MASH e diabete

Va bene, c'è MASH - Che si fa?

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Conflict of Interest
last 3 years

Speaker in Scientific Events

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

Scientific AB

Amgen
Bruno Farmaceutici
EG
Lilly
Merck
Novartis
Novo Nordisk
Pfizer
PikDare

Table 4.2—Assessment and treatment plan

Assessing risk of diabetes complications

- ASCVD and heart failure history
- ASCVD risk factors and 10-year ASCVD risk assessment
- Staging of chronic kidney disease (see **Table 11.1**)
- Hypoglycemia risk (see Section 6, "Glycemic Goals and Hypoglycemia")
- Assessment for retinopathy
- Assessment for neuropathy
- Assessment for NAFLD/NASH *

Goal setting

- Set A1C/blood glucose/time in range
- If hypertension is present, establish blood pressure goal
- Weight management and physical activity goals
- Diabetes self-management goals

Therapeutic treatment plans

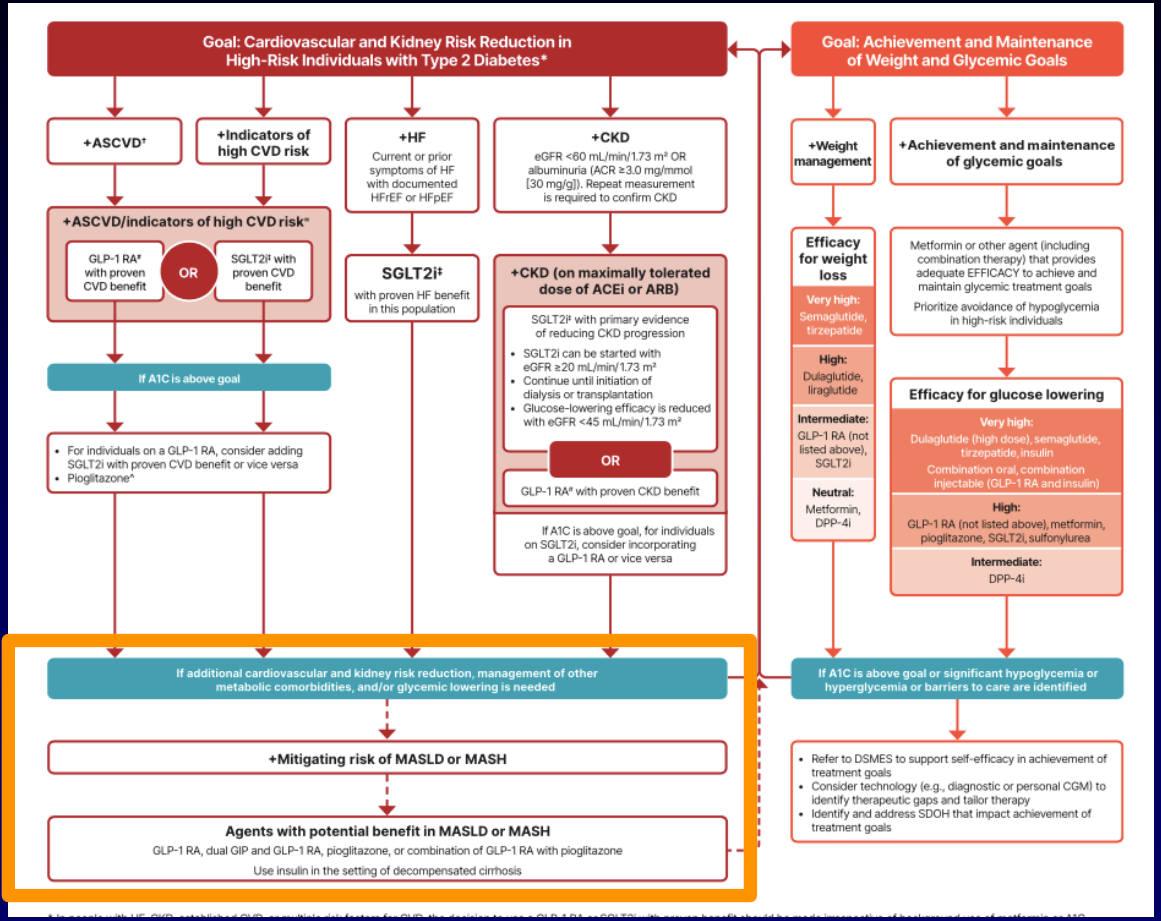
- Lifestyle management
- Pharmacologic therapy: glucose lowering
- Pharmacologic therapy: cardiovascular and kidney disease risk factors
- Weight management with pharmacotherapy or metabolic surgery, as appropriate
- Use of glucose monitoring and insulin delivery devices
- Referral to diabetes education, behavioral health, and medical specialists

Assessment and treatment planning are essential components of initial and all follow-up visits. ASCVD, atherosclerotic cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

2024
A new era

ADA Standard of Care, Diabetes Care, 2024

ADA Standards of Care 2025



ADA Standards of Care, Diabetes Care, 2025

Che si fa?

