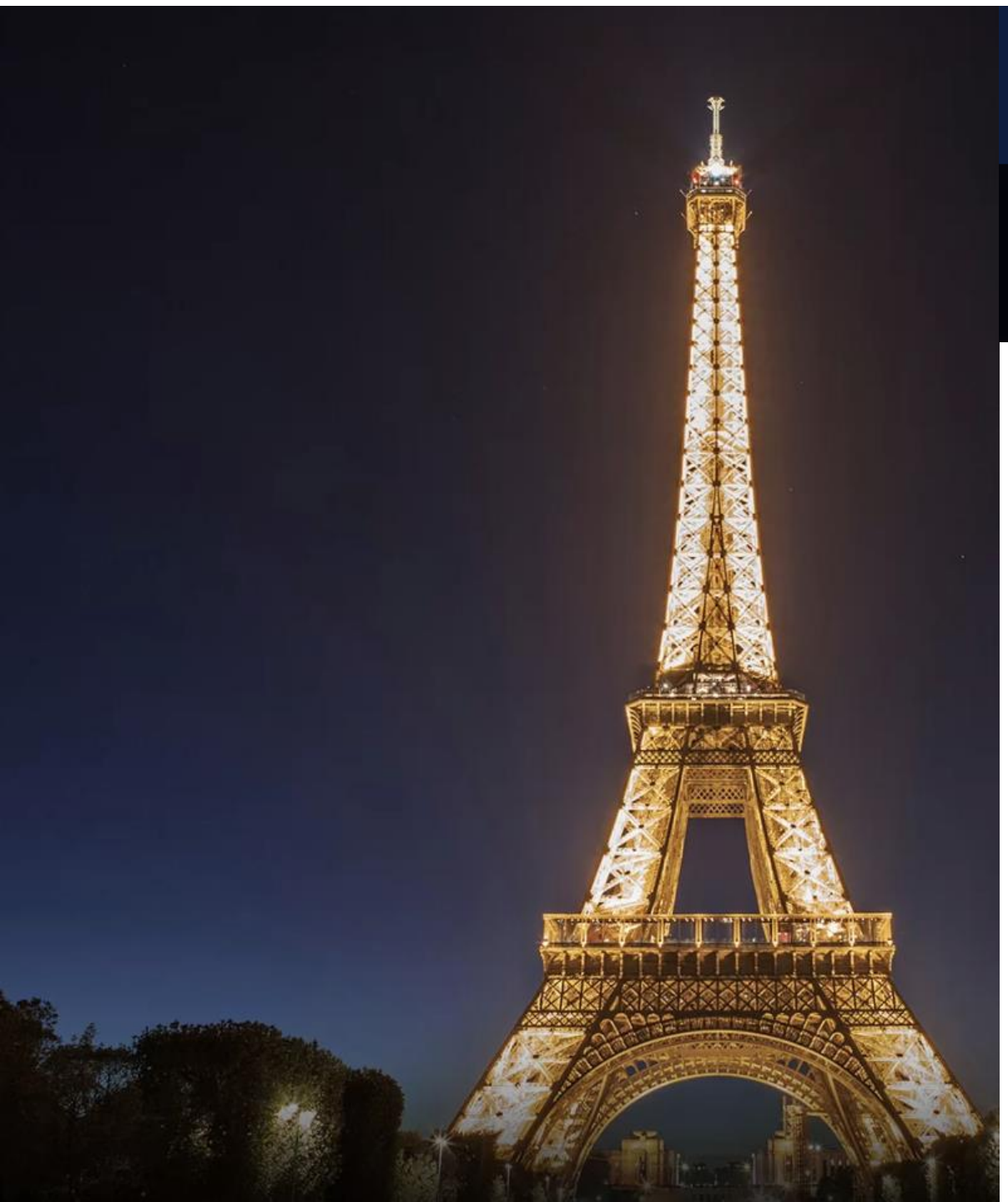


APHC Association for the Promotion of Hepatologic Care

APHC Association for the Promotion of Hepatologic Care

Benefit of weight loss in MASH

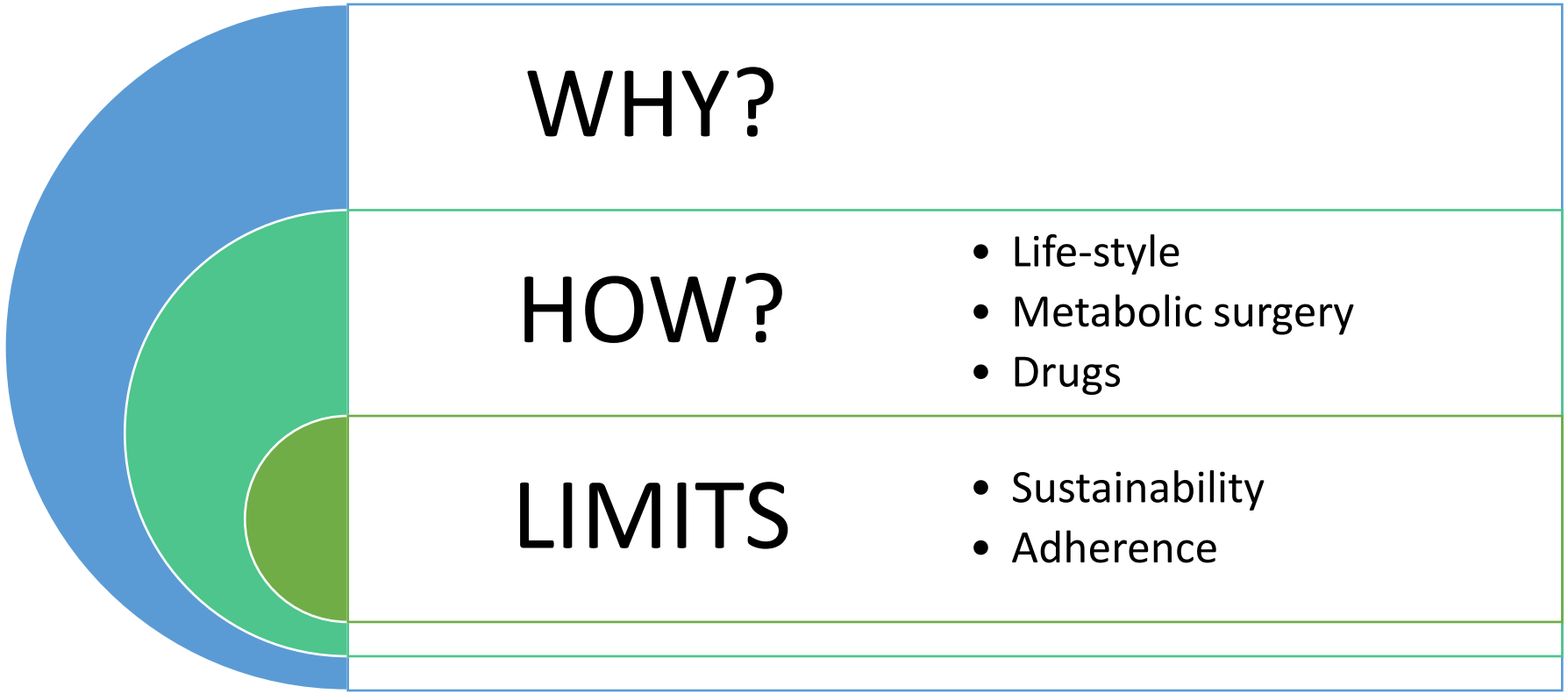
Dr Raluca Pais

Pitié Salpêtrière, & ICAN
Paris, France

IHU ICAN Fondation pour l'Innovation en Cardiométabolisme et Nutrition

Hôpital Pitié-Salpêtrière AP-HP

Benefit of weight loss in MASH

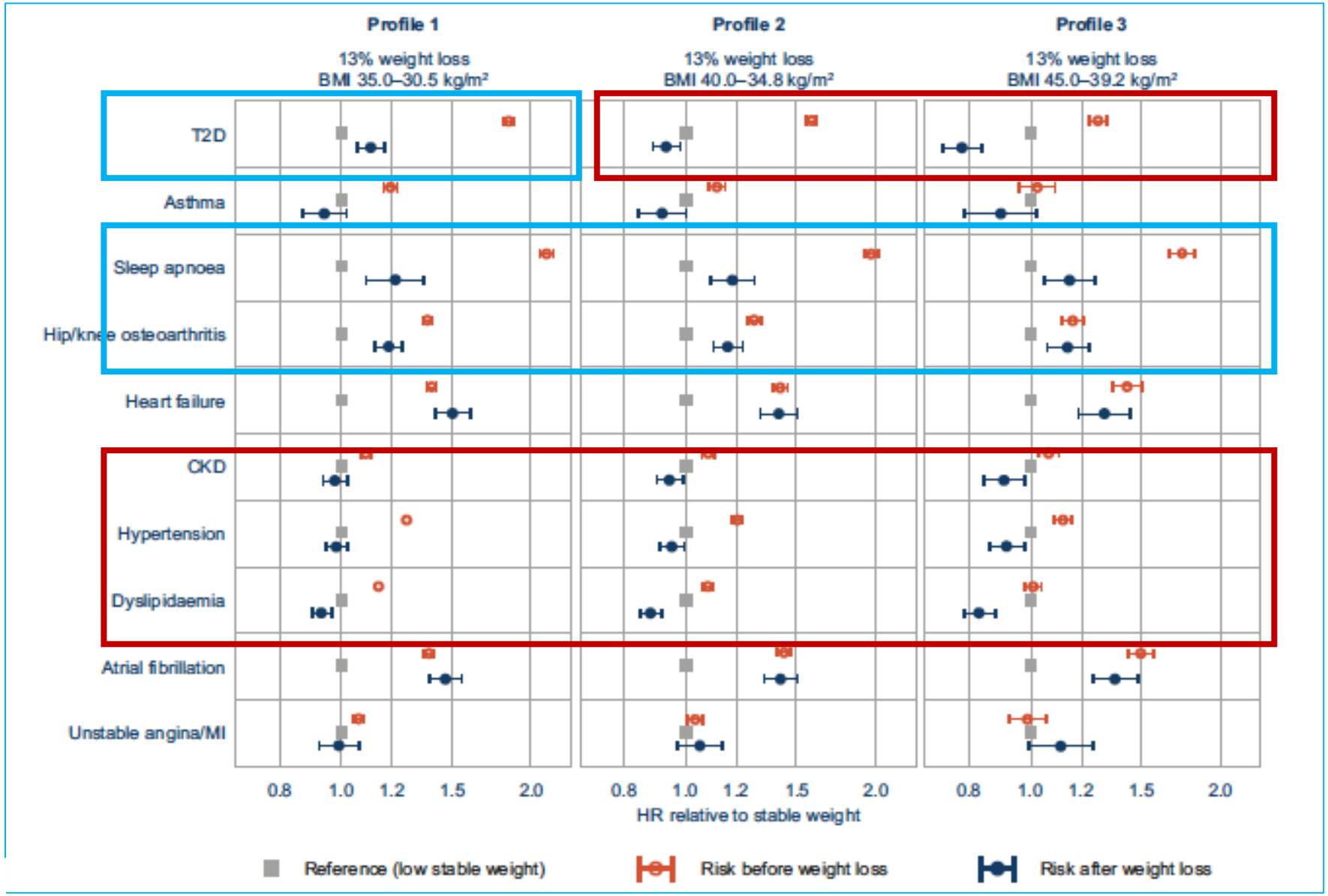


Benefits of weight loss

UK primary care database: 0.5 million people

- **Additional benefit:** The risk after weight loss was significantly lower than the risk for an individual with the corresponding stable lower BMI.

