MASLD: una nuova frontiera terapeutica per i GLP-1 RA?

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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

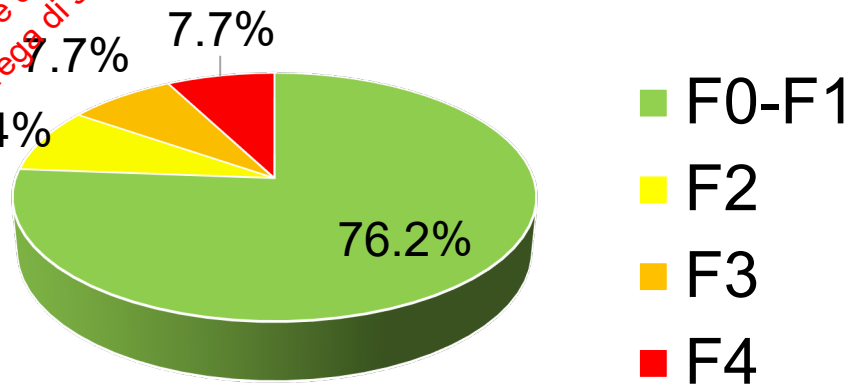
Scientific AB

Amgen
Bruno Farmaceutici
EG
Lilly
Merck
Novartis
Novo Nordisk
Pfizer
PikDare
Sanofi

Screening steatosis and fibrosis in T2D

- 825 pats with DMT2: transient elastography
- Steatosis (CAP≥274 dB/m): 73.8%

- Fibrosis
  - ≥ F2: 8.2 kPa
  - ≥ F3: 9.7 kPa
  - F4: 13.6 kPa



Ciardullo S et al. Diabetes Care 2021

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

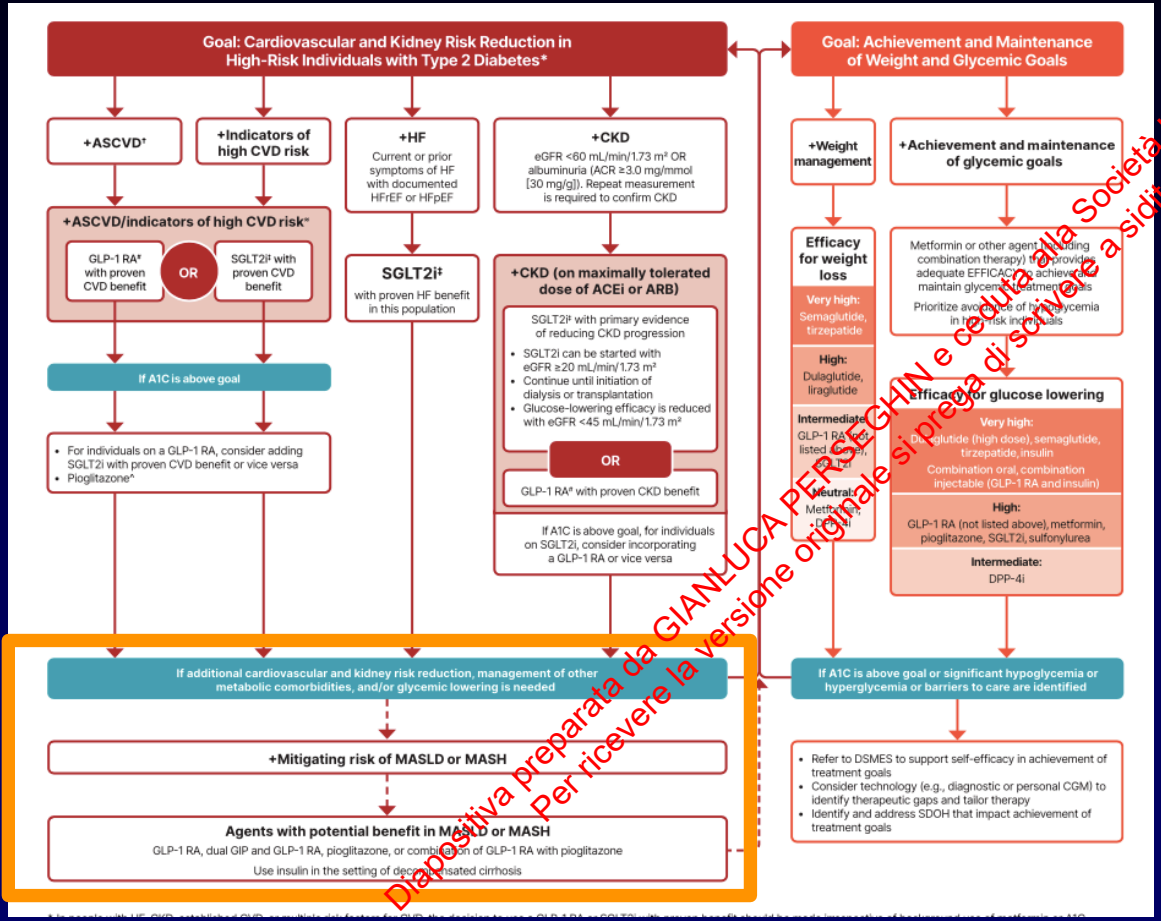
Therapeutic treatment plans
- Lifestyle management
- Pharmacologic therapy: glucose lowering
- Pharmacologic therapy: cardiovascular and kidney disease risk factors
- Weight management with pharmacotherapy or metabolic surgery, as appropriate
- Use of glucose monitoring and insulin delivery devices
- 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

