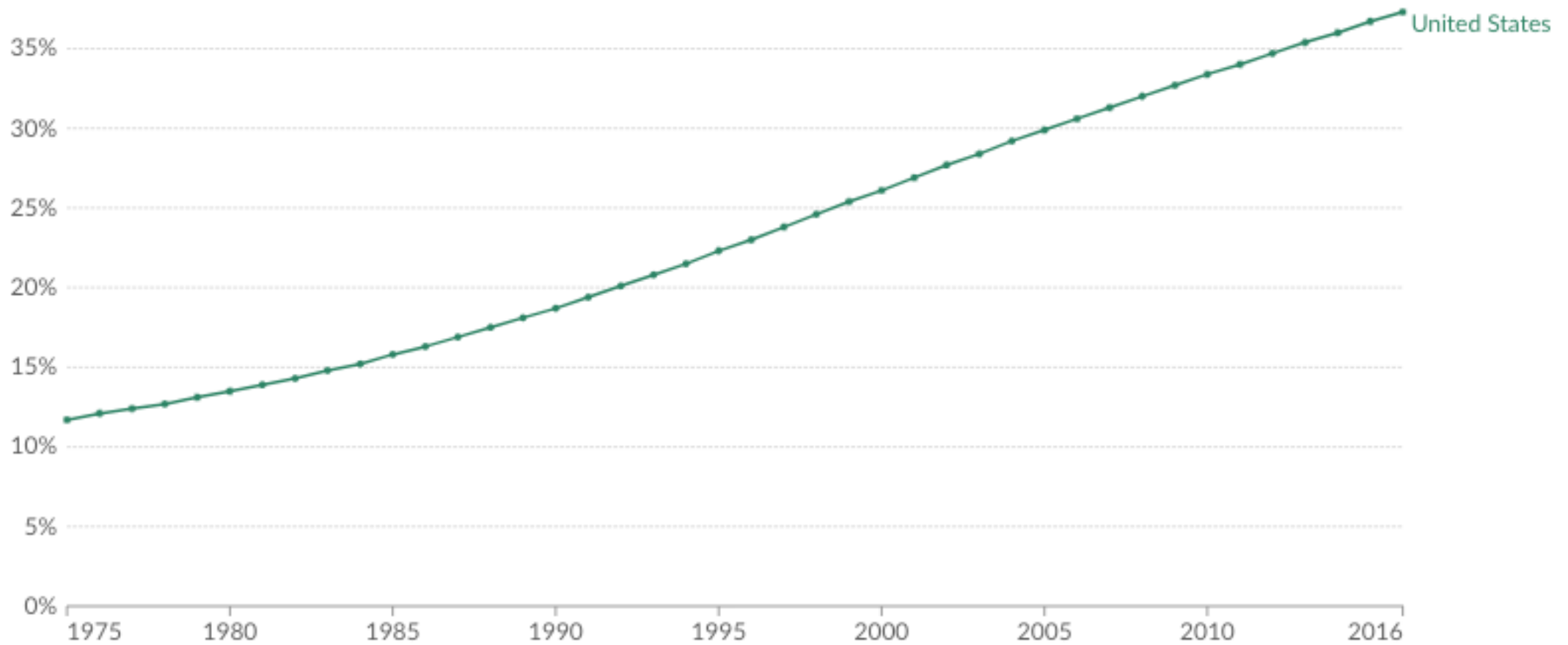


Use of Anti-Obesity Medications in Post-Operative Metabolic and Bariatric Surgery (MBS) Patients

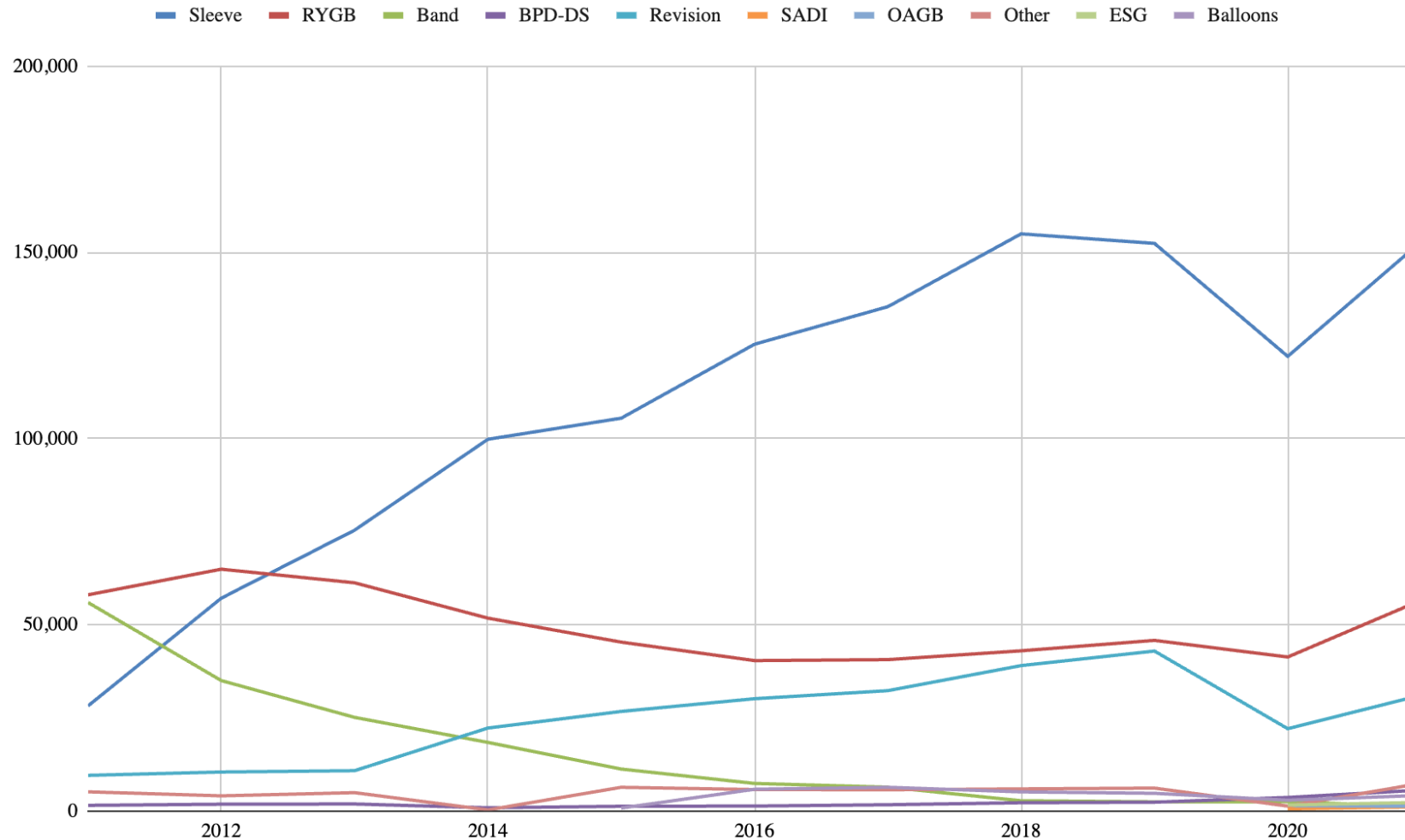
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February 21, 2024