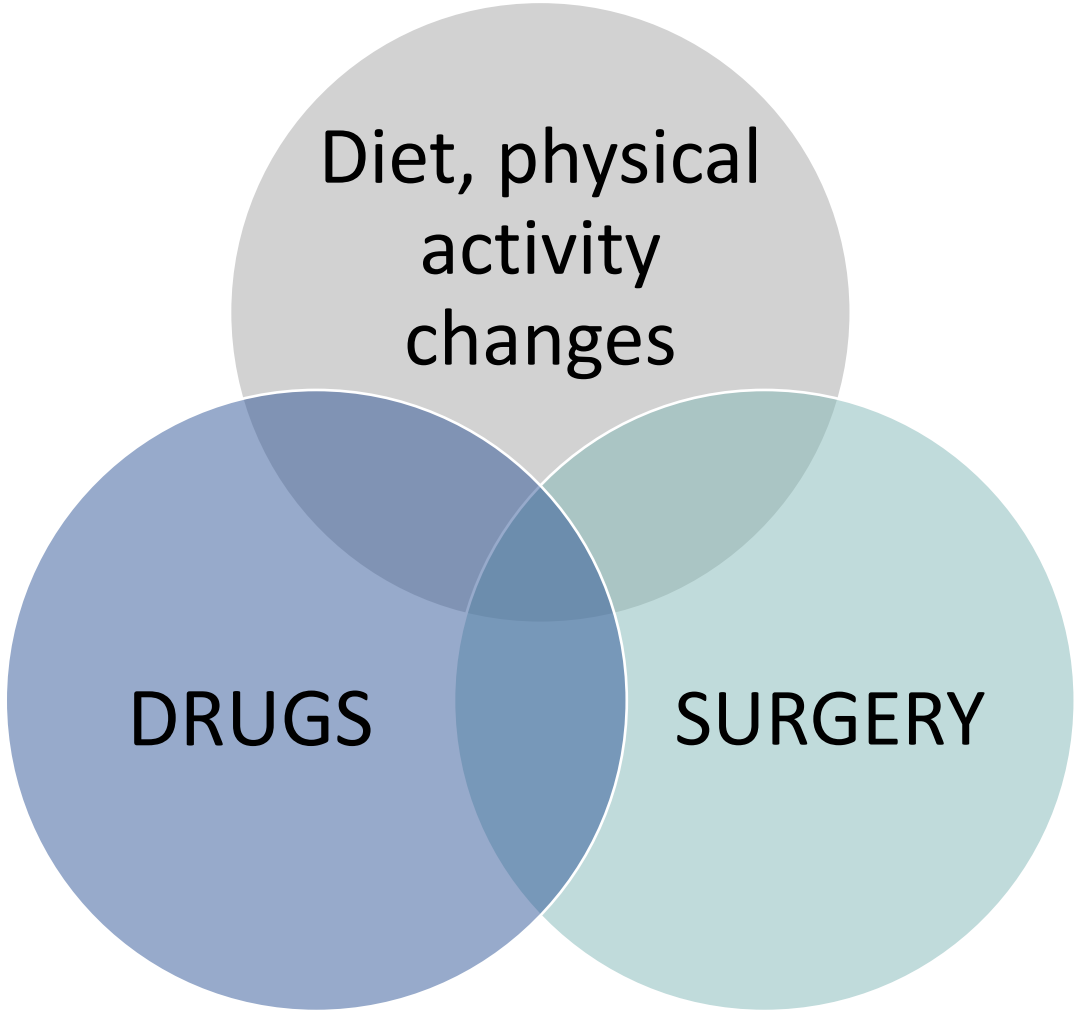
- **Benefit with residual risk:** The risk after weight loss was significantly lower than the risk before weight loss; but significantly higher than the risk for an individual with the corresponding stable lower BMI



Haase, Int J of Obesity 2021

Weight loss therapy

HOW?



Associated comorbidities

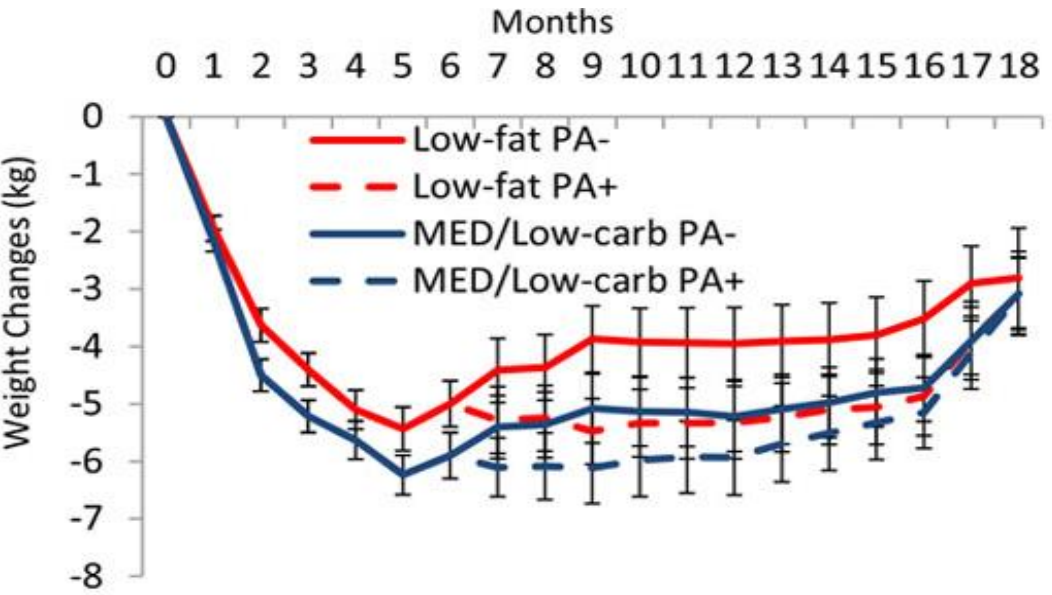
Target Outcomes

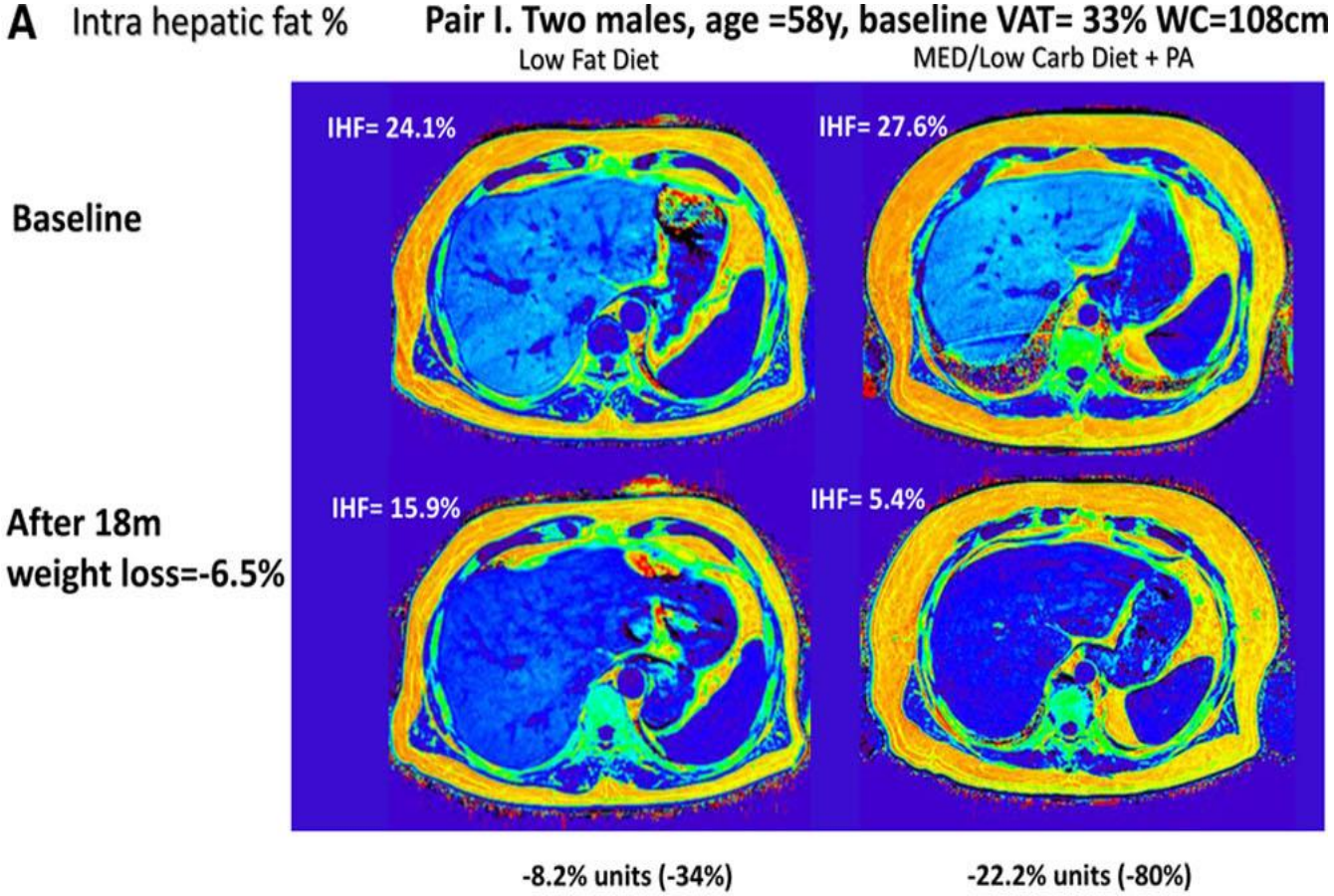
Reimbursement policies

Patients' choice

Effect of diet with or without physical activity on intrahepatic fat content

18 month RCT
278 obeses adults



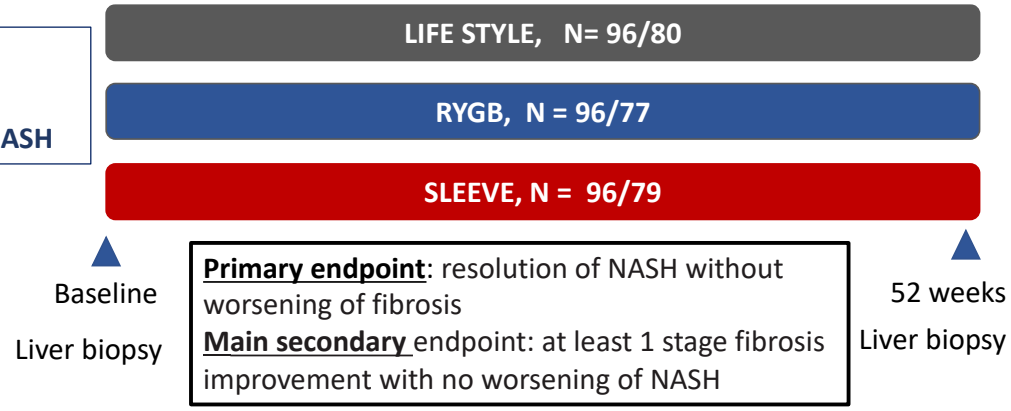


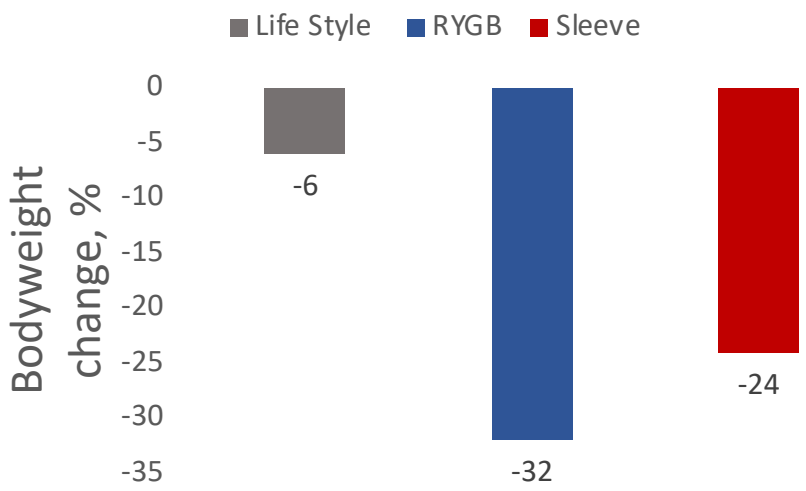
Gepner, Circulation, 2018

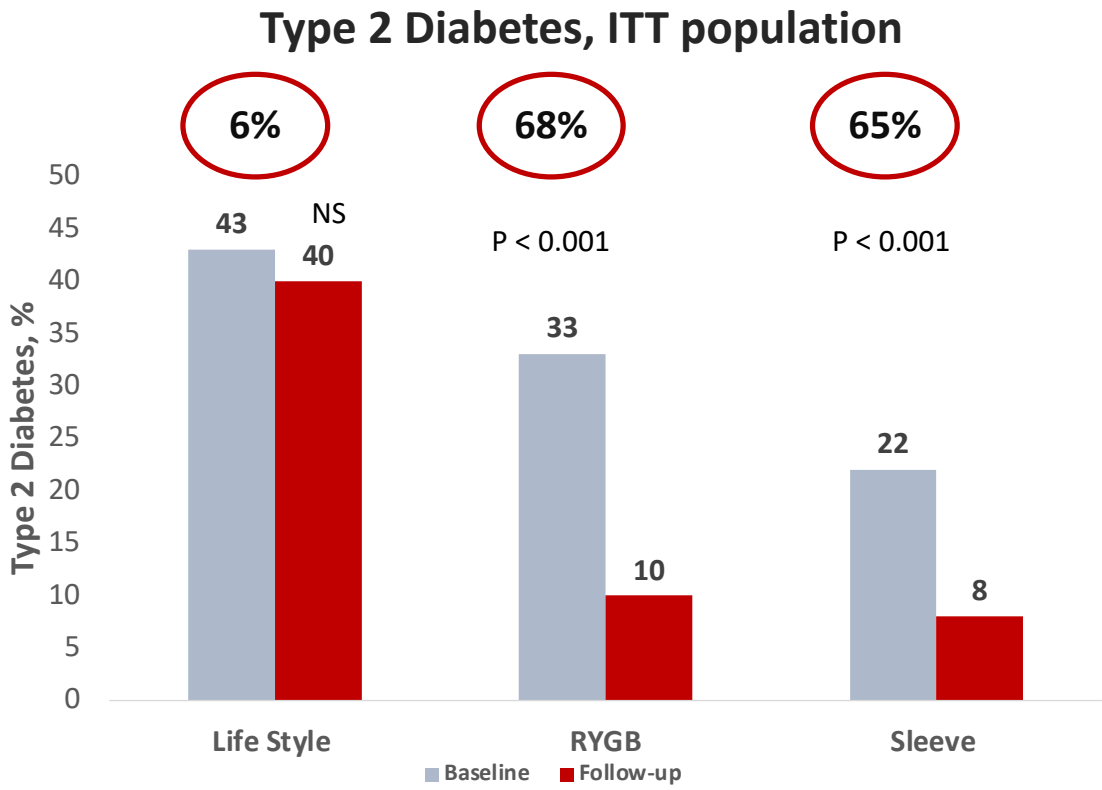
Bariatric–metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial

Ornella Verrastro, Simona Panunzi*, Lidia Castagneto-Gissey, Andrea De Gaetano, Erminia Lembo, Esmeralda Capristo, Caterina Guidone, Giulia Angelini, Francesco Pennestrì, Luca Sessa, Fabio Maria Vecchio, Laura Riccardi, Maria Assunta Zocco, Ivo Boskoski, James R Casella-Mariolo, Pierluigi Marini, Maurizio Pompili, Giovanni Casella, Enrico Fiori, Francesco Rubino, Stefan R Bornstein, Marco Raffaelli, Geltrude Mingrone*

Inclusion criteria:
- ✓ BMI 30–55 kg/m²
- ✓ Histologically confirmed NASH







Bariatric–metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial

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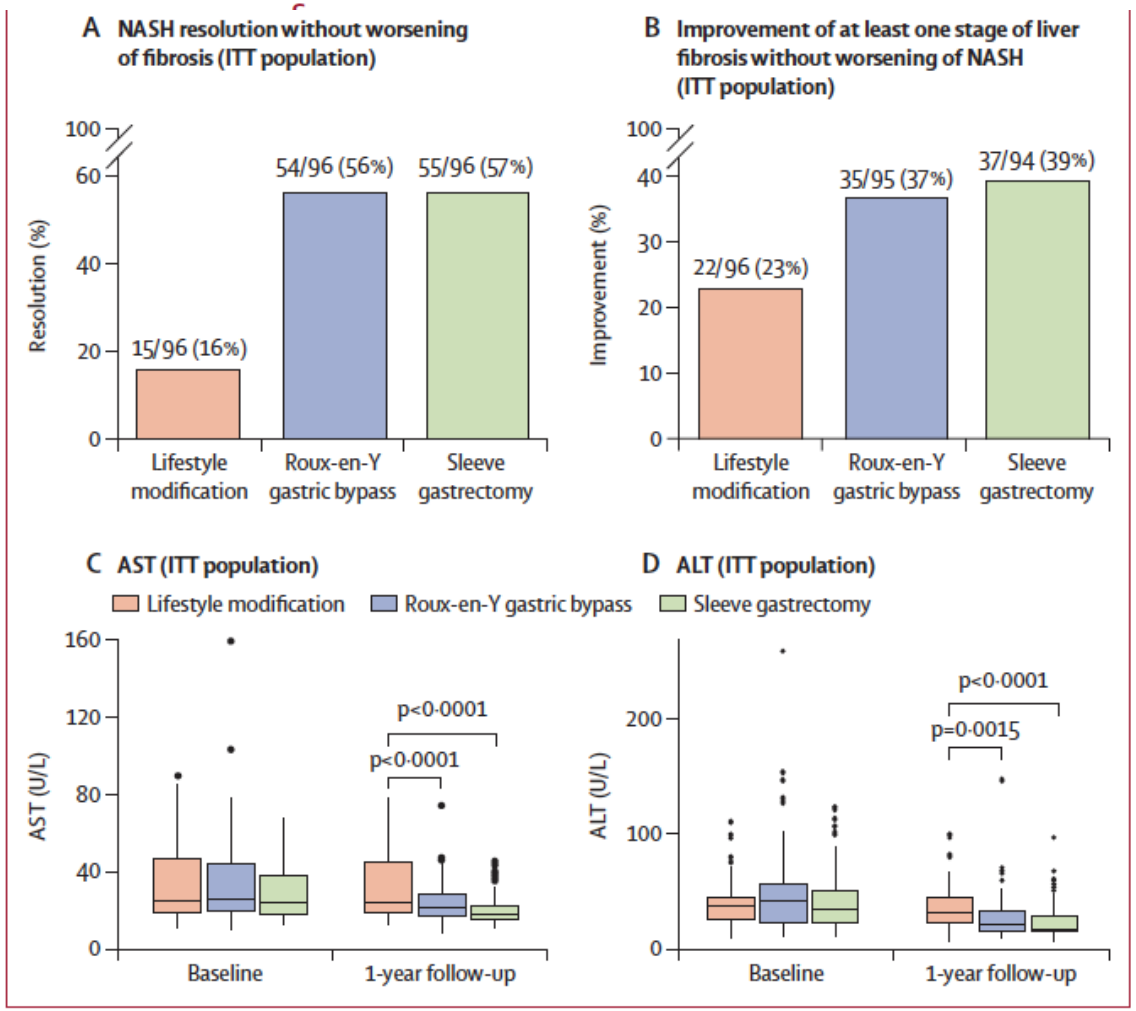
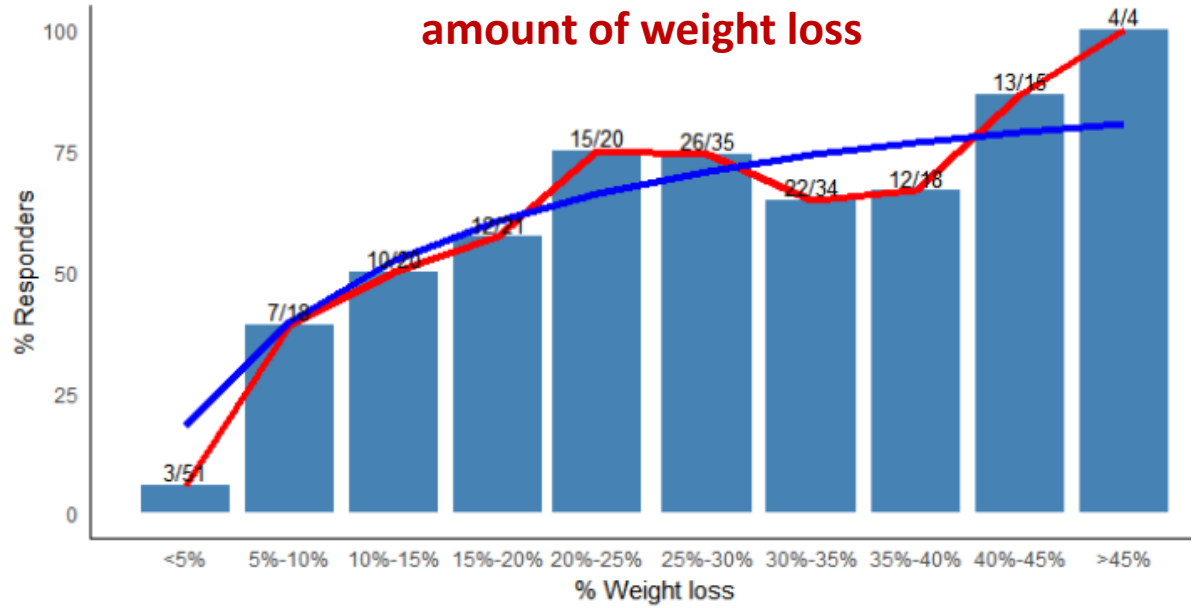


NASH resolution according to the amount of weight loss



88% - F1F2

11% - F3

EASL CONGRESS
Vienna, Austria
21–24 June 2023

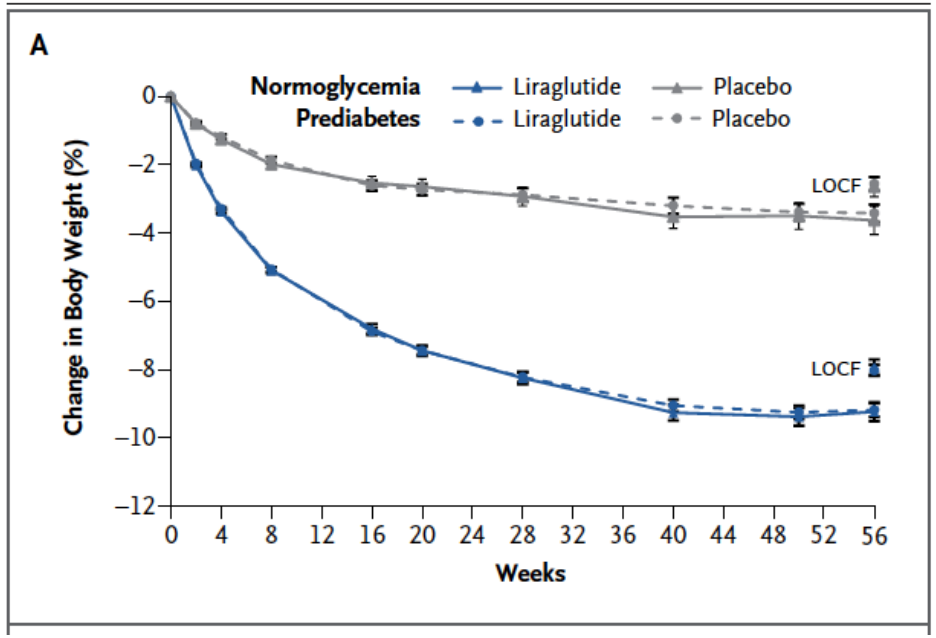
MECHANISM OF ACTION OF GLP1 RECEPTORS AGONIST

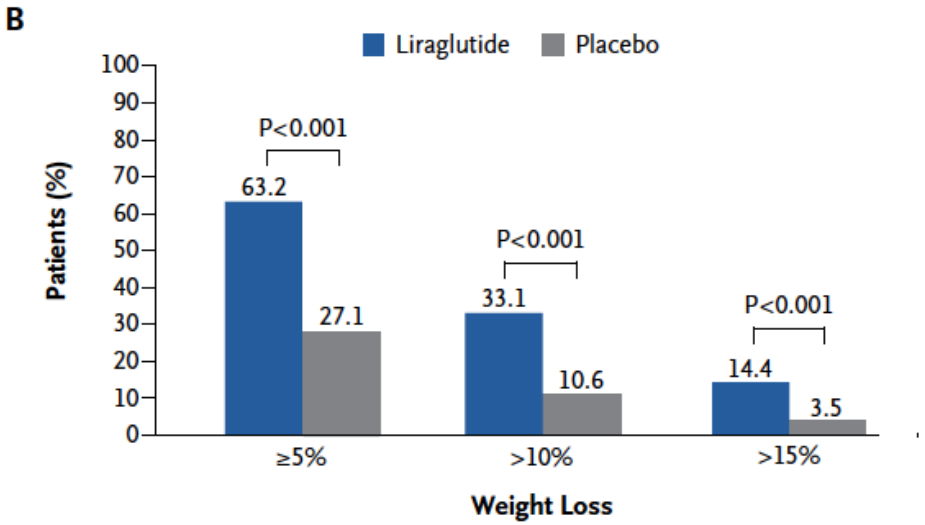
GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist.

1. Campbell, Drucker. *Cell Metab* 2013;17:819–37; 2. Baggio, Drucker. *J Clin Invest* 2014;124:4223–6; 3. Flint et al. *J Clin Invest* 1998;101:515–20;
4. Blundell et al. *Diabetes Obes Metab* 2017;19:1242–51; 5. Tong, D'Alessio. *Diabetes* 2014;63:407–9; 6. Armstrong et al. *J Hepatol* 2016;64:399–408;
7. Armstrong et al. *Lancet* 2016;387:679–90; 8. MacDonald et al. *Diabetes* 2002;51(Suppl 3):S434–42; 9. Drucker. *Cell Metab* 2016;24:15–30.