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

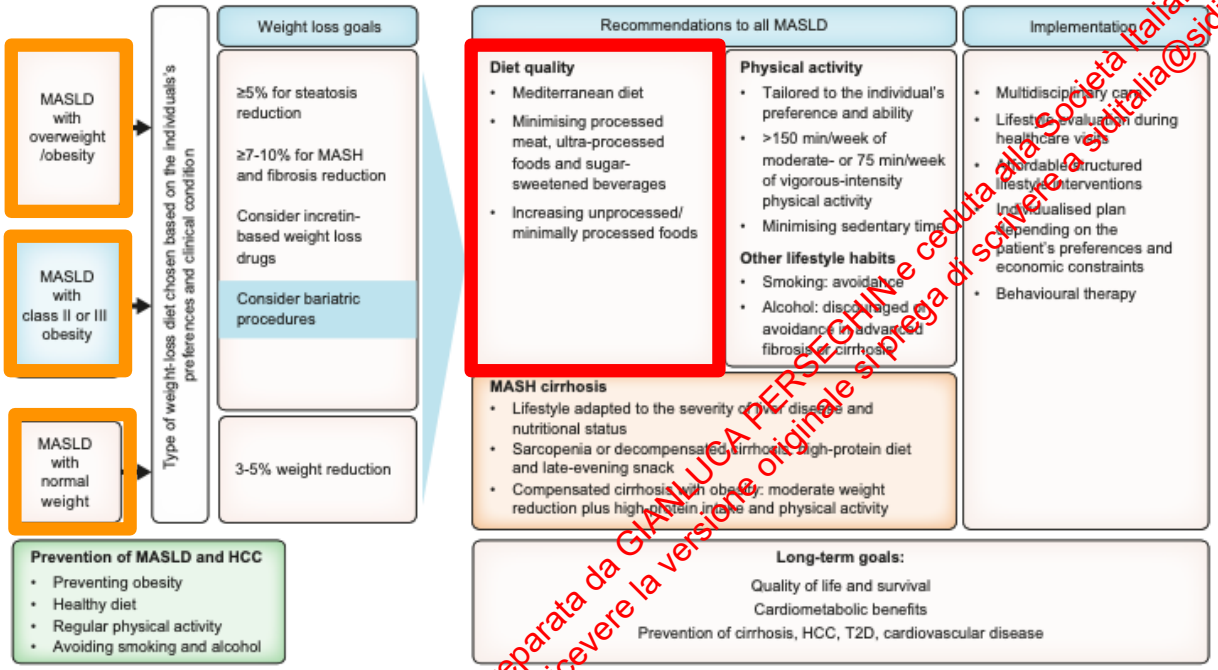


Fig. 3. Lifestyle management algorithm for MASLD. Note: Behavioural therapy includes: self-monitoring, clinicians providing affected individuals with self-efficacy and motivation, setting realistic negotiable goals, and overcoming barriers. Examples of unprocessed/minimally processed foods: vegetables, 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.

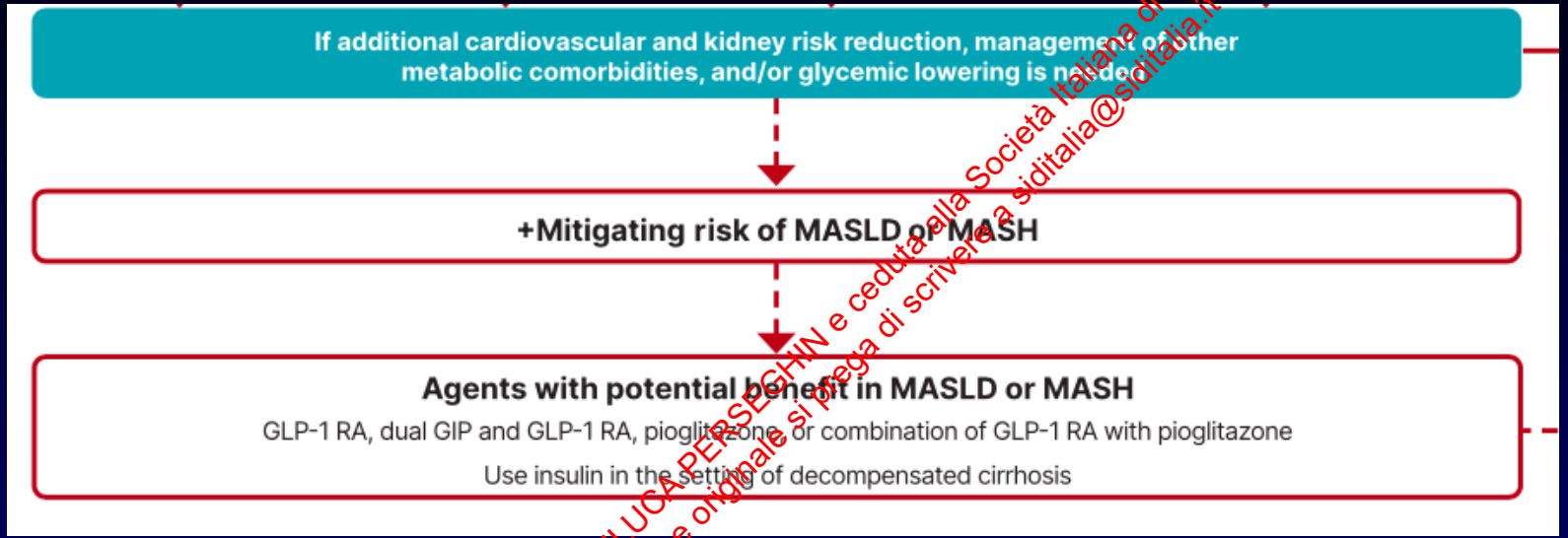
Regardless of diabetes

Weight loss !

