Weight-regain
la gestione farmacologica

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Conflict of Interest

Honorarium as a speaker in Scientific Events

AstraZeneca
Bayer
Boheringer Ingelheim
Daiichi Sankyo
Echosens
Lilly
Menarini Diag
MSD
Novartis
Novo Nordisk
PikDare
Roche Diag
Sanofi
Servier

Scientific advisory boards

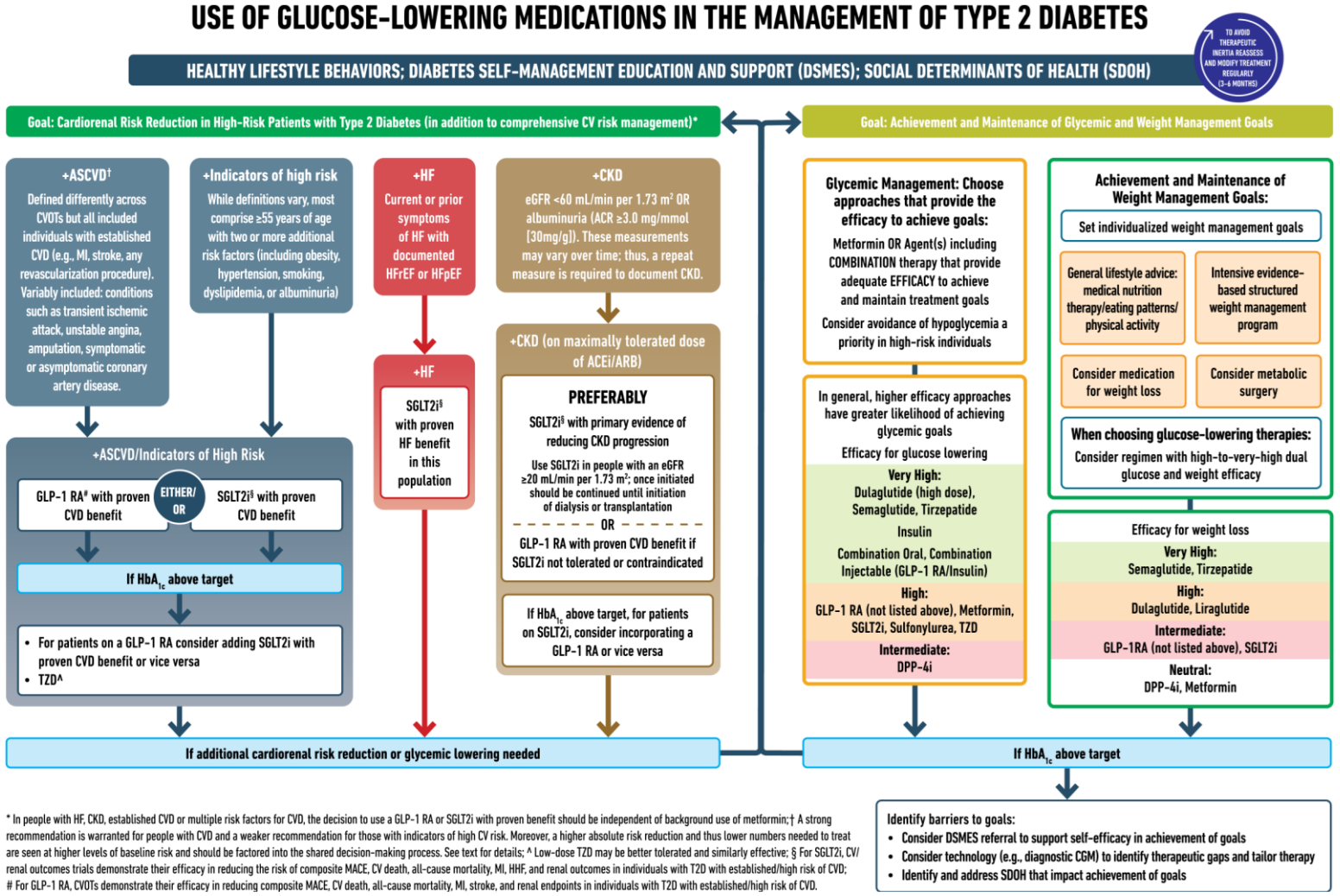
AstraZeneca
Intercept
Lilly
Merck
Novartis
Novo Nordisk
Pfizer
PikDare
Sanofi

Weight loss – treat to target

American Diabetes Association®

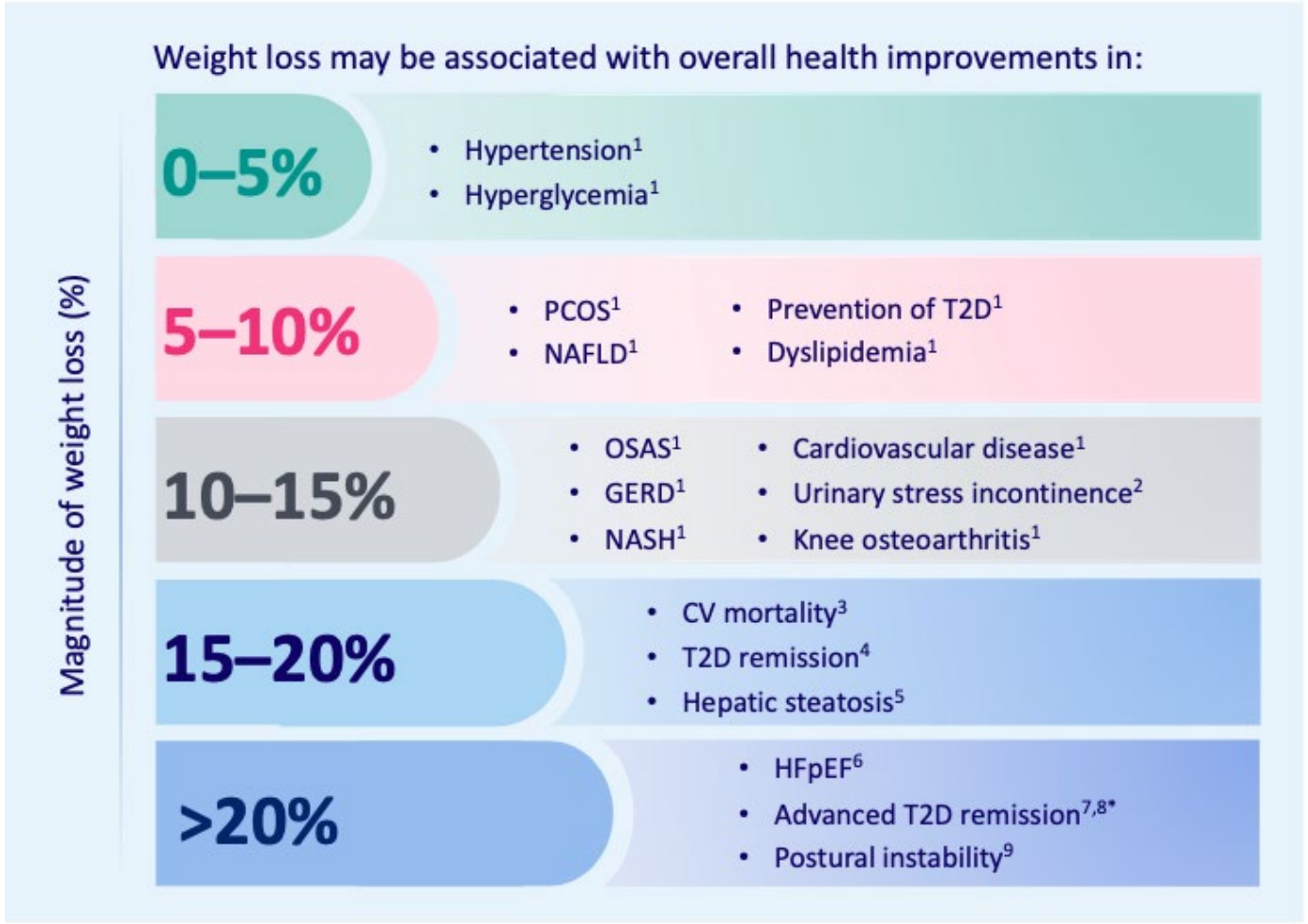
From: **Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)**

Diabetes Care. 2022;45(11):2753-2786. doi:10.2337/dci22-0034



Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin/creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione.

Greater weight loss is associated with better health outcomes



*T2D remission rates have been found to plateau at 20–25% total weight loss where 25% total weight loss did not confer additional benefits;

BP, blood pressure; CV, cardiovascular; GERD, gastro-oesophageal reflux disease; HbA1c, glycated hemoglobin; HFpEF, heart failure with preserved ejection fraction; NAFLD; non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome; PwO, people with obesity; T2D, type 2 diabetes; TG, triglycerides. 1. Horn D et al. Postgrad Med. 2022;134:359–75; 2. Garvey WT et al. Endocr Pract. 2016;22(Suppl. 3):1–203; 3. Look AHEAD Research Group, Gregg EW et al. Lancet Diabetes Endocrinol. 2016;4:913–21; 4. Lean ME et al. Lancet. 2018;391:541–51; 5. Sundström J et al. Circulation. 2017;135:1577–85;
6. Benraoune F & Litwin SE. Curr Opin Cardiol. 2011;26:555–61; 7. Meerasa A & Dash S. Diabetes Care 2022;45:28–30; 8. Teasdale, N et al. Int J Obes 2007;31:153–160; 9. Ryan DH and Yockey SR. Curr Obes Rep 2017;6:187–94.

2 problems

1) T2DM patients lose less weight

2) Weight regain

Problem 1: T2DM pats loose less

Metabolic and Psychological Features are Associated with Weight Loss 12 Months After Sleeve Gastrectomy

Emanuele Muraca,[1] Alice Oltolini,[1] Alberto Binda,[2] Mattia Pizzi,[3] Stefano Ciardullo,[1,4] Giuseppina Manzoni,[1] Francesca Zerbini,[1] Eleonora Bianconi,[1] Rosa Cannistraci,[1,4] Silvia Perra,[1] Pietro Pizzi,[3] Guido Lattuada,[1] Gianluca Perseghin,[1,4] and Matteo Villa[2]

was considered. Multivariable stepwise regression analysis showed that younger age, lower impulsiveness, higher-than-normal urinary free cortisol, and lower HbA1c were associated with higher %TWL, explaining about 31.5% of the weight loss.

Muraca E et al J Clin Endocrinol & Metab, 2021

Problem 1: T2DM, IFG/IGT pats loose less

TABLE 3. 24 months follow-up weight loss in the study population segragated by glucose tolerance condition

		Entire population		NOR	IFG	T2DM
TWL (%)	6 months	25.3 ± 6.8		27.3 ± 6.8 [c,d]	24.7 ± 6.6	23.4 ± 7.1
	12 months	31.7 ± 8.7		35.3 ± 8.5 [c,d]	31.0 ± 8.1	27.9 ± 9.1
	24 months	32.4 ± 11.5		38.1 ± 11.3 [c,d]	31.6 ± 11.0 [b]	26.4 ± 10.3
DBMI	6 months	11.6 ± 3.5		12.6 ± 3.3 [a,d]	11.3 ± 3.5	10.7 ± 3.3
	12 months	14.7 ± 4.6		16.5 ± 4.2 [c,d]	14.3 ± 4.5	13.0 ± 4.4
	24 months	15.2 ± 6.0		18.0 ± 5.3 [c,d]	14.7 ± 6.0	12.4 ± 5.5
EWL (%)	6 months	57.8 ± 18.5		61.8 ± 19.2 [b]	56.3 ± 17.4	54.5 ± 18.8
	12 months	71.7 ± 22.3		78.7 ± 23.0 [a,d]	70.7 ± 20.5	63.3 ± 21.8
	24 months	72.5 ± 26.6		84.0 ± 25.9 [a,d]	71.6 ± 24.7 [b]	59.2 ± 24.1