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)☆

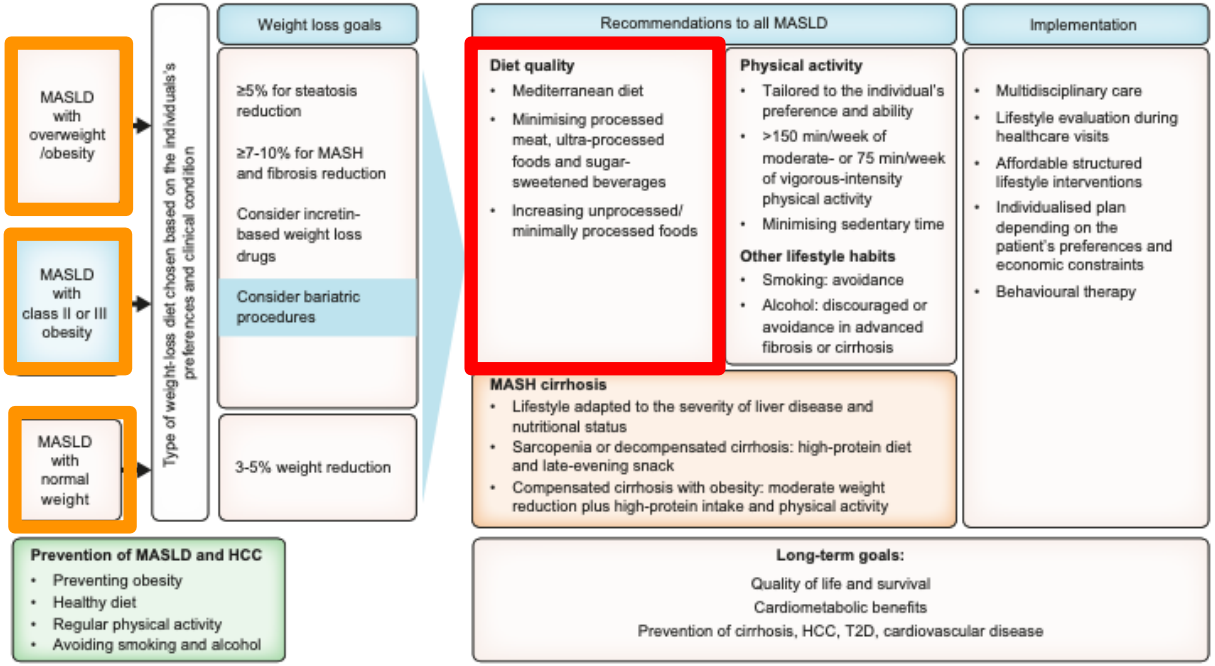


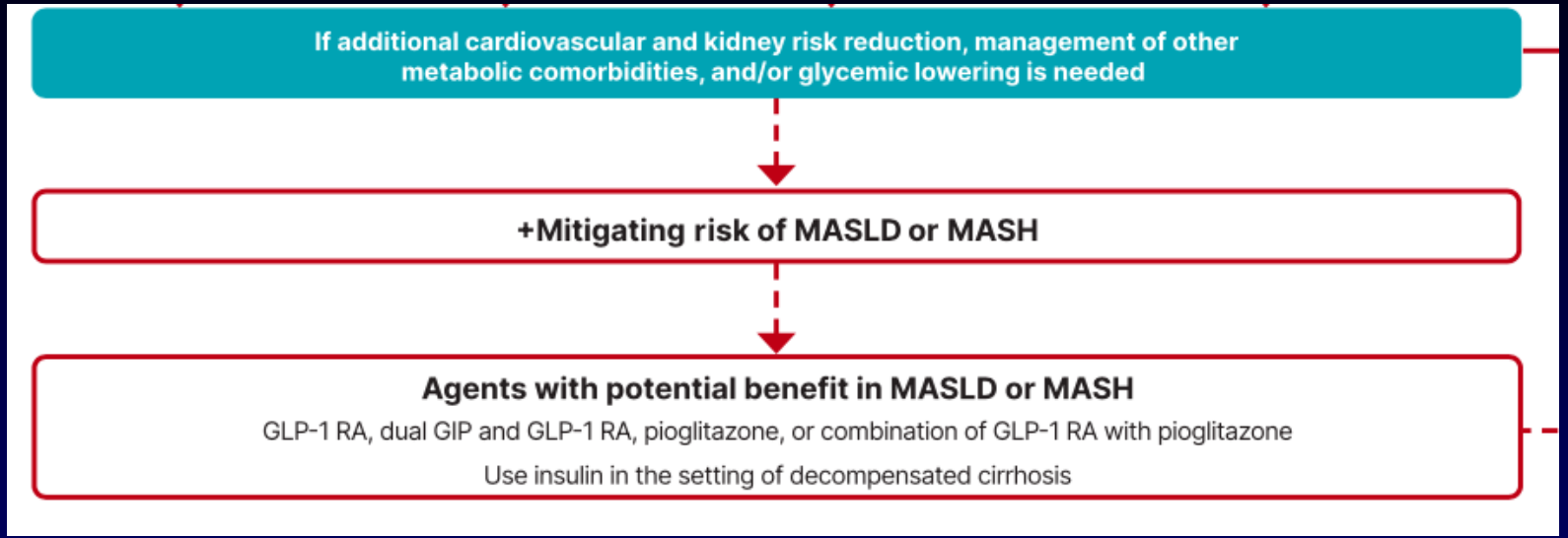
Fig. 3. Lifestyle management algorithm for MASLD. Note: Behavioural therapy includes: self-monitoring, clinicians providing affected individuals with self-efficacy and motivation, setting realistic negotiable goals, and overcoming barriers. Examples of unprocessed/minimally processed foods: vegetables, fruits (not juice), low-fat dairy, nuts, olive oil, legumes, unprocessed fish and poultry. Overweight/obesity: Overweight: BMI of 25–29.9 kg/m^2 (non-Asian) or 23–24.9 (Asian), Obesity: ≥30 kg/m^2 (non-Asian) ≥25 kg/m^2 (Asian). Class II obesity: BMI ≥35 kg/m^2 (non-Asian) or BMI ≥30 kg/m^2 (Asian). Normal weight: BMI<25 kg/m^2 (non-Asian) or <23 kg/m^2 (Asian). BMI, body-mass index; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; T2D, type 2 diabetes.

Regardless of diabetes

Weight loss !

EASL–EASD–EASO
J Hepatol, 2024

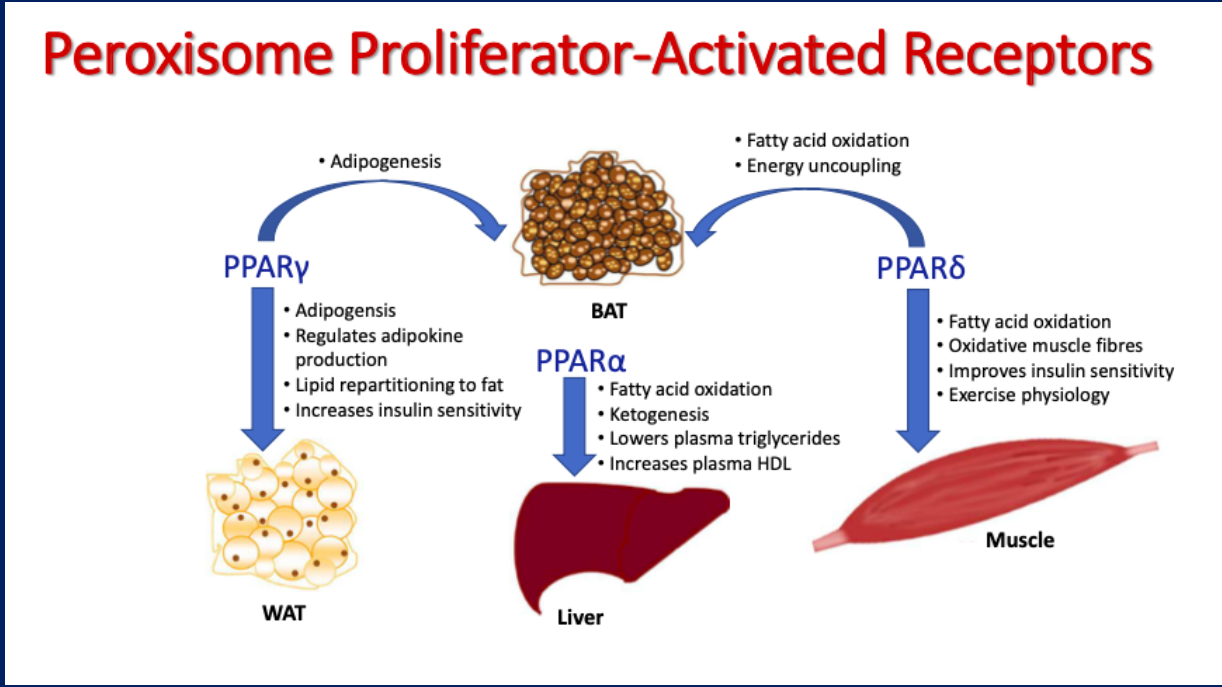
ADA Standards of Care 2025



- GLP1-RA
- GIP/GLP1-RA
- Pioglitazone
- GLP1-RA + Pioglitazone

ADA Standards of Care, Diabetes Care, 2025

Pioglitazone



Belfort R et al N Engl J Med, 2006 - Sanyal AJ et al CRN N Engl J Med, 2007
Cusi K et al Ann Int Med, 2016