EASL–EASD–EASO
J Hepatol, 2024

Special task for the diabetologist

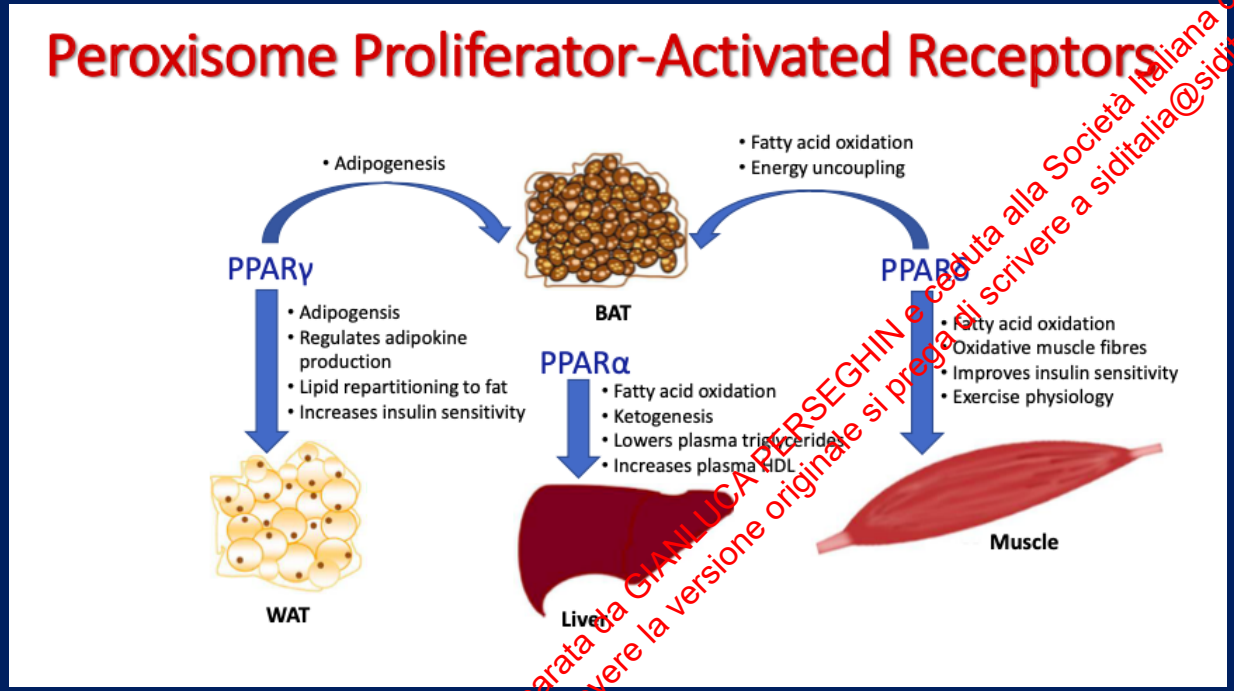
ADA Standards of Care 2025



- 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

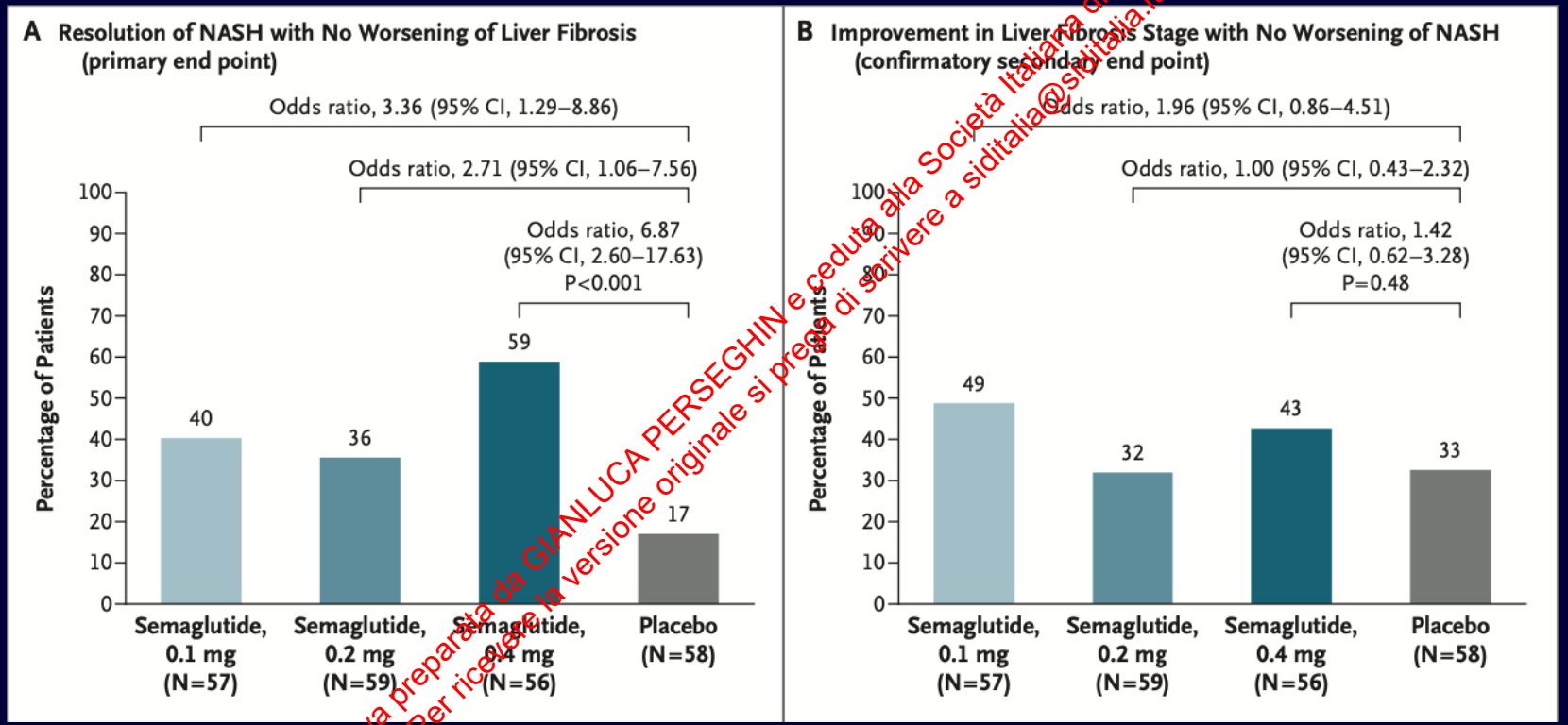
Liraglutide

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, Derken 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

ESSENCE

Semaglutide 2.4 once weekly

ESSENCE is an ongoing phase 3 trial comparing once-weekly subcutaneous semaglutide 2.4 mg versus placebo in participants with biopsy-defined MASH and fibrosis stage 2 or 3

Here, we report interim efficacy and safety* results from the first 800 patients who completed 72 weeks of treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis

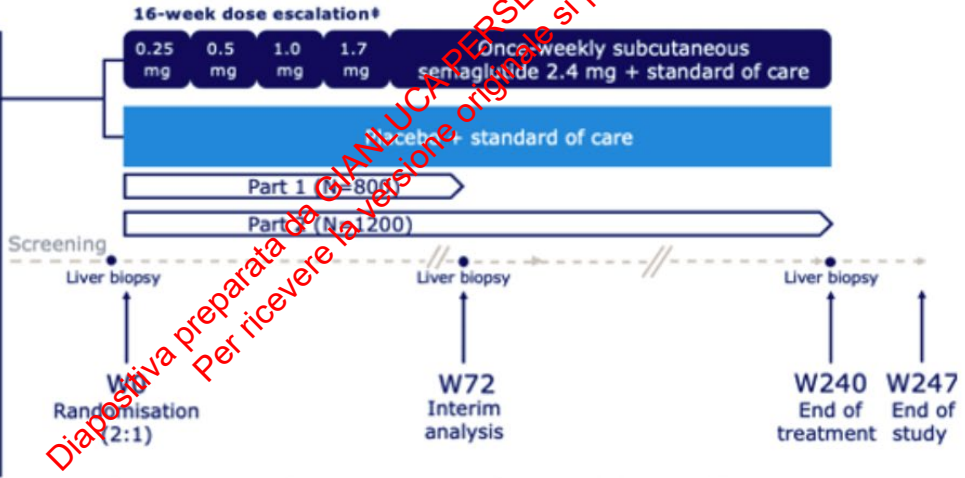
Arun J. Sanyal, M.D.,[1] Philip N. Newsome, M.B., Ch.B., Ph.D.,[2,3] Iris Kliers, M.D.,[4] Laura Harms Østergaard, M.Sc.,[4] Michelle T. Long, M.D.,[4] Mette Skalshøi Kjær, M.D., Ph.D.,[4] Anna M.G. Cali, M.D.,[4] Elisabetta Bugianesi, M.D., Ph.D.,[5] Mary E. Rinella, M.D.,[6] Michael Roden, M.D.,[7-9] and Vlad Ratziu, M.D., Ph.D.,[10] for the ESSENCE Study Group*