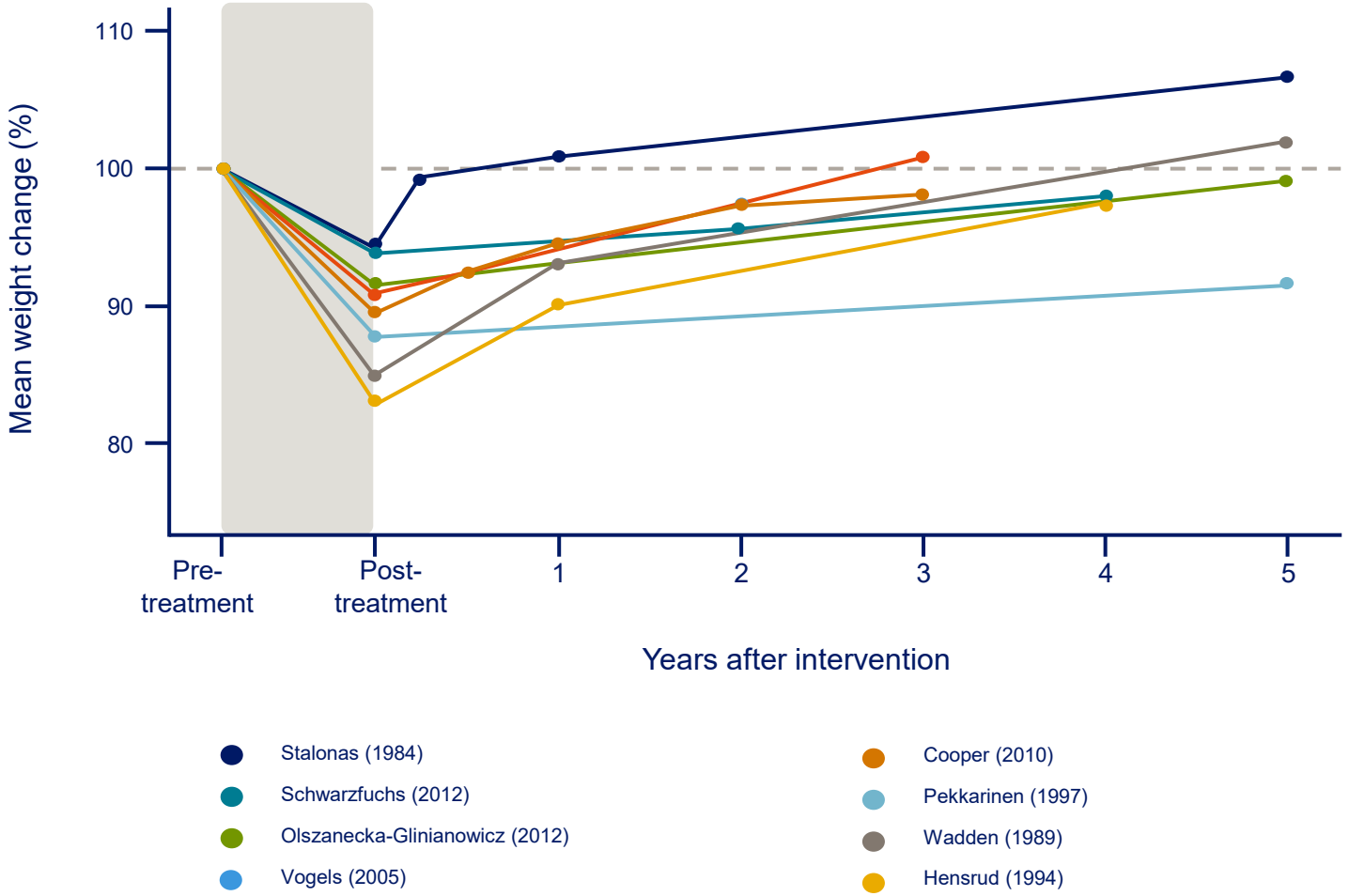
Pearson chi-square test with post hoc Bonferroni adjustment was used for categorical variables.
Kruskal-Wallis test and Dunn-Bonferroni approach for pairwise comparison or ANOVA test and post hoc Sidak-Bonferroni test was applied for continuos variables.
TWL = total weight loss, BMI = body mass index, EWL = excess weight loss
[a] $p \leq 0.05$ vs IFG
[b] $p \leq 0.05$ vs T2DM
[c] $p \leq 0.01$ vs IFG
[d] $p \leq 0.01$ vs T2DM

Sleeve gastrectomy
2 years follow-up

Muraca E et al (in preparation)

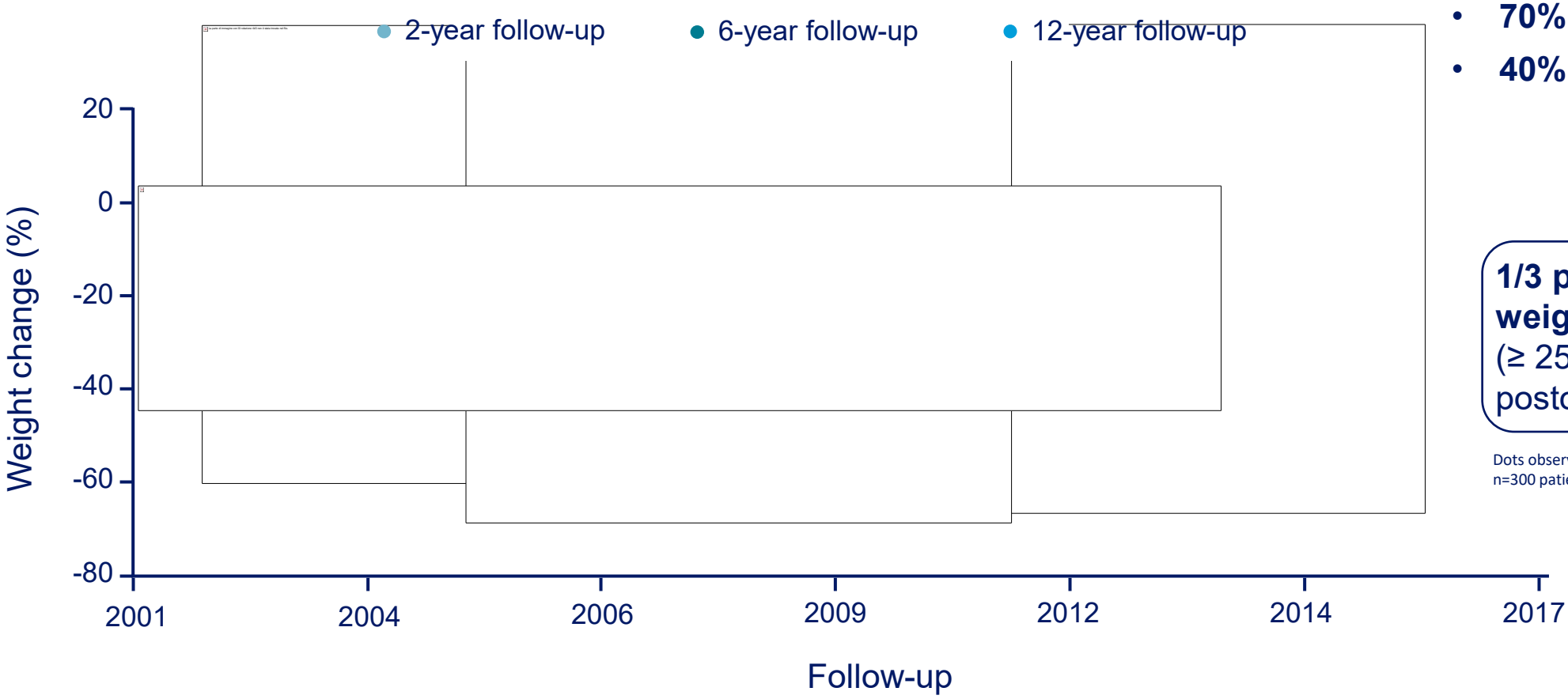
Obesity is a relapsing disease

Maintenance of weight loss



Nordmo et al. Obes Rev, 2019
Fothergill E et al Obesity, 2016
Sumithran P et al N Engl J Med, 2011

Bariatric surgery is also associated with weight re-gain



Weight loss maintenance at 12y:

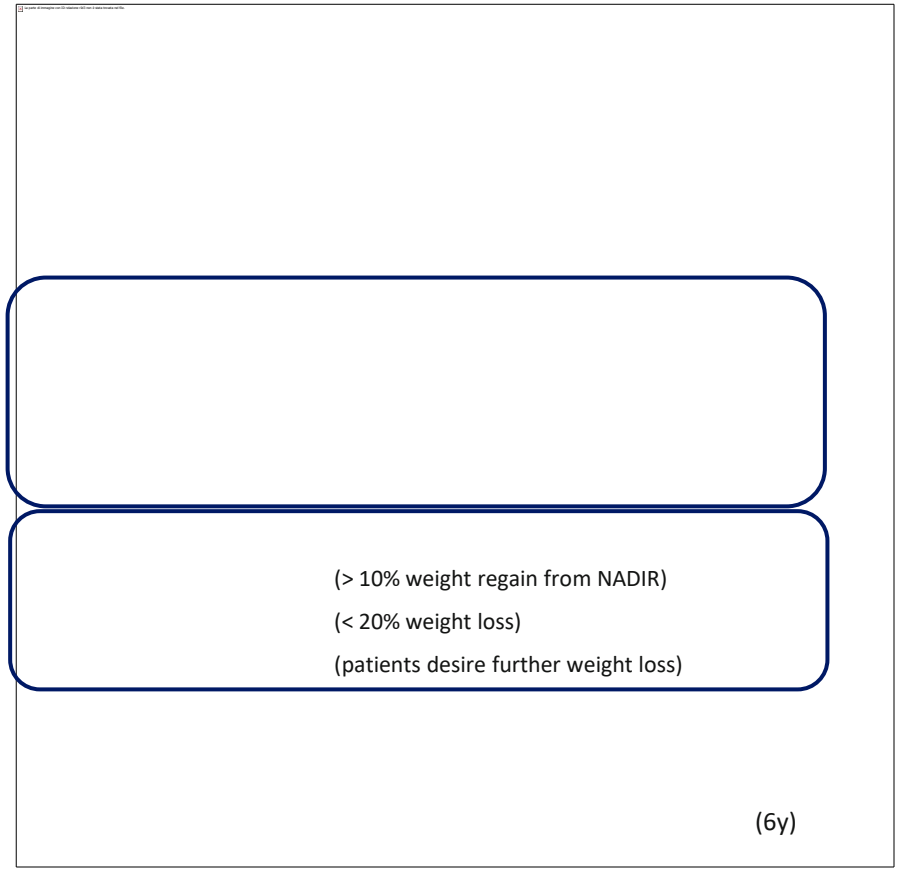
- **93%** of patients **≥ 10% WL**
- **70%** of patients **≥ 20% WL**
- **40%** of patients **≥ 30% WL**

1/3 patients experienced **weight regain** (≥ 25 weight loss) from postoperative year 1

Dots observed in a post-operative follow up period of 7±5 years
n=300 patients who underwent Roux-en-Y gastric bypass (RYBG)

Adams et al, N Engl J Med 2017
Cooper TC et al, Obes Surg 2015

Efficacy of Liraglutide 3.0 mg in Patients with Prior Bariatric Surgery



Median weight at each time point

50% of participants achieved a **28-week weight lower** than their **nadir post-surgical weight**

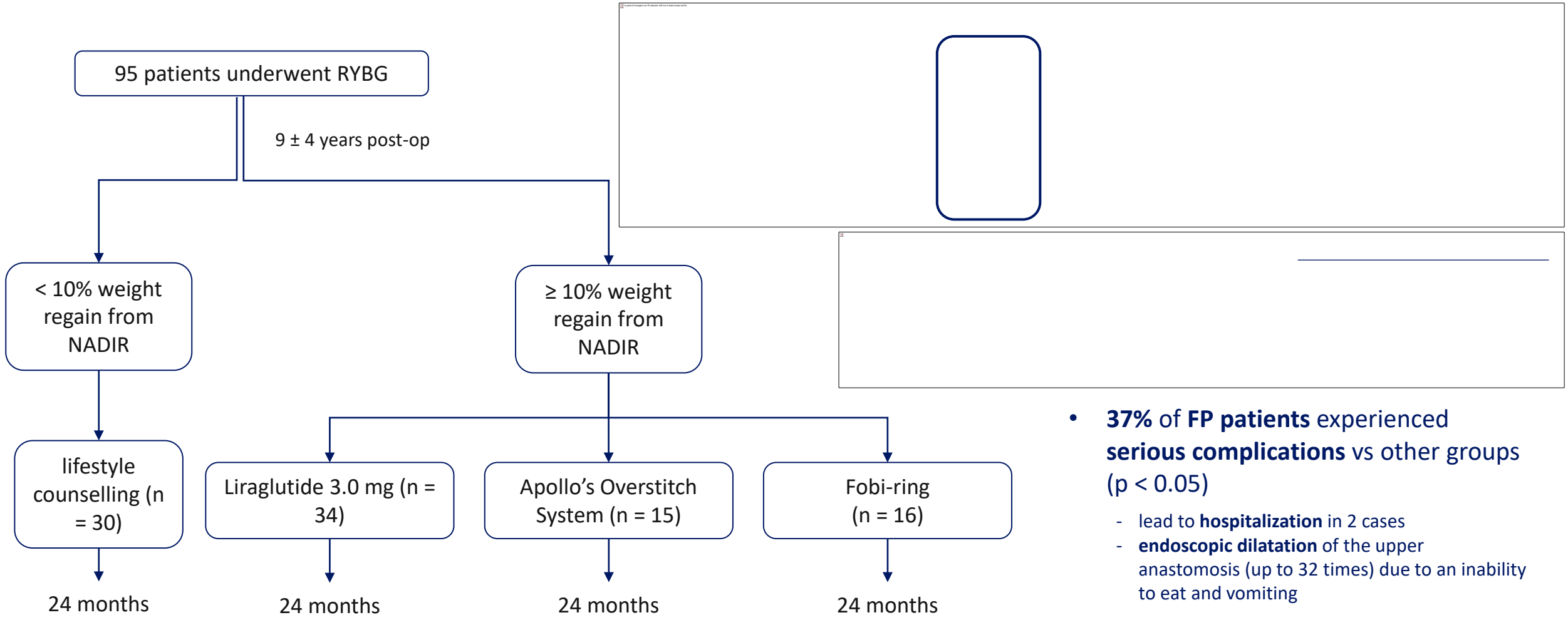
-7.1 %

-9.7 %

RYGB, roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy; VBG, vertical banded gastroplasty; AGB adjustable gastric band.

Rye P, et al. Obes Surg. 2018;28(11):3553-3558.