A growing and large proportion of the US population is obese (BMI > 30)



Consistent increases in MBS volume and dominance of sleeve gastrectomy (SG) in the US



There is an unmet clinical need for effective therapeutics in patients struggling to lose weight post-MBS

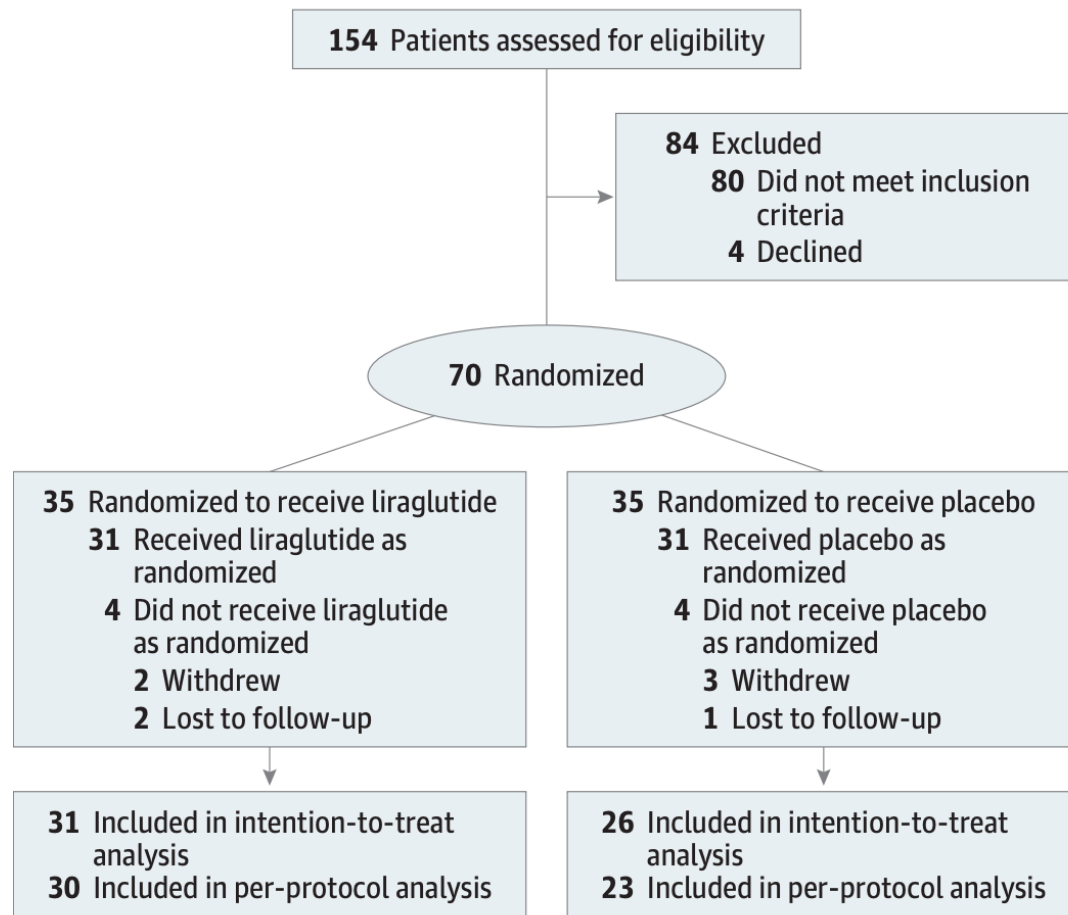
- Data from 22 trials shows bariatric surgery compared with any nonsurgical intervention is more effective in promoting weight loss and improvement in co-morbid outcomes ([Sudlow et al 2019](#))
- While on a population level metabolic surgery is highly effective, on an individual level the response is highly variable
- **Poor weight loss or weight regain**, resulting in less than 20% weight loss, **affect up to 1 in 4 patients** who undergo metabolic surgery ([Mok et al 2023](#))

Overview of anti-obesity medications

Table 1
Summary of the most commonly prescribed FDA-approved antiobesity medications*