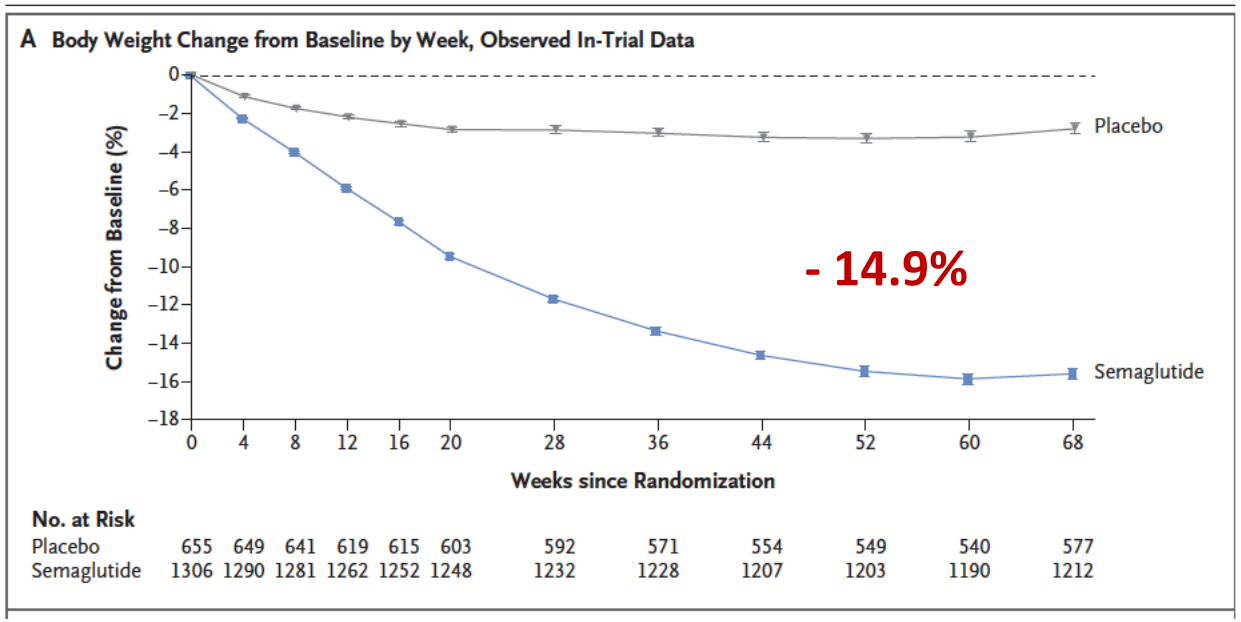
WEIGHT LOSS WITH GLP1 RA

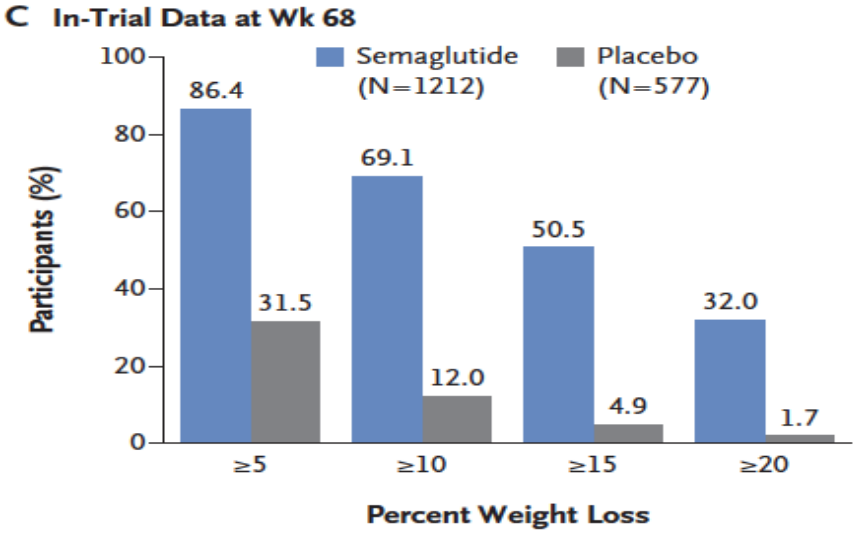
LIRA - 1





STEP - 1



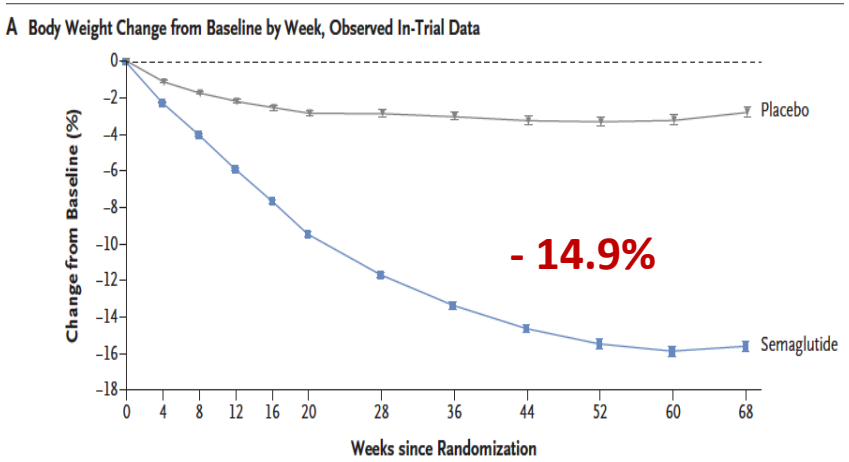


Sunyer, NEJM 2015

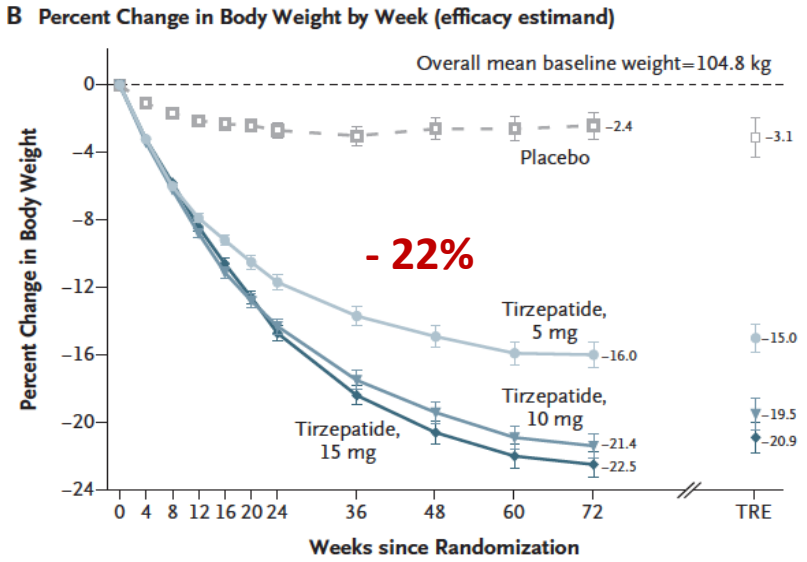
Wilding, NEJM 2021

Weight loss with GLP-1RA, double and triple RA

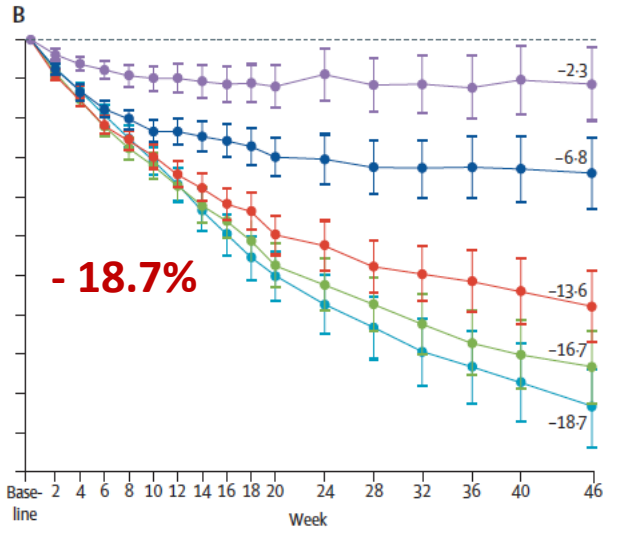
SEMAGLUTIDE



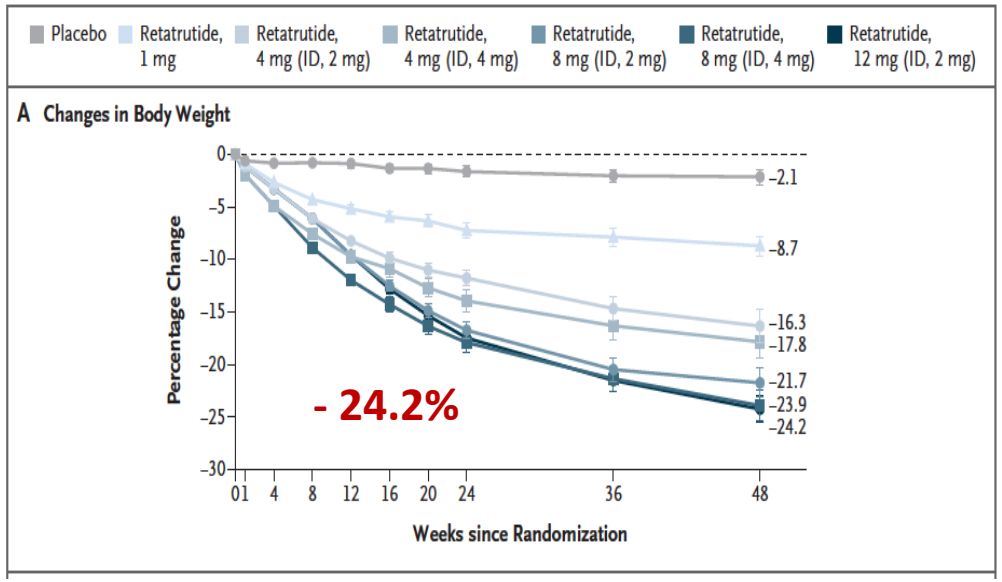
TIRZEPATIDE



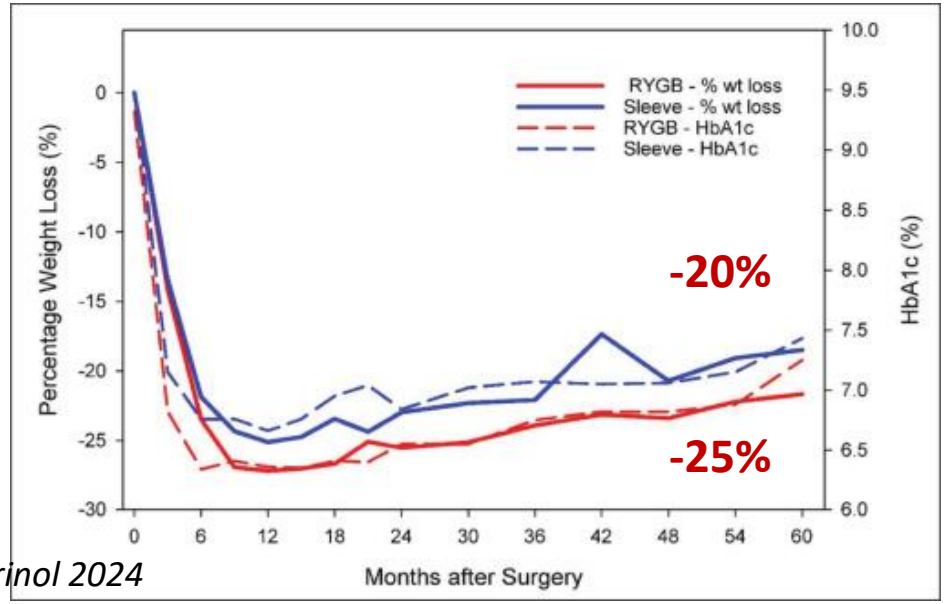
SURVODUTIDE



RETATRUTIDE



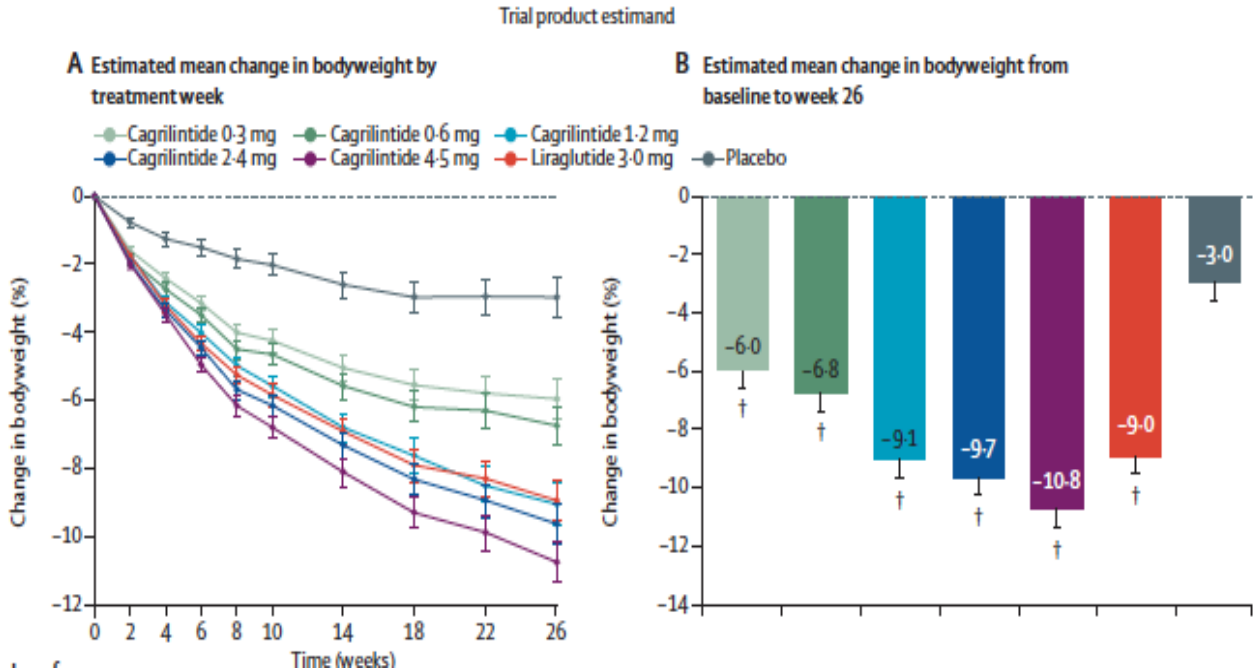
Wilding, NEJM 2015
Jastreboff, NEJM 2022
Jastreboff, NEJM 2023
Zhou, Endocrine Practice 2019
LeRoux, Lancet Diabetes&Endocrinol 2024



Cagrilintide - long-acting amylin analogue

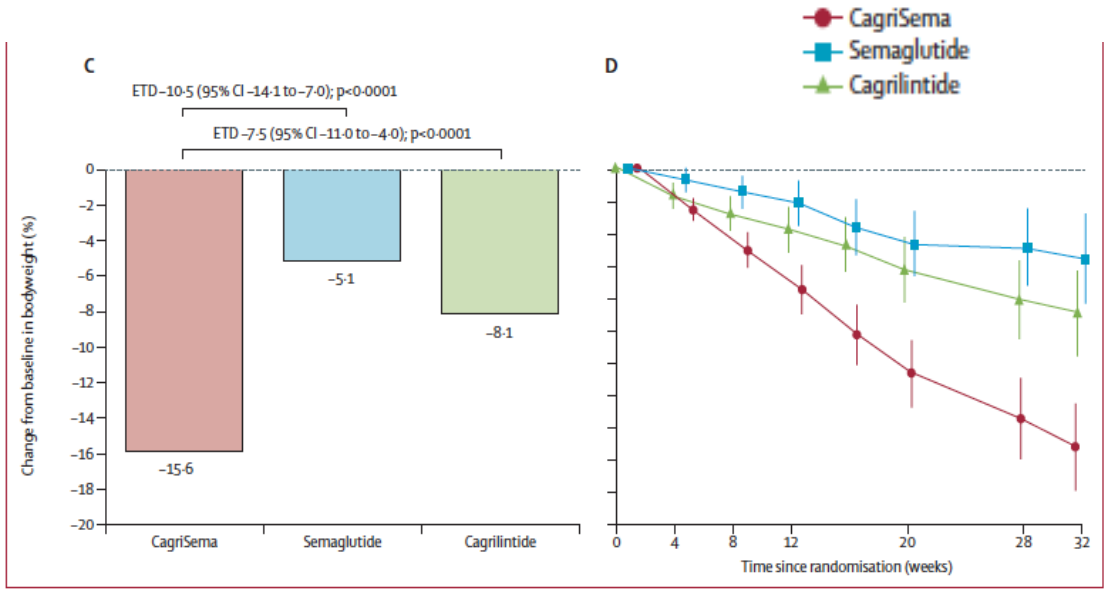
Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial

David C W Lau, Lars Erichsen, Ann Marie Francisco, Altynai Satylganova, Carel W le Roux, Barbara McGowan, Sue D Pedersen, Kirsi H Pietiläinen, Domenica Rubino, Rachel L Batterham