Liraglutide 3.0 mg or Surgical Revision in Long-Term Weight Regain After RYBG

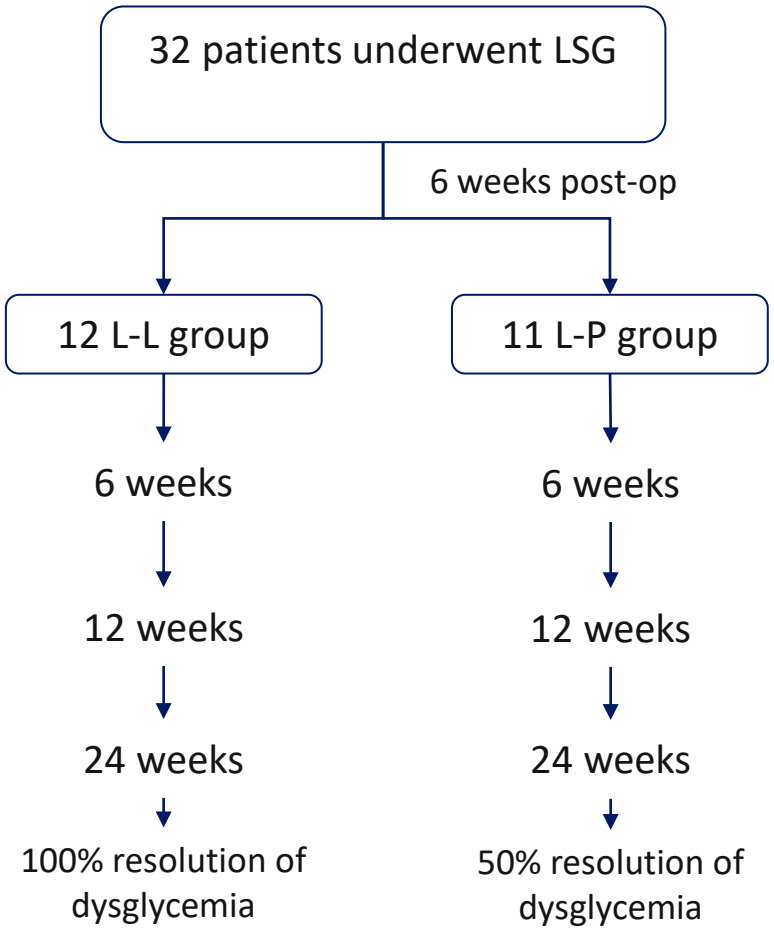


- **37%** of **FP patients** experienced **serious complications** vs other groups ($p < 0.05$)
  - lead to **hospitalization** in 2 cases
  - **endoscopic dilatation** of the upper anastomosis (up to 32 times) due to an inability to eat and vomiting

Horber FF, et al. Epub 2020 Jul 21. Erratum in: Obes Surg. 2021;31(7):3386.

RYGB, roux-en-Y gastric bypass.

LSG + liraglutide 3.0 mg for patients desiring further weight loss



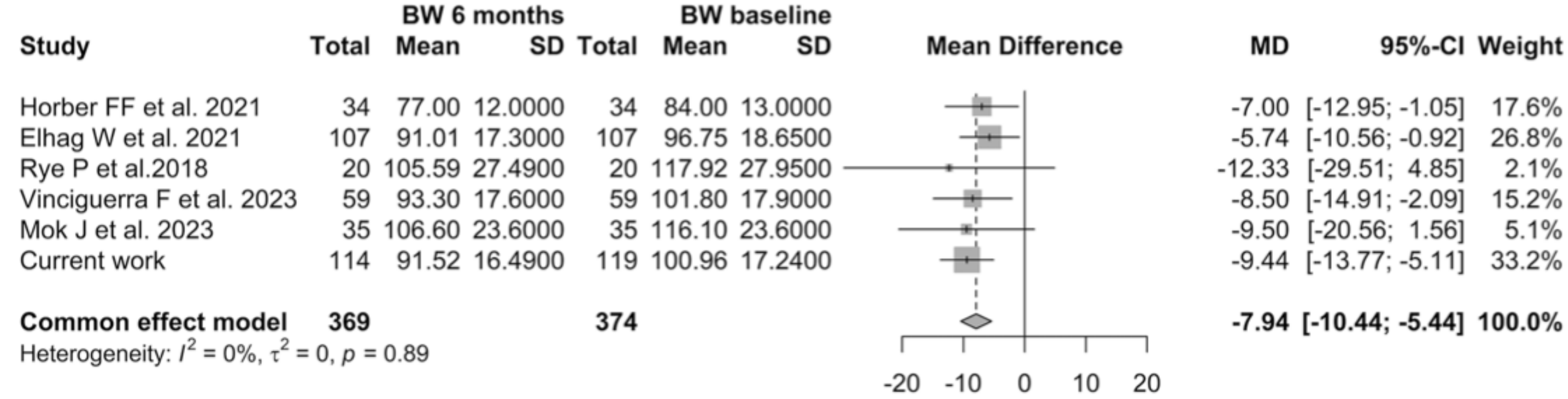
Thakur U, et al. Obes Surg. 2021;31(1):84-92.

Obesity Surgery
https://doi.org/10.1007/s11695-023-07053-9

ORIGINAL CONTRIBUTIONS

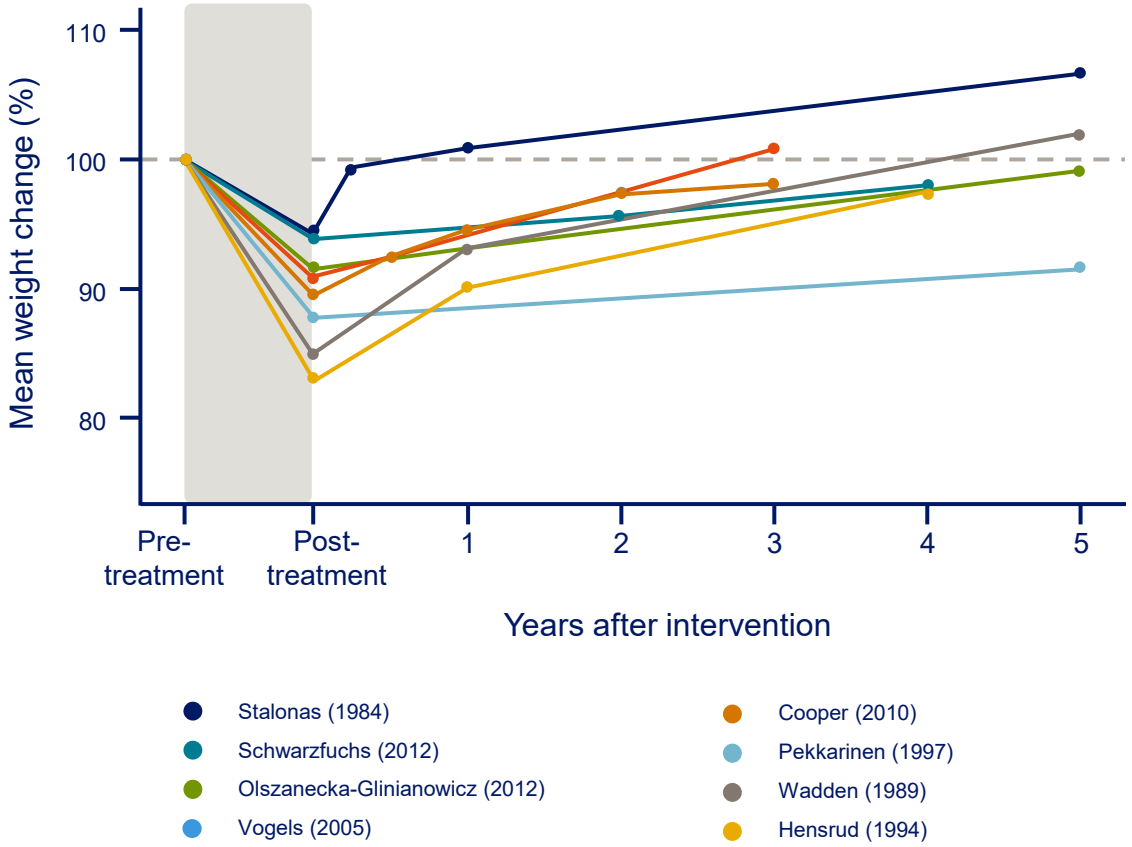
Efficacy of High-dose Liraglutide 3.0 mg in Patients with Poor Response to Bariatric Surgery: Real-world Experience and Updated Meta-analysis

Federica Vinciguerra[1] · Carla Di Stefano[2] · Roberto Baratta[3] · Alfredo Pulvirenti[4] · Giuseppe Mastrandrea[5] · Luigi Piazza[2] · Fabio Guccione[6] · Giuseppe Navarra[6] · Lucia Frittitta[1,7]

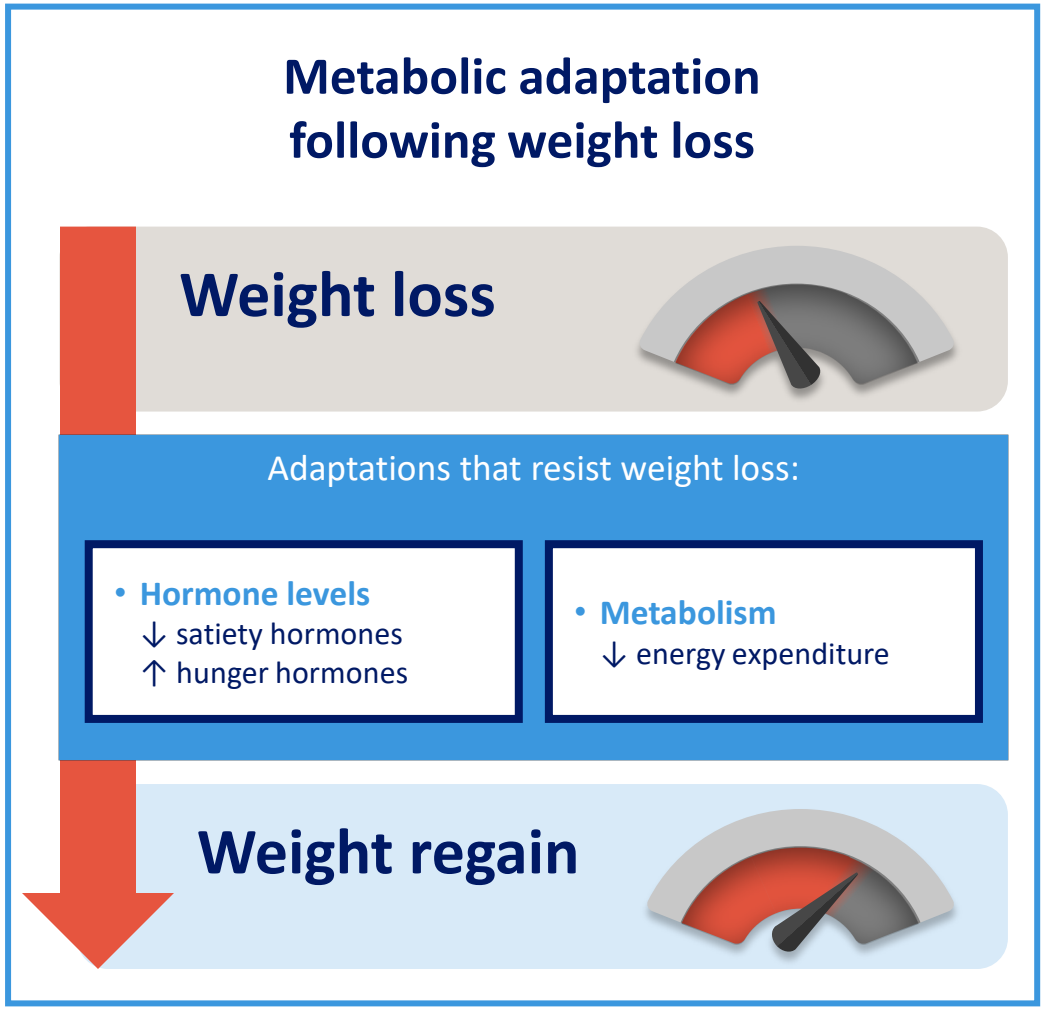


Obesity is a relapsing disease

Maintenance of weight loss



Metabolic adaptation following weight loss



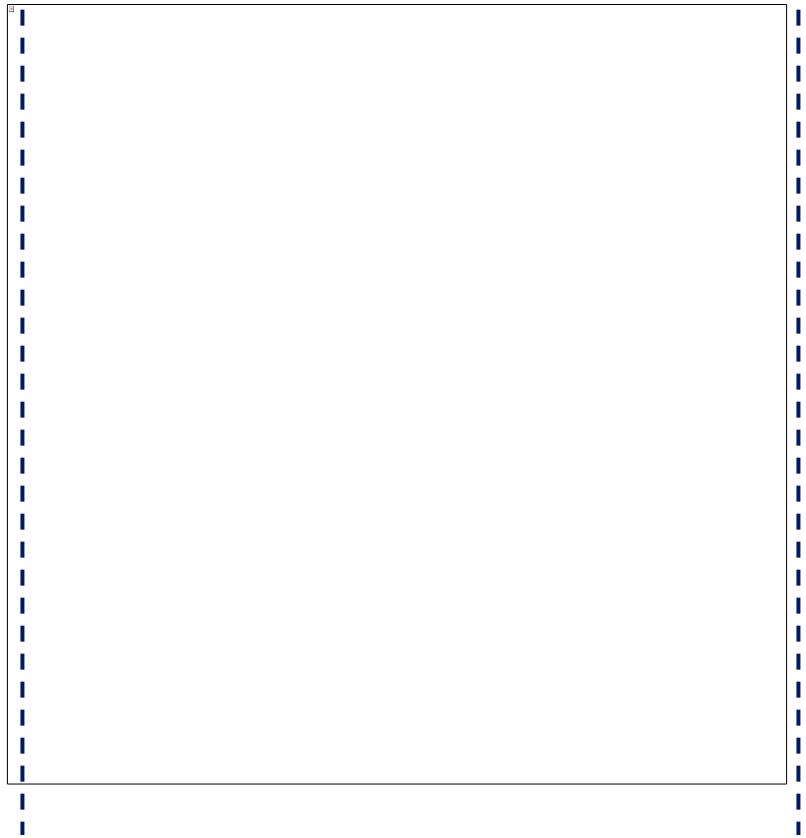
Nordmo et al. Obes Rev 2019. doi: 10.1111/obr.12949. Fothergill E, Guo J, Howard L, et al. Obesity (Silver Spring). 2016;24:1612– 1619; Sumithran P, Prendergast LA,

The Role of Pharmacotherapy

Pre Bariatric Surgery

1. **Treat Metabolic Syndrome:**
   - ↑ EWL post-op [1]
   - ↓ Reduce hospital stay [1]
   - ↓ Post-op complications [2]
2. **Reduce Risk in Anesthesia**
3. **BMI > 65*** pre-surgical weight loss is mandatory to **reduce intra-abdominal volume** and **achieve operability** [3]
4. **Patients non-responsive to lifestyle intervention** [4]

* BMI > 55 main risk factor for unfavourable outcomes (SICOB guidelines 2016)



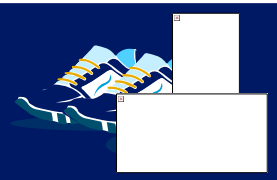
Post Bariatric Surgery

1. **Weight Regain** [5] (≥ 25 weight loss)
2. **Insufficient Weight Loss** [5] (< 50% EWL)
3. **Patients desiring further weight loss** [6]

- **Patients with no indication for bariatric surgery** [7] (BMI < 40): endoscopic surgery

1. Hutcheon DA et al. J Am Coll Surg. 2018;226(4):514-524; 2. Cassie S et al. Surg Obes Relat Dis. 2011;7(6):760-7; 3. Stier et al. Diabetes 2015;64:A43; 4. Malone et al. Ann Pharmacother 2012;46:779–84; 5. Vinciguerra F, et al. 2021 Apr 1. doi: 10.23736/S2724-6507.21.03311-3; 6. Thakur U, et al. Obes Surg. 2021;31(1):84-92; 7. Badurdeen D, et al. Gastrointest Endosc. 2021 Jun;93(6):1316-1324.e1.