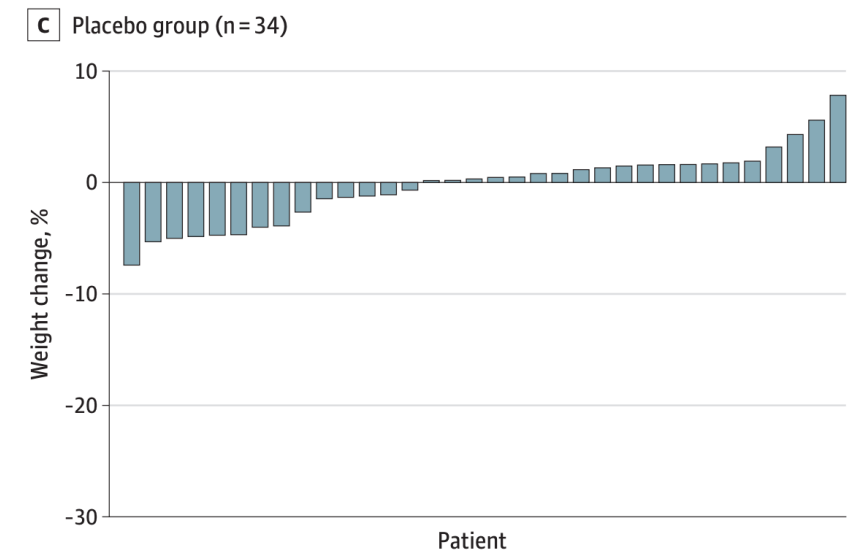
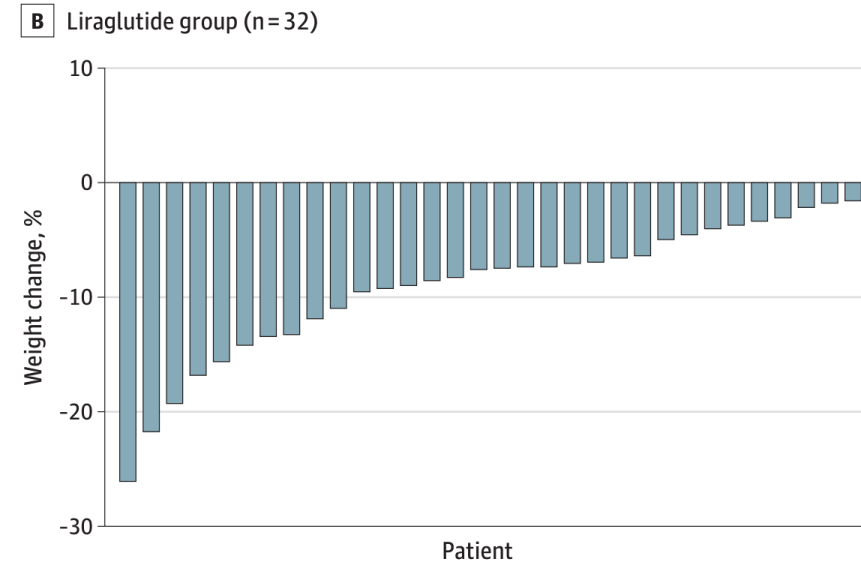
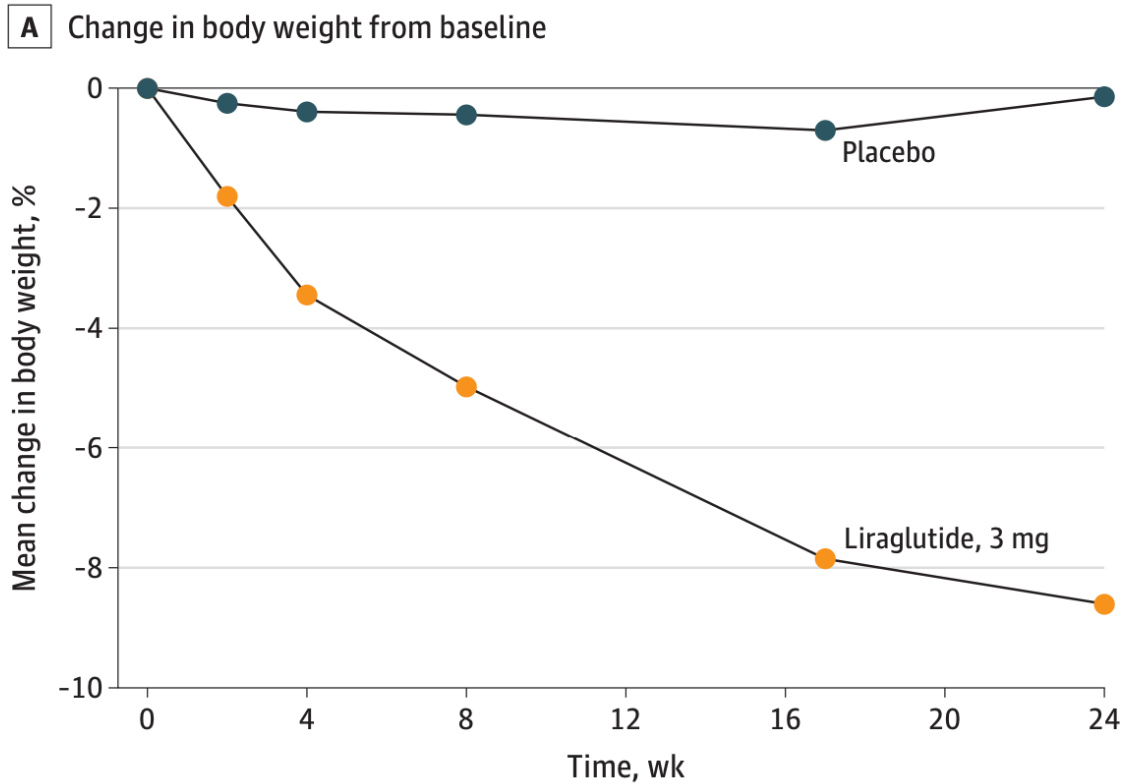
Category	Orlistat	Phentermine	Phentermine-topiramate	Naltrexone-bupropion	Liraglutide	Semaglutide
Class	Lipase inhibitor	Sympathomimetic amine	Sympathomimetic amine-antiepileptic	Antidepressant-opioid receptor antagonist	Glucagon-like peptide 1 analogue	Glucagon-like peptide 1 analogue
Administration	PO	PO	PO	PO	SQ	SQ
Renal adjustment	No	Maximum daily dose (MDD) of 15 mg. Avoid in dialysis or ESRD	MDD of 7.5–46 mg. Avoid use with severe impairment.	MDD of 1 tablet bid. Avoid use in ESRD.	Use with caution. Postmarketing report of acute kidney injury.	Use with caution. Postmarketing report of acute kidney injury.
Hepatic adjustment	No	No	MDD of 7.5–46 mg. Avoid use with severe impairment.	MDD of 1 tablet bid.	Use with caution.	Use with caution.
Contraindications	Chronic malabsorption syndrome, cholestasis	Cardiovascular disease, hyperthyroidism, glaucoma, agitated states, history of drug abuse, within 14 d of MAOI	Glaucoma, hyperthyroidism, or within 14 d of MAOI	Uncontrolled hypertension, seizure disorders, eating disorders (anorexia nervosa or bulimia), chronic opioid therapy, within 14 d of MAOI, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 3
Drug interactions	Cyclosporine, fat-soluble vitamins, levothyroxine, warfarin	MAOI, alcohol, adrenergic neuron blockers	Oral contraceptives, CNS depressants (i.e., alcohol), non-potassium-sparing diuretics	CYP2D6 metabolizer (i.e., antidepressants, antipsychotics, beta-blockers, and type 1C antiarrhythmics), CYP2B6 inhibitors, CYP2B6 inducers, drugs that lower seizure threshold, dopaminergic drugs	May slow down absorption of oral medications	May slow down absorption of oral medications