GLP1-RA

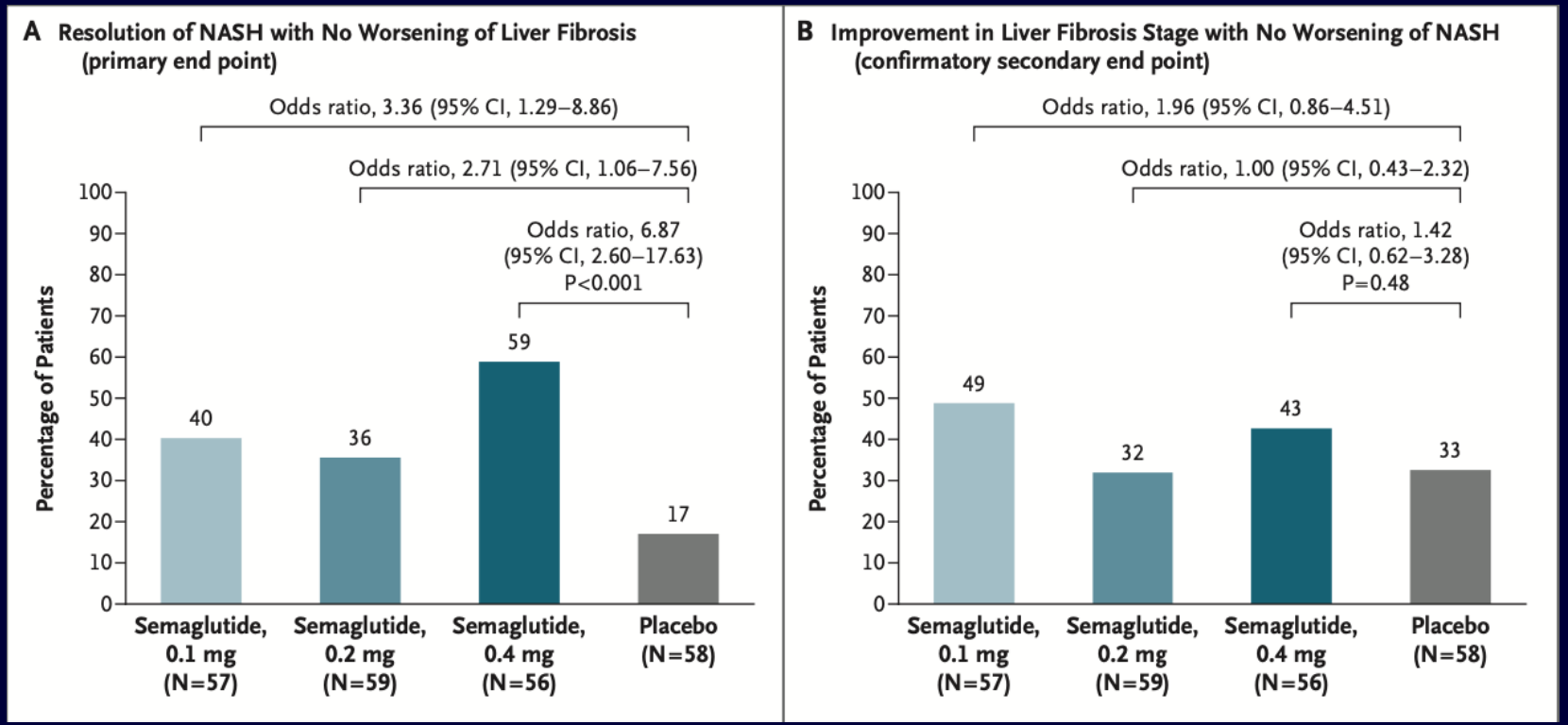
Liraglutide

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

Matthew James Armstrong, Piers Gaunt, Guruprasad P Aithal, Darren Barton, Diana Hull, Richard Parker, Jonathan M Hazlehurst, Kathy Guo, LEAN trial team, George Abouda, Mark A Aldersley, Deborah Stocken, Stephen C Gough, Jeremy W Tomlinson, Rachel M Brown, Stefan G Hübscher, Philip N Newsome*

Armstrong MJ et al, Lancet, 2016

GLP1-RA – Semaglutide 0.4 die



Newsome P et al, N Engl J Med, 2020

company announcement

Semaglutide 2.4 mg demonstrates superior improvement in both liver fibrosis and MASH resolution in the ESSENCE trial

Bagsværd, Denmark, 1 November 2024 – Novo Nordisk today announced the headline results from part 1 of the ongoing ESSENCE trial, a pivotal phase 3, 240-week, double-blinded trial in 1,200 adults with metabolic dysfunction-associated steatohepatitis (MASH) and moderate to advanced liver fibrosis (stage 2 or 3)[1]. Part 1 of the ESSENCE trial evaluated the effect of once-weekly semaglutide 2.4 mg on liver tissue (histology) compared to placebo on top of standard of care for the first 800 randomised people at 72 weeks.

The trial achieved its primary endpoints by demonstrating a statistically significant and superior improvement in liver fibrosis with no worsening of steatohepatitis, as well as resolution of steatohepatitis with no worsening of liver fibrosis with semaglutide 2.4 mg compared to placebo. At week 72, 37.0% of people treated with semaglutide 2.4 mg achieved improvement in liver fibrosis with no worsening of steatohepatitis compared to 22.5% on placebo[2]. 62.9% of people treated with semaglutide 2.4 mg achieved resolution of steatohepatitis[3] with no worsening of liver fibrosis compared to 34.1% on placebo[2].

In the trial, semaglutide 2.4 mg appeared to have a safe and well-tolerated profile in line with previous semaglutide 2.4 mg trials.

"We are very pleased about the ESSENCE clinical trial results and the potential of semaglutide to help people living with MASH" said Martin Holst Lange, executive vice president and head of Development at Novo Nordisk. "Among people with overweight or obesity, one in three live with MASH. This has a serious impact on their health and represents a significant unmet need."