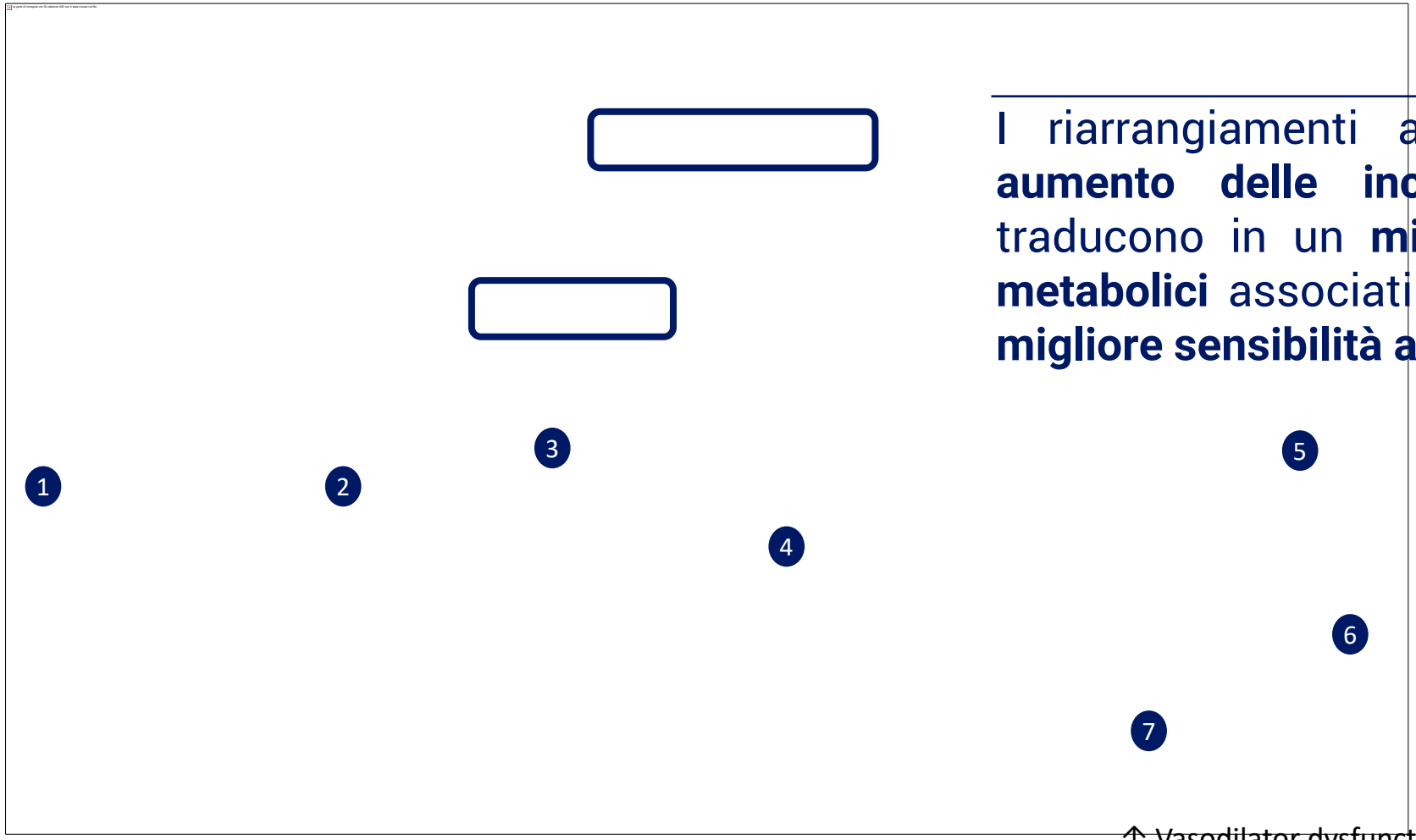
Stepped approach to obesity management

	BMI 25–26.9 kg/m²	BMI 27–29.9 kg/m²	BMI 30–34.9 kg/m²	BMI 35–39.9 kg/m²	BMI ≥40 kg/m²
Surgery 			When optimal medical and behavioural management has been insufficient	With adiposity-related complications	+
Pharmacotherapy 		With adiposity-related complications	+	+	+
Behavioural modification 	+	+	+	+	+
	All individuals, regardless of body size or composition, benefit from a healthy, well-balanced eating pattern and regular physical activity				

BMI, body mass index.

Wharton S et al. CMAJ 2020;192:E875–91.

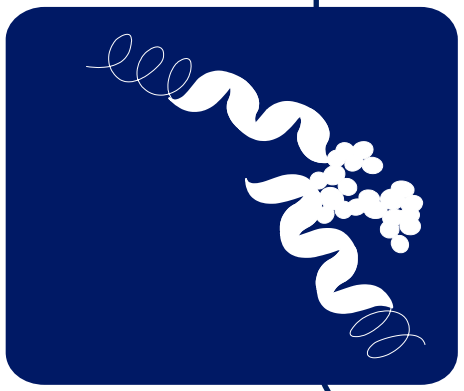
Bariatric surgery is the most effective treatment for sustained weight loss in morbid obesity



I riarrangiamenti anatomici portano ad un **aumento delle incretine** che alla fine si traducono in un **miglioramento dei parametri metabolici** associati alla perdita di peso e una **migliore sensibilità all'insulina**

GLP-1, glucagon-like peptide 1; OSA, obstructive sleep apnea: PYY, peptide YY.

Casimiro I, et al. Physiol Rep. 2019;7(10):e14111.



Liraglutide 3.0 mg

What is GLP-1?

- GLP-1 is a peptide comprised of 31 amino acids
- Member of incretin family
- Secreted predominantly from L-cells in the gut, but also the brain (nucleus tractus solitarius)

Human endogenous GLP-1

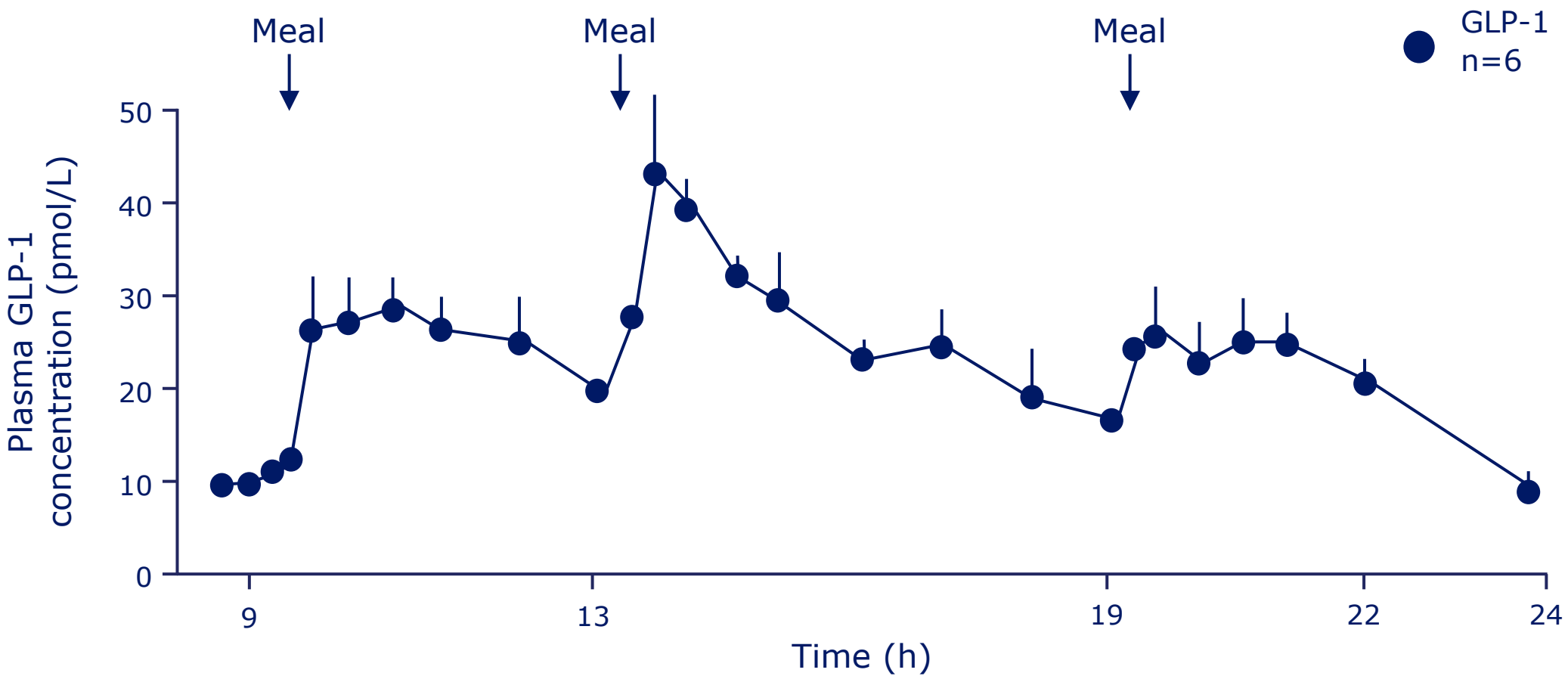
Enzymatic degradation by DPP-4

$t_{½}$=1.5–2 min

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; $t_{½}$, half-life

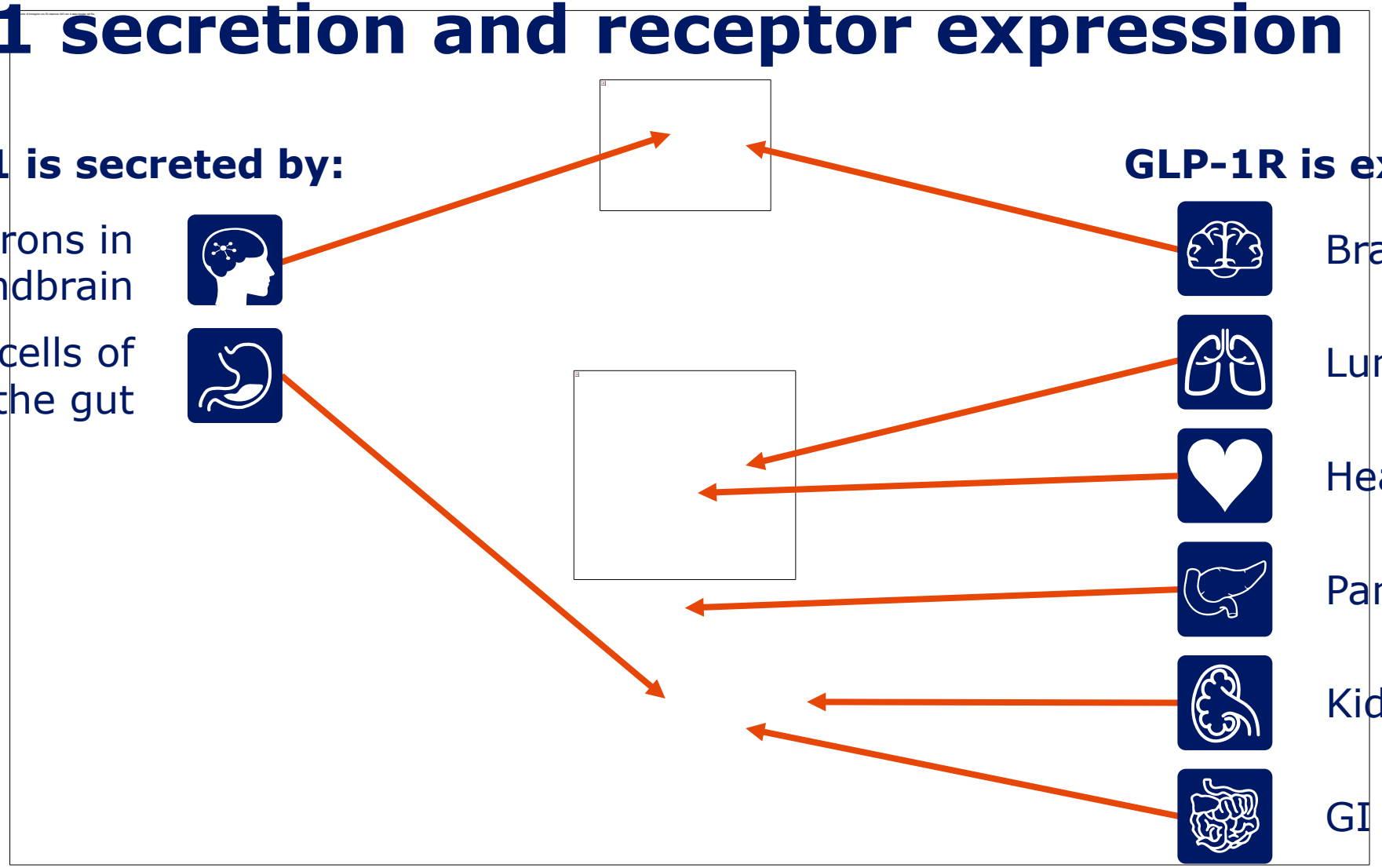
Merchenthaler *et al. J Comp Neurol* 1999;403:261–80; Baggio, Drucker. *Gastroenterology* 2007;132:2131–57; Ducker, Nauck. *Lancet* 2006;368:1696–705