BARI-OPTIMISE Trial: Liraglutide 3.0mg against placebo in patients with poor weight loss



Characteristic	Mean (SD)		
	Placebo (n = 35)	Liraglutide, 3.0 mg (n = 35)	Overall trial (N = 70)
Age, y	48.4 (10.6)	46.7 (10.8)	47.6 (10.7)
Sex, No. (%)			
Female	26 (74)	26 (74)	52 (74)
Male	9 (26)	9 (26)	18 (26)
Diabetes status, No. (%)			
Type 2 diabetes	4 (11)	5 (14)	9 (13)
No diabetes	31 (89)	30 (86)	61 (87)
Metabolic surgical procedure, No. (%)			
RYGB	3 (9)	2 (6)	5 (7)
SG	32 (91)	33 (94)	65 (93)
Duration since surgery, mo	49.1 (33.7)	55.1 (33.3)	52.1 (33.4)
Percentage weight loss since surgery	7.4 (7.4)	7.0 (7.8)	7.2 (7.6)
Body mass index ^a	44.6 (8.3)	41.6 (6.9)	43 (7.5)
Body mass index, ^a No. (%)			
<30	0	0	0
≥30 to <35	3 (7)	4 (11)	7 (10)
≥35 to <40	10 (29)	13 (33)	23 (33)
≥40	22 (62)	18 (51)	40 (57)
Race and ethnicity, ^b No. (%)			
Asian	1 (3)	4 (11)	5 (7)
Black	9 (26)	5 (14)	14 (20)
White	22 (63)	22 (63)	44 (63)
Asian and White	0	1 (3)	1 (1)
Black Caribbean and White	1 (3)	2 (6)	3 (4)
Other multiple races or ethnicities ^c	2 (6)	1 (3)	3 (4)
Weight, kg	123.5 (24.8)	116.1 (23.6)	119.8 (24.3)
Fat mass, kg ^d	54.2 (15.1)	49.4 (11.3)	51.9 (13.5)
Lean mass, kg ^d	67.1 (13.1)	63.7 (11.0)	65.5 (12.2)
Bone density, g/cm ^{2d}	1.2 (0.1)	1.2 (0.1)	1.2 (0.1)
Fasting glucose, mmol/L	5.3 (1.5)	5.0 (1.3)	5.2 (1.4)
HbA _{1c} , %	6.0 (0.9)	5.8 (0.7)	5.9 (0.8)
Heart rate, beats/min	77.3 (11.5)	74.0 (13.6)	75.7 (12.6)
Systolic BP, mm Hg	131.3 (14.5)	131.3 (15.0)	131.3 (14.7)
Diastolic BP, mm Hg	76.2 (11.2)	75.9 (10.4)	76 (10.7)
CRP, mg/L	5.3 (4.9)	6.3 (6.9)	5.9 (6)
Cholesterol, mmol/L	4.7 (0.9)	5.3 (1.2)	5 (1.1)
LDL, mmol/L	2.6 (0.9)	3.3 (0.9)	2.9 (1)
HDL, mmol/L	1.5 (0.4)	1.4 (0.4)	1.5 (0.4)
Triglyceride, mmol/L	1.4 (0.9)	1.4 (0.8)	1.4 (0.8)
Active GLP-1, pmol/L			
0 min	8.3 (8.9)	7.2 (4.4)	7.8 (7.0)
30 min	13.7 (9.8)	12.5 (6.2)	13.1 (7.2)

BARI-OPTIMISE: 8% weight loss with Liraglutide after 24 weeks compared to 0.5% reduction on placebo



Notable side-effect differences (Placebo vs. Liraglutide):