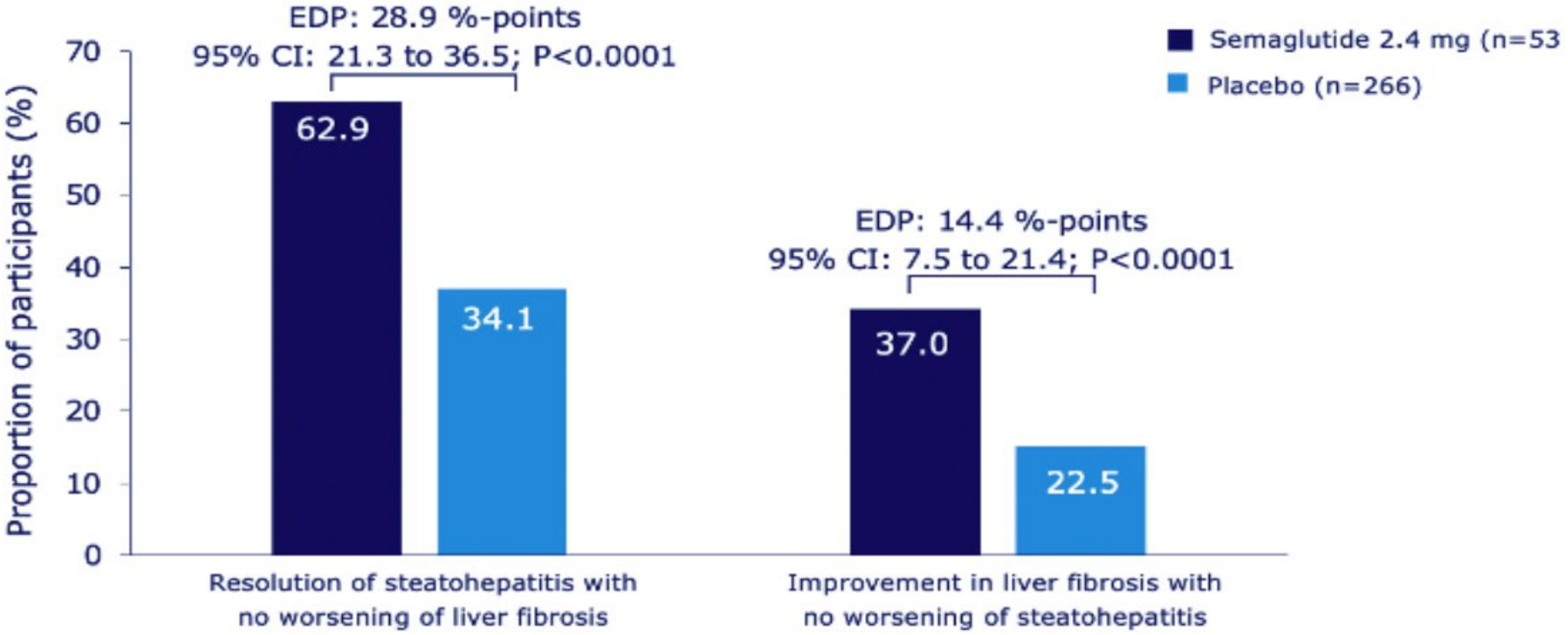
Novo Nordisk expects to file for regulatory approvals in the US and EU in the first half of 2025. The detailed results from ESSENCE will be presented at a scientific conference in 2024. Part 2 of the ESSENCE trial will continue with expected readout in 2029.

Semaglutide 2.4 once weekly

Press release

ESSENCE
semaglutide | effects and outcomes in NASH

Primary endpoints (ITT population)

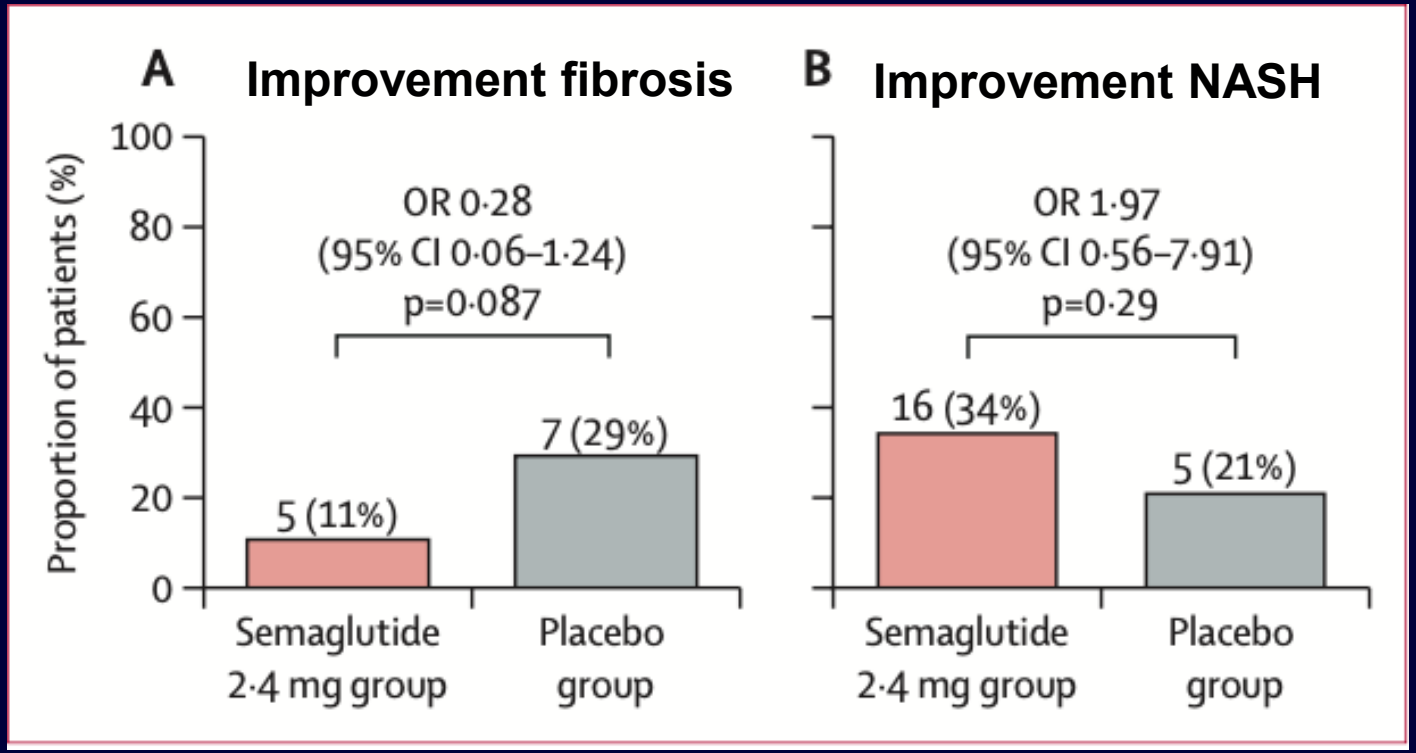


CI, confidence interval; EDP, estimated difference in responder proportions; ITT, intention-to-treat..