GLP-1 is released in response to food intake



Adapted from: Orskov *et al. Scand J Gastroenterol* 1996;31:665–70

GLP-1 secretion and receptor expression



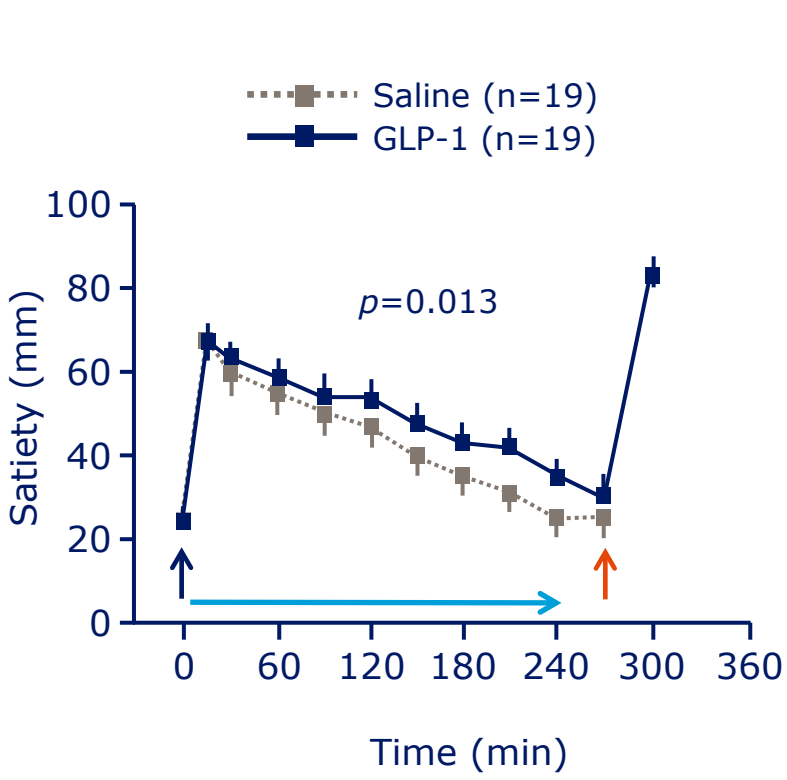
AV, atrioventricular; GI, gastrointestinal; GLP-1R, glucagon-like peptide-1 receptor

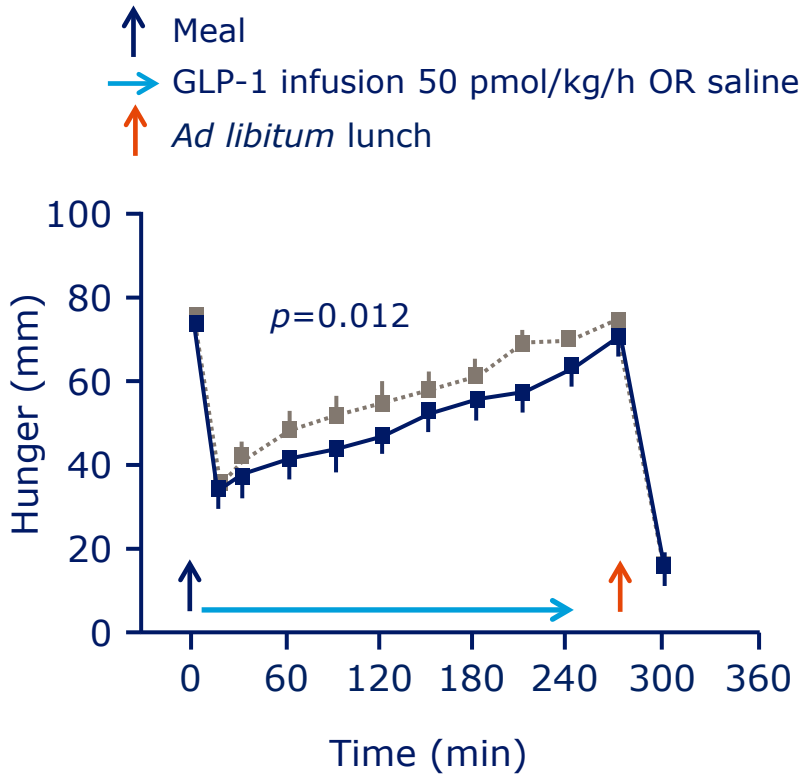
Merchenthaler *et al. J Comp Neurol* 1999;403:261–80; Baggio, Drucker. *Gastroenterology* 2007;132:2131–57; Ban *et al. Circulation* 2008;117:2340–50; Vrang *et al. Prog Neurobiol* 2010;92:442–62; Pyke *et al. Endocrinology* 2014;155:1280–90

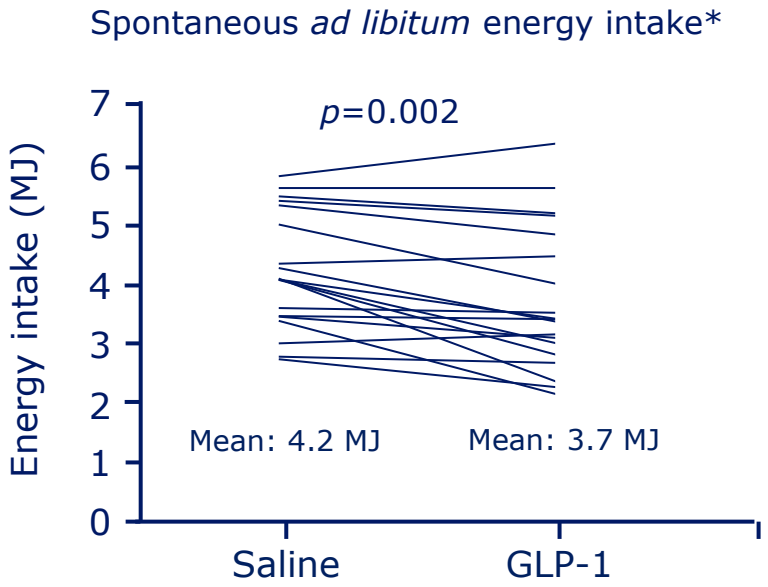
GLP-1 increases satiety and reduces hunger

In normal weight subjects

- Infusion increased plasma GLP-1 from 10 pmol/L to 60–90 pmol/L





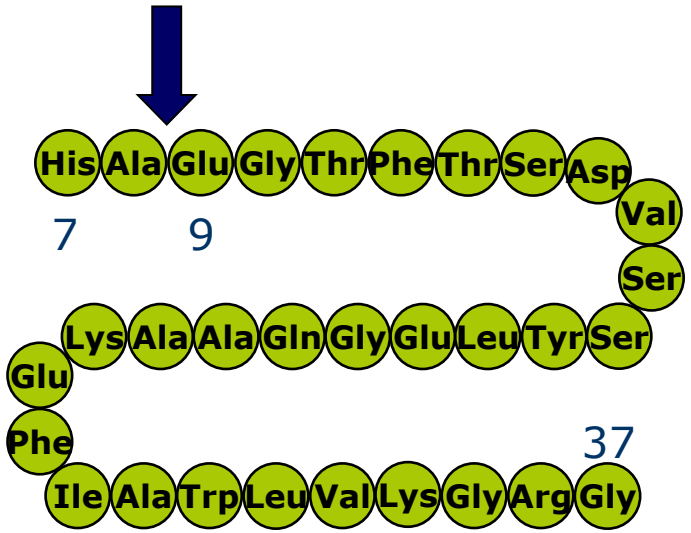


*At an *ad libitum* lunch during GLP-1 or saline infusion in 19 healthy normal-weight male subjects. Data are mean ± SEM. GLP-1, glucagon-like peptide-1; SEM, standard error of mean

Adapted from: Flint *et al. J Clin Invest* 1998;101:515–20

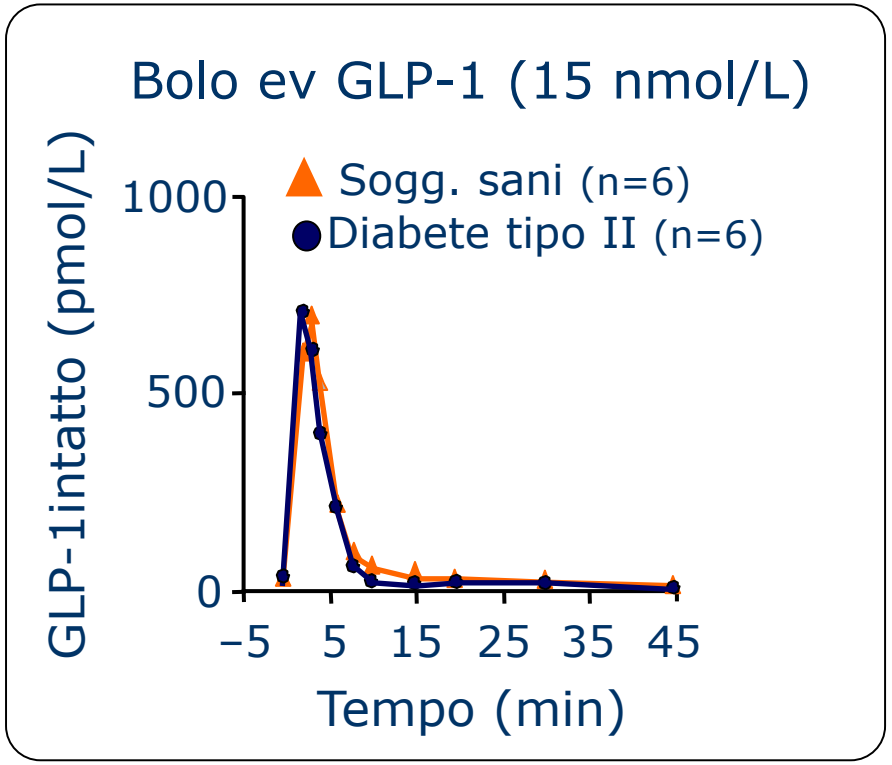
Il GLP-1 ha valore clinico limitato per la sua breve emivita

Inattivazione proteolitica
da parte di DPP-IV



Clivaggio enzimatico

Clearance elevata
(4–9 L/min)



$t_{½}$=1.5–2.1 min
(bolo ev 2.5–25.0 nmol/L)

Adapted from Vilsbøll et al. J Clin Endocrinol Metab 2003;88:220–4.