- 20% vs 51% nausea
- 6% vs 26% constipation
- 6% vs 14% fatigue

Robust 6-month weight loss (10%) in patients struggling with post-MBS weight loss given Semaglutide once weekly 0.5mg

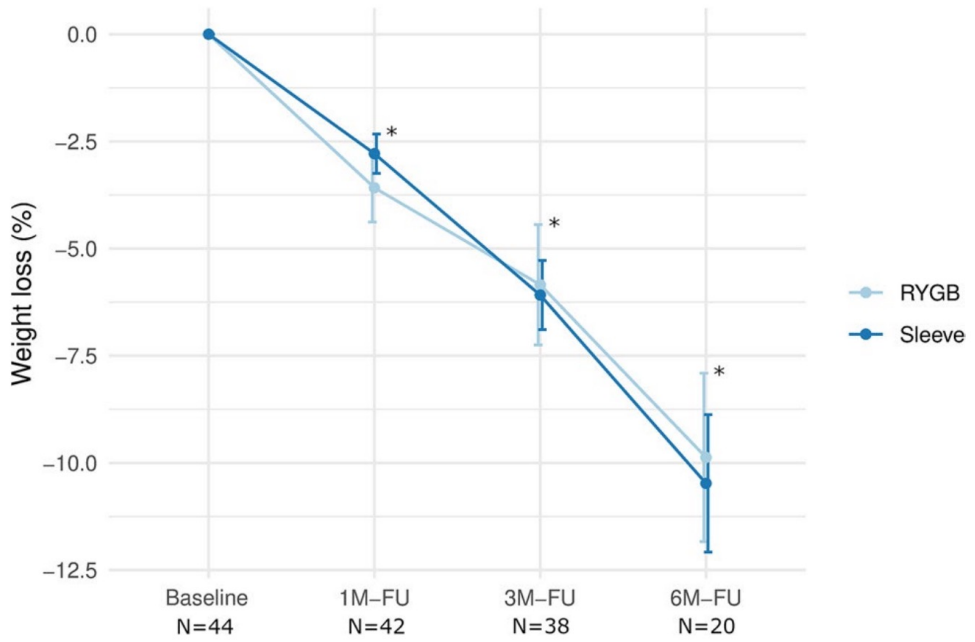
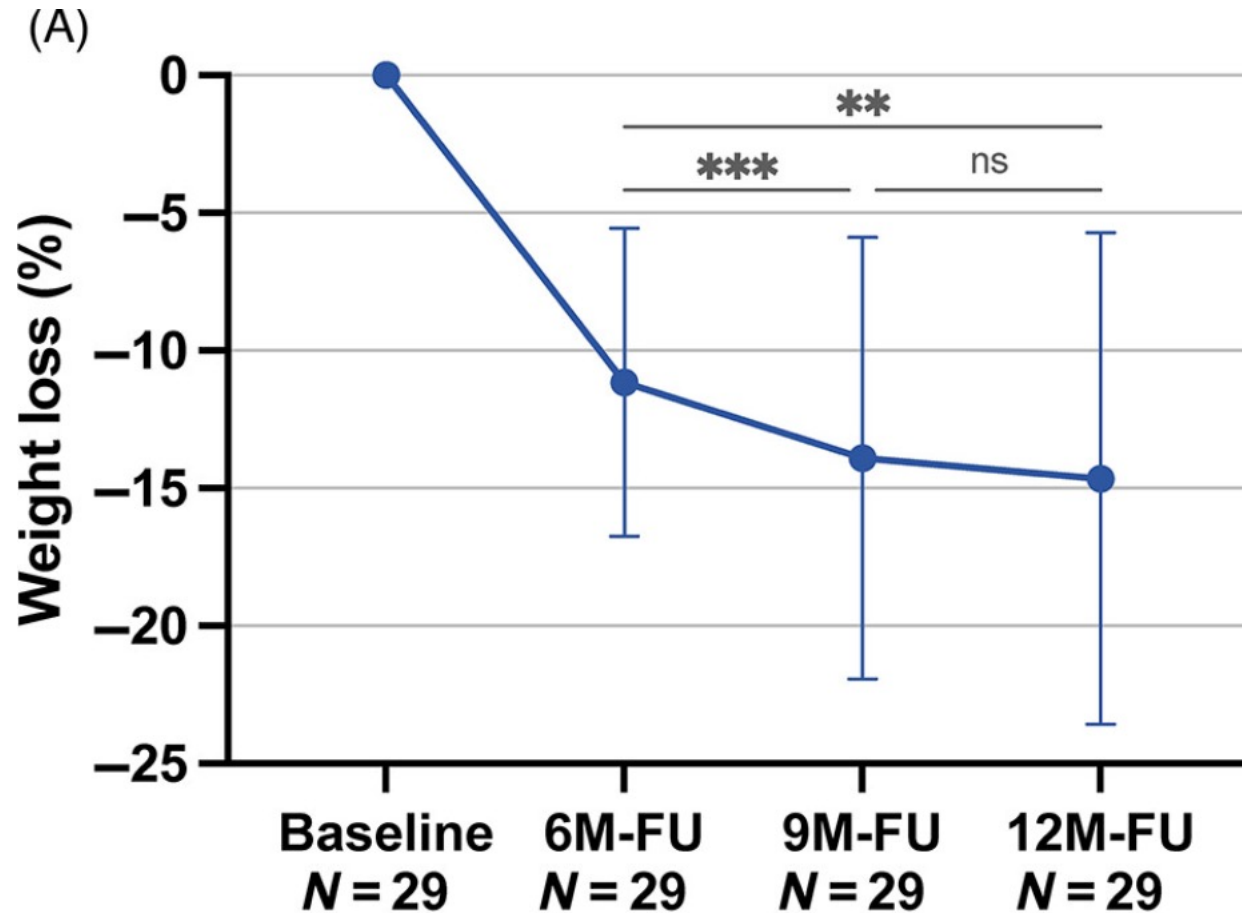