Yet to be published

GLP1-RA in compensated cirrhosis - Semaglutide

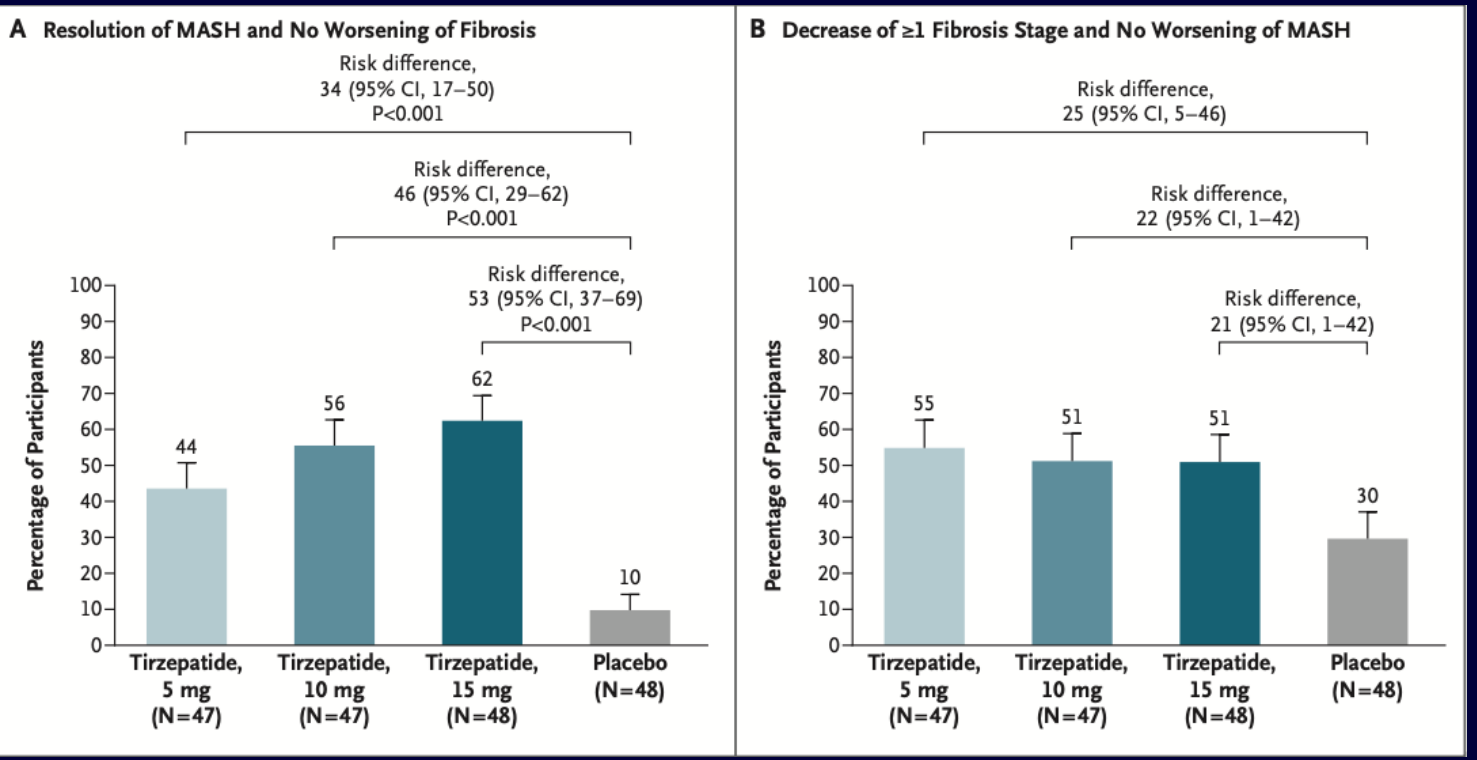
Phase 2:
71 patients
48 weeks



Loomba R et al, Lancet Diabetes Endocrinol, 2023

Dual-agonists

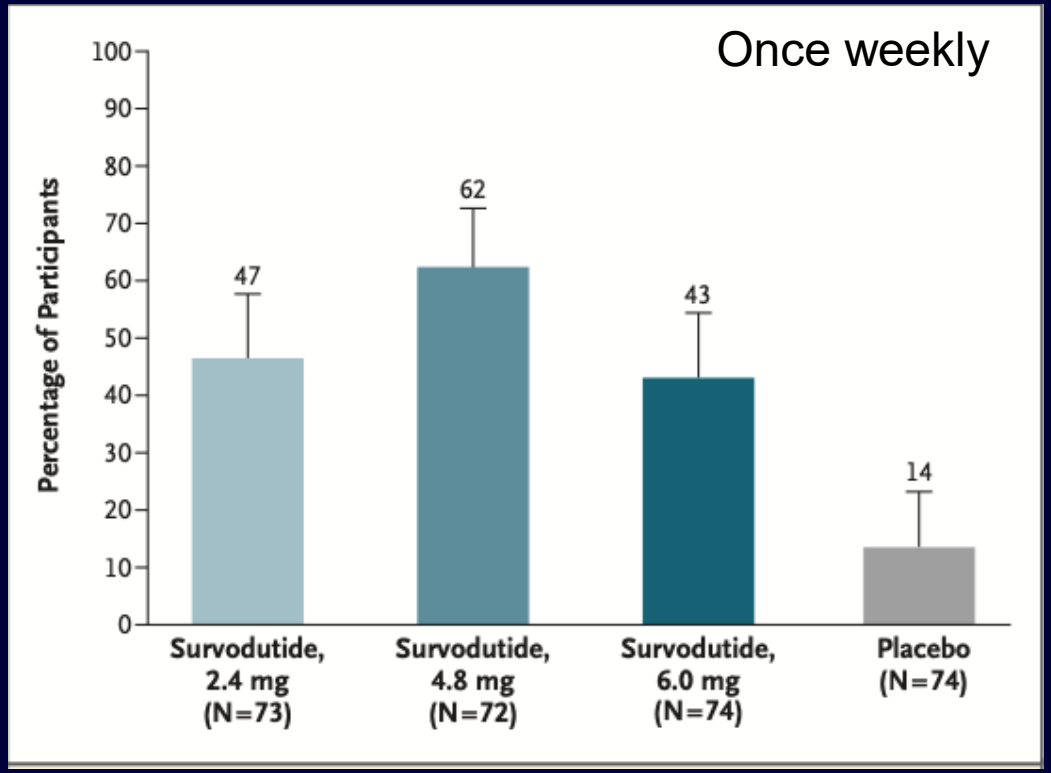
GLP1/GIP RA: Tirzepatide



Phase 2:
190 pats
54 weeks

Loomba R et al, N Engl J Med, 2024

GLP1/Glucagon RA: Survodutide

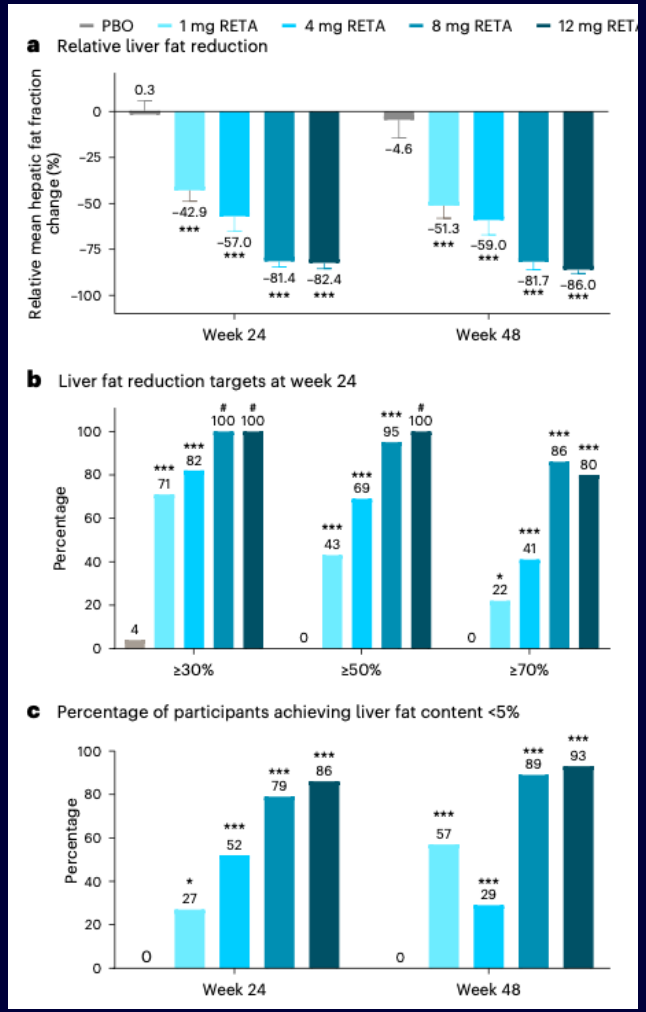


Phase-2, 48 weeks