Liraglutide is a once-daily, human GLP-1 analogue

Human endogenous GLP-1

$T_{½}$= ~2 mins

C-16 fatty acid (palmitoyl)

Liraglutide

97% amino acid homology to human GLP-1; improved PK: albumin binding through acylation; heptamer formation

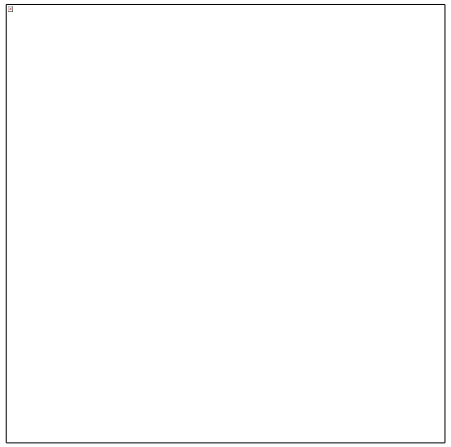
↓

Slow absorption from subcutis
Resistant to DPP-4
Long plasma half-life
($T_{½}$=13 h)

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PK, pharmacokinetics; $T_{½}$, plasma half-life

Knudsen *et al. J Med Chem* 2000;43:1664–9; Degn *et al. Diabetes* 2004;53:1187–94

Liraglutide 3.0 mg

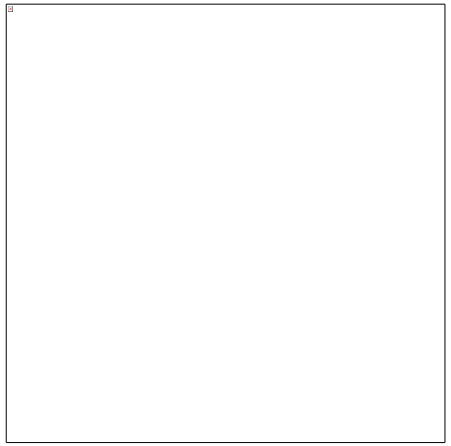


es. h: 1.61 m, w: 70 kg

Overweight

BMI ≥ 27 kg/m²

+ ≥ 1 comorbidities
[such as dysglycaemia (prediabetes or T2D), hypertension, dyslipidaemia or OSAS]



es. h: 1.61 m, w: 78 kg

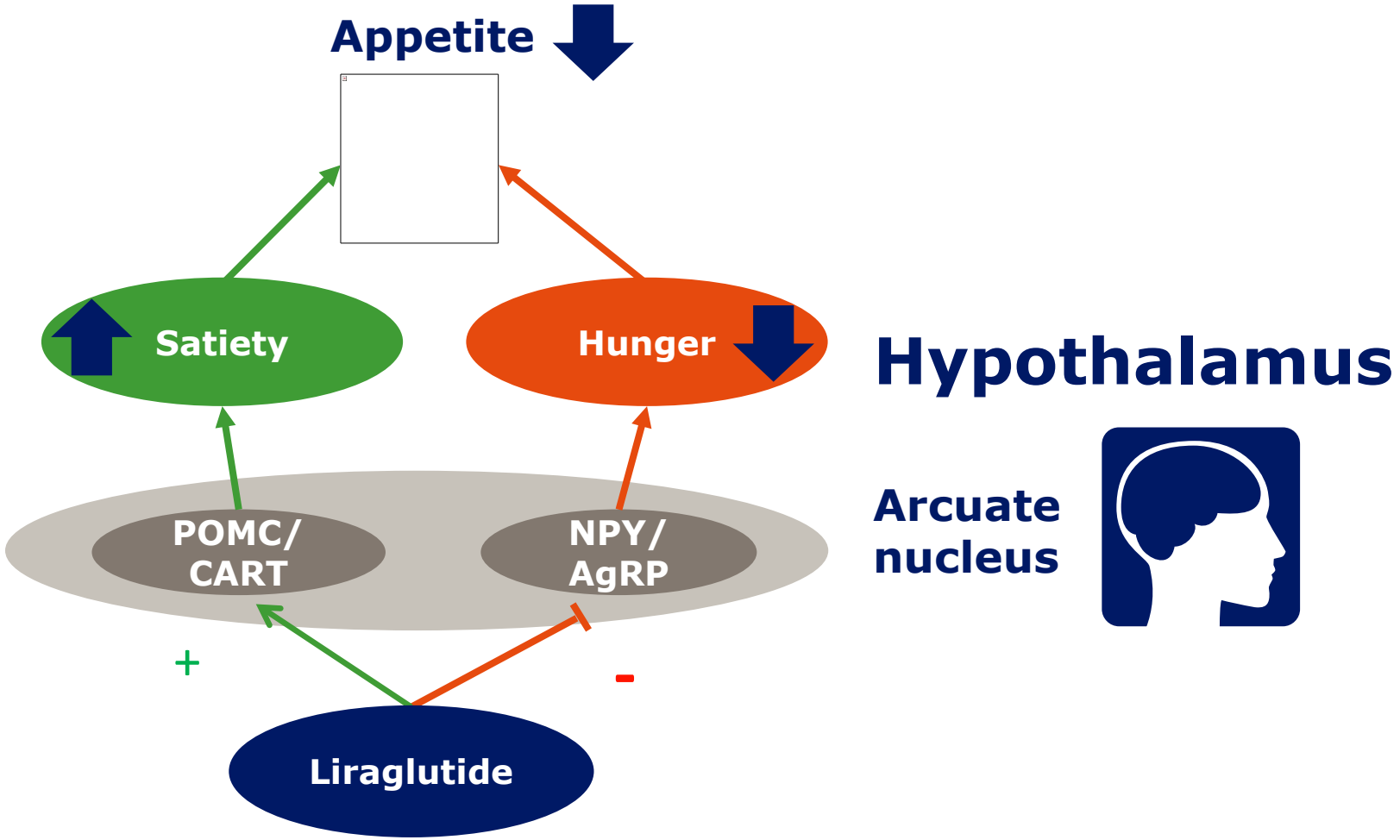
Obesity

BMI ≥ 30 kg/m²

T2D, type 2 diabetes; OSAS, obstructive sleep apnoea.

Liraglutide increases satiety and reduces hunger

Via neurons in the arcuate nucleus



GABA, gamma-aminobutyric acid; GLP-1R, glucagon-like peptide-1 receptor; NPY, neuropeptide Y; POMC, pro-opiomelanocortin

Secher et al. J Clin Invest 2014;124:4473–88

The Role of Pharmacotherapy

Pre Bariatric Surgery

1. **Treat Metabolic Syndrome:**
   - ↑ EWL post-op [1]
   - ↓ Reduce hospital stay [1]
   - ↓ Post-op complications [2]
2. **Reduce Risk in Anesthesia**
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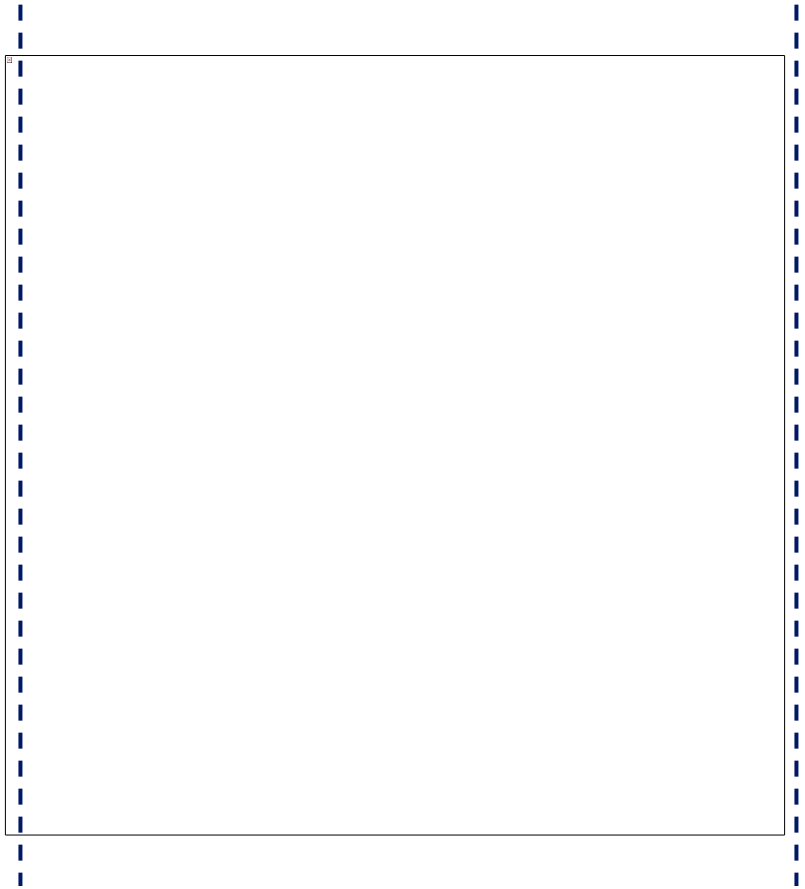
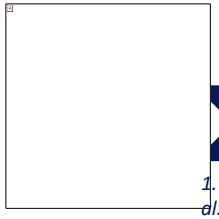
4. **Patients non-responsive to lifestyle intervention** [4]



* BMI > 55 main risk factor for unfavourable outcomes (SICOB guidelines 2016)



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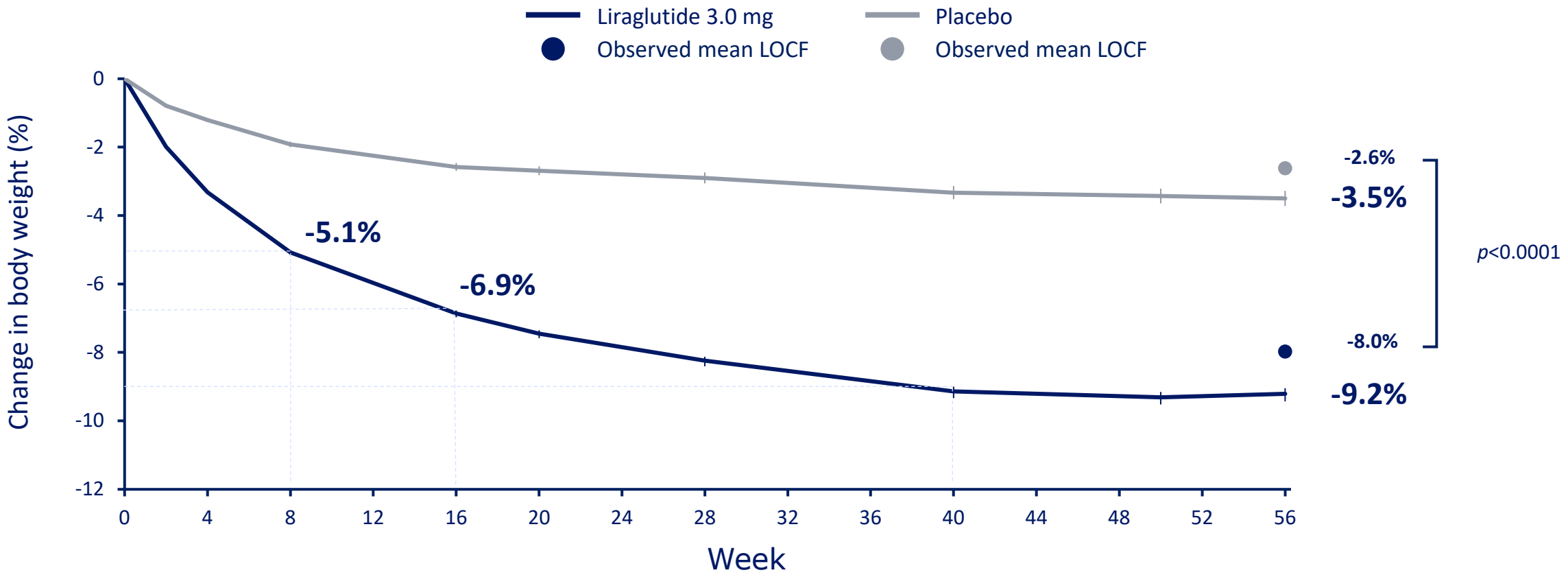
Change in body weight (%)

SCALE Obesity and Prediabetes: 0-56 weeks

Mean baseline weight: 106 kg



FAS, fasting visit data only. Line graphs are observed means (±SE). Statistical analysis is ANCOVA.
FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

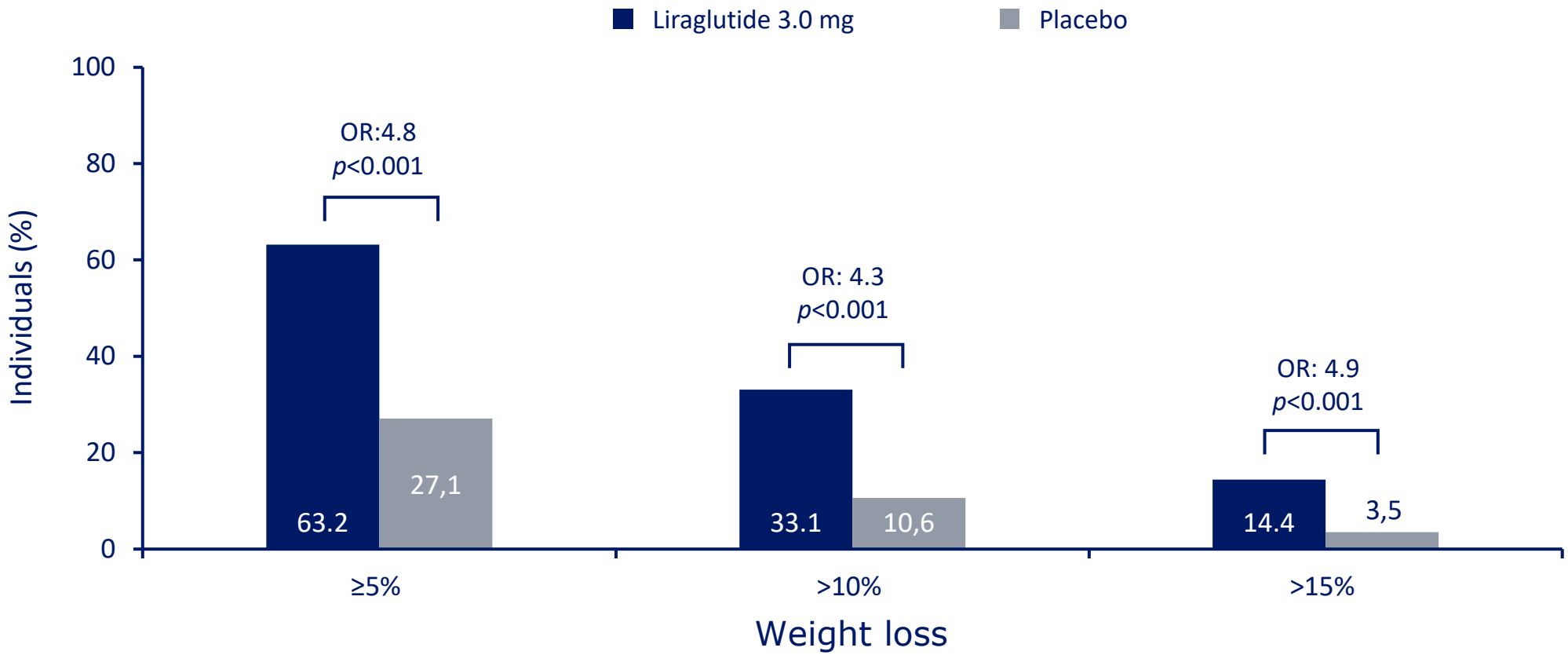
Lifestyle intervention: -500 kcal/day diet + 150 min/week physical activity

