

Obesity and metabolism Post-Endo 2022

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Obesity and metabolism Endo 2022

(SY047) Novel Aspects in Incretin and Glucagon Biology: From Basic to Clinical Applications

- Julio Rosenstock: Emerging Dual-Peptide Incretin Receptor Agonists: How Far Have We Gone with “Twincretins“?



(SY005) Exploring New Diagnostic and Treatment Options for Fatty Liver Disease From Pediatrics to Adult Care

- NAFLD and What’s In Development Today: Kenneth Cusi

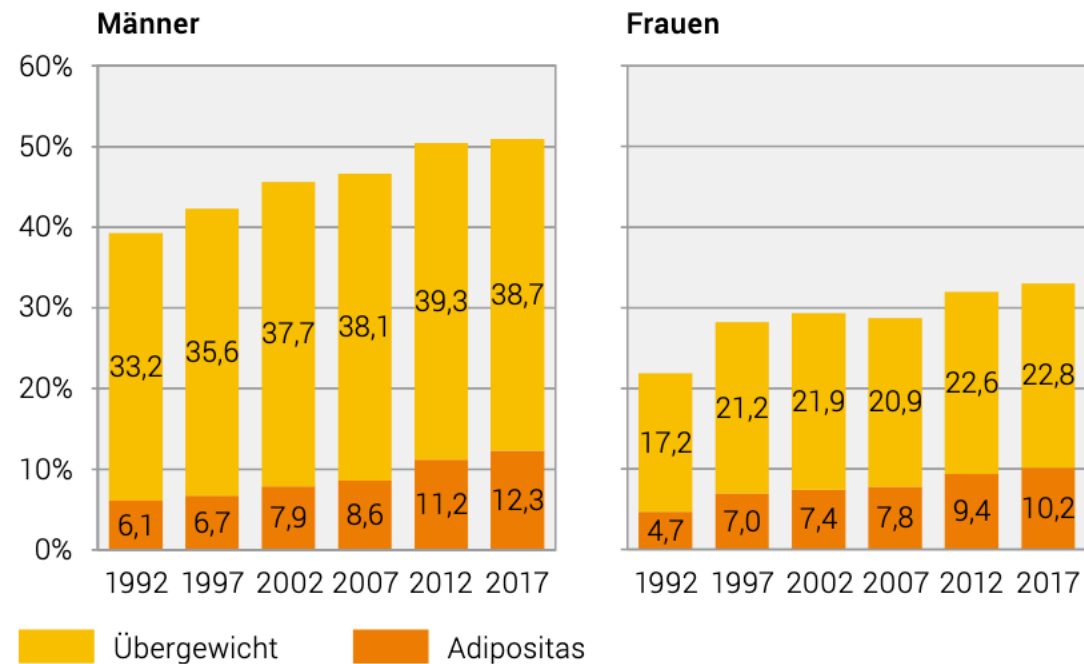


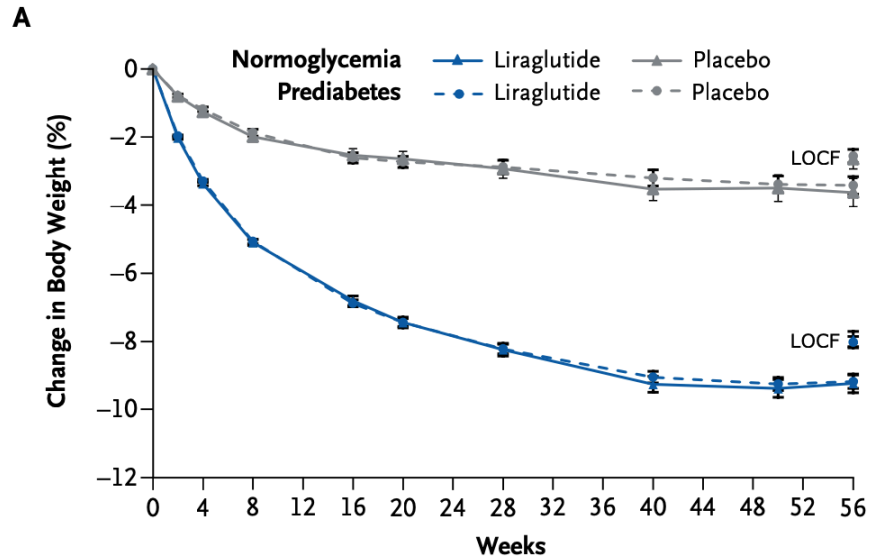
Overweight and Obesity in Switzerland

Übergewicht und Adipositas, 1992–2017

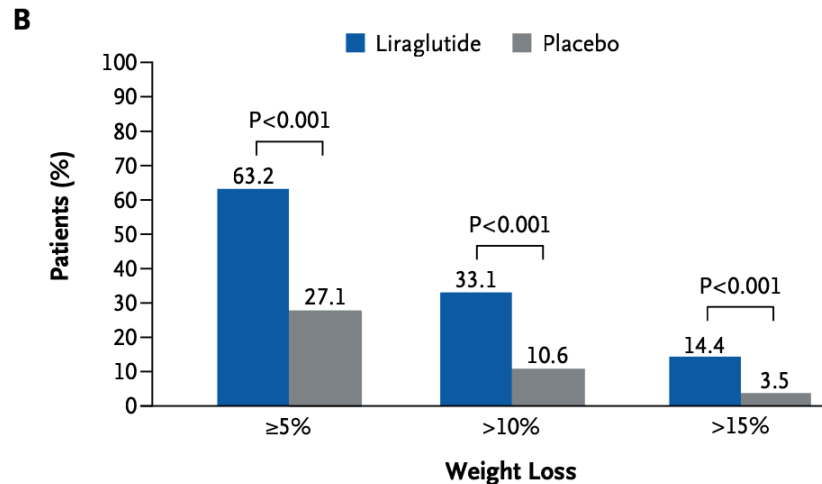
Bevölkerung ab 15 Jahren in Privathaushalten

G1





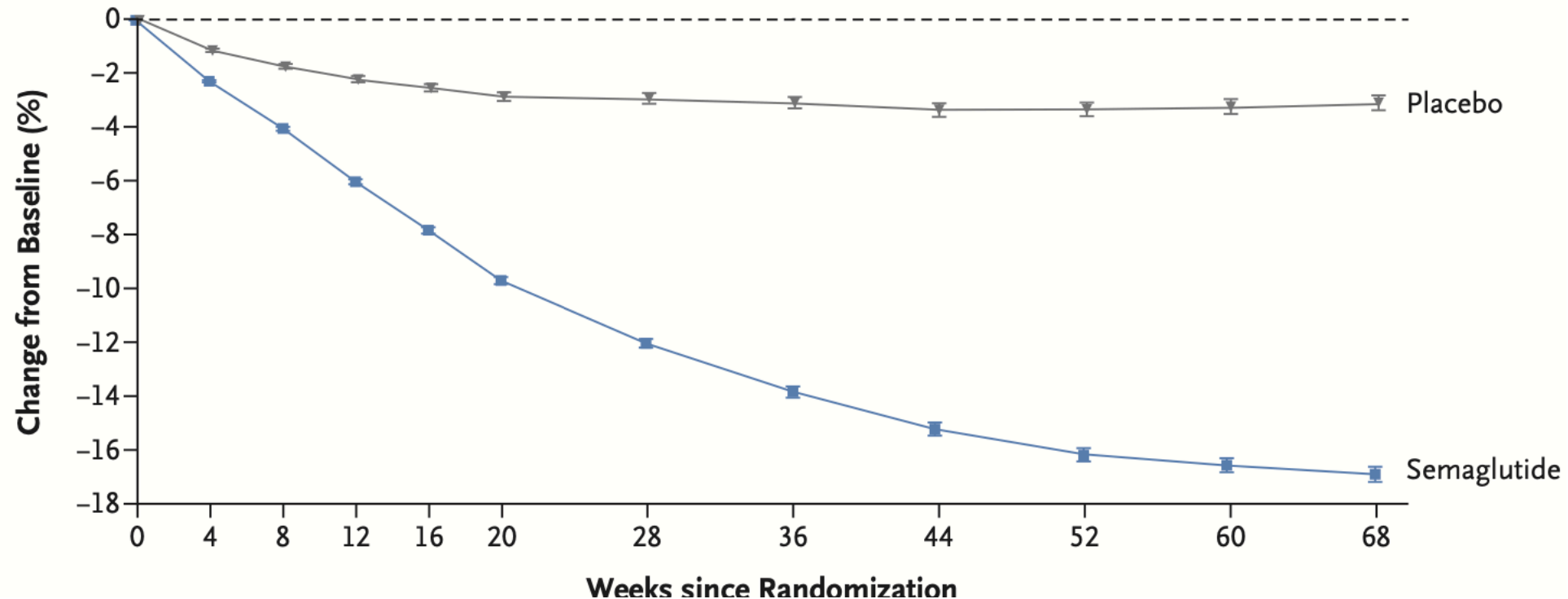
A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management (SCALE)



Pi-Sunyer et al, NEJM 2015 SCALE

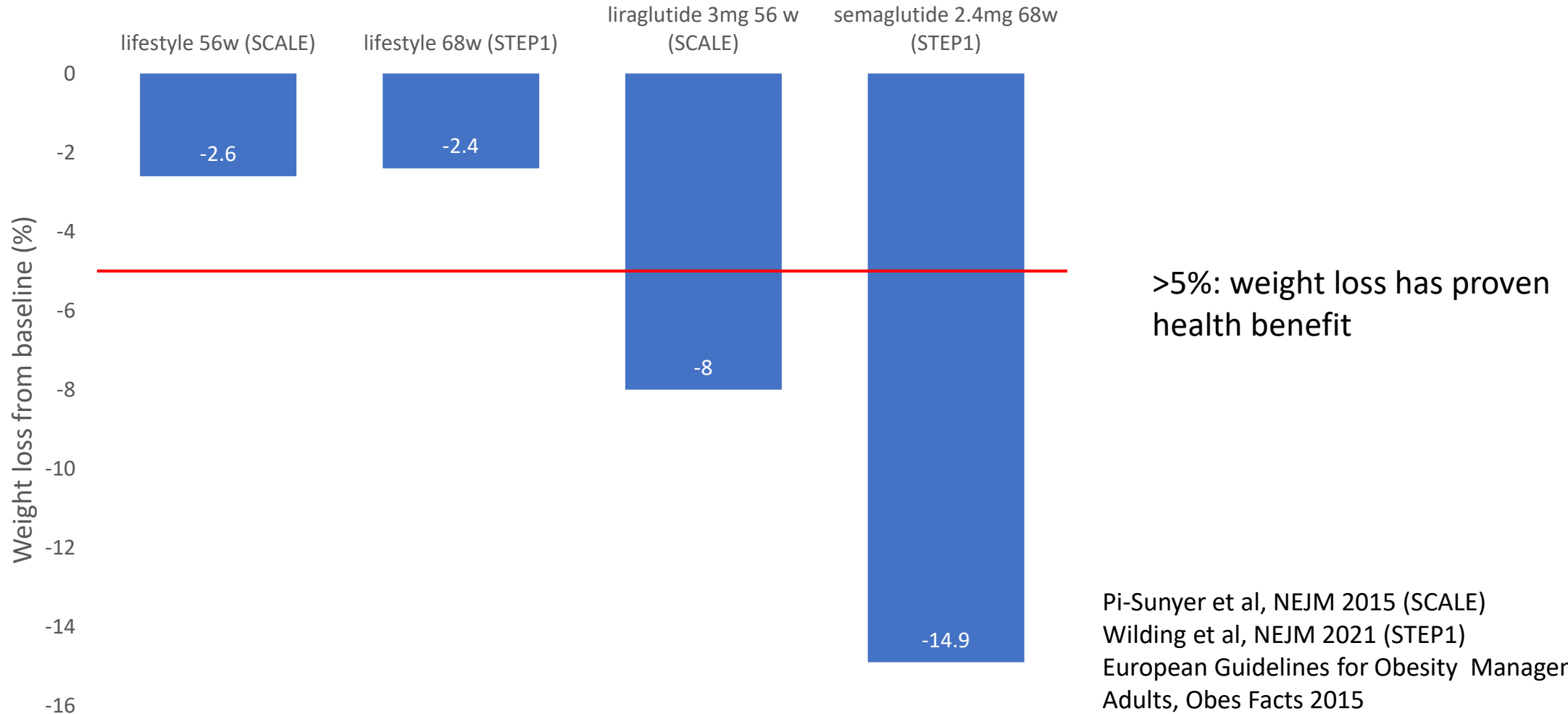
Once-Weekly Semaglutide in Adults with Overweight or Obesity (STEP1)

Body Weight Change from Baseline by Week, Observed On-Treatment Data



Wilding et al, NEJM 2021 (STEP1)

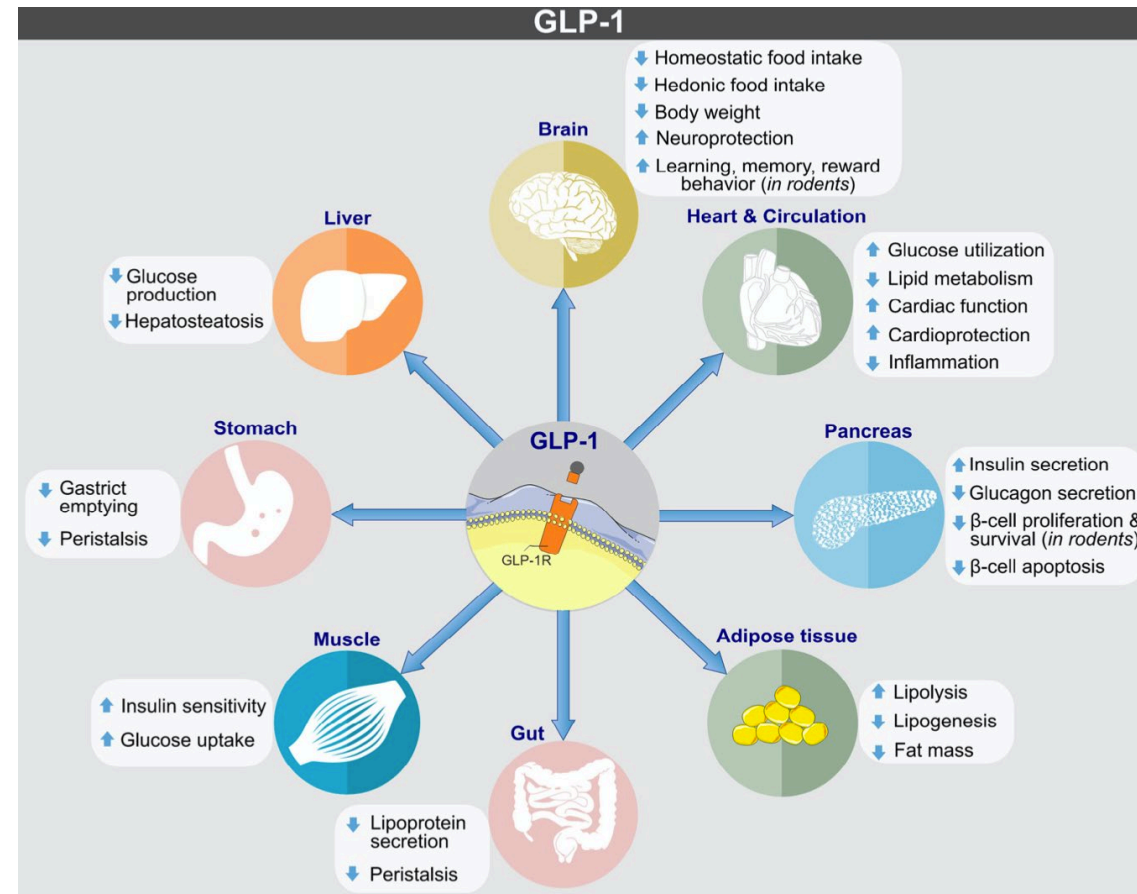
Weight loss with Liraglutide and Semaglutide



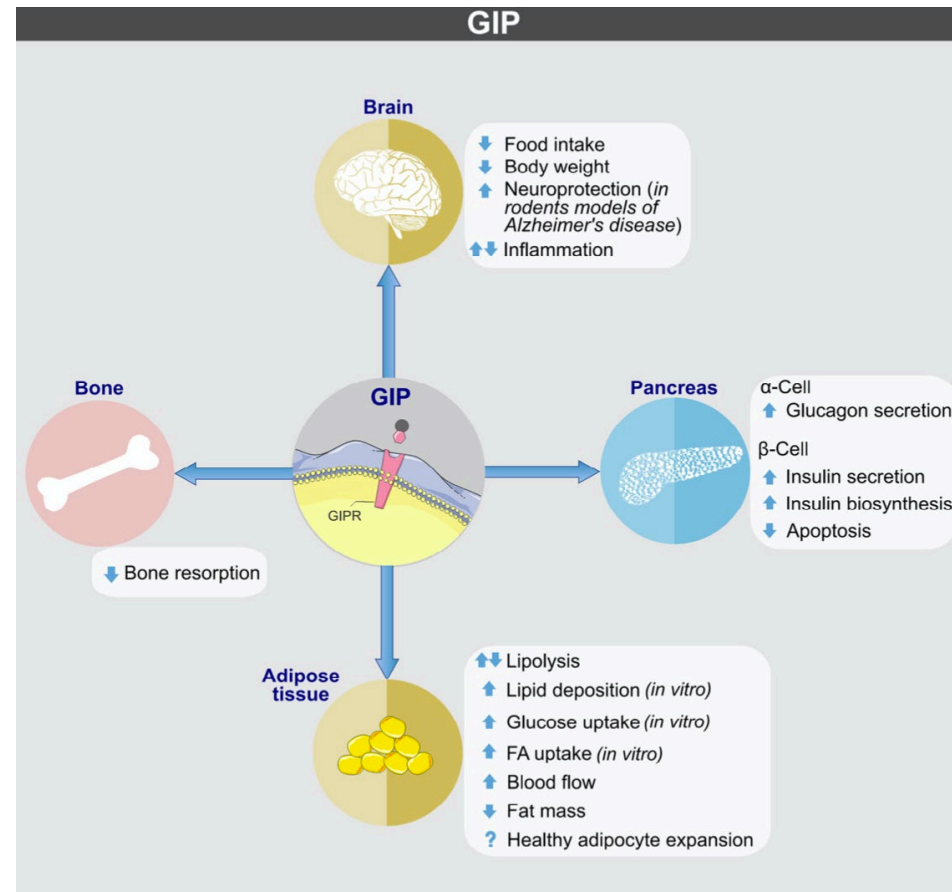
Glucagon-like peptide-1 receptor co-agonists for treating metabolic disease

- Amylin
- Cholecystokin
- Fibroblast Growth Factors
- Glucagon
- Glucose-dependent insulinotropic polypeptide
- Insulin
- Leptin
- Peptide YY

GLP-1: pleiotropic hormone

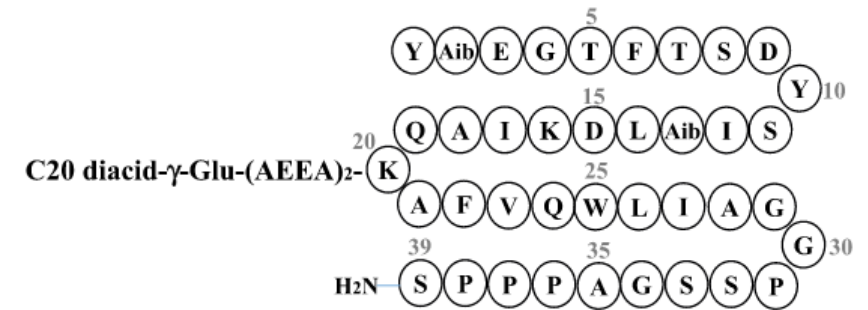


Glucose-dependent insulinotropic polypeptide



Tirzepatide LY3298176 (once-weekly GLP1-GIP-RA)

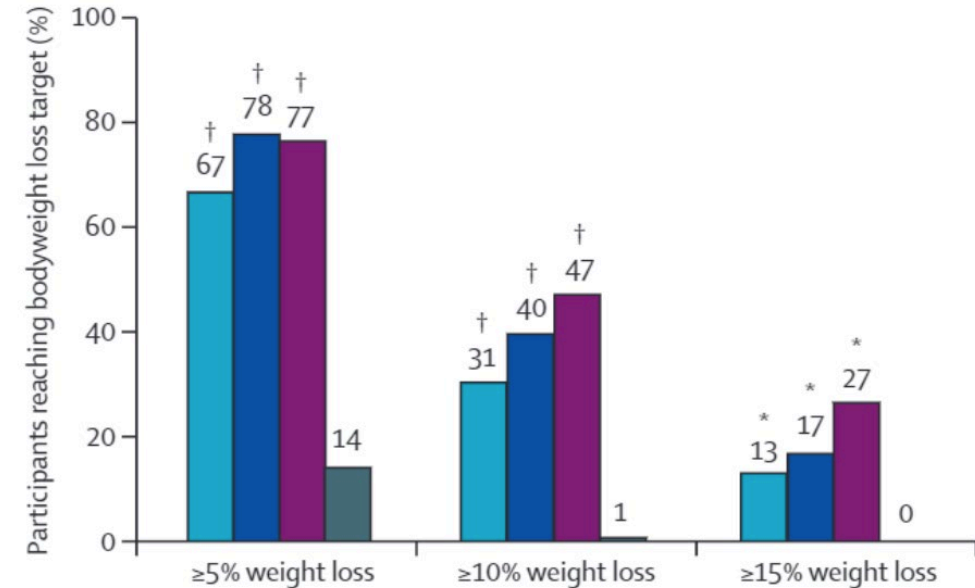
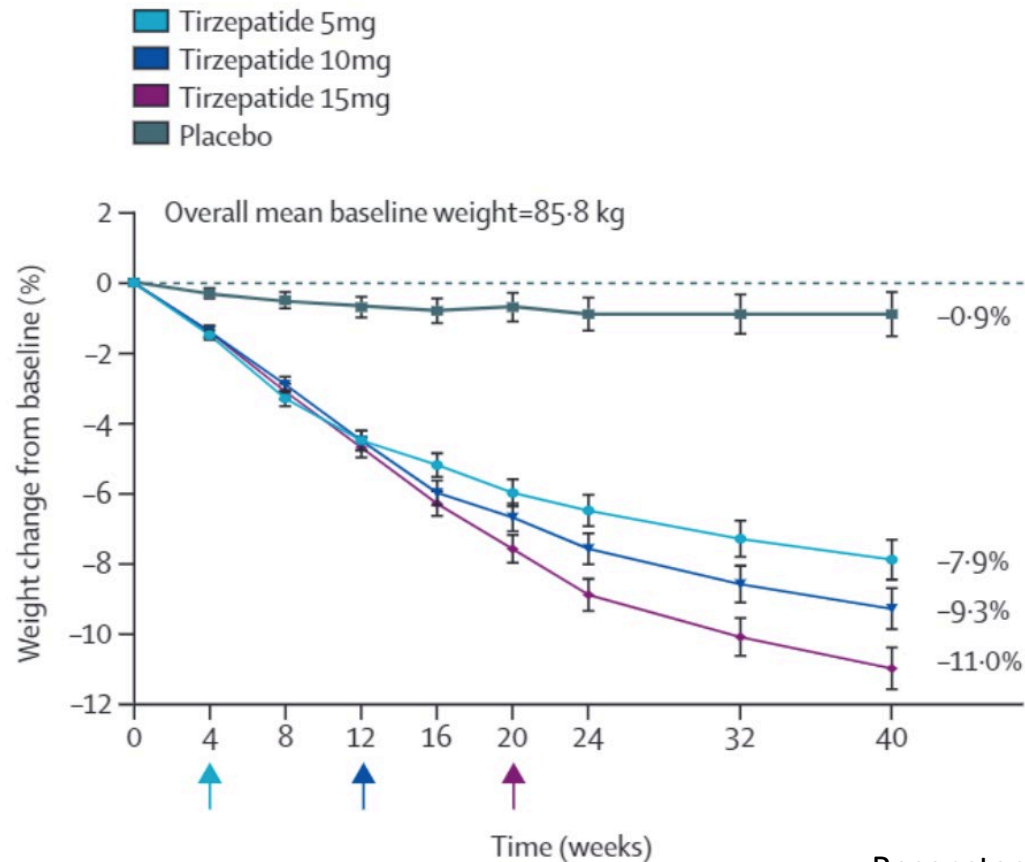
- novel dual GIP- and GLP-1 RA that consists of a 39-amino acid synthetic peptide¹
- Acylation technology enables albumin binding which provides once-weekly dosing regimen²
- Elimination half-life of appr. 5 days (irrespective of renal function)¹
- In vitro: greater potency for the GIPR²



¹Urva et al, Clinical Pharmacokinetics 2021

²Tan Q et al, Frontiers in Endocrinology 2022

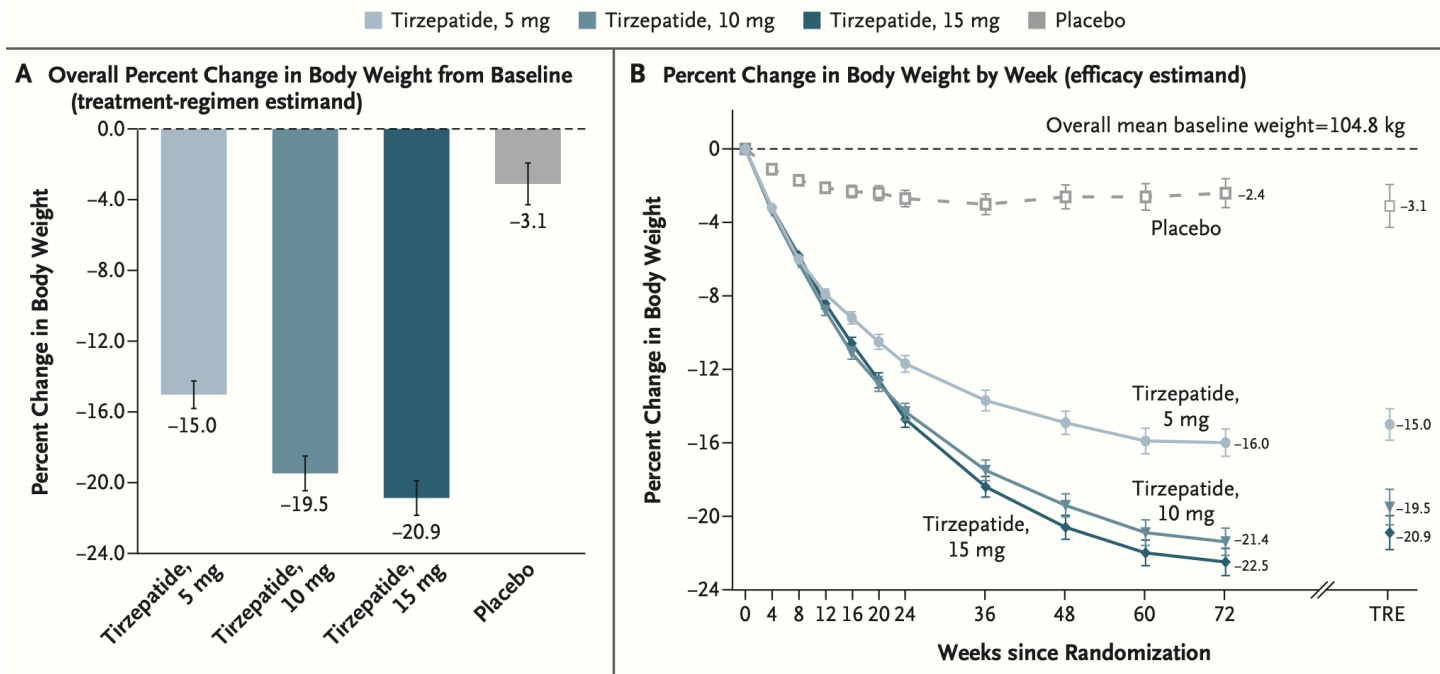
SURPASS-1: Weight loss with tirzepatide in T2DM



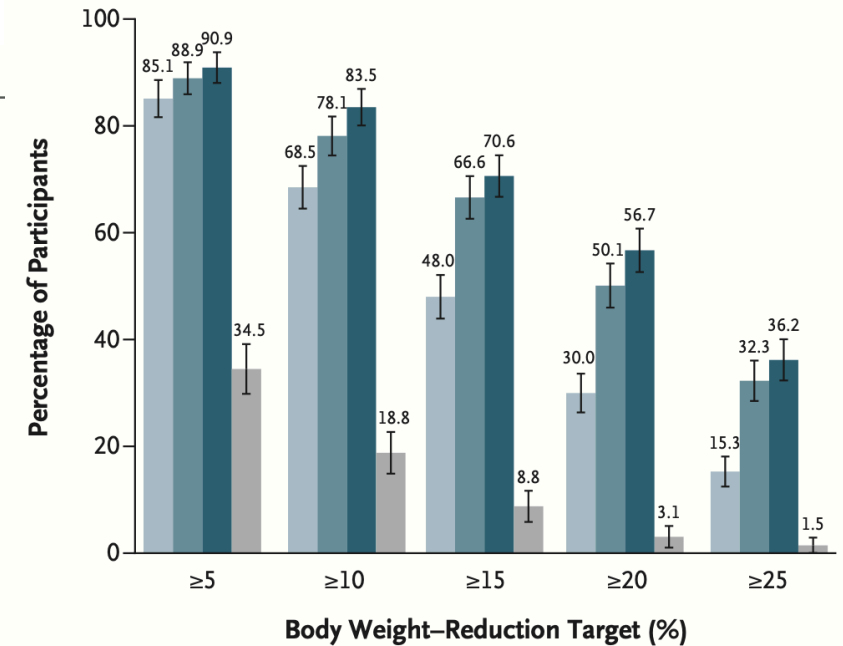
Rosenstock et al , Lancet 2021

Weight loss (%)

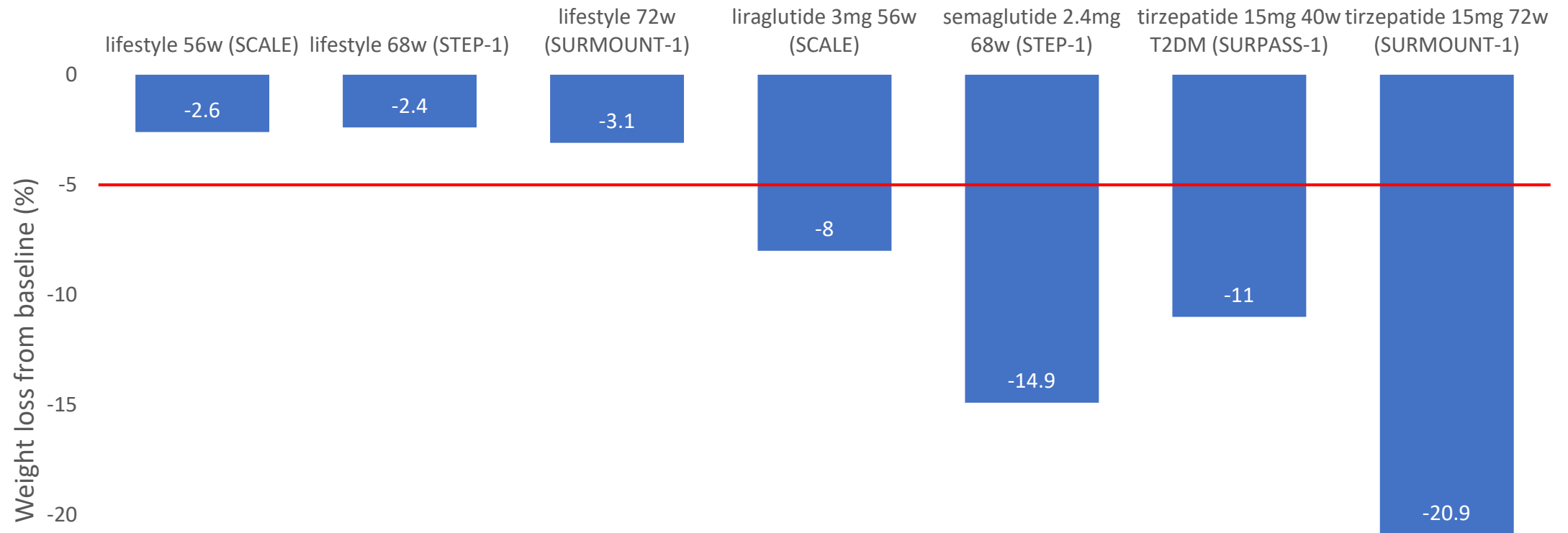
SURMOUNT-1: Tirzepatide for the treatment of obesity



C Participants Who Met Weight-Reduction Targets



Weight loss with GLP1-RA +Co-agonists



Pi-Sunyer et al, NEJM 2015 (SCALE)

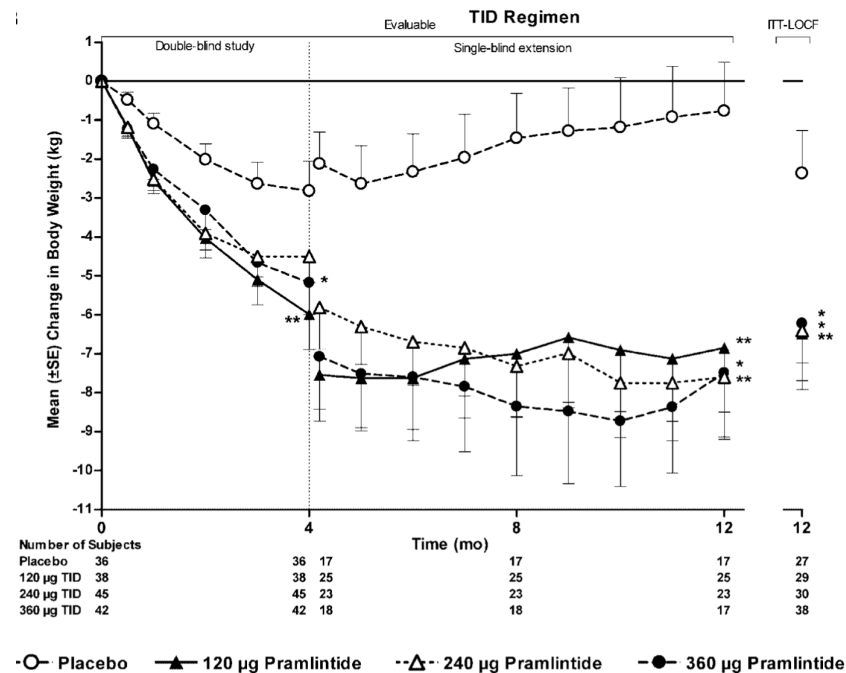
Wilding et al, NEJM 2021 (STEP1)

-25 Rosenstock et al, Lancet 2021 (SURPASS-1)

Jastreboff et al, NEJM 2022 (SURMOUNT-1)

Pramlintide

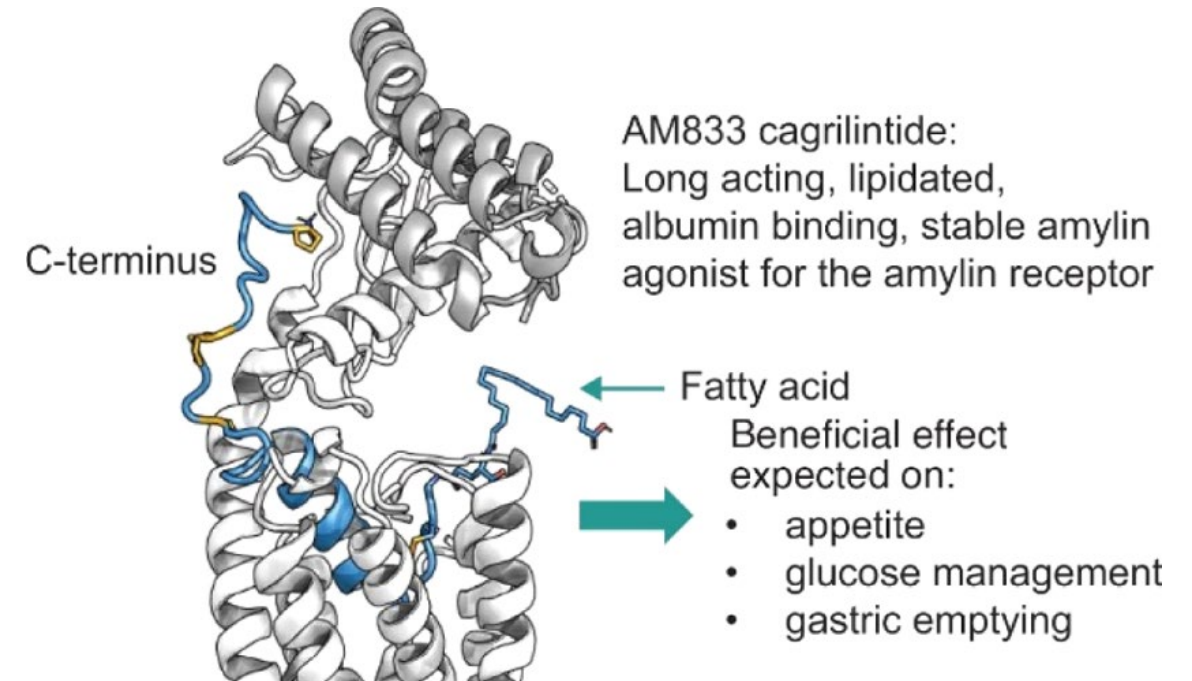
Synthetic analog of human amylin



Smith et al, Diabetes care 2008

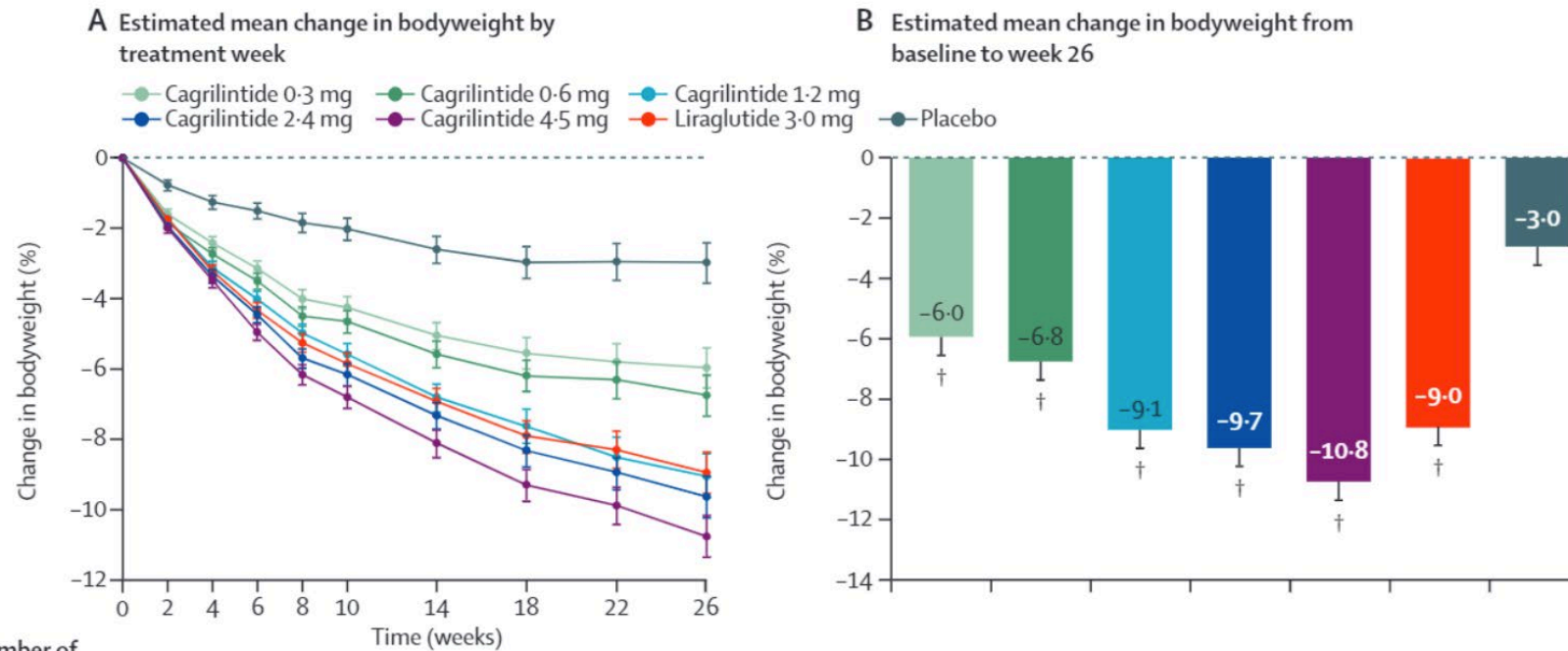
Cagrilintide

Long acting amylin analogue



Kruse et al, J Med Chem 2021

Cagrilintide for weight management in patients with overweight and obesity (dose-finding phase 2)

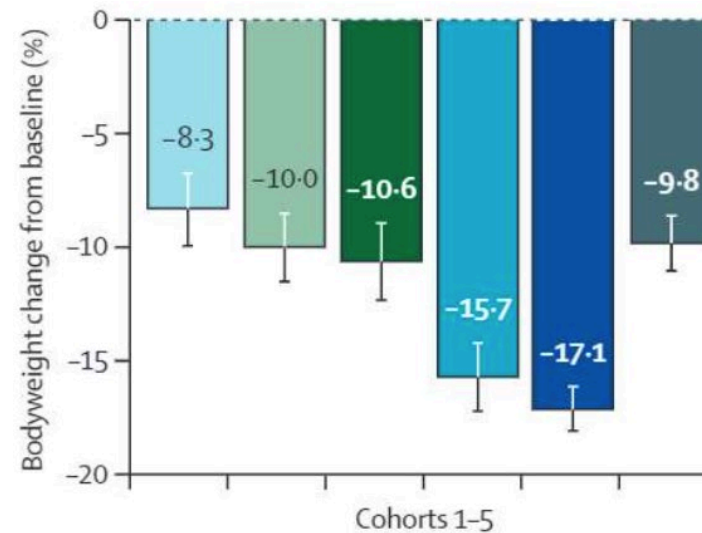
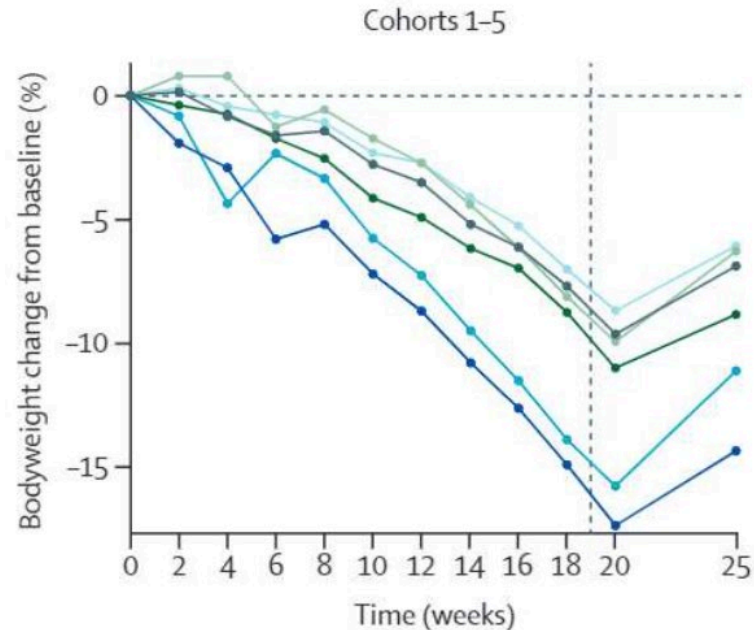


	0	2	4	6	8	10	14	18	22	26
Number of participants										
Cagrilintide 0.3 mg	101	100	97	100	98	99	98	98	98	96
Cagrilintide 0.6 mg	100	99	98	96	98	97	97	94	95	97
Cagrilintide 1.2 mg	102	101	98	96	99	100	98	96	95	98
Cagrilintide 2.4 mg	102	101	100	99	100	99	99	98	97	99
Cagrilintide 4.5 mg	101	100	99	99	97	97	96	94	93	97
Liraglutide 3.0 mg	99	99	99	98	97	95	94	96	93	95
Placebo	101	101	100	95	97	94	94	91	90	95

Cagrilintide and Semaglutide: Phase 1

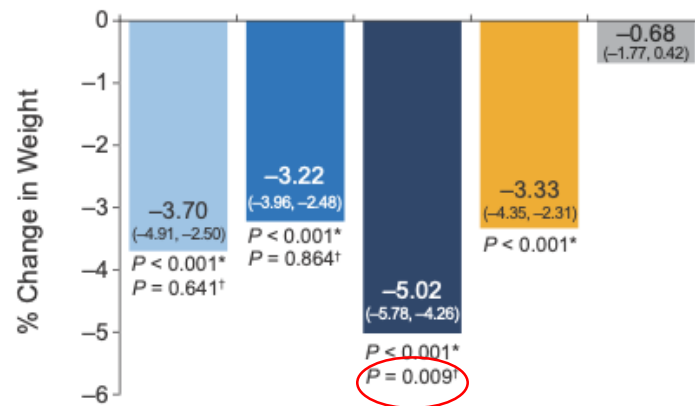
Cagrilintide: (long-acting amylin analogue) + Semaglutide 2.4mg

- Cagrilintide 0-16 mg plus semaglutide 2.4 mg
- Cagrilintide 0-30 mg plus semaglutide 2.4 mg
- Cagrilintide 0-60 mg plus semaglutide 2.4 mg
- Cagrilintide 1-2 mg plus semaglutide 2.4 mg
- Cagrilintide 2-4 mg plus semaglutide 2.4 mg
- Pooled placebo plus semaglutide 2.4 mg

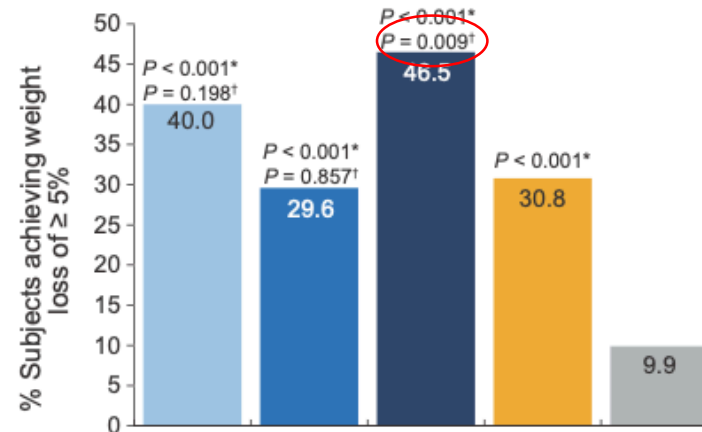


Cotadutide: dual GLP-1 and Glucagon Receptor Agonist: Phase 2 Übergewicht und T2DM

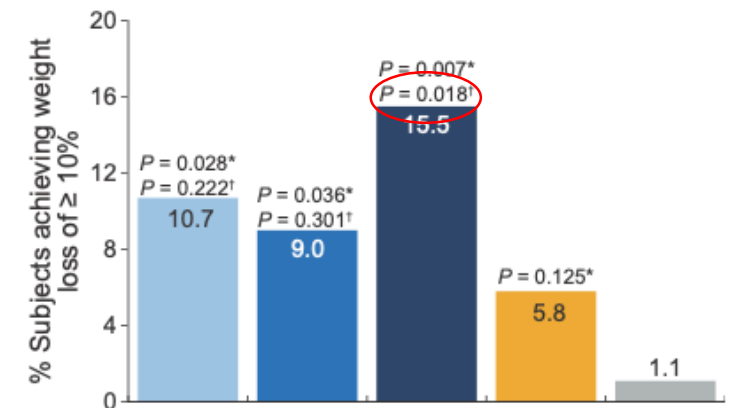
% change in weight



Weight loss $\geq 5\%$



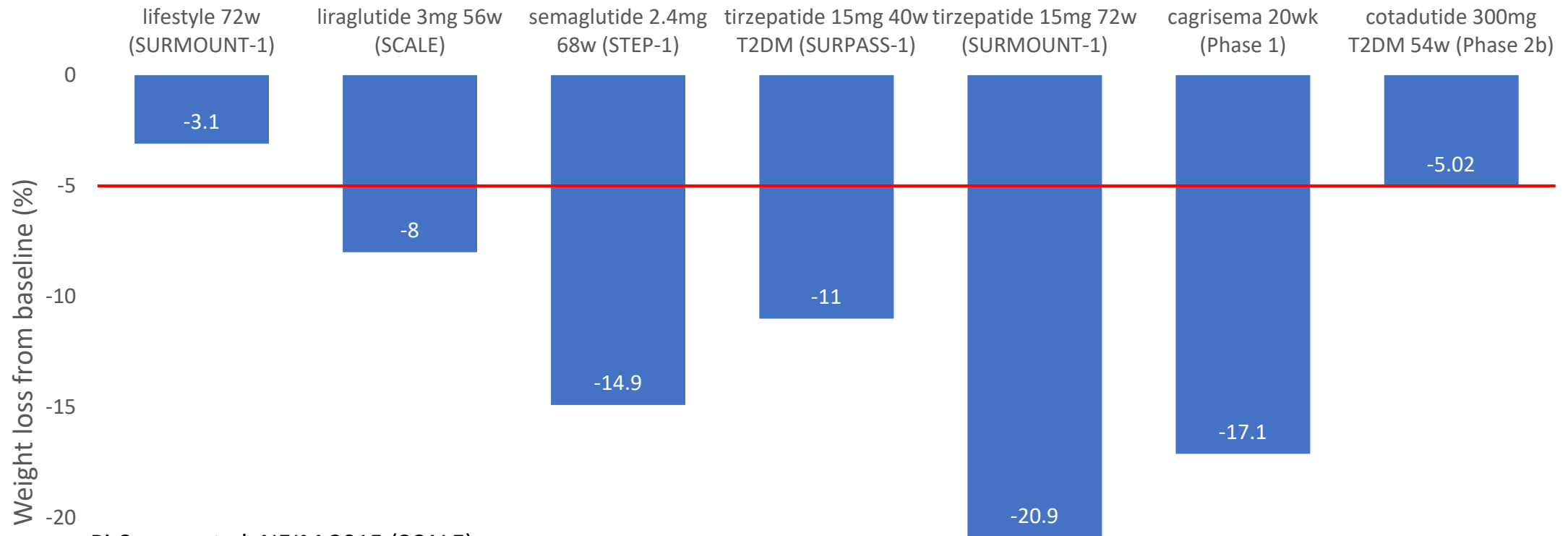
Weight loss $\geq 10\%$



■ Cotadutide 100 µg ■ Liraglutide 1.8 mg
■ Cotadutide 200 µg ■ Placebo
■ Cotadutide 300 µg

*vs. placebo
† vs. liraglutide

Weight loss „Twincretins“ vs GLP1-RA



Pi-Sunyer et al, NEJM 2015 (SCALE)

Wilding et al, NEJM 2021 (STEP1)

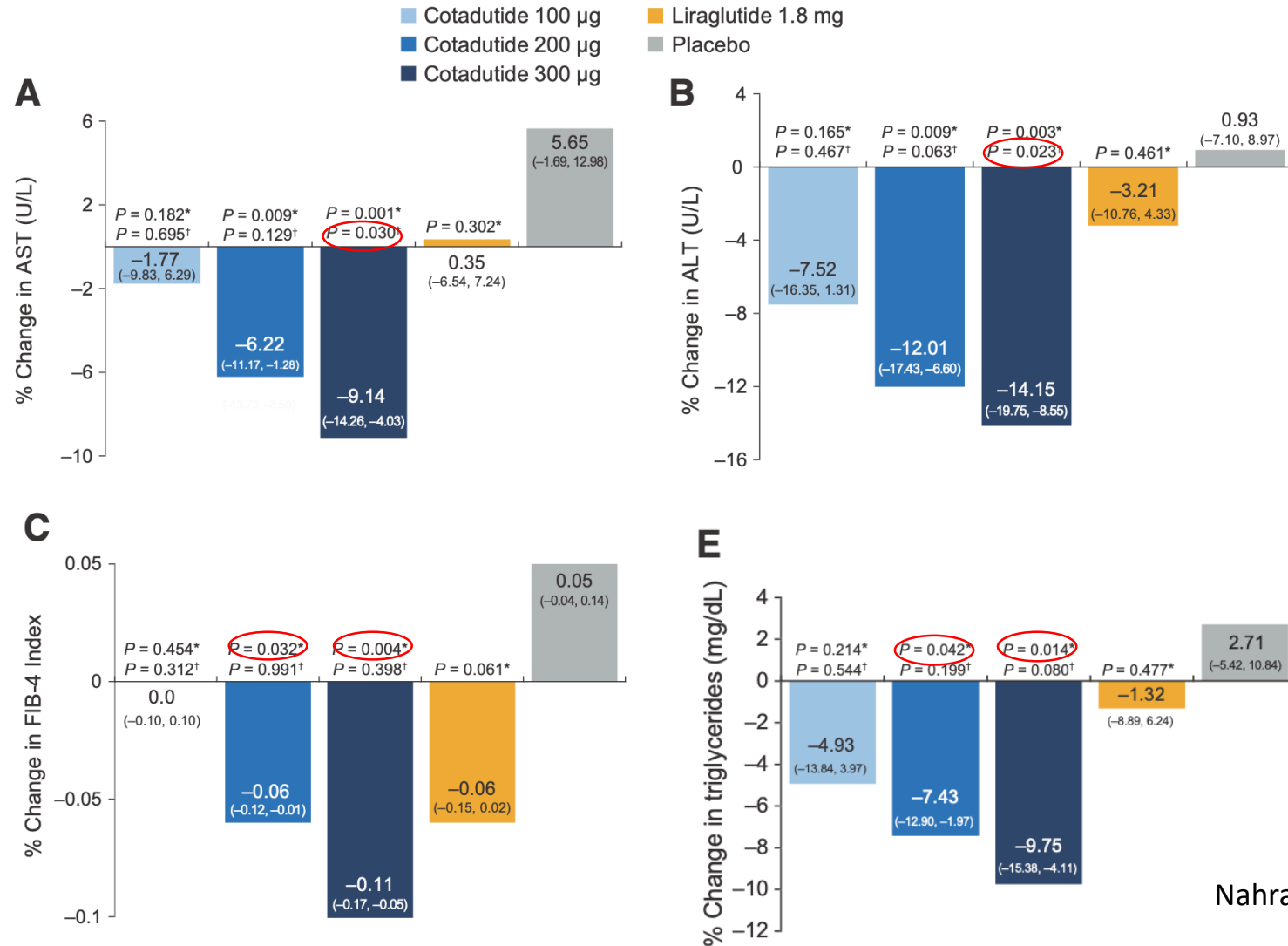
Rosenstock et al, Lancet 2021 (SURPASS-1)

Jastreboff et al, NEJM 2022 (SURMOUNT-1)

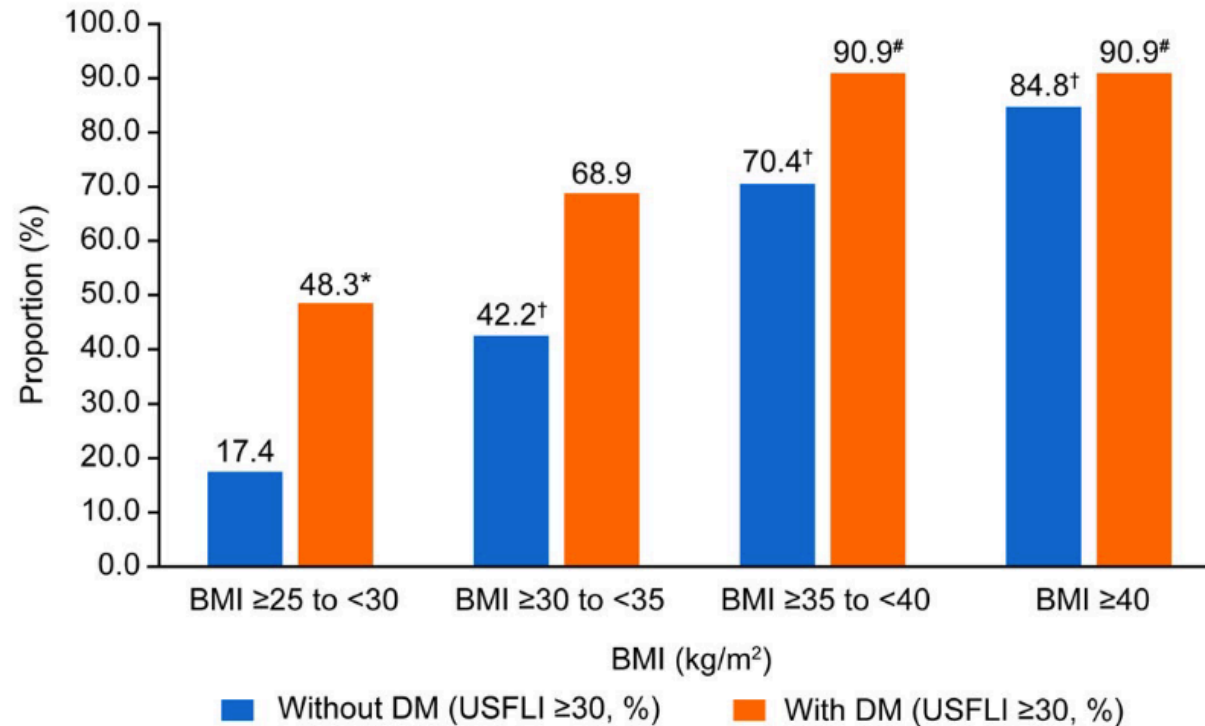
Enebo et al, Lancet 2021 (cagrisema)

Nahra et al, Diabetes care 2021 (cotadutide)

Cotadutide reduces transaminases



Risk for NASH in Obesity and T2DM



Prevalence of steatosis by BMI

USFLI = United States Fatty Liver Index

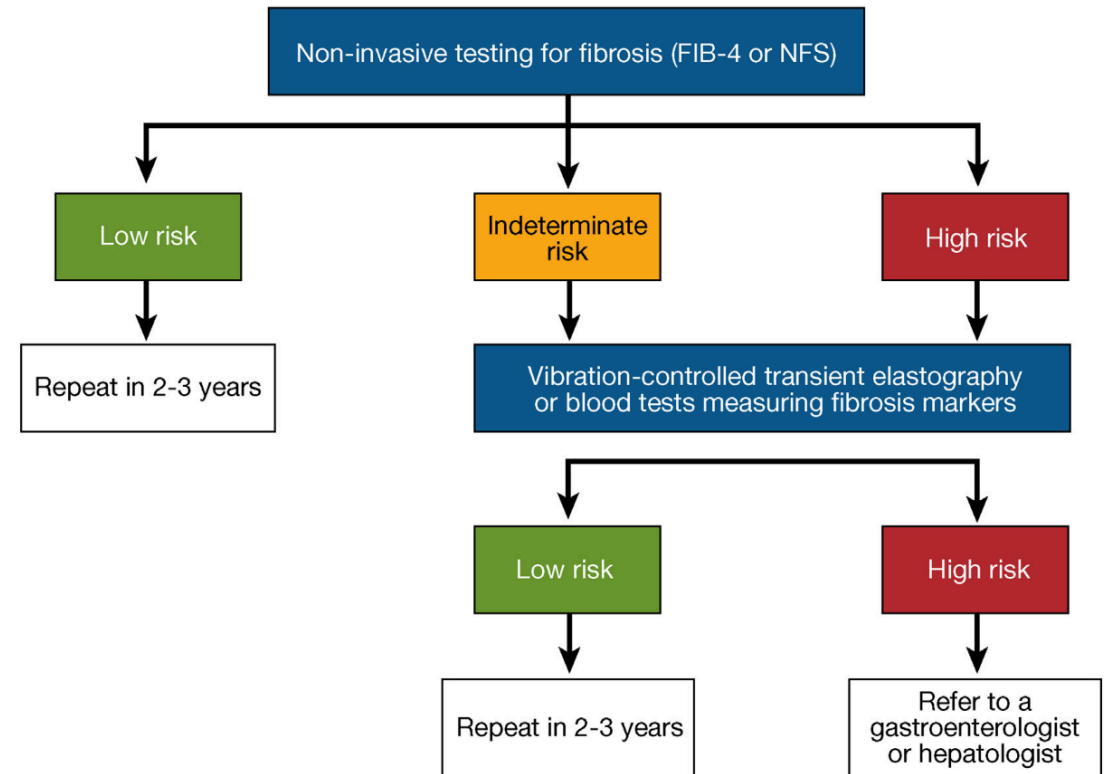
Non-invasive testing for fibrosis

ADA-guidelines 2021

Nonalcoholic Fatty Liver Disease

Recommendation

4.10 Patients with type 2 diabetes or prediabetes and elevated liver enzymes (ALT) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**



Screening for hepatic fibrosis using FIB-4 Index

Risk for advanced fibrosis is low when FIB4-score is less than 1.3

Screening for hepatic fibrosis using Fibrosis-4 Index in subjects with type 2 diabetes

Hannah Loher¹, Janina Tuetsch¹, Anina Neidhardt¹, Mirko Birbaumer², Nadine Stanek³, Patrik Aepli³, Christoph Henzen¹, Stefan Fischl¹

¹Department of Endocrinology, Diabetes and Clinical Nutrition, Luzerner Kantonsspital, ²Department of Technology and Architecture, Hochschule Luzern, ³Department of Gastroenterology and Hepatology, Luzerner Kantonsspital

Introduction/Background

- Screening for diabetic complications (i.e., retinopathy, nephropathy) is part of the annual check-up in diabetic patients.
- Non-alcoholic fatty (NAFLD) liver disease is a frequent comorbidity, especially in subjects with type 2 diabetes (T2DM). In this context it can be interpreted as a diabetes-related end-organ damage.
- In clinical practice there is lack of screening guidelines/procedures regarding

Conclusion

- The FIB-4 score is frequently elevated in patients with T2DM
- A dedicated hepatologic work-up in persons at risk is essential
- Lack of statin therapy is associated with an increased FIB-4 score. This finding is consistent with current studies on the treatment of non-alcoholic steatohepatitis. Longitudinal studies and larger datasets are needed to support the conclusions.

metformin and 60.5% with statins.

- 51 (42.9%) subjects had a FIB-4-score ≥ 1.3 and 4 (3.4%) had a FIB-4-score ≥ 3.25 .

- Subjects treated with statins had a

response variable and BMI, diabetes duration, basal insulin dose, use of SGLT 2-inhibitors, GLP1-receptor agonist, metformin and statin therapy as predictor variables has been carried out.

Best subset selection has been applied to the linear regression model in order to detect the most influential predictor variables

duration: 11.49 (± 8.6) years, mean BMI: 31.05 (± 5.5) kg/m²

- 70.6% of the subjects were treated with insulin, 18.5% with SGLT2-inhibitors, 37.8% with GLP-1-receptor agonists, 55.5% with Metformin and 60.5% with statins.
- 51 (42.9%) subjects had a FIB-4-score ≥ 1.3 and 4 (3.4%) had a FIB-4-score ≥ 3.25 .
- Subjects treated with statins had a significantly lower FIB-4-score ($p < 0.05$)
- other variables (BMI, diabetes duration and type of glucose lowering therapy) didn't show a significant effect (Fig. 1).

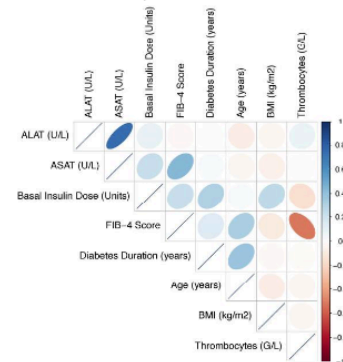


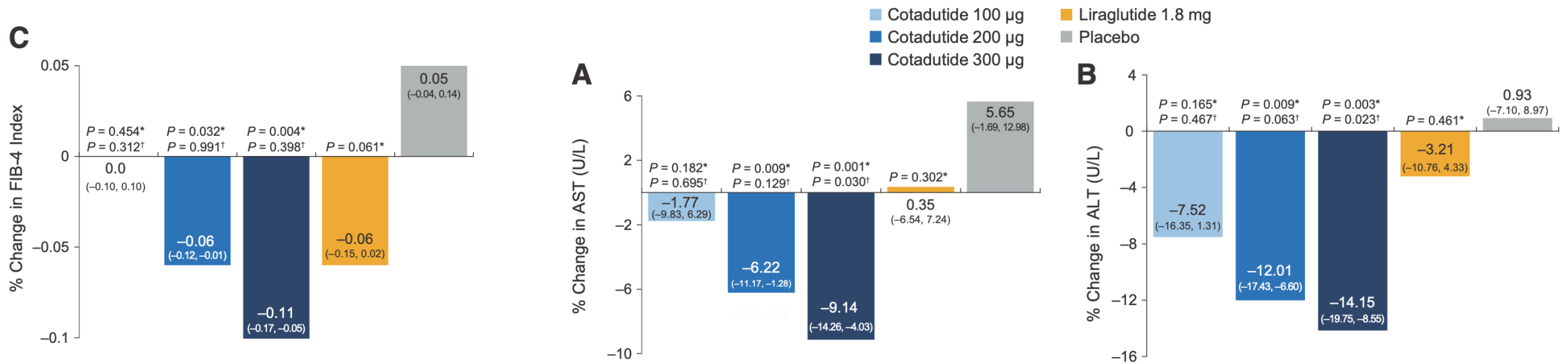
Figure 1: Correlation matrix of factors influencing FIB-4 Score

Literature

- Z. Younossi et al.: The global epidemiology of NAFLD and NASH in patients with type 2 diabetes; A systematic review and meta-analysis. J Hepatol. 2019 Oct;71(4):793-801
- L. Eslami et al.: Statins für non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Cochrane Database Syst. Rev. 2013 Dec 27

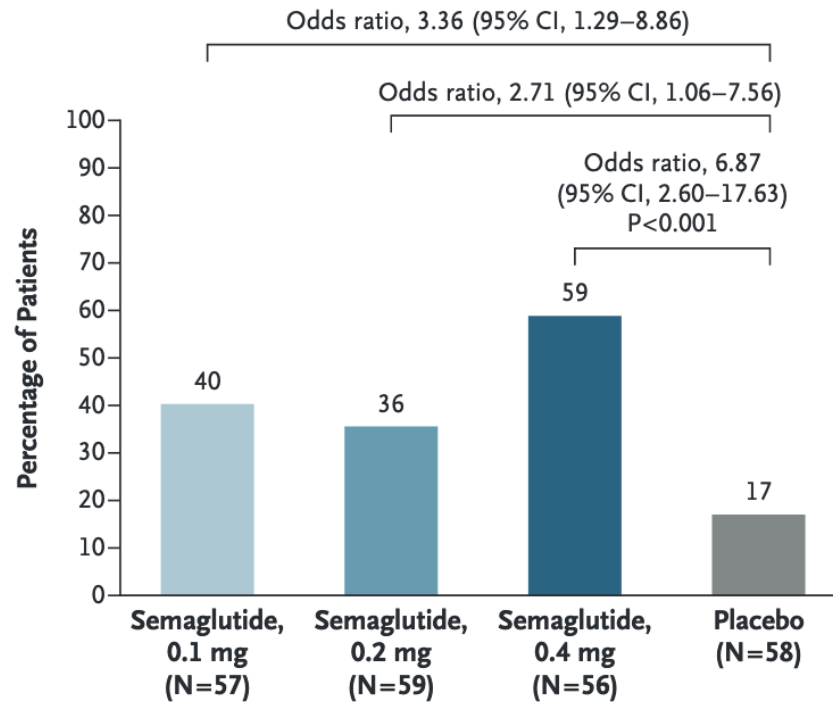
Cotadutide: dual GLP1- and Glucagon Receptor Agonist

- Reduces transaminases and FIB-4-Index
- But to date no studies with biopsy-proven effect in humans

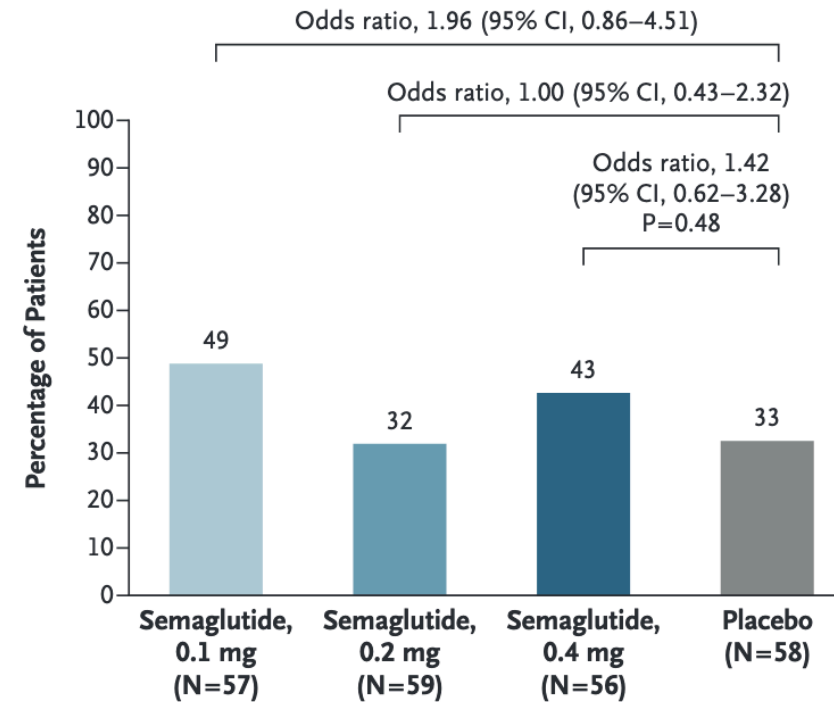


Semaglutide in Nonalcoholic Steatohepatitis

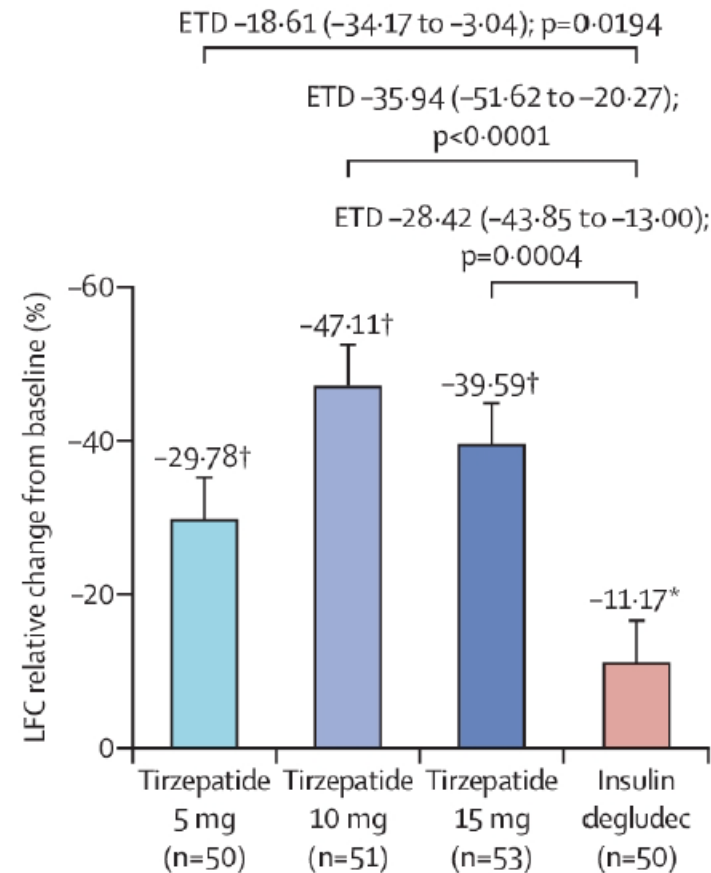
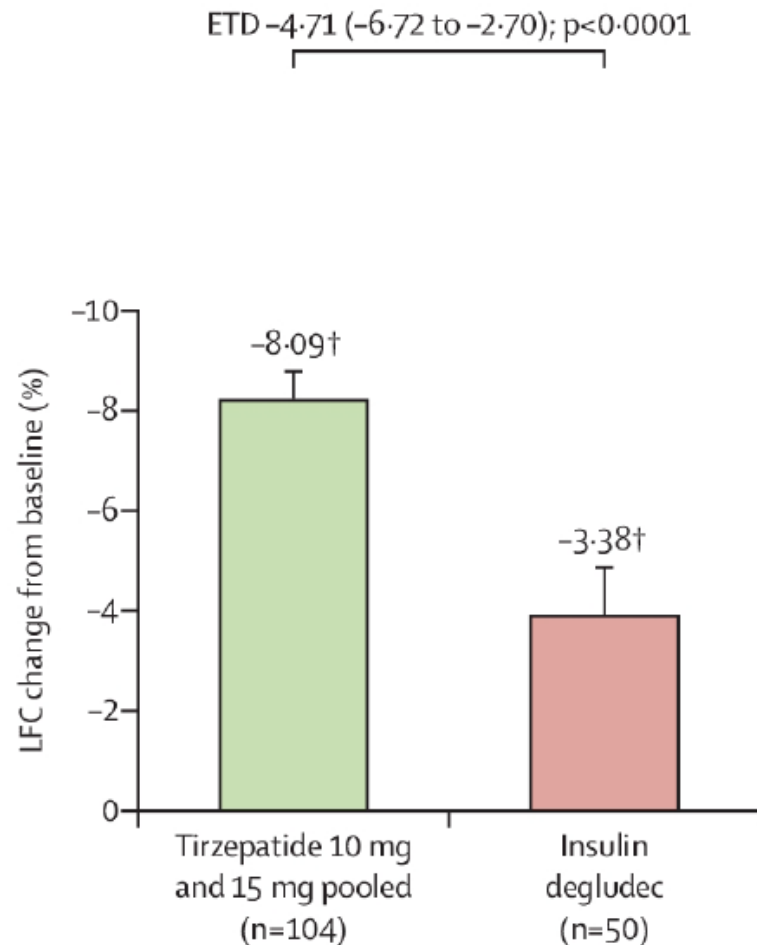
A Resolution of NASH with No Worsening of Liver Fibrosis (primary end point)



B Improvement in Liver Fibrosis Stage with No Worsening of NASH (confirmatory secondary end point)



Tirzepatide vs basal insulin NASH: effect on liver fat content (SURPASS 3-MRI)



Conclusion

- Semaglutide 2.4mg weekly: weight loss of 14.9% vs liraglutide 3mg (8%)
- Tirzepatide 15mg: weight loss of 20.9%: closing the gap between medications now available for weight reduction and bariatric surgery
- Promising drugs currently being investigated in trials: Cagrilintide with Sema 2.4mg weekly (weight loss) and Cotadutide (weight loss/NAFLD)
- Screening for NAFLD in obese patients and subjects with Type 2 Diabetes
- GLP-1 might have a beneficial effect on NASH, but combination of medication might be superior (tirzepatide, cotadutide)