Histologic improvement in MASH, with no worsening of fibrosis

Sanyal AJ et al, N Engl J Med, 2024

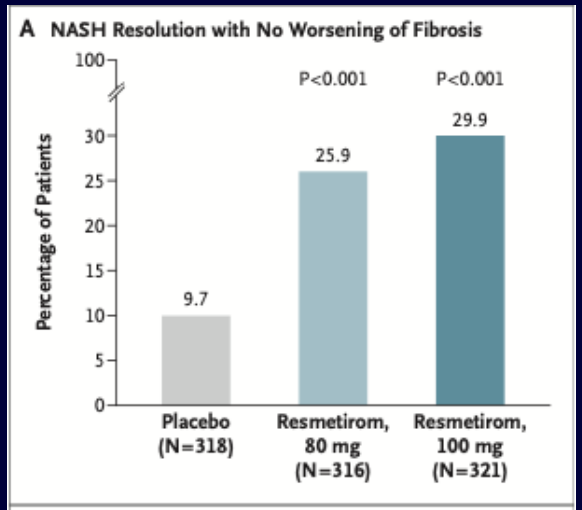
Triple-agonists

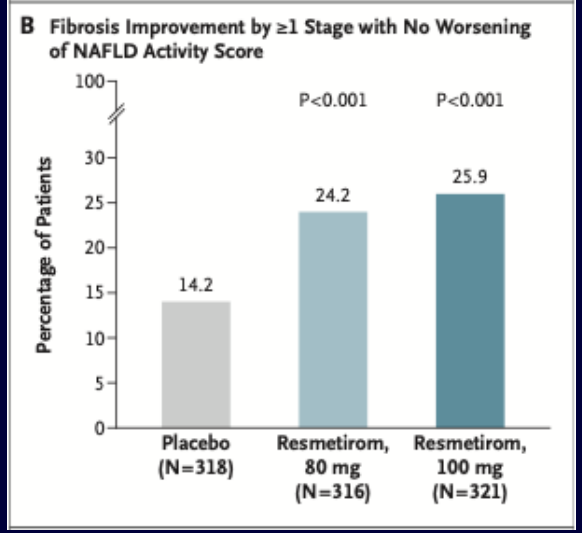
GLP1/GIP/Glucagon – RA (Retatrutide)



Liver fat reductions were significantly related to changes in body weight, abdominal fat and metabolic measures associated with improved insulin sensitivity and lipid metabolism