Methods

Trial design

Key inclusion criteria
- Age ≥18 years old
- Histological evidence of fibrosis stage 2 or 3*
- NAS ≥4†

Key exclusion criteria
- Chronic liver diseases other than MASLD
- Known or suspected excessive consumption of alcohol (>20 g/day for women or >30 g/day for men)
- Treatment with GLP-1RAs or unstable use of other glucose-lowering, lipid-lowering or weight loss medications within 90-days prior to screening



Sanyal A et al
N Engl J Med, 2025

ESSENCE: End-point

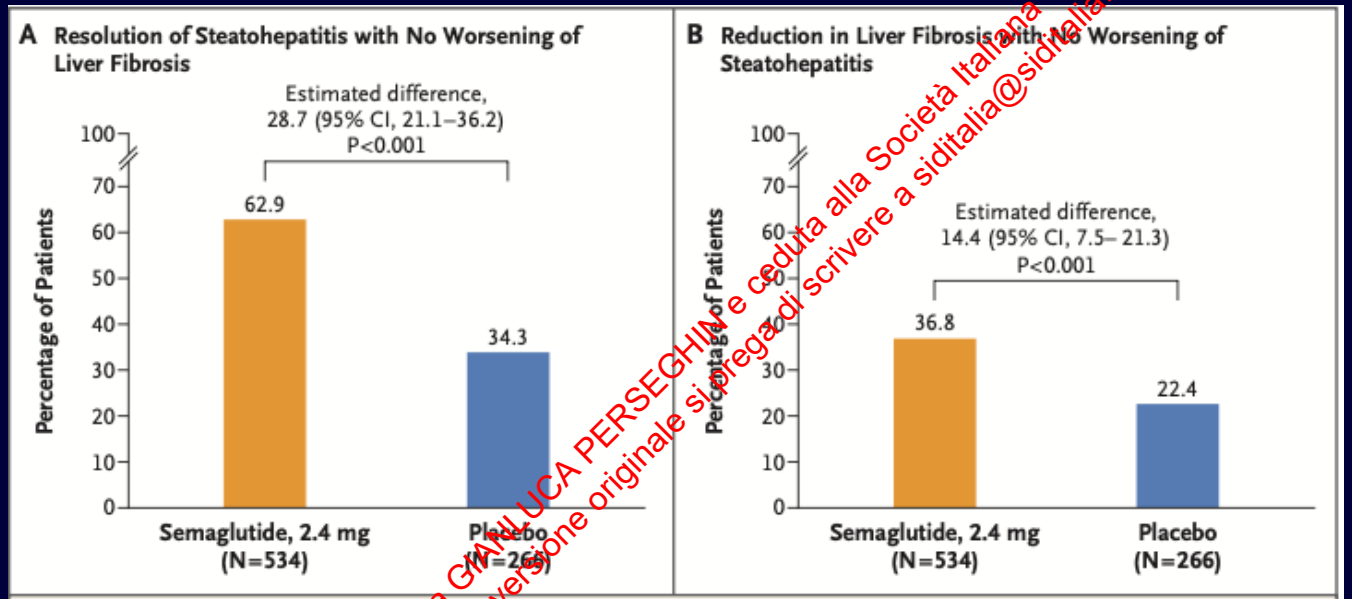


Figure 1. Primary End Points.

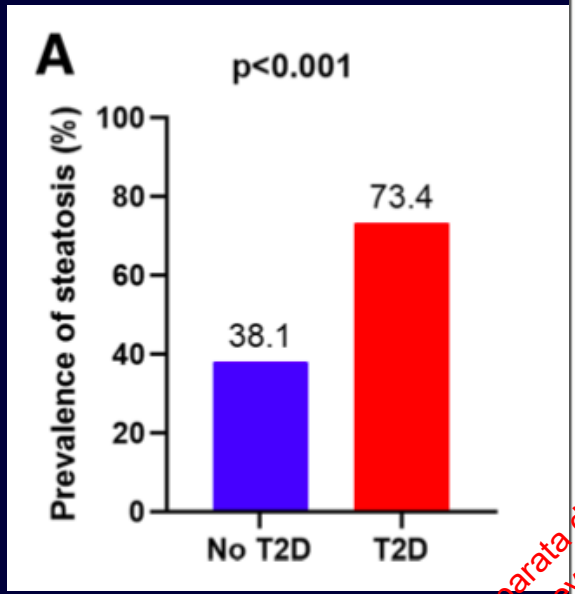
The figure shows the percentage of patients with fibrosis stage 2 or 3 who had resolution of steatohepatitis with no worsening of liver fibrosis (Panel A) and reduction in liver fibrosis with no worsening of steatohepatitis (Panel B) after 72 weeks, with the estimated difference expressed in percentage points.