Fig. 1 Weight loss over time following adjunct treatment with semaglutide once-weekly by type of surgery. SG, sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; FU, follow-up; N, number of individuals. Results are expressed as means and standard deviation. *Significantly different from baseline regardless of surgical group ($p < 0.001$)

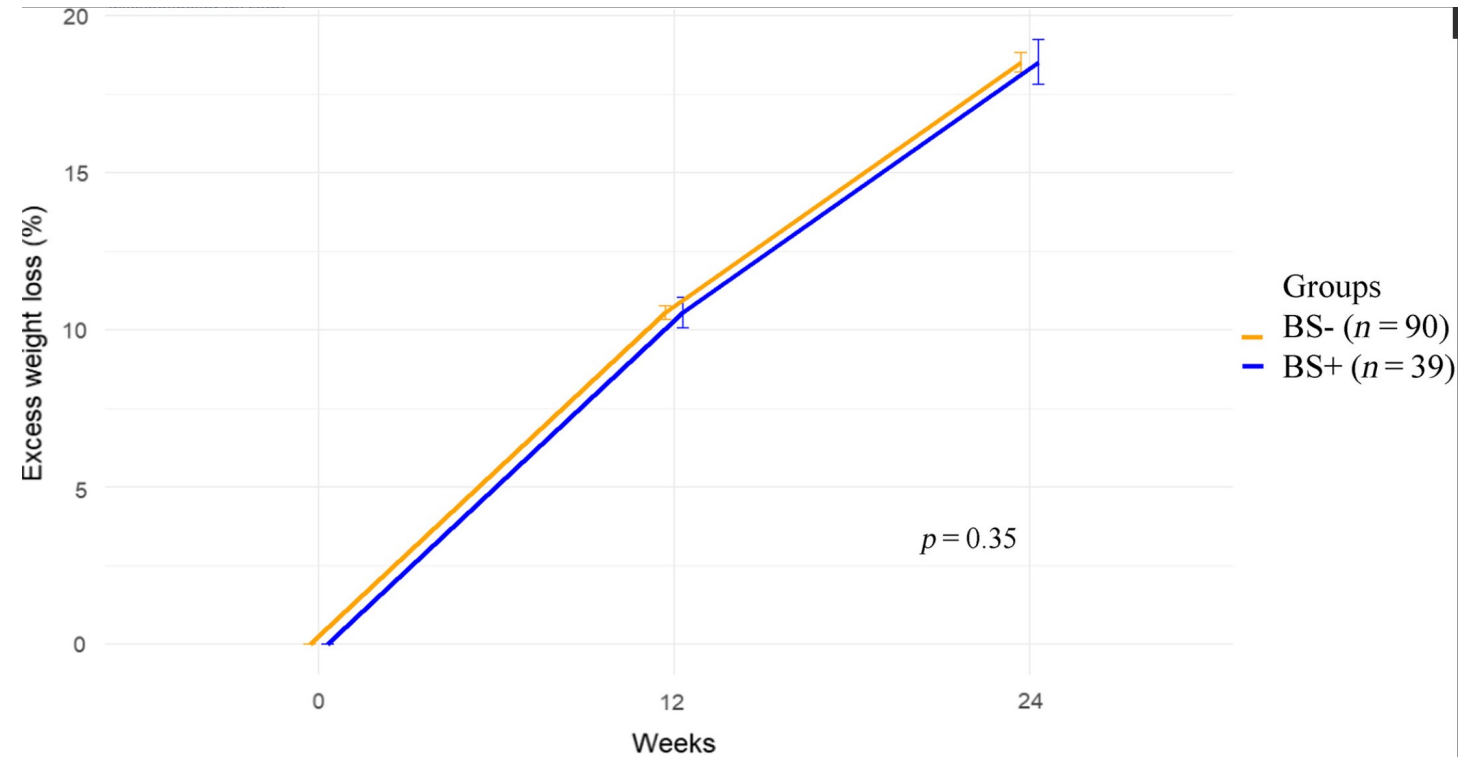
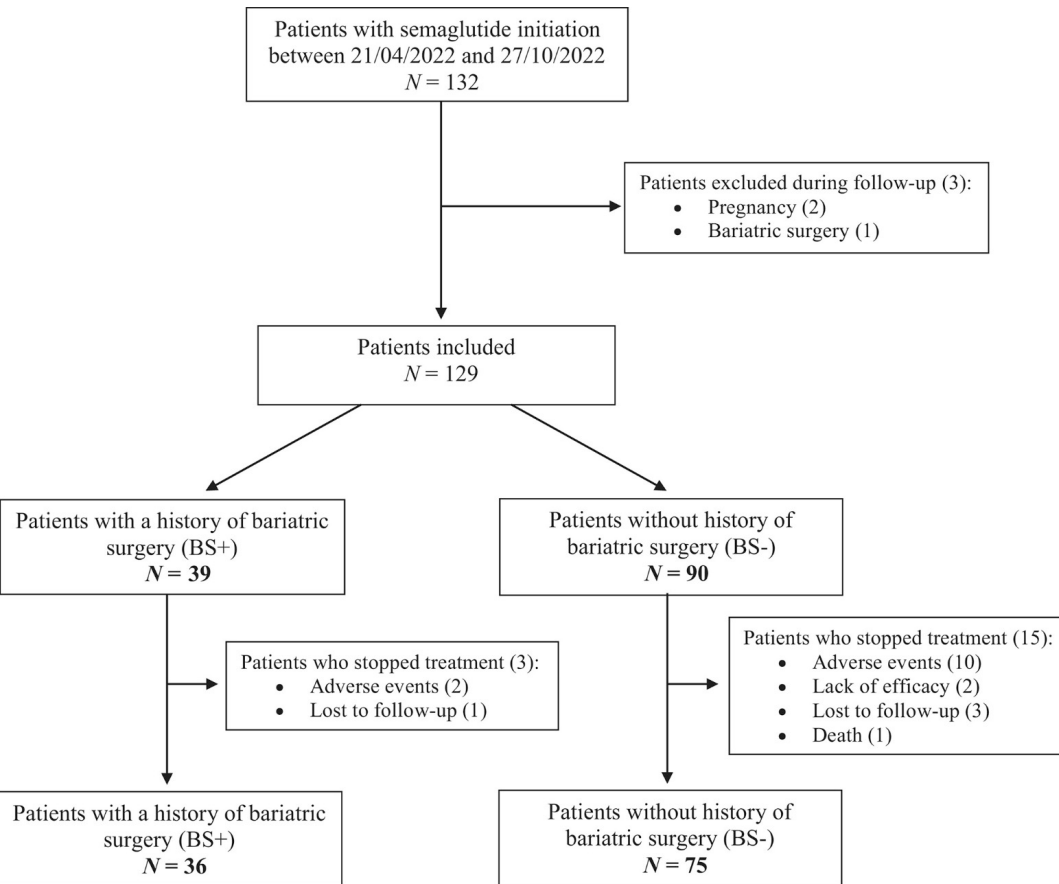
Retrospective study with 44 patients, 15 RYGB and 29 SG