Sanyal AJ et al, Nature Med, 2024





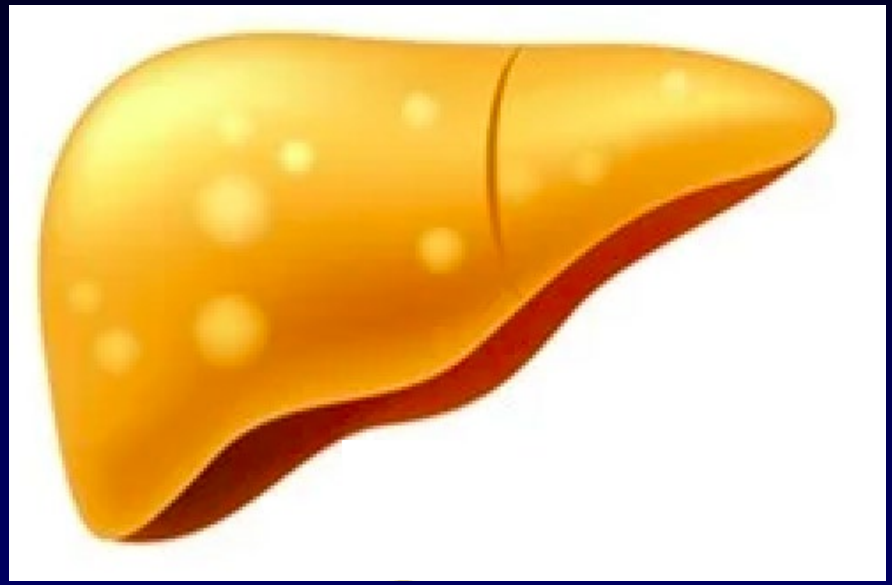
Resmetirom

MAESTRO – Phase 3

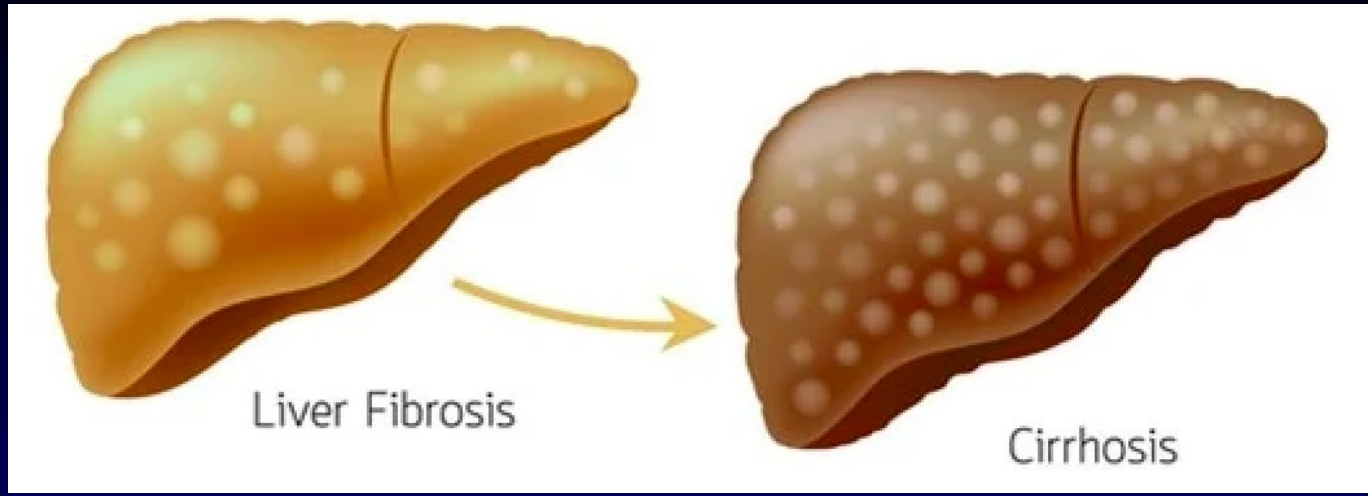
Resmetirom is an oral, liver-directed, thyroid hormone receptor beta (THR-β) – selective agonist

Harrison SA et al, N Engl J Med, 2024

Conclusions

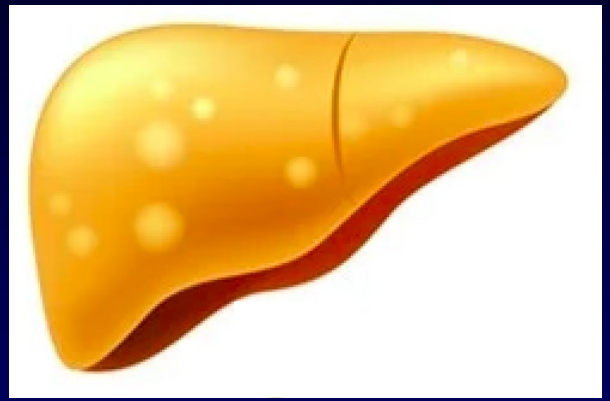


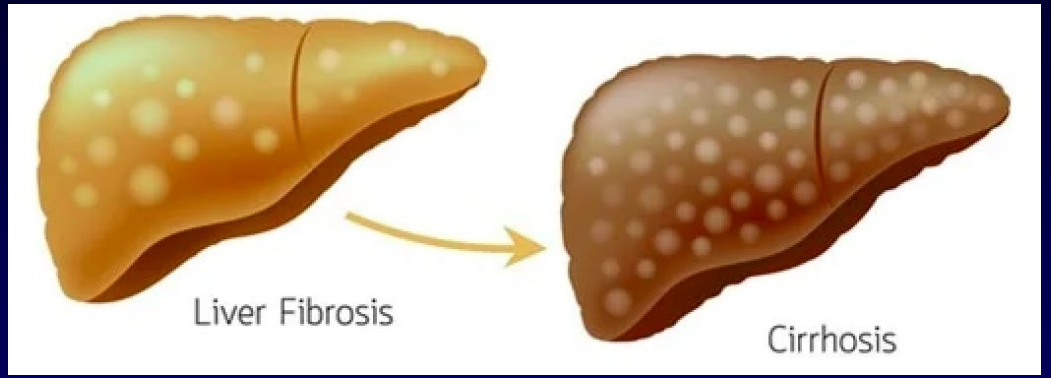
Anti metabolic therapy



Anti inflammatory and anti fibrotic therapy

Combination/sequential therapy





Anti metabolic therapy

Anti inflammatory and anti fibrotic therapy

Anti inflammatory and anti fibrotic therapy

Anti metabolic therapy

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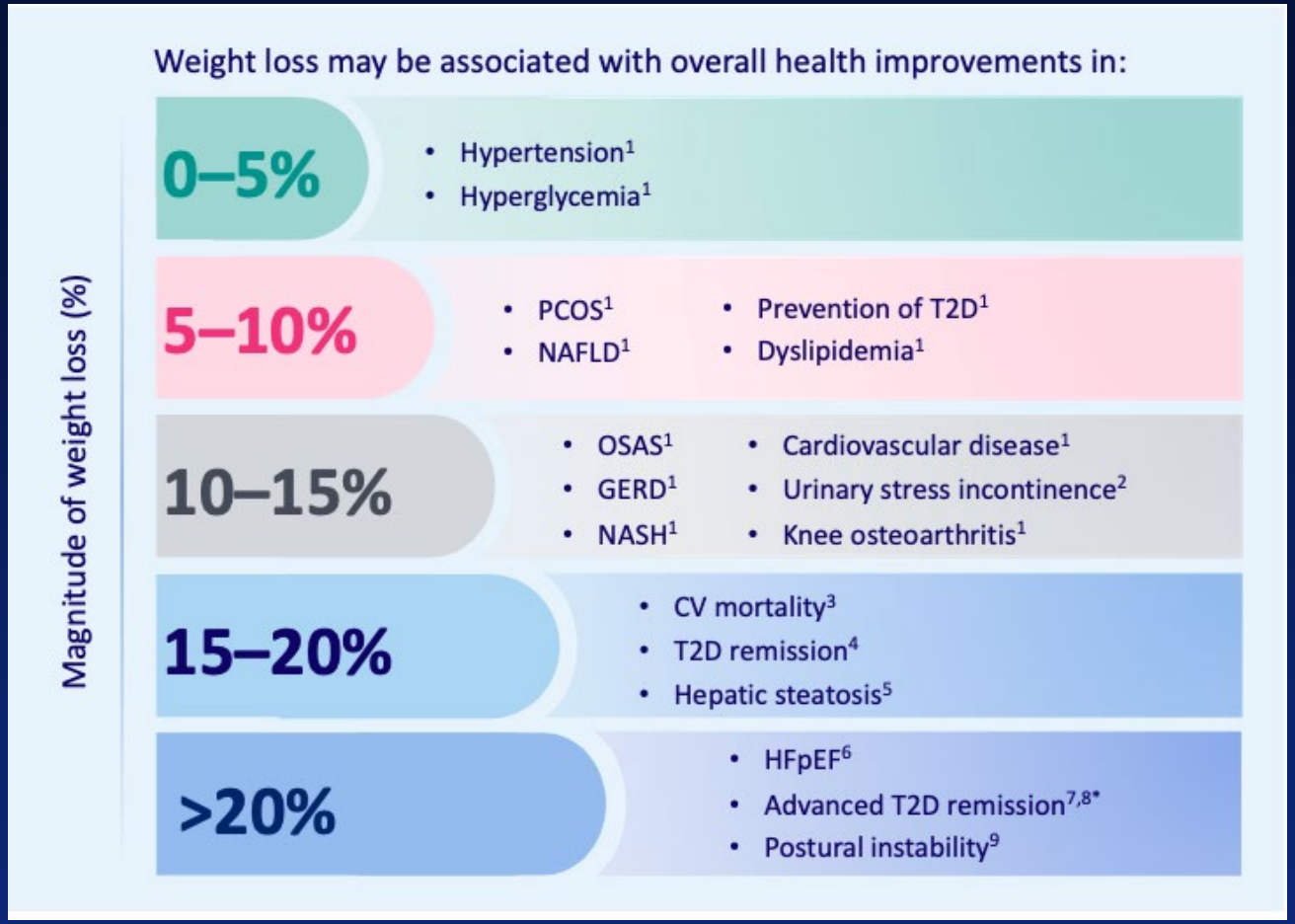