Sanyal A et al N Engl J Med, 2025

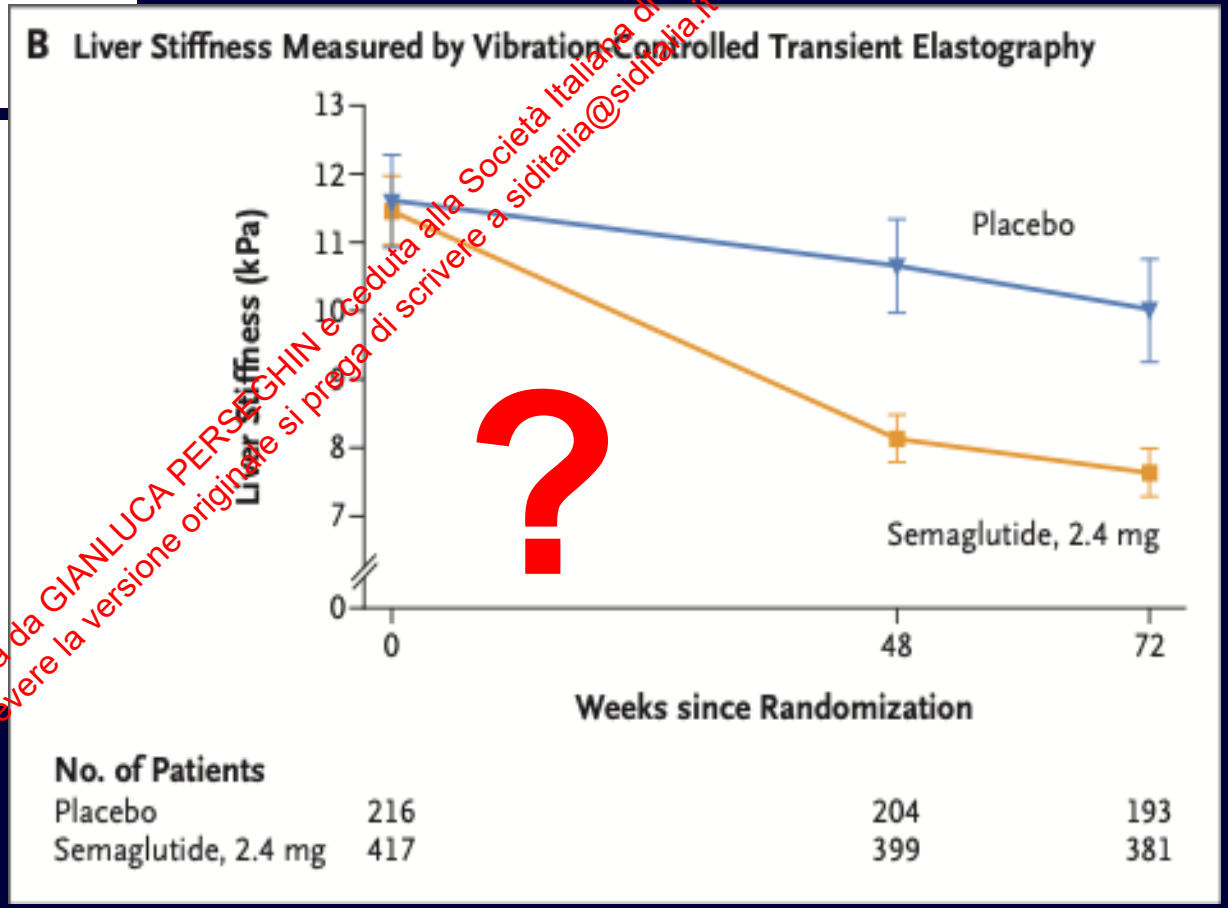
Prevalence of Noninvasively Detected Clinically Significant Portal Hypertension Among U.S. Adults With and Without Diabetes

