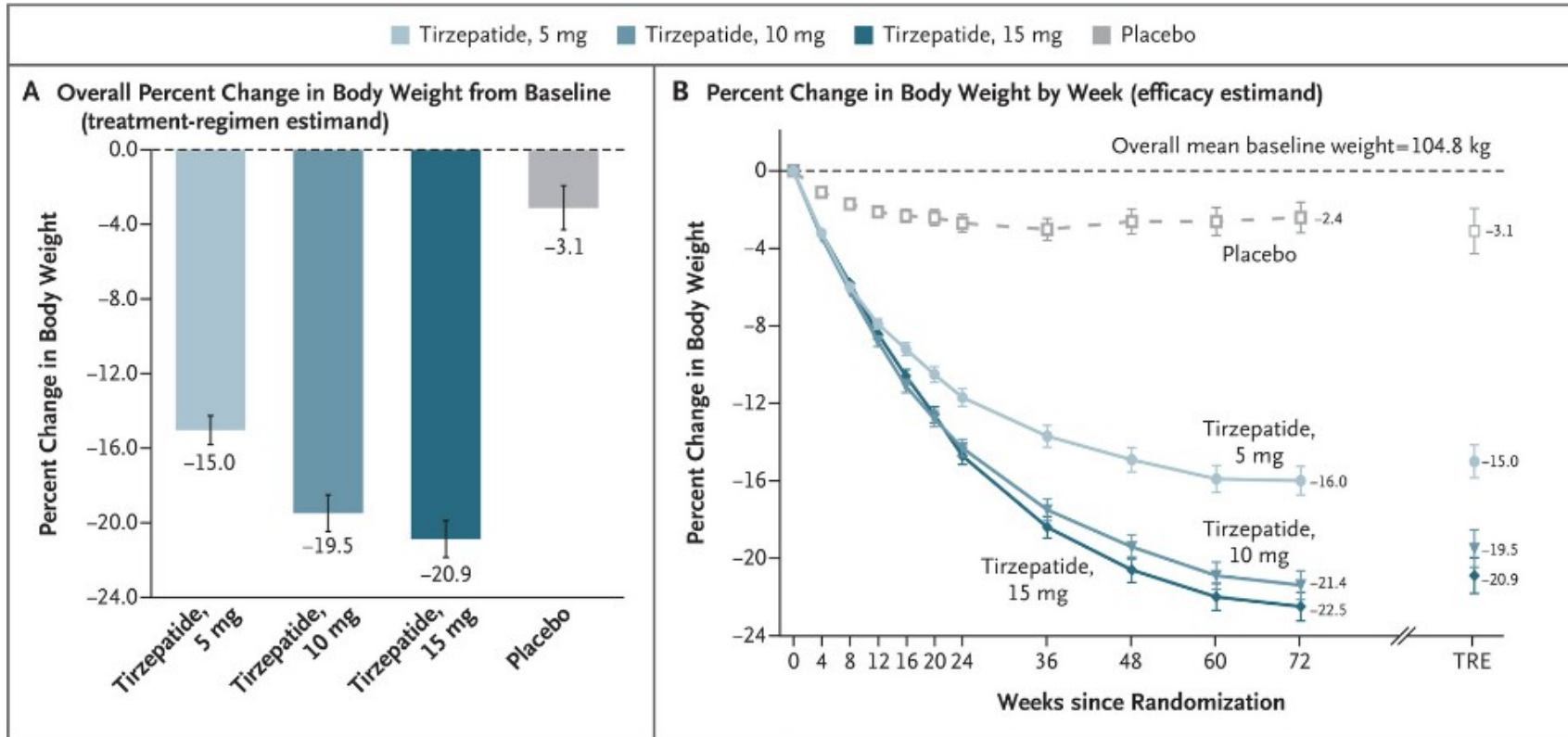




**GLP-1/GIP
Tirzepatide
(Mounjaro®)**



Tirzepatide - vikteffekt



- N2500
- bmi 30 or 27 with comorbidity
- non-diabetics

N Engl J Med 2022; 387:205-216

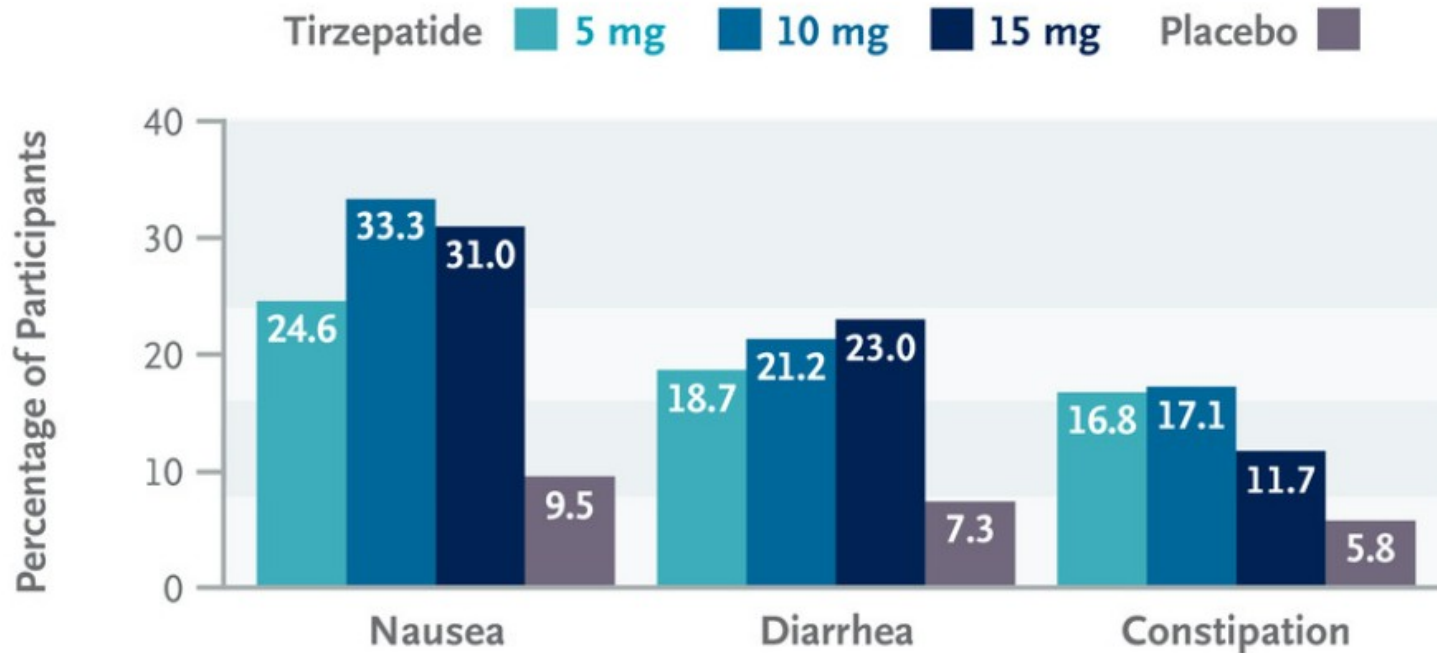
Tirzepatide Once Weekly for the Treatment of Obesity

Ana M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Akihiro Kiyosue, M.D., Ph.D., Shuju Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Ilavick, M.D., Ph.D., and Adam Stefanik, M.D., Ph.D. for the SURMOUNT-1 Investigators*