Pi-Sunyer et al. N Engl J Med 2015;373:11–22; 2

Categorical weight loss

SCALE Obesity and Prediabetes: At week 56

Mean baseline weight: 106.2 kg

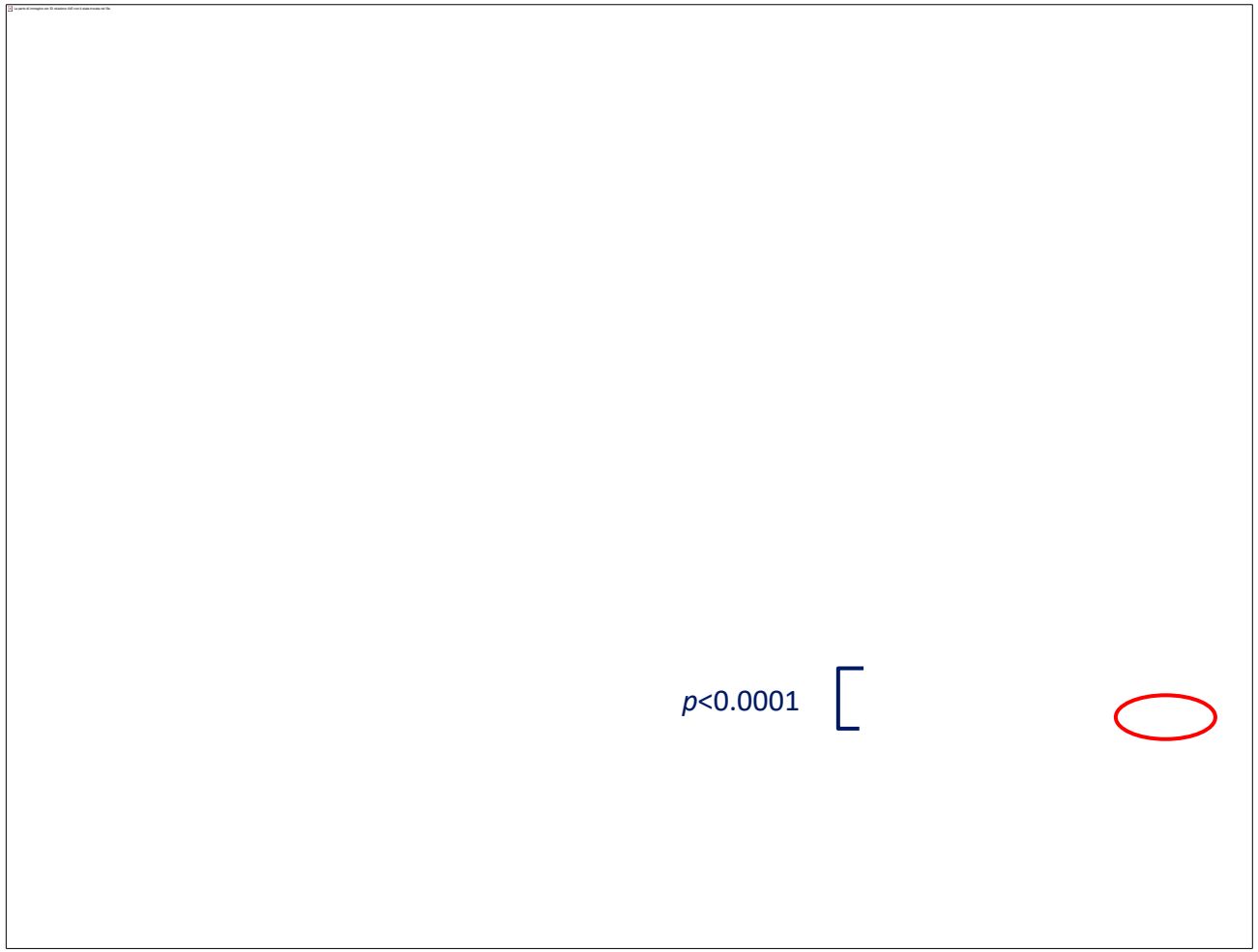


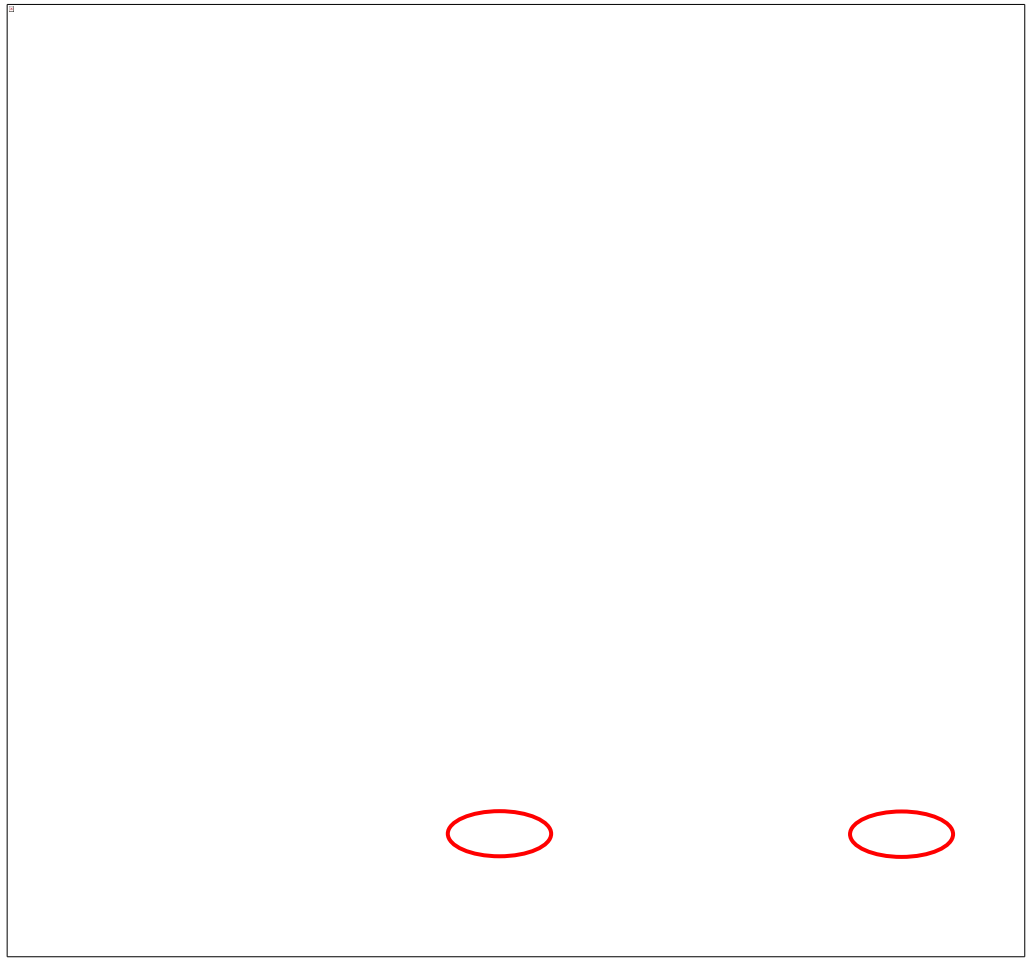
Data are observed means for the full analysis set (with LOCF) and the odds ratios (OR) shown are from a logistic regression analysis (the analysis for achieving 15% weight loss was performed post hoc). LOCF, last observation carried forward; OR, odds ratio

Pi-Sunyer et al. N Engl J Med 2015;373:11–22;

Visceral fat and ectopic fat reduction by MRI

One mechanism associated with benefits on infertility

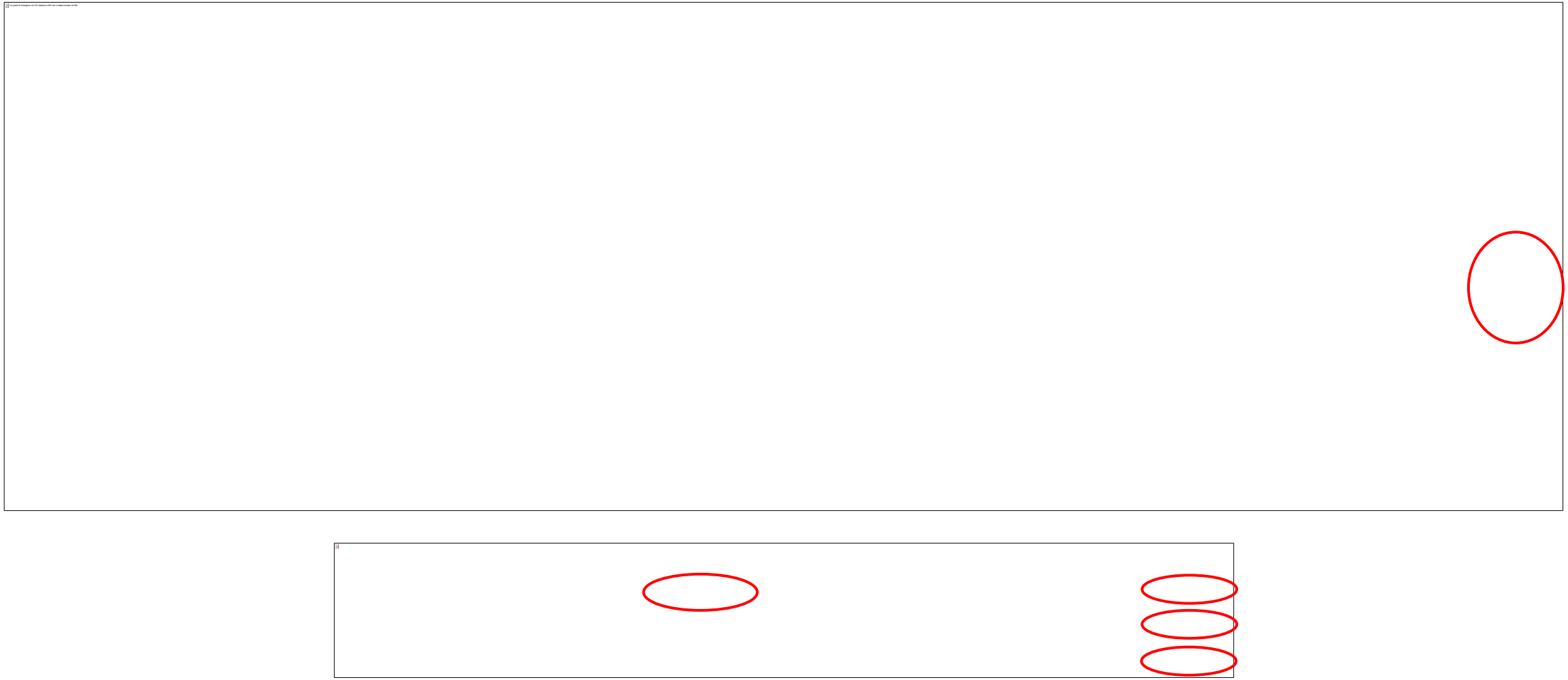




Neeland IJ et al. Lancet Diabetes Endocrinol. 2021 Sep;9(9):595-605.

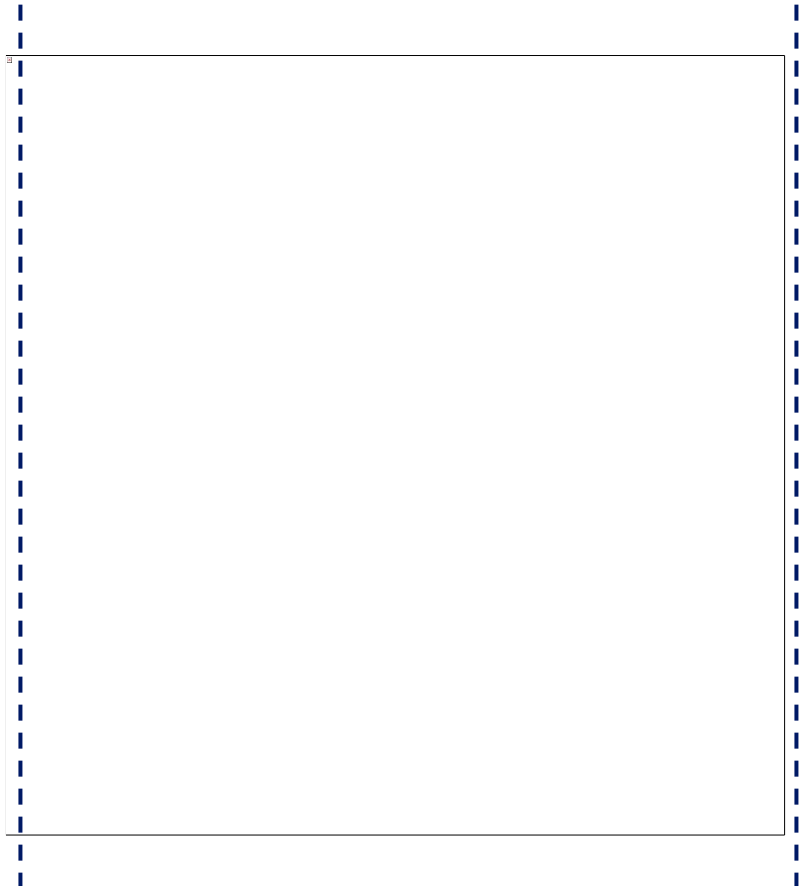
Change in fasting glucose and fasting insulin

SCALE Obesity and Prediabetes: At week 172



le Roux CW, et al. Lancet. 2017;389(10077):1399-1409.