https://doi.org/10.2337/dc24-1341

Ciardullo S, Perseghin G. Diabetes Care, 2024

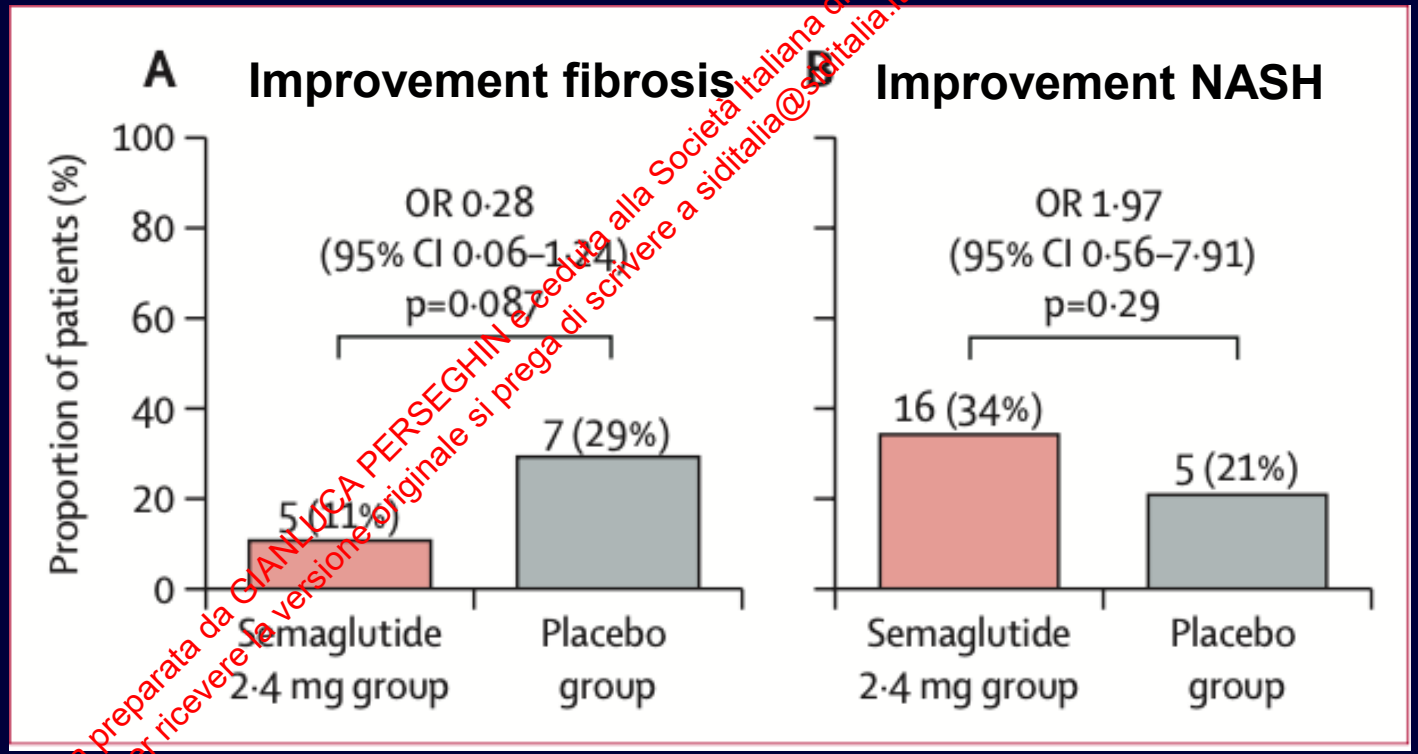


MASLD/MASH



GLP1-RA in compensated cirrhosis (F4) - Semaglutide

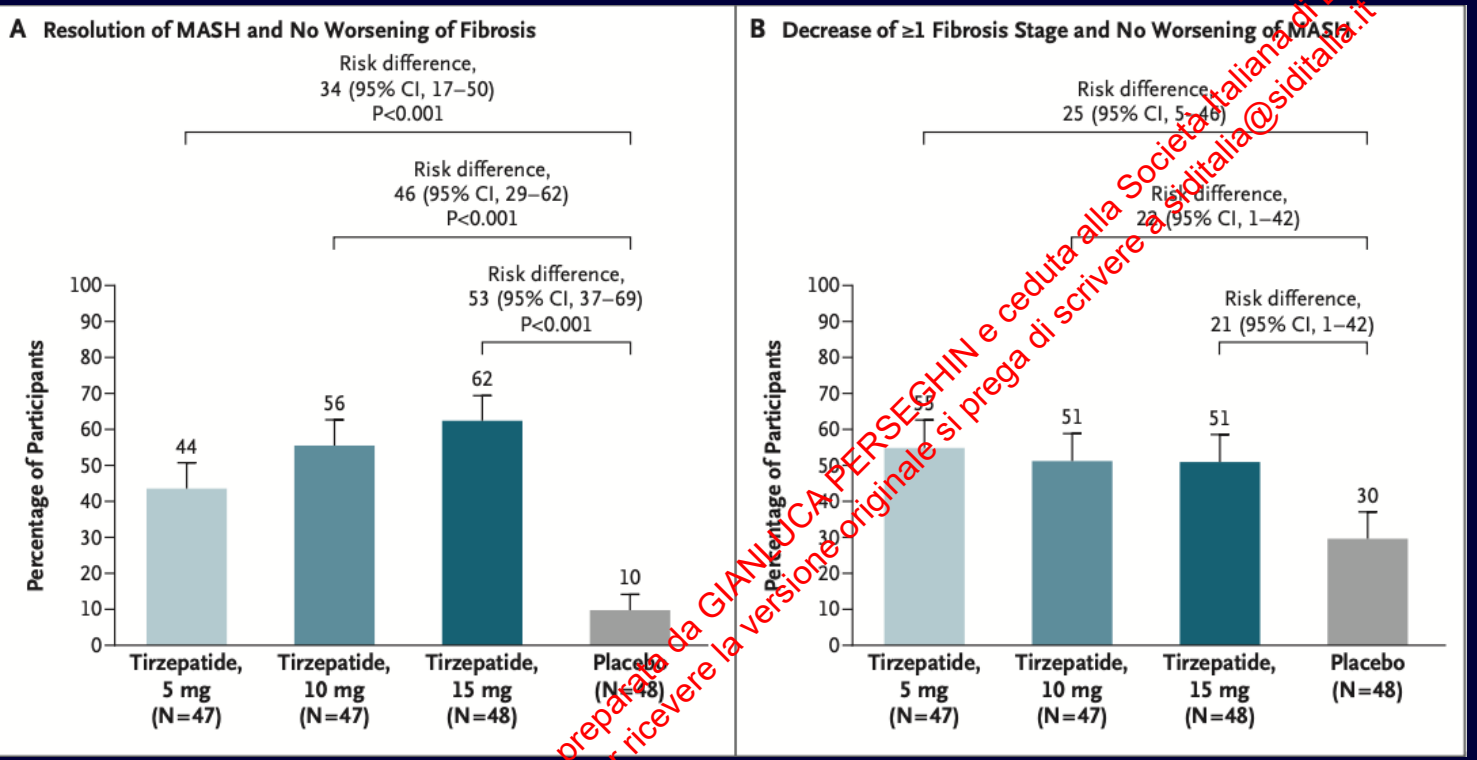
Phase 2:
71 patients
48 weeks



Loomba R et al, Lancet Diabetes Endocrinol, 2023

Dual-agonists

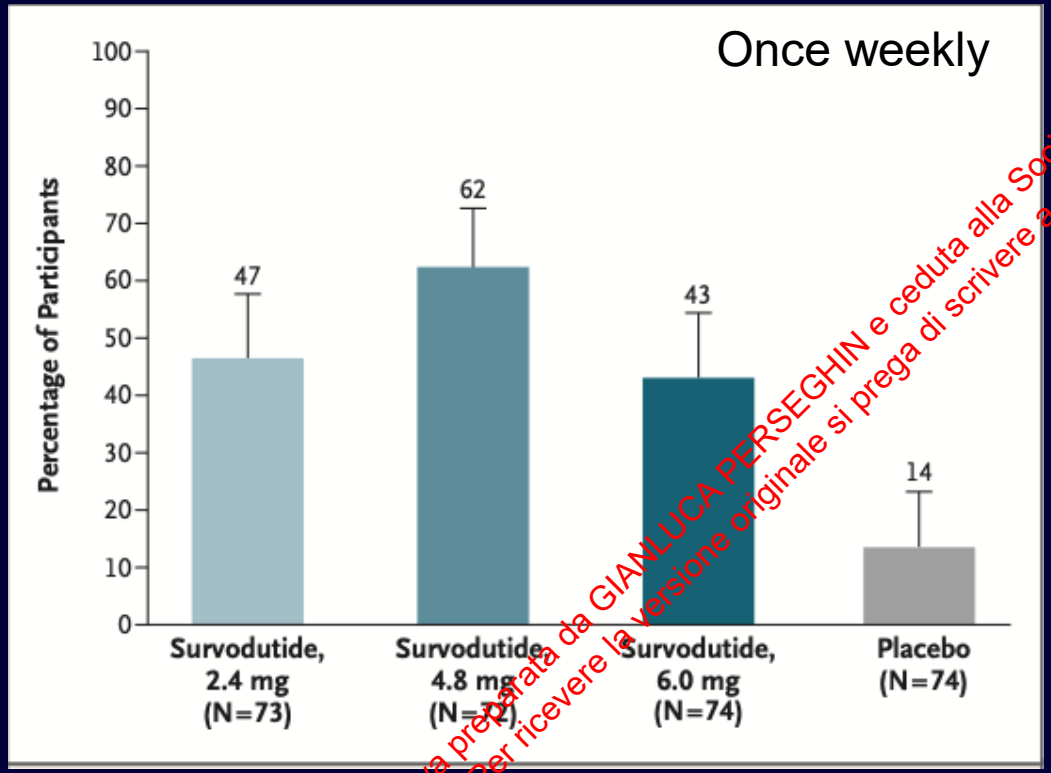
GLP1/GIP RA: Tirzepatide



Phase 2:
190 pats
54 weeks

Loomba R et al, N Engl J Med, 2024

GLP1/Glucagon RA: Survodutide

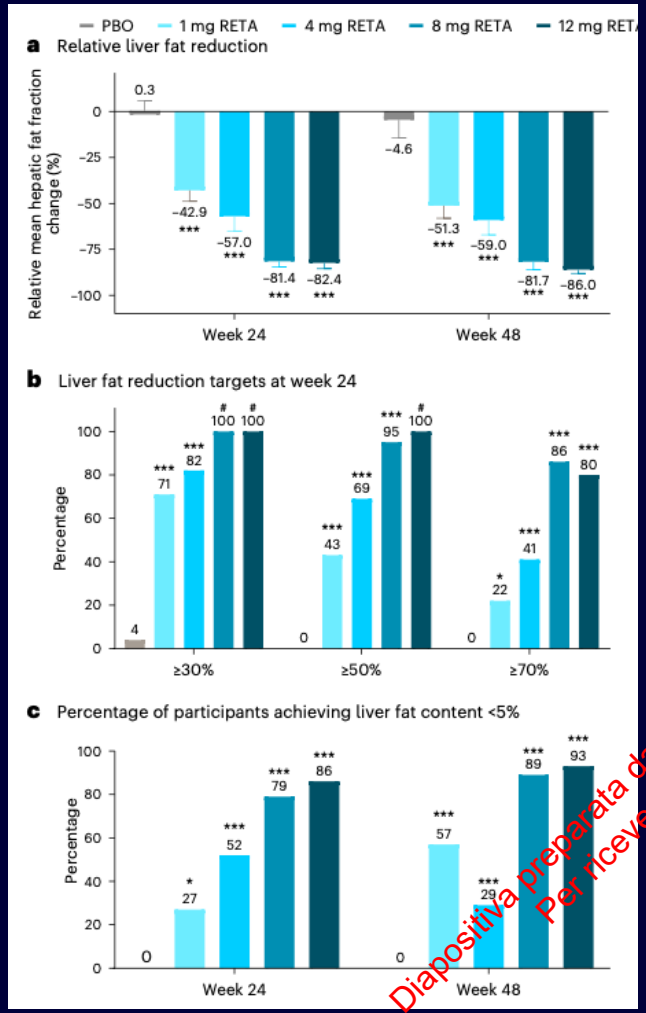


Phase-2, 48 weeks
Histologic improvement in MASH, with no worsening of fibrosis

Sanyal AJ et al, N Engl J Med, 2024

Triple-agonists

GLP1/GIP/Glucagon – RA (Retatrutide)

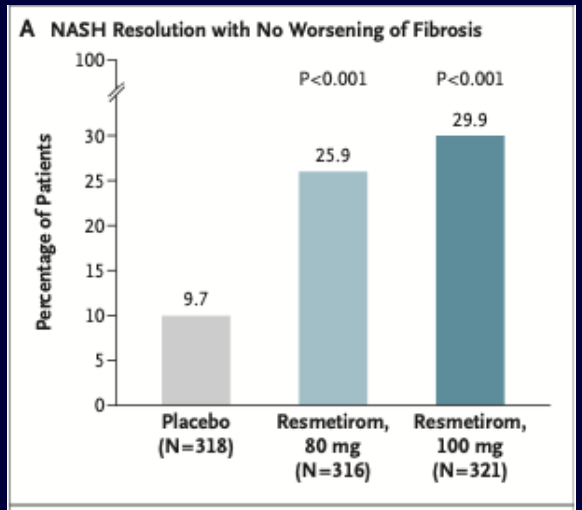


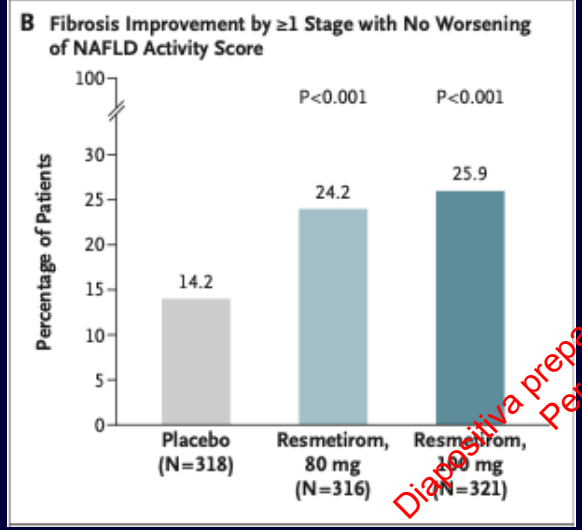
Liver fat reductions were significantly related to changes in body weight, abdominal fat and metabolic measures associated with improved insulin sensitivity and lipid metabolism

Sanyal AJ et al, Nature Med, 2024

Resmetirom

MAESTRO – Phase 3

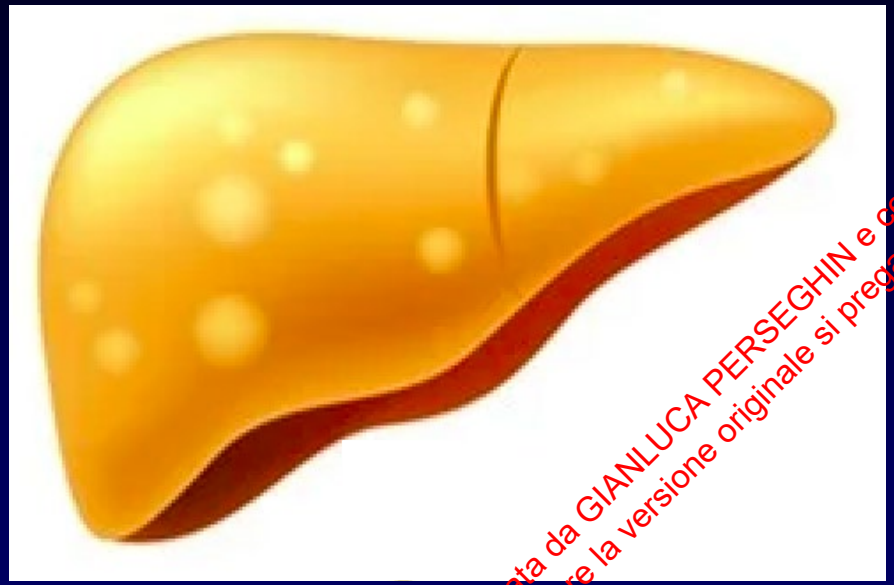




Resmetirom is an oral, liver-directed, thyroid hormone receptor beta (THR-β) – selective agonist

Harrison SA et al, N Engl J Med, 2024

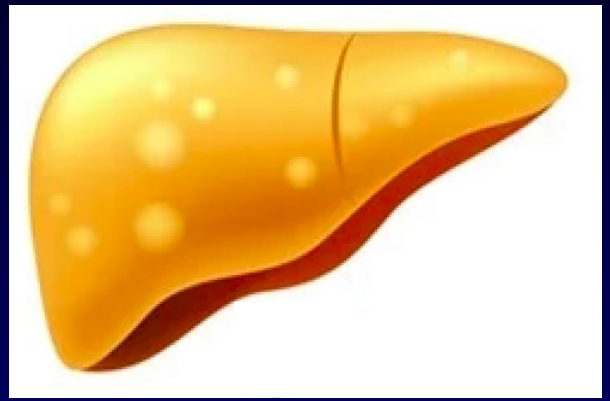
Conclusions

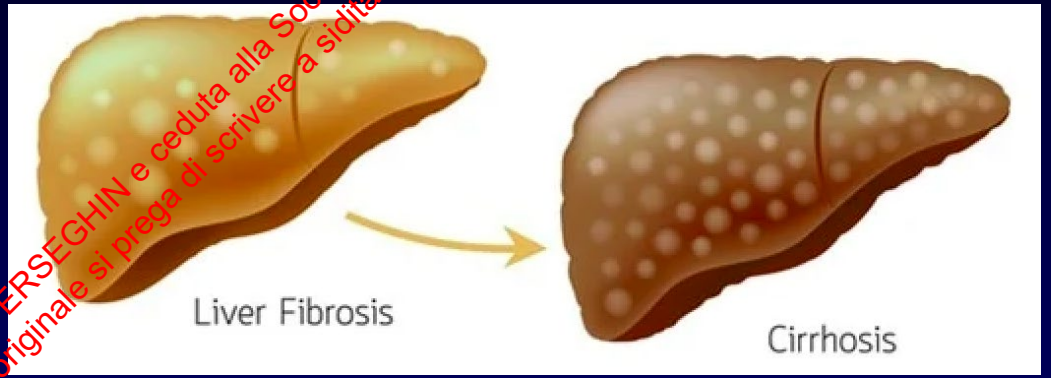


Anti metabolic therapy

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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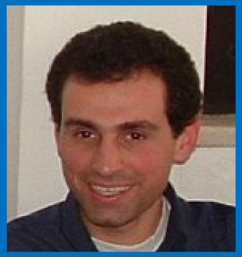
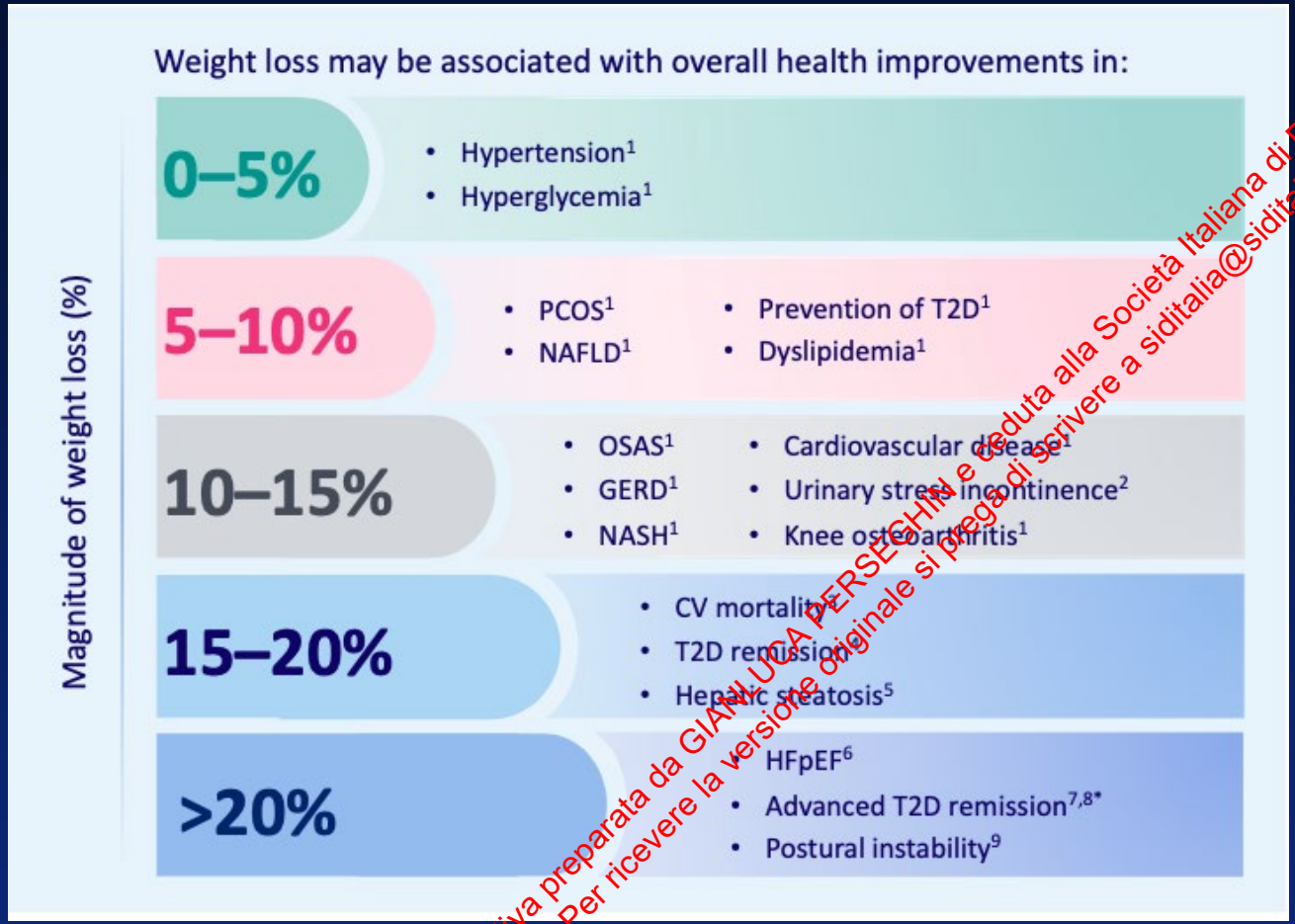