Tirzepatide - biverkningar

Adverse Events Occurring in $\geq 5\%$ of Participants

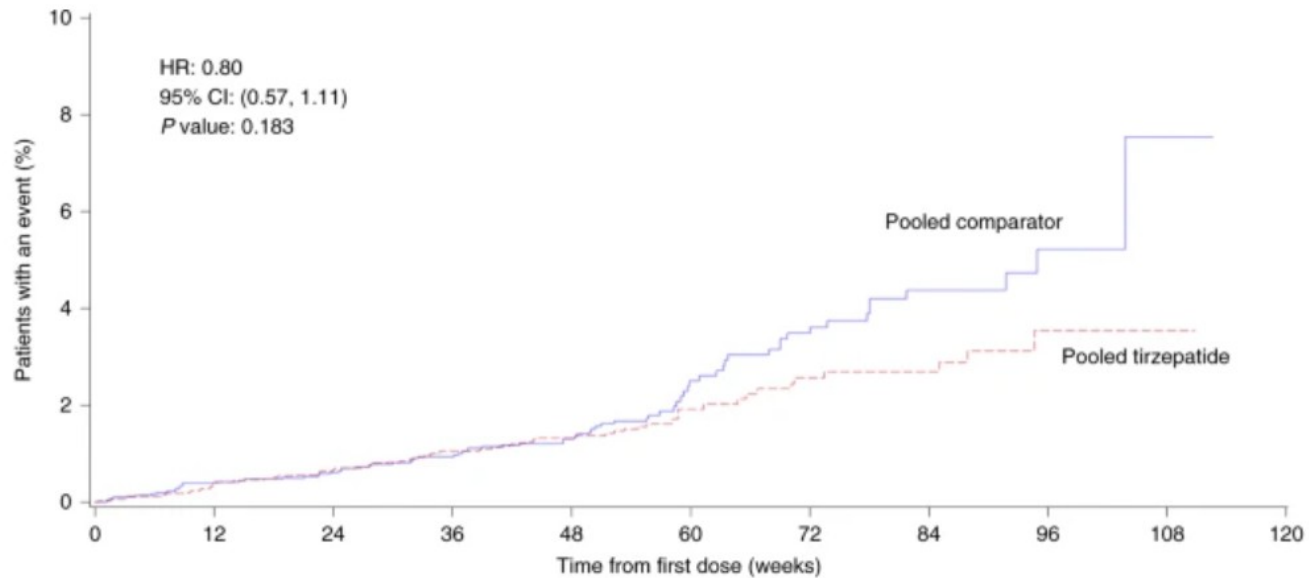


Variable	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)
	<i>number (percent)</i>			
Participants with ≥ 1 adverse event during treatment period	510 (81.0)	520 (81.8)	497 (78.9)	463 (72.0)



Tirzepatide - mortalitetsdata

Fig. 2: Adjusted Kaplan–Meier plot of pooled tirzepatide versus pooled comparator effect on time to first occurrence of adjudication-confirmed MACE-4 (primary outcome).



Planned follow-up period

GPGB (30 weeks)

SURPASS-1, -2 and -5 (44 weeks)

SURPASS-3 and J-mono (56 weeks)

SURPASS-4 (56–108 weeks)

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

Naveed Sattar  Darren K. McGuire, Imre Pavo, Govinda J. Weerakkody, Hiroshi Nishiyama, Russell J. Wiese & Sophia Zoungas 

Nature Medicine 28, 591–598 (2022) | [Cite this article](#)



Kommande inkretiner/Tarmhormoner



Oralt Semaglutide

- 50mg tablett (istf 14 mg för diabetes)
- 15% viktnedgång jmf placebo



Survodutide

- Glukagon/GLP1-agonist
- Aptitnedgång
- Ökar leverns energiomsättning
- Magsäckstömning
- 19% viktnedgång på 46v i högdos, ej platåfas då
- GI-biverkningar 90%
- Inga allvarliga jmf med placebo