Semaglutide (up to 1mg) in weight recurrent post-MBS patients creates >10% weight loss at 6 months



Retrospective study of 29 MBS patients (11 RYGB, 18 SG)

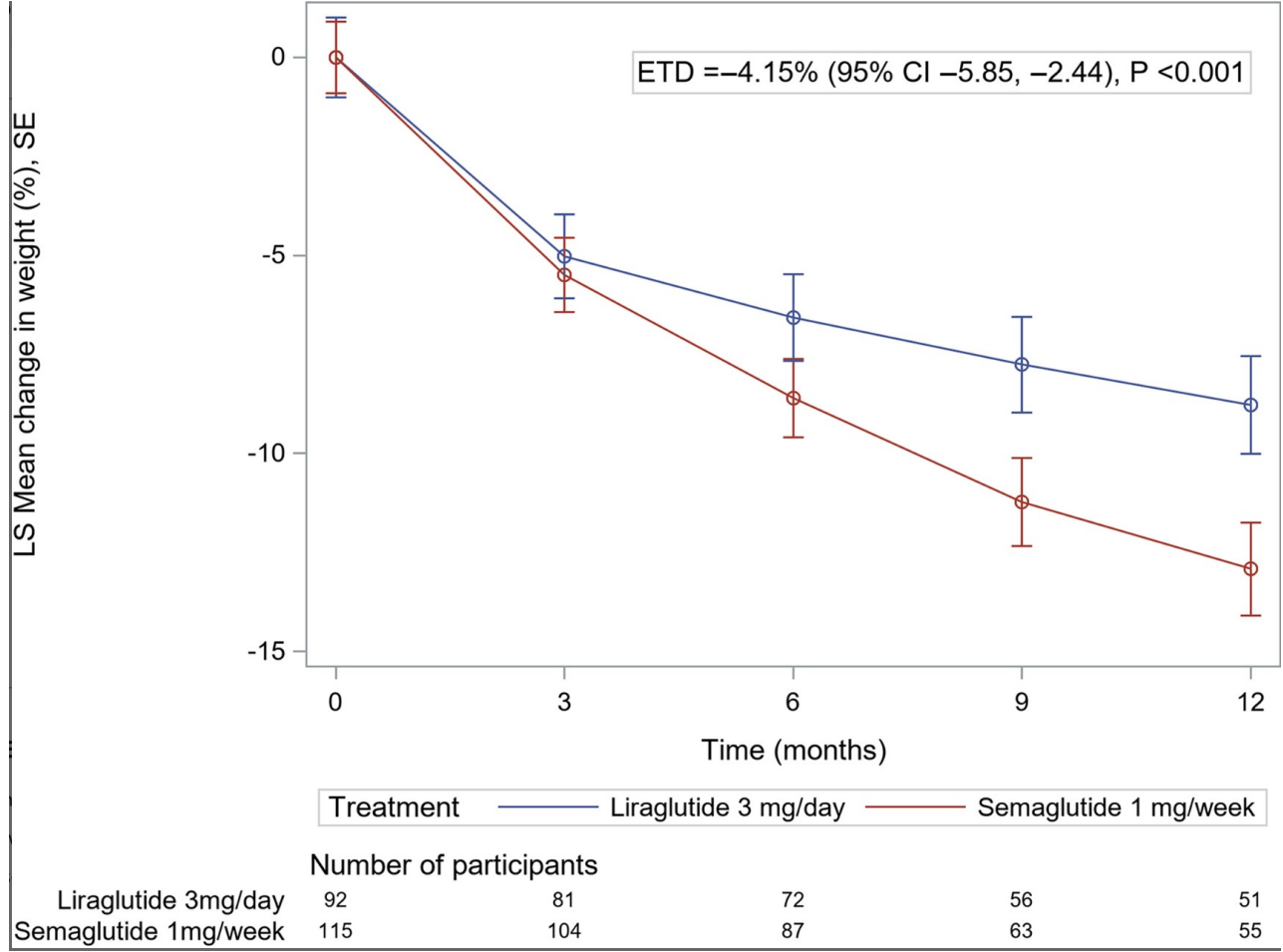
2.4mg Semaglutide in weight recurrent post-MBS patients results in 9.8% weight loss in 6 months; similar to non-MBS individuals



The %EWL was calculated as $((\text{pre-surgery weight} - \text{follow-up weight}) / (\text{operative excess weight})) \times 100$

Operative excess weight = (pre-surgery weight – ideal weight)

Semaglutide 1mg/week results in significantly greater weight loss than Liraglutide 3mg/day



Retrospective 207 adult, Semaglutide (n = 115), Liraglutide (n = 92)
-12.92% weight loss at 12 months vs -8.77%, respectively

GLP-1 drugs can help weight recurrent post-MBS patients consistently lose weight (5-10% in 6 months)

Table 1. Summary of studies in the literature evaluating glucagon-like peptide-1-receptor agonist use in patients who regained weight or lost insufficient weight after metabolic bariatric surgery.