The Role of Pharmacotherapy



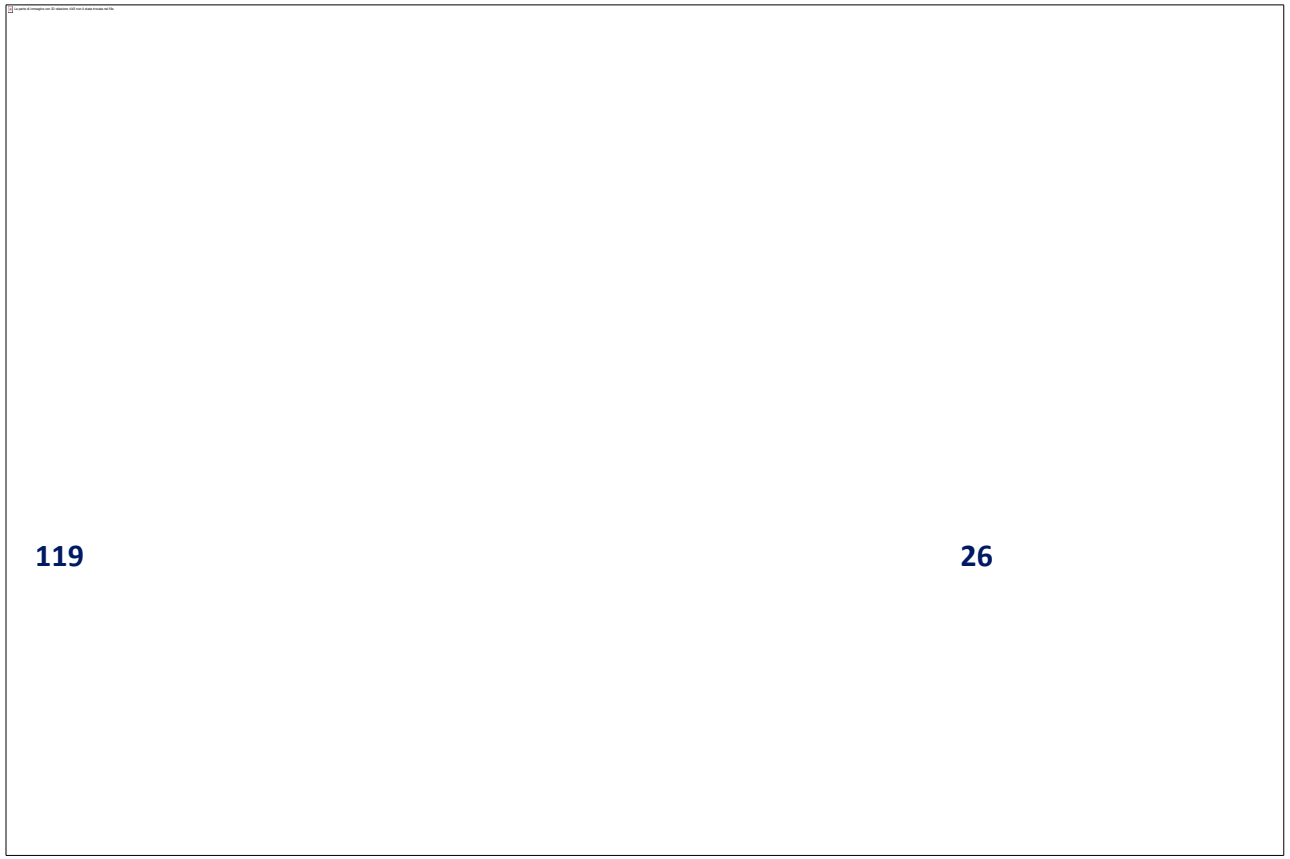
Post Bariatric Surgery

1. **Weight Regain** [5] (≥ 25 weight loss)
2. **Insufficient Weight Loss** [5] (< 50% EWL)
3. **Patients desiring further weight loss** [6]

- **Patients with no indication for bariatric surgery** [7] (BMI < 40): endoscopic surgery

1. Hutcheon DA et al. J Am Coll Surg. 2018;226(4):514-524; 2. Cassie S et al. Surg Obes Relat Dis. 2011;7(6):760-7; 3. Stier et al. Diabetes 2015;64:A43; 4. Malone et al. Ann Pharmacother 2012;46:779–84; 5. Vinciguerra F, et al. 2021 Apr 1. doi: 10.23736/S2724-6507.21.03311-3; 6. Thakur U, et al. Obes Surg. 2021;31(1):84-92; 7. Badurdeen D, et al. Gastrointest Endosc. 2021 Jun;93(6):1316-1324.e1.

Liraglutide 3.0 mg in inadequate weight loss (IWL) or weight regain (WR) after primary or revisional surgery

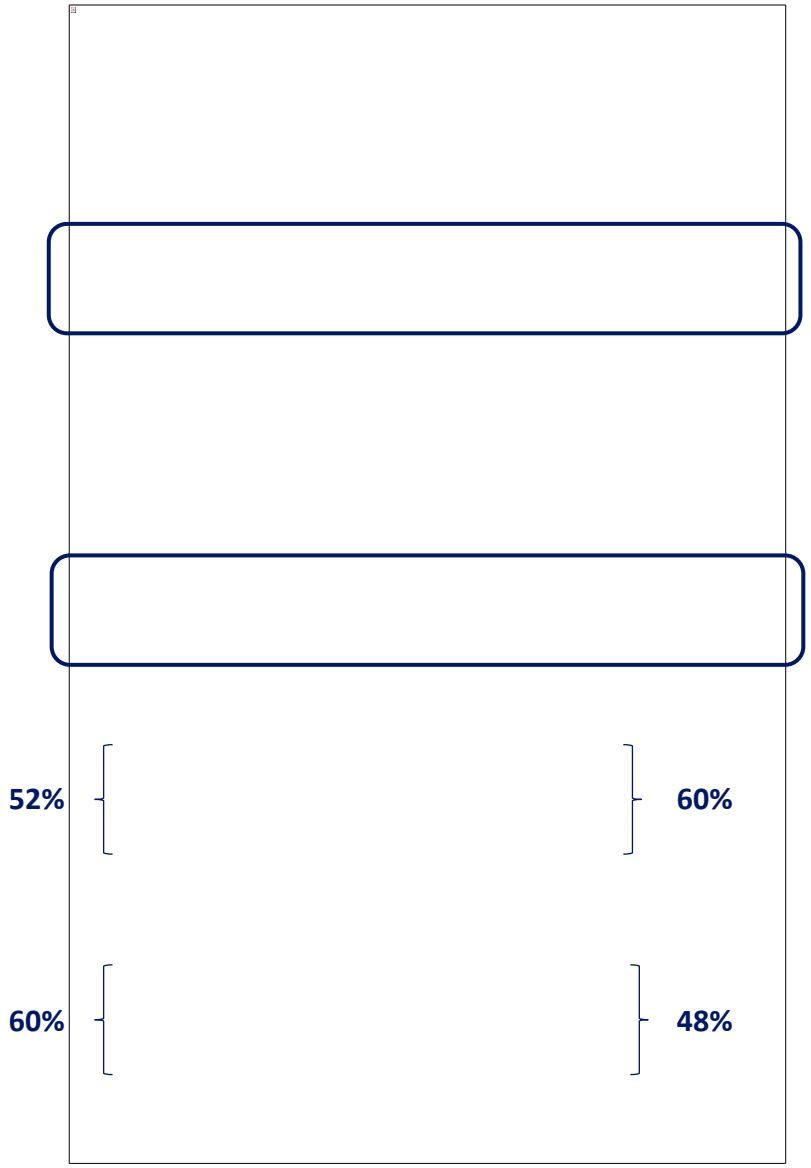


- 22% inadequate weight loss
- 78% weight regain

Liraglutide start: 56 months postop

- 42% inadequate weight loss
- 58% weight regain

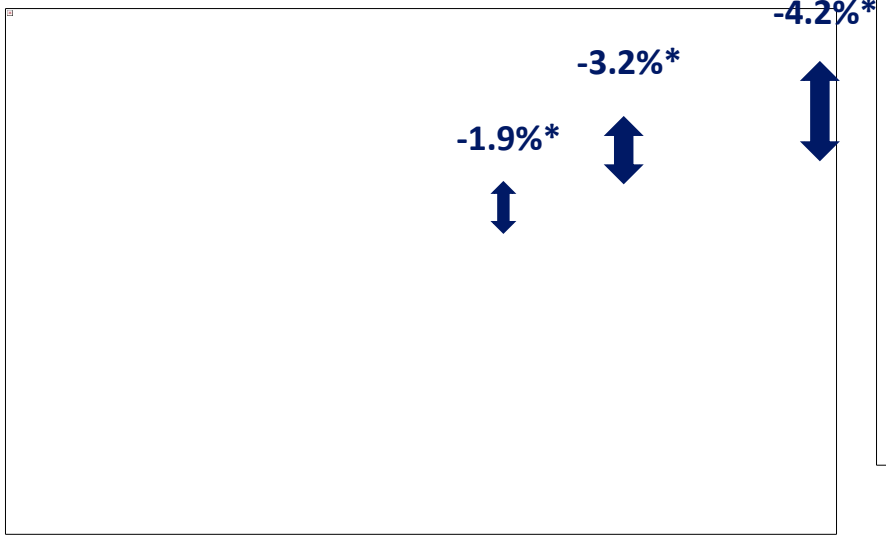
Liraglutide start: 42 months postop

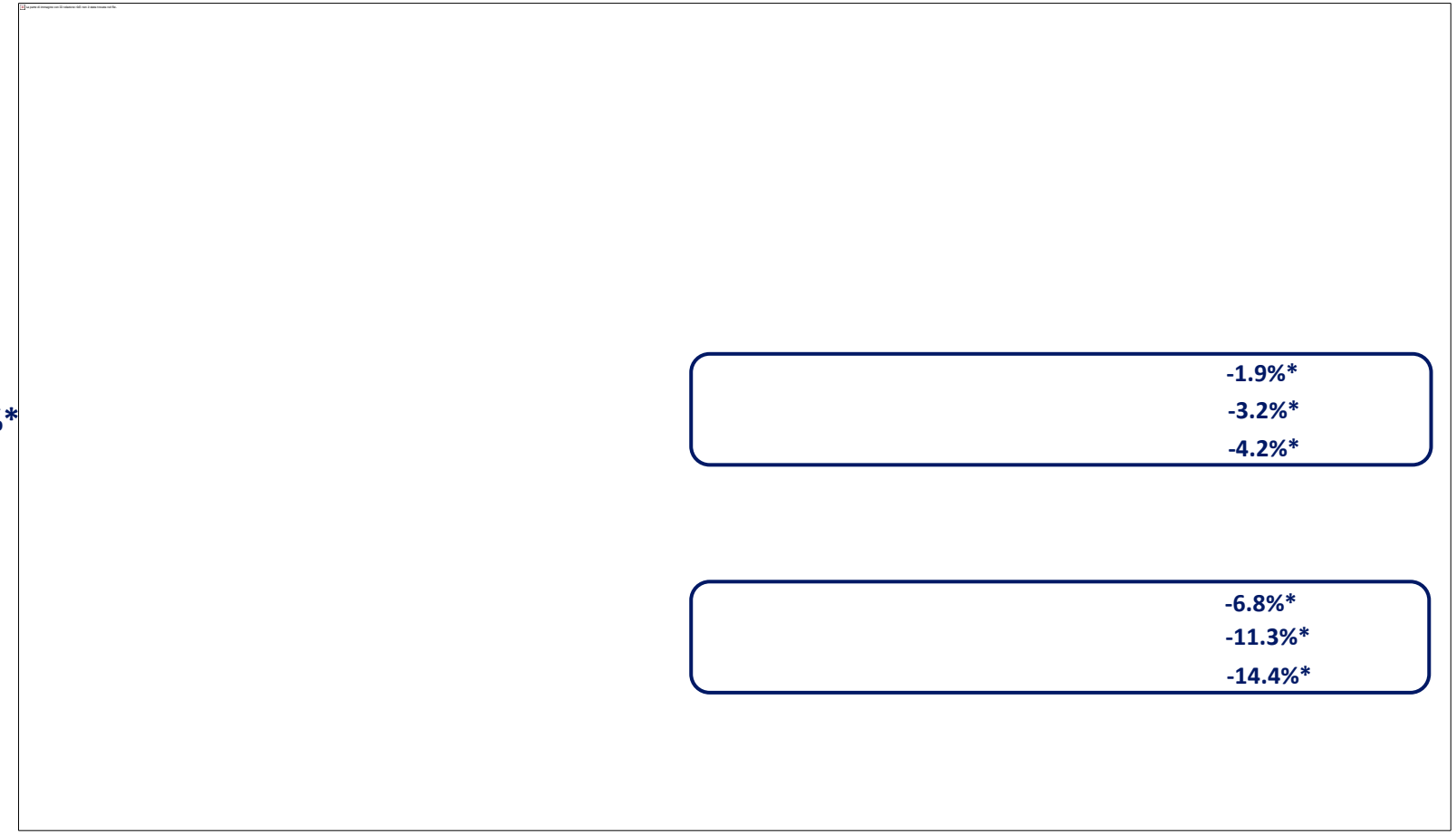


RYGB, Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy; LAGB, laparoscopic adjustable gastric banding; SADI, single-anastomosis duodeno-ileal bypass .

Elhag W, et al. Obes Surg. 2022 Jan 20. doi: 10.1007/s11695-021-05884-y.

Endoscopic sleeve gastroplasty plus liraglutide 3.0 mg vs endoscopic sleeve gastroplasty alone for weight loss





Badurdeen D, et al. Gastrointest Endosc. 2021;93(6):1316-1324.e1.