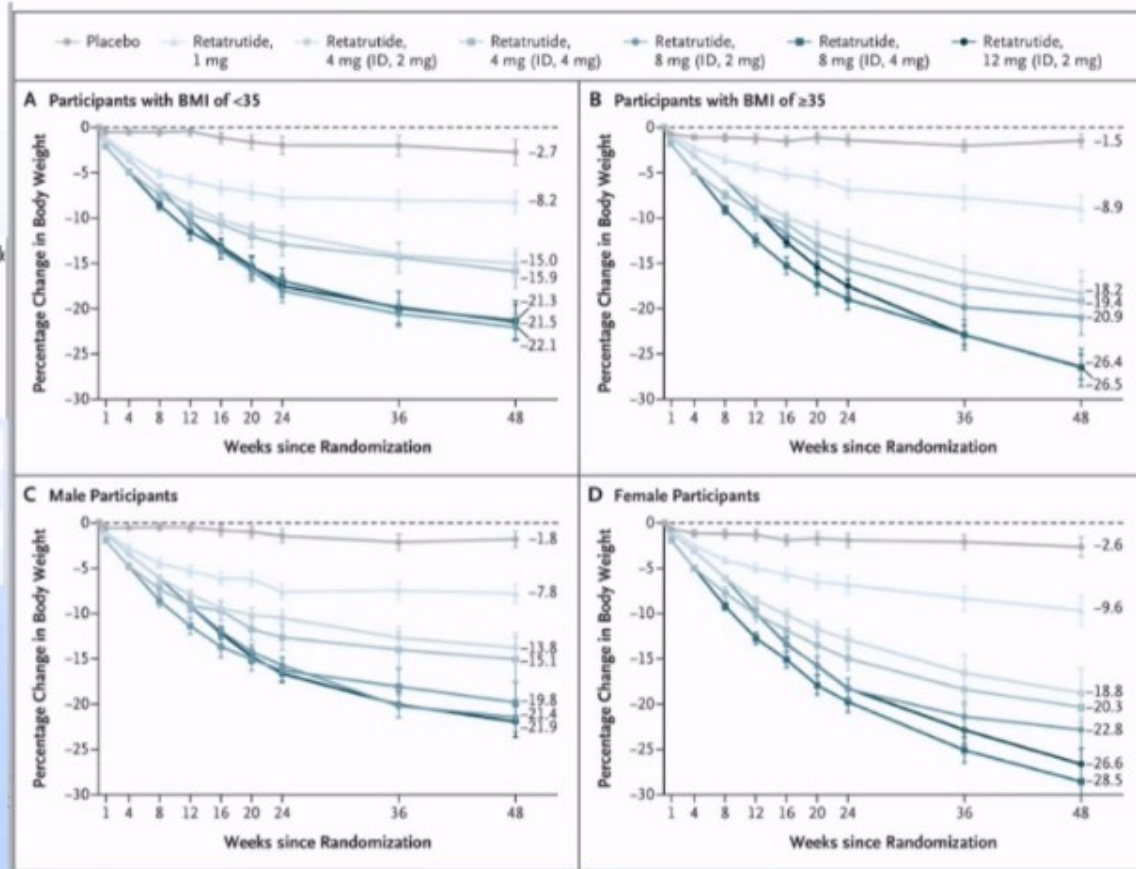


Trippelagonist Retatrutide. GLP-1/GIP/Glukagon

Triple-Hormone-Receptor Agonist Retatrutide for Obesity — Phase 2 Trial

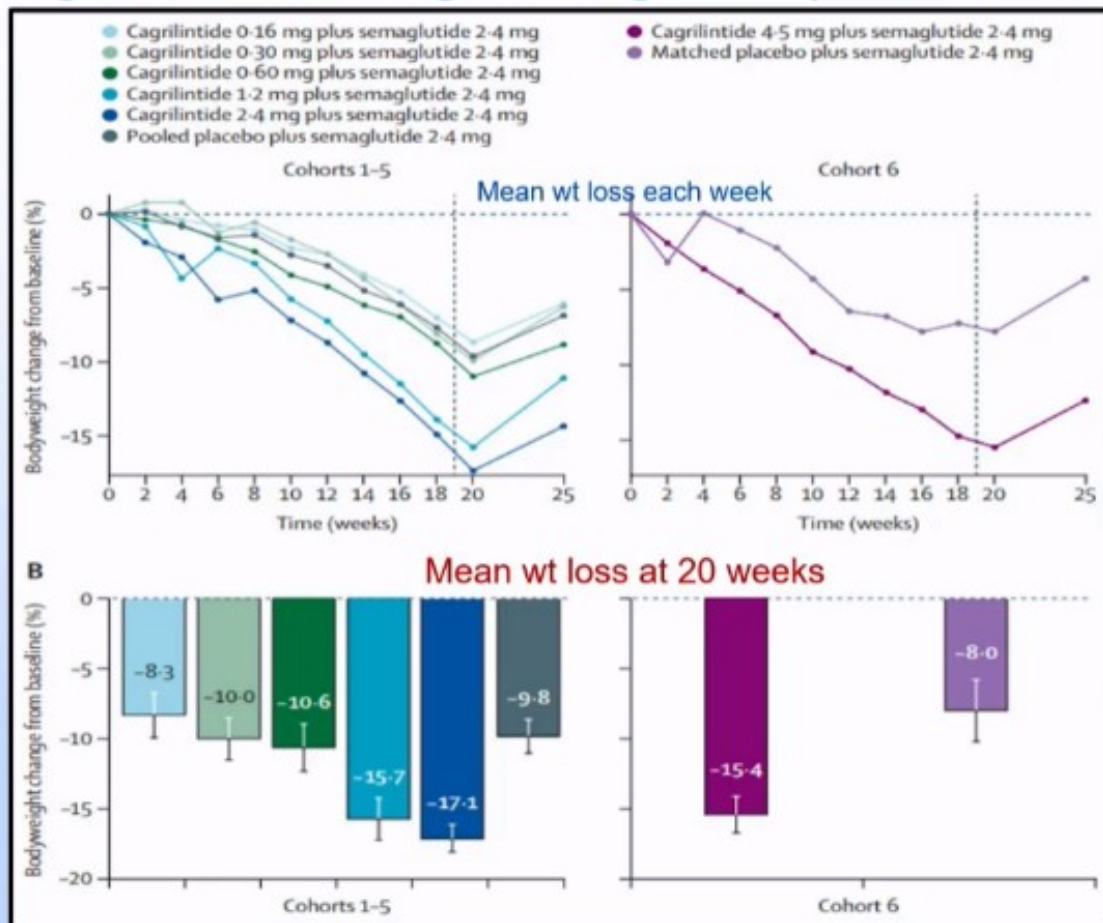
Adverse Event	Placebo Group (N=70)	Retatrutide		
		1 mg (N=69)	4 mg (ID, 2 mg) (N=33)	4 mg (ID, 4 mg) (N=33)
Nausea	8 (11)	10 (14)	6 (18)	12 (36)
Covid-19	14 (20)	13 (19)	4 (12)	6 (18)
Decreased appetite	6 (9)	9 (13)	6 (18)	8 (24)
Diarrhea	8 (11)	6 (9)	4 (12)	4 (12)

Most common AEs with retatrutide were GI; dose-related, mostly mild to moderate in severity, and partially mitigated with a lower starting dose (2 mg vs. 4 mg).



Cagrilintide with semaglutide 2.4 mg SQ/week for weight management: phase 1b RCT

- mean estimated treatment differences at 20 wks 6, 7.2, and 7.2% for 1, 2.4 and 4.5mg cagrilintide + semaglutide compared to placebo + semaglutide
- PK $T_{1/2}$ of cagrilintide: 159–195 h, with median T_{max} of 24–72 h consistent with weekly administration



Enebo, Berthelsen, et al. *Lancet*. 2021;397:1736-1748

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Amylin-analog som tillägg till semaglutide





Framtid

GLP-1/Glukagon
GLP-1/GIP/Glukagon
GLP-1/GIPantagonist(sic)
GLP-1/PYY
GLP-1/FGF-21
GLP-1/GLP-2
GLP-1/Amylin

Centrala droger, Leptin-analoger, FGF-21,
Vaccin (Ghrelin, Somatostatin,
Adenovirus36)