Studies	Study design	Number of subjects	Type of surgery	Inclusion criteria	Time since the operation	Type of GLP-1-RA	Time on GLP-1-RA treatment	Weight loss under GLP-1-RA treatment
Rye et al. [34]	Retrospective	20	RYGB/LSG/VBG/AGB	WR > 10% WL < 20% reached plateau	6.3 years	Liraglutide 3 mg/day	28 weeks	-9.7%
Wharton et al. [35]	Retrospective	117	RYGB/AGB/SG	Received liraglutide 3 mg in the clinic and gained 58% average maximal weight postoperatively	7.8 years	Liraglutide 3 mg/day	7.6 months	-5.5%
Suliman et al. [36]	Retrospective	76	RYGB/SG/Other	Treated in ICLDC clinic and received liraglutide 3 mg	4 years	Liraglutide 3 mg/day	213 days	-6.1%
Abrahamsson et al. [37]	Retrospective	13	GBS	<50% EBWL in 15-20 months	≥2 years	Liraglutide 3 mg/day	15-20 months	-10.4%
Creange et al. [38]	Retrospective	25	LAGB/RYGB/LSG/LAGB and RYGB	Had previous BS and started liraglutide 3 mg	—	Liraglutide 3 mg/day	24 weeks	-9.45%
Rigas et al. [39]	Retrospective	48	LAGB/LSG/GBP	Reached plateau early than expected	—	Liraglutide 3 mg/day	7 months	-13.4%
Talbot et al. [40]	Retrospective	32	Not specified	Gained 15% of weight loss postoperatively	1.1 years	Liraglutide 3 mg/day	9 months	-7.2%
Shehadeh et al. [41]	Retrospective	25	SG/GB/GBP/Last both	Gained >25% of weight loss and did not respond to lifestyle intervention	—	Liraglutide 3 mg/day	3 months	-10%
Muratori et al. [42]	Retrospective	20	LSG/RYGB/LAGB	Gained in BMI postoperative weight loss	4.5 years	Liraglutide 3 mg/day	10.9 months	-5.2 kg/m ²
Colbourne et al. [43]	Retrospective	68	RYGB/SG/AGB/revisional surgery	IWL after BS: >25% after LSG/RYGB or >20% after LAGB	>1 year after LSG/RYGB or >2 years after LAGB	Liraglutide 3 mg/day	13 months	-5.3%
Lautenbach et al. [45]	Retrospective	44	RYGB/SG	Those with continuous WR after nadir of IWL (EWL < 50% after BS) without type 2 DM	64.7 months	Semaglutide 0.5 mg/week	6 months	-10.3%
Jensen et al. [46]	Retrospective	50	RYGB/SG	Those with WR after BS	72 months	29: Liraglutide 3 mg/day 21: Semaglutide 1 mg/week	6 months	-8.8%
Murvelashvili et al. [47]	Retrospective	207	RYGB/VSG/AGB	Those were prescribed medication after BS due to BMI > 30 kg/m ² or >27 kg/m ² with obesity related comorbidities	8 years	92: Liraglutide 3 mg/day 115: Semaglutide 1 mg/week	12 months	-12.92% by semaglutide -8.77% by liraglutide
Mok et al. [49]	Prospective, randomized, placebo-controlled	70 35: liraglutide + life style intervention 35: placebo + lifestyle intervention	RYGB/SG	WL < 20% from the day of surgery Suboptimal GLP-1 response (<2x increase in meal stimulated GLP-1 levels)	52.1 months	Liraglutide 3 mg/day vs. placebo saline injection	24 weeks	-8.82% vs. -0.54% Estimated treatment difference: -8.03%

AGB adjustable gastric banding, BMI body mass index, BS bariatric surgery, DM diabetes mellitus, EBWL estimated body weight loss, EWL excess weight loss, GB gastric banding, GBP gastric bypass, GLP-1 glucagon-like peptide-1, GLP-1-RA glucagon-like peptide-1-receptor agonist, ICLDC imperial college London diabetes center, IWL insufficient weight loss, LAGB laparoscopic adjustable gastric banding, LSG laparoscopic sleeve gastrectomy, RYGB Roux-en-Y gastric bypass, SG sleeve gastrectomy, VBG vertical banded gastroplasty, VSG vertical sleeve gastrectomy, WL weight loss, WR weight regain.

Takeaways

- Poor weight loss and weight regain affect 1 in 4 MBS patients (~60,000 patients / year in the US)
- GLP-1 analogs (liraglutide, semaglutide) may help weight recurrent post-MBS patients lose weight reliably on the order of 10% in 6 months
- 5% weight loss in obese patients meaningfully reduce cardiovascular risk, a measure GLP-1 drugs achieve in post-MBS weight recurrent patients
- Semaglutide may be more effective than liraglutide in post-MBS patients (note: data is retrospective)
- Liraglutide is off patent June 2024 which will make it more accessible for patients
- **GLP-1 drugs (liraglutide, semaglutide, and tirzepatide) may be useful as standard therapy in treating weight recurrent post-MBS patients**

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