Efficacy and safety of co-administered once-weekly cagrilintide 2·4 mg with once-weekly semaglutide 2·4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial

Juan P Frias, Srikanth Deenadayalan, Lars Erichsen, Filip K Knop, Ildiko Lingvay, Stanislava Macura, Chantal Mathieu, Sue D Pedersen, Melanie Davies

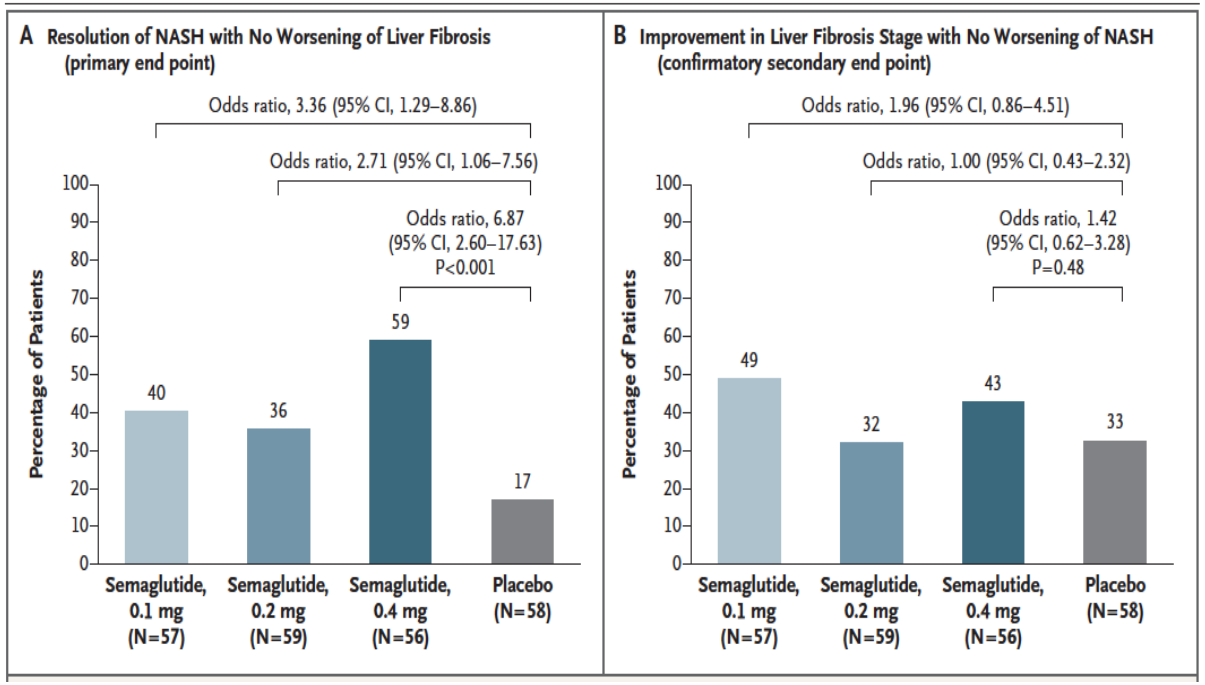


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

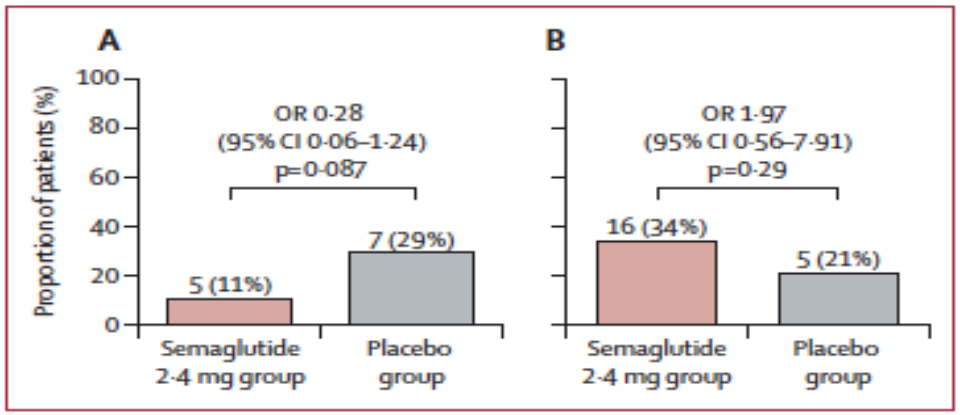
A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

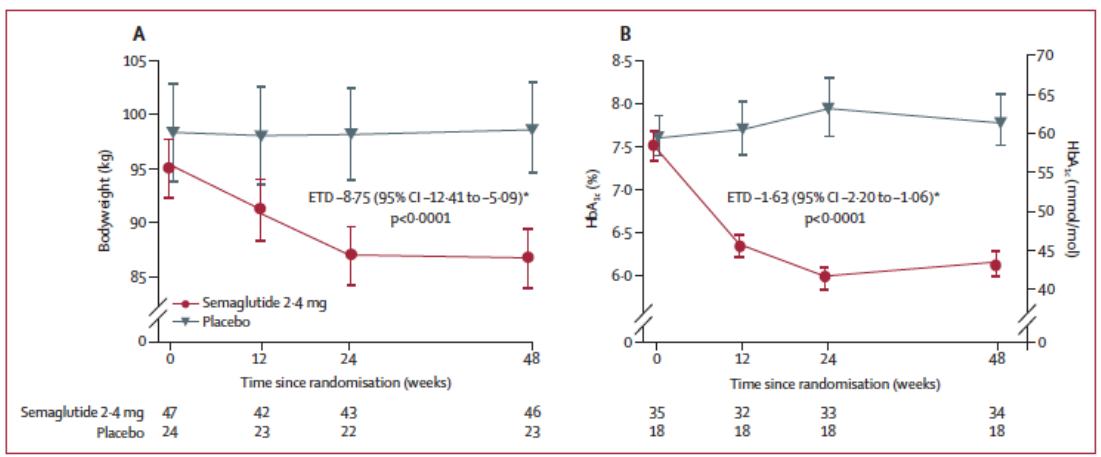
P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*



Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial

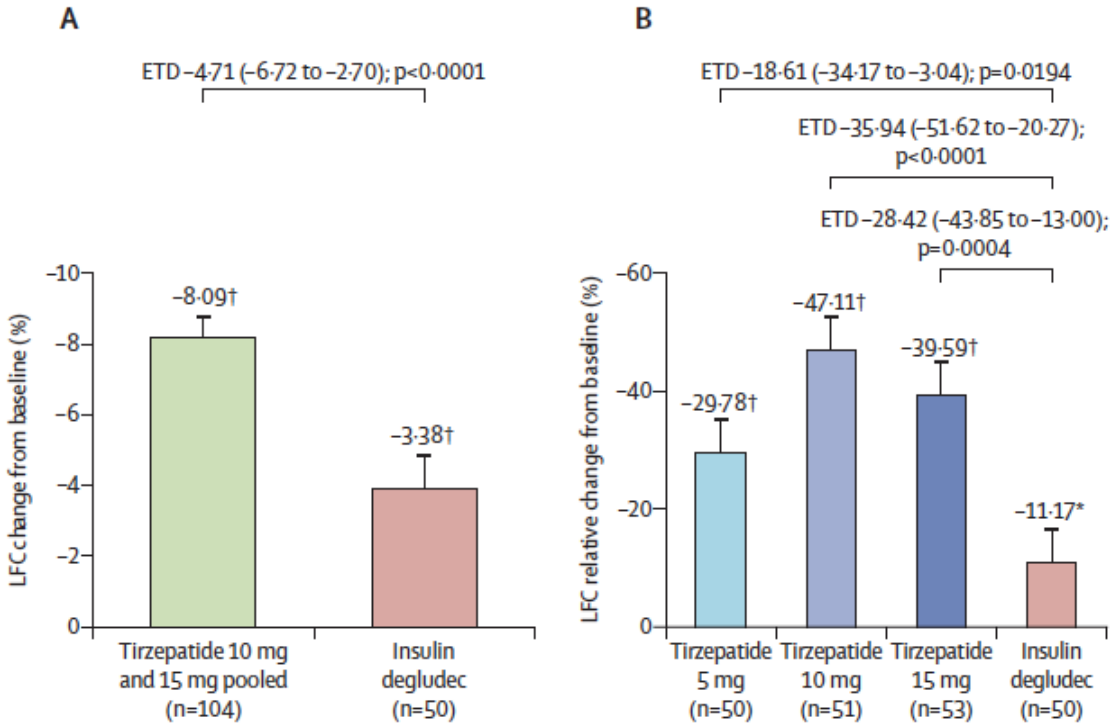
Rohit Loomba*, Manal F Abdelmalek, Matthew J Armstrong, Maximilian Jara, Mette Skalshøi Kjær, Niels Krarup, Eric Lawitz, Vlad Ratziu, Arun J Sanyal, Jörn M Schattenberg, Philip N Newsome*, on behalf of the NN9931-4492 investigators†





Effect of dual and triple RA on liver fat content

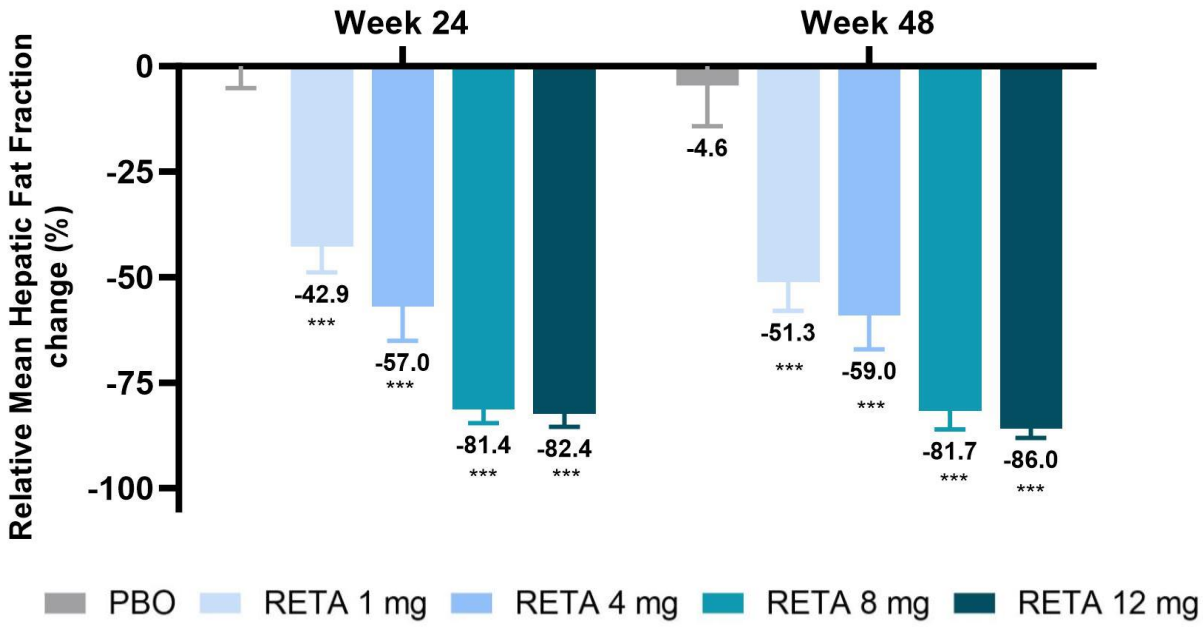
TIRZEPATIDE – SURPASS-3 MRI



Gastaldelli, Lancet 2022

RETATRUTIDE

- Mean relative liver fat reduction was >80% with RETA 8 mg and 12 mg

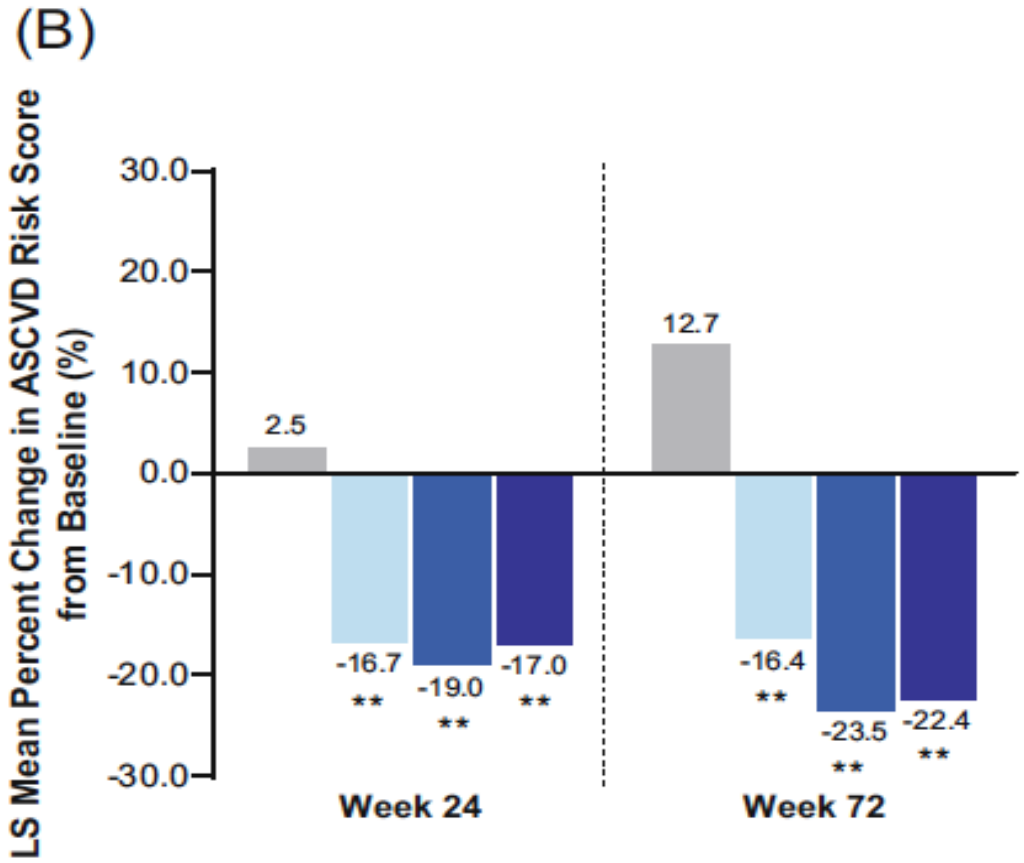


Sanyal, AASLD 2023

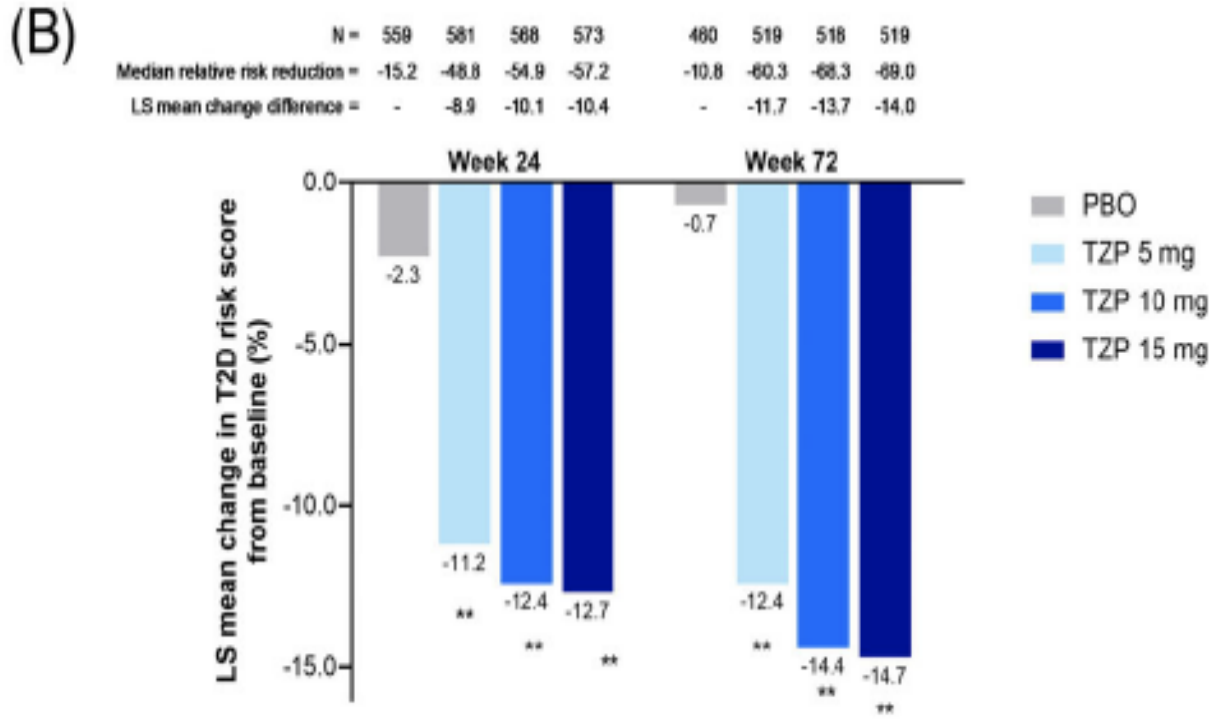
Tirzepatide reduces the predicted risk of atherosclerotic cardiovascular disease and improves cardiometabolic risk

Tirzepatide reduces the predicted risk of developing type 2 diabetes

Post hoc analysis of the SURMOUNT-1 trial



Hankosky, Diabetes Obes Metab 2024



Hankosky, Diabetes Obes Metab 2024

GLP1 – Receptors Agonists: The Holy Grail to lose weight?

- ❖Weight loss
- ❖Liver fat content
- ❖CV risk
- ❖T2DM risk

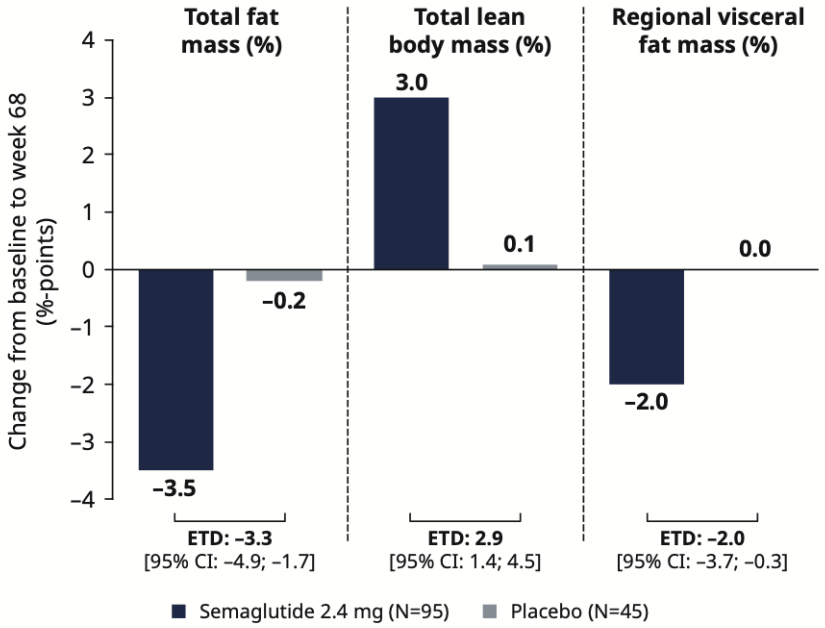
- ❖Effect on adipose tissue distribution
- ❖Sustainability of weight loss
- ❖Non or inadequate response
- ❖Adherence?
- ❖Costs

Effect of a single GLP1 - RAs and dual RAs on adipose tissue distribution

Once-weekly semaglutide in adults with overweight or obesity

	Semaglutide 2.4 mg once weekly (N=1306)	Placebo once weekly (N=655)	Treatment comparison for semaglutide vs. placebo [95% CI]
Co-primary endpoint assessed in the overall population			
Body weight change from baseline to week 68 – %	−16.86	−2.44	ETD: −14.42 [−15.29; −13.55]
Body weight reduction ≥5% – proportion of participants (%) at week 68	92.4	33.1	OR: 37.0 [28.0; 49.0]

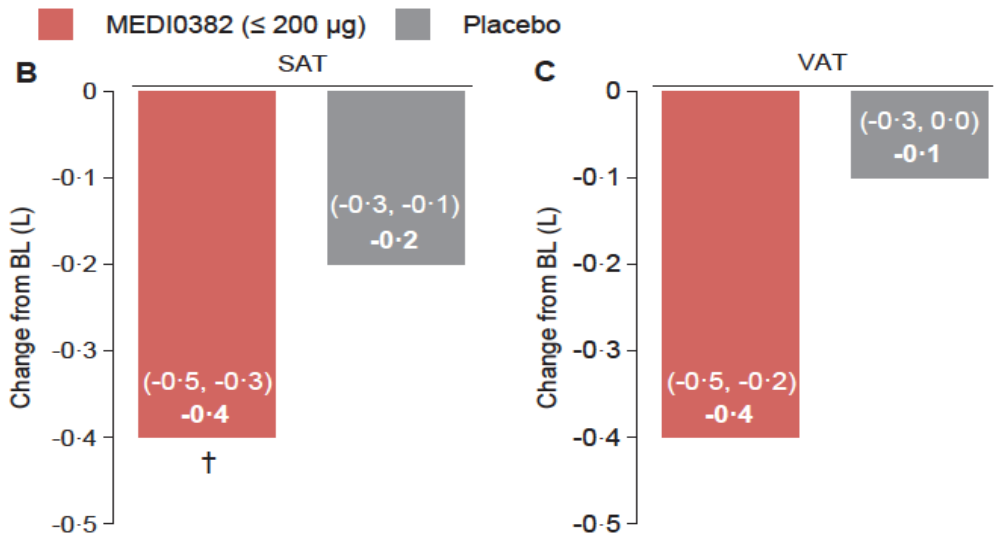
Figure 1: Change in body composition from baseline to week 68



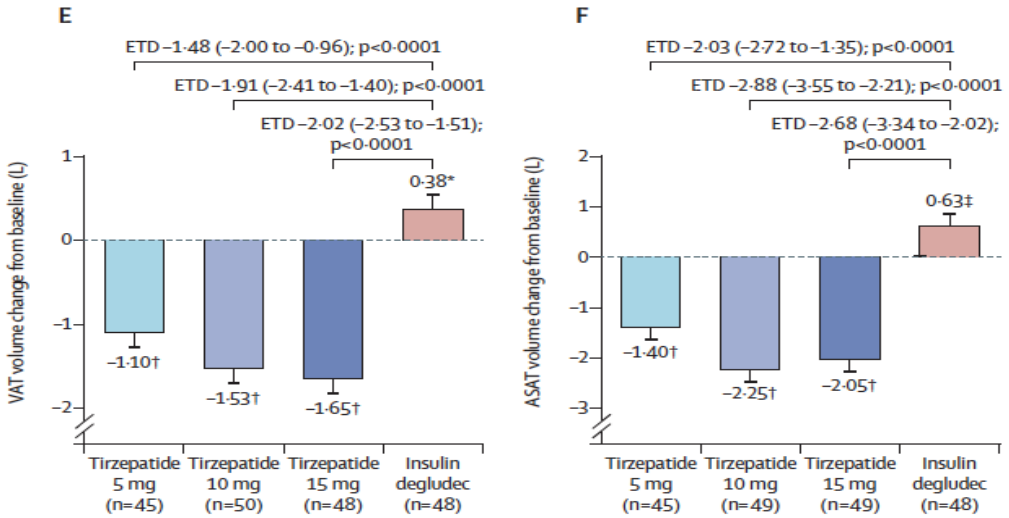
CI, confidence interval; ETD, estimated treatment difference.

Wilding, NEJM 2021

Ambery et al. Lancet 2018; 391:2607–18



Gastaldelli, Lancet 2022



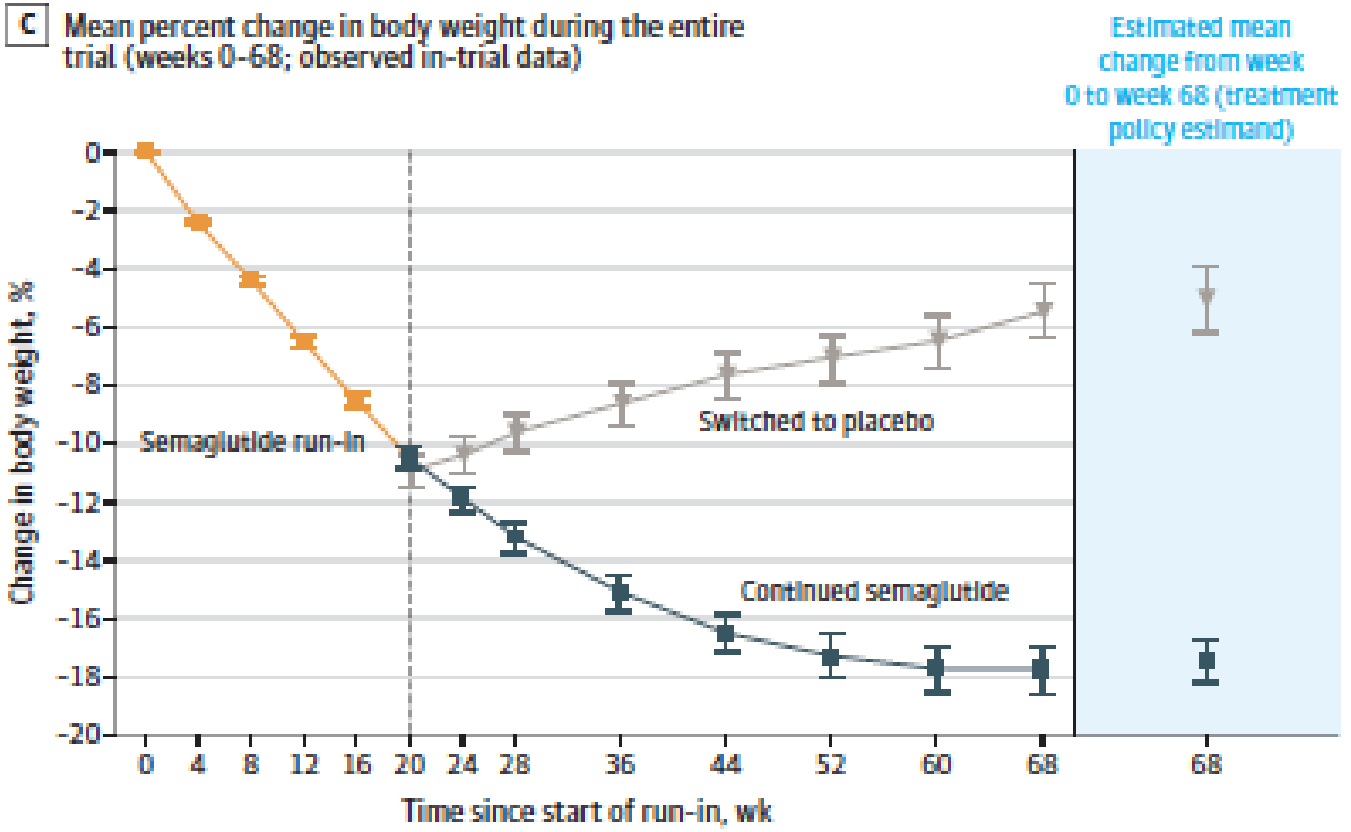
Weight loss sustainability after stopping GLP1-RAs

Research

JAMA | Original Investigation

Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity
The STEP 4 Randomized Clinical Trial

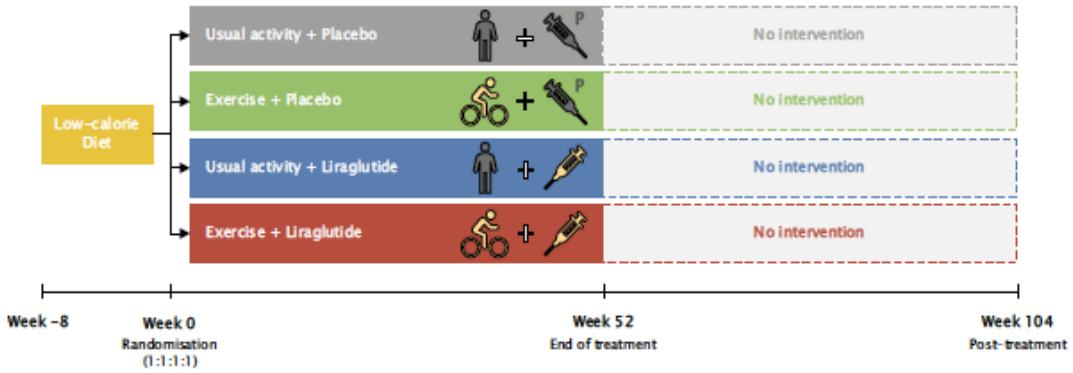
C Mean percent change in body weight during the entire trial (weeks 0-68; observed in-trial data)

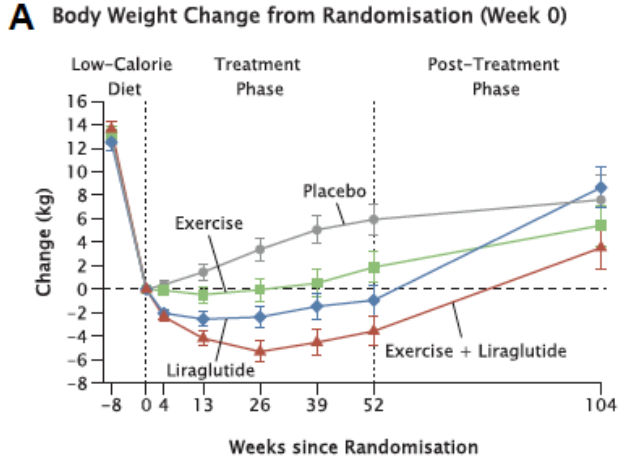


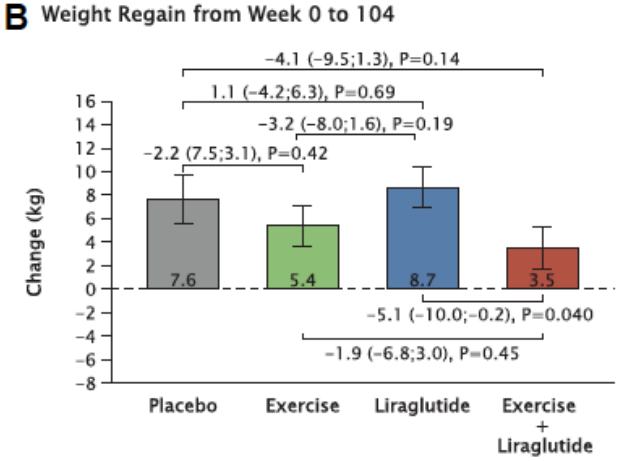
No. of participants

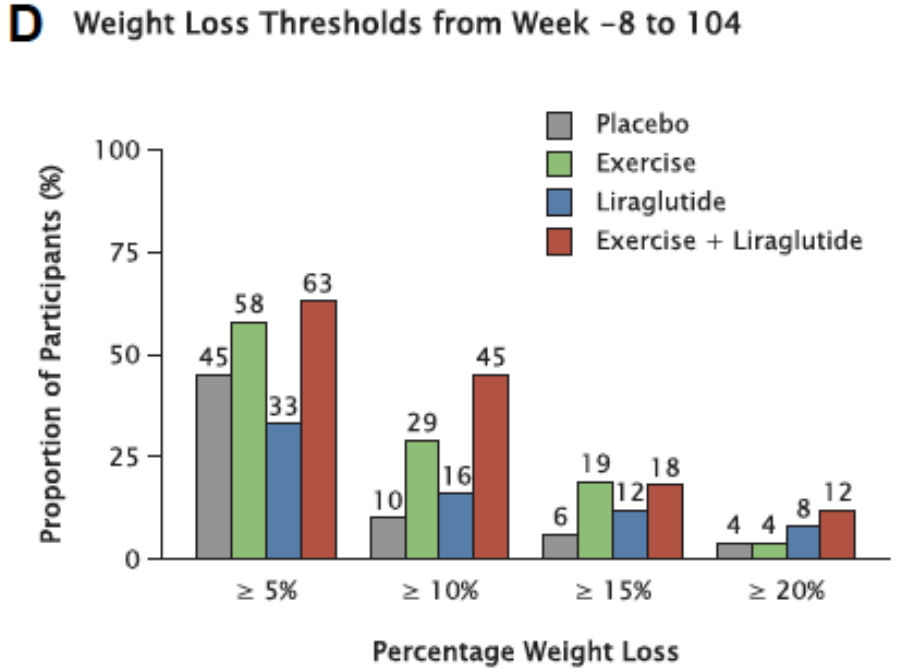
Semaglutide run-in	803	803	803	802	801			
Continued semaglutide	535	527	531	525	523	521	516	520	535
Switched to placebo	268	267	265	258	260	254	246	250	268

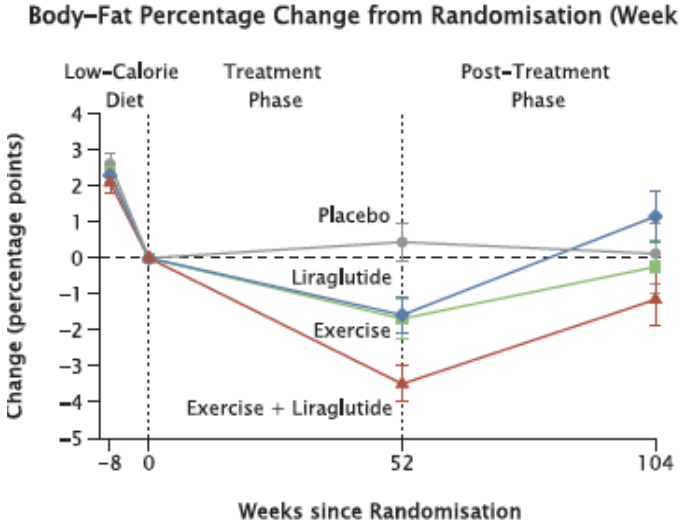
Weight loss sustainability after stopping GLP1-RAs

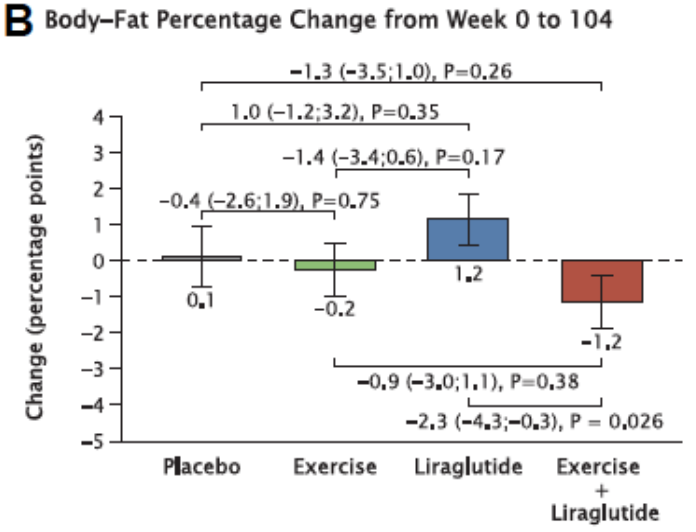






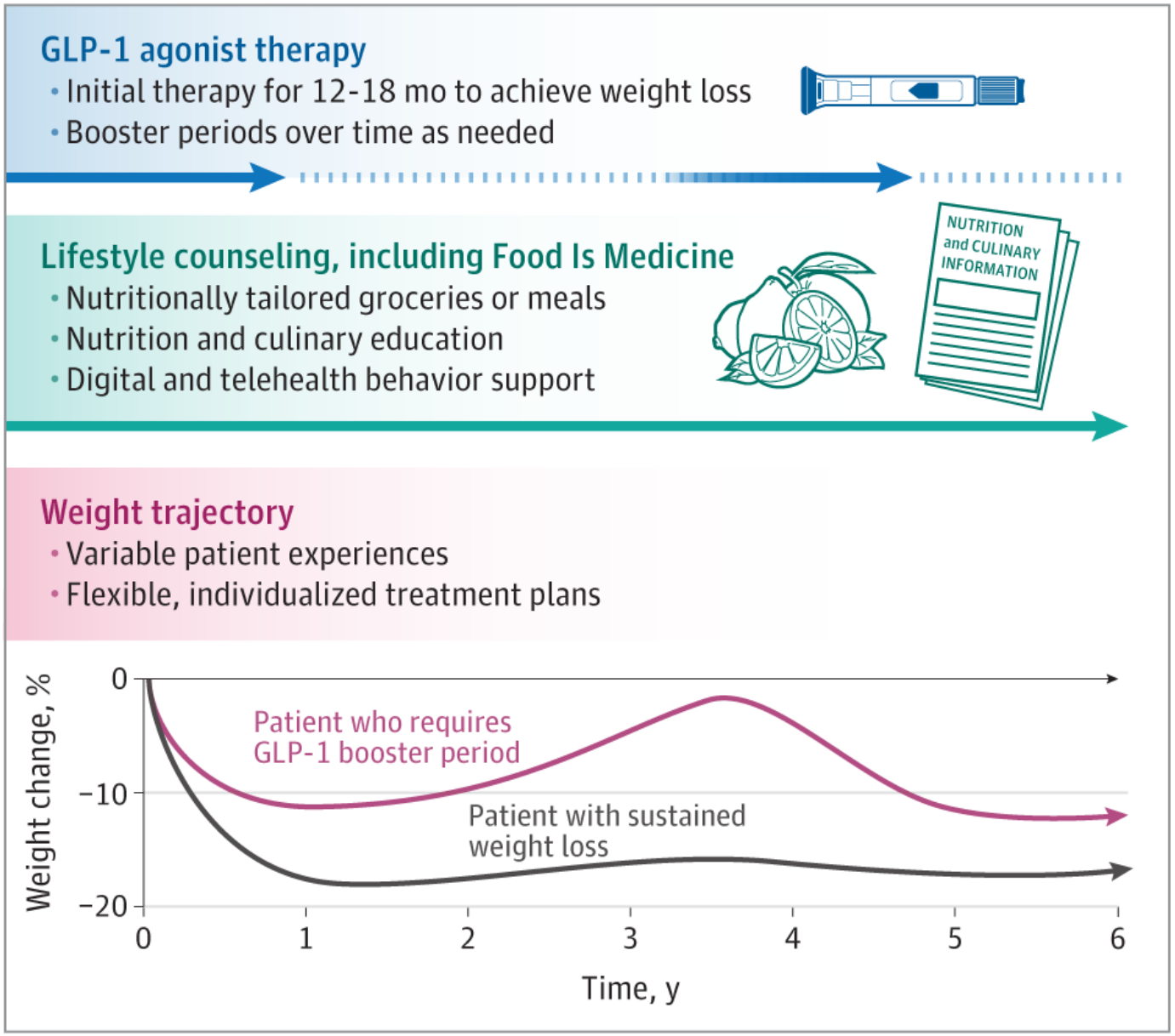






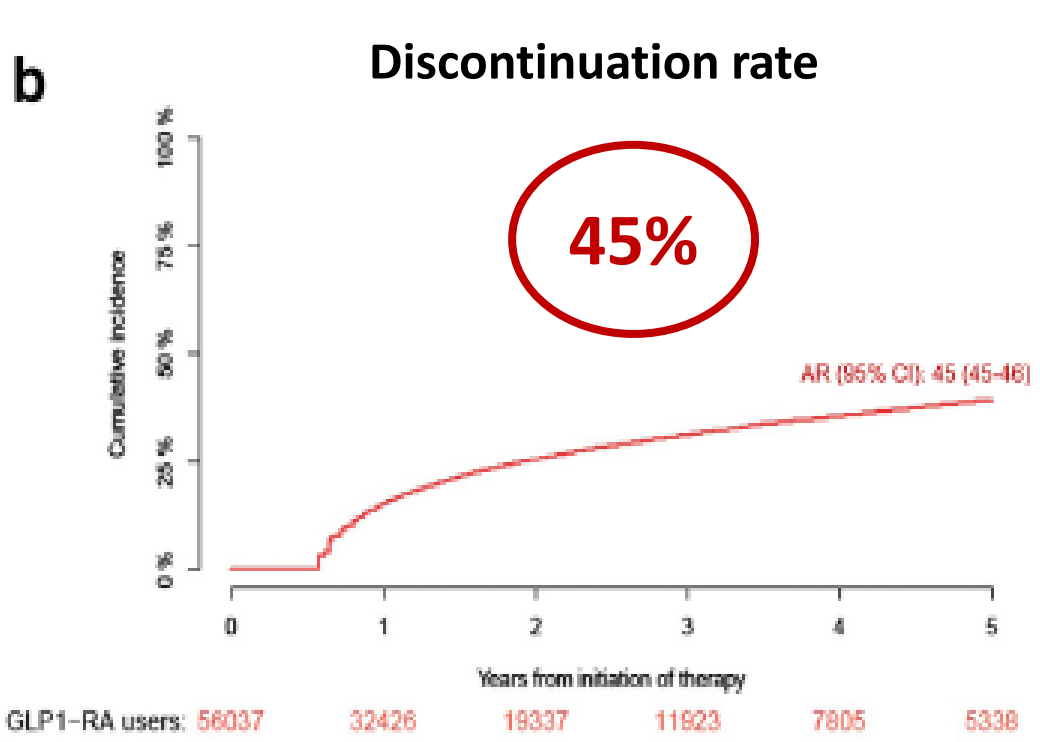
Jensen, Lancet 2024

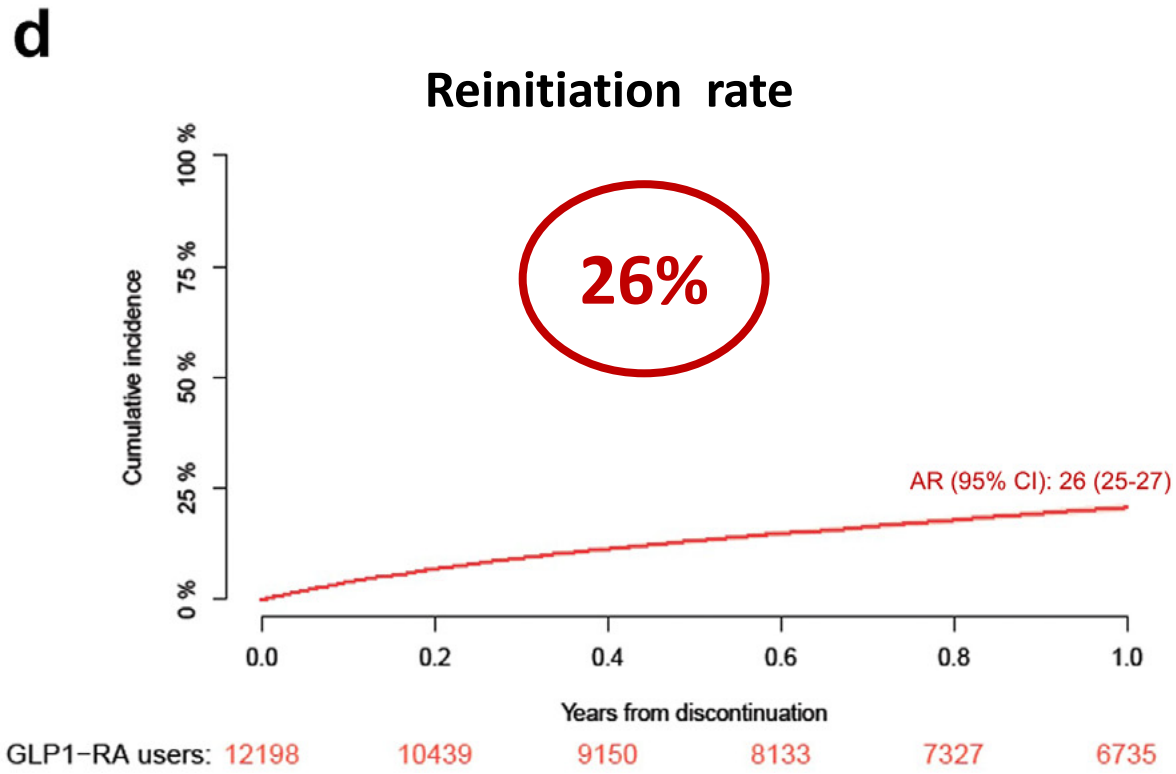
Weight loss sustainability after stopping GLP1-RAs



Mozaffarian, JAMA, February 2024

Discontinuation and reinitiation of GLP-1R agonists in patients with type 2 diabetes: a nationwide study from 2013 to 2021





Malik, Lancet 2023

Conclusion

- Weight loss strategies not only provides opportunities to treat obesity itself but also offers a potential treatment for its complications, such as T2D and MASLD

- Glucagon-like peptide-1 receptor agonists (GLP1-RAs):
  - promote **significant weight loss** but also offers promising therapeutic options for MASLD
  - backbone of future MASH/combination therapies
  - Strategies combining life-style measures / booster periods for GLP1?

- Bariatric surgery:
  - Significant cardiometabolic benefits
  - Significant histological improvement correlated to the amount of weight loss (> 20%)
  - Feasibility of bariatric surgery in patients with cirrhosis (HTP?)