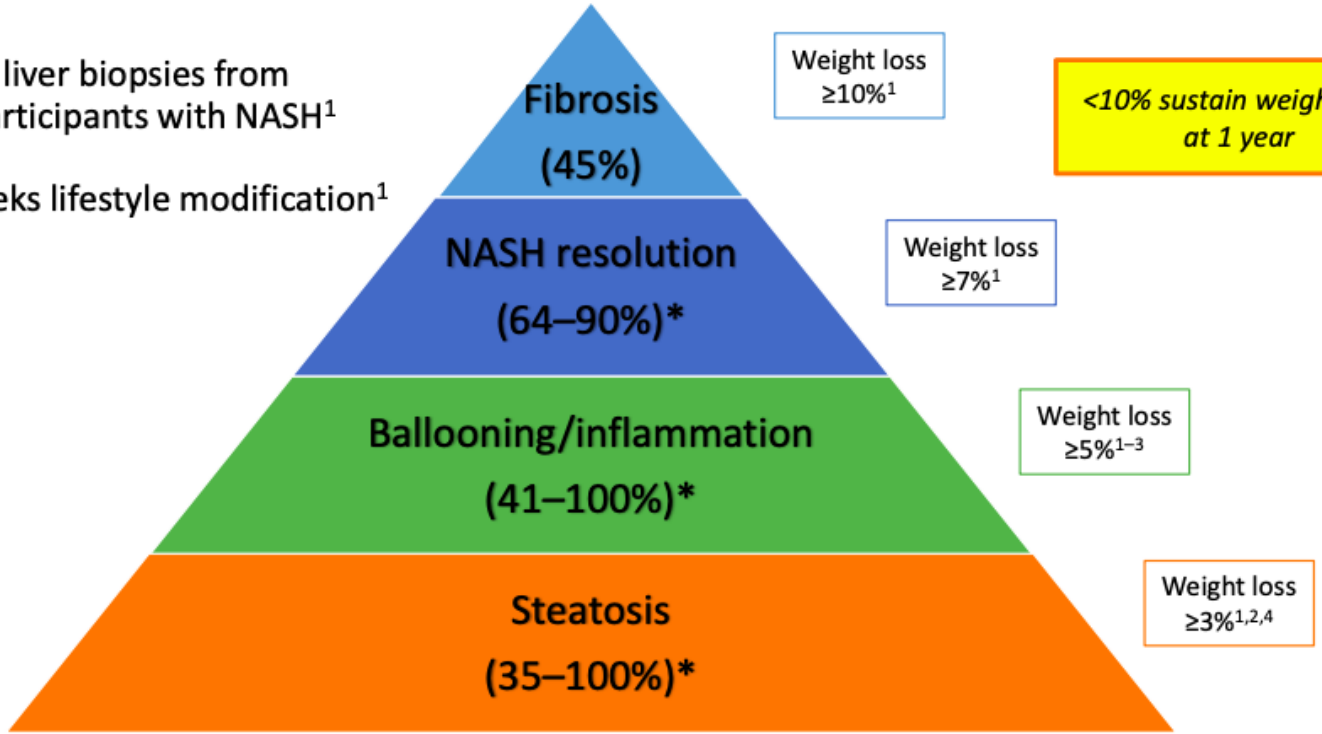
Greater weight loss = better liver health outcomes

*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.

Lifestyle Modification and Histology in NAFLD

- Paired liver biopsies from 261 participants with NASH[1]
- 52 weeks lifestyle modification[1]



Cortesia di Elisabetta Bugianesi (UNITO)

Recommendations

4.27 Adults with type 2 diabetes or prediabetes, particularly with overweight or obesity, with nonalcoholic fatty liver disease (NAFLD) should be recommended lifestyle changes that promote weight loss, ideally within a structured nutrition plan and physical activity program for cardiometabolic benefits **B** and histological improvement. **C**

4.28 For adults with type 2 diabetes, particularly with overweight or obesity, with NAFLD, consider using a glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated benefits in nonalcoholic steatohepatitis (NASH) as an adjunctive therapy to lifestyle interventions for weight loss. **B**

4.29 Pioglitazone or GLP-1 receptor agonists are the preferred agents for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven NASH or those at high risk with clinically significant liver fibrosis using noninvasive tests. **A**

4.30a In adults with type 2 diabetes and NAFLD, use of glucose-lowering therapies other than pioglitazone or GLP-1 receptor agonists may be continued as clinically indicated, but these therapies lack evidence of benefit in NASH. **B**

4.30b Insulin therapy is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis. **C**

4.31a Adults with type 2 diabetes and NAFLD are at increased cardiovascular risk; therefore, comprehensive management of cardiovascular risk factors is recommended. **B**

4.31b Statin therapy is safe in adults with type 2 diabetes and compensated cirrhosis from NAFLD and should be initiated or continued for cardiovascular risk reduction as clinically indicated. **B** Statin therapy should be used with caution and close monitoring in people with decompensated cirrhosis, given limited safety and efficacy data. **B**

4.32a Consider metabolic surgery in appropriate candidates as an option to treat NASH in adults with type 2 diabetes **B** and to improve cardiovascular outcomes. **B**

4.32b Metabolic surgery should be used with caution in adults with type 2 diabetes with compensated cirrhosis from NAFLD **B** and is not recommended in decompensated cirrhosis. **B**

ADA Standard of Care, Diabetes Care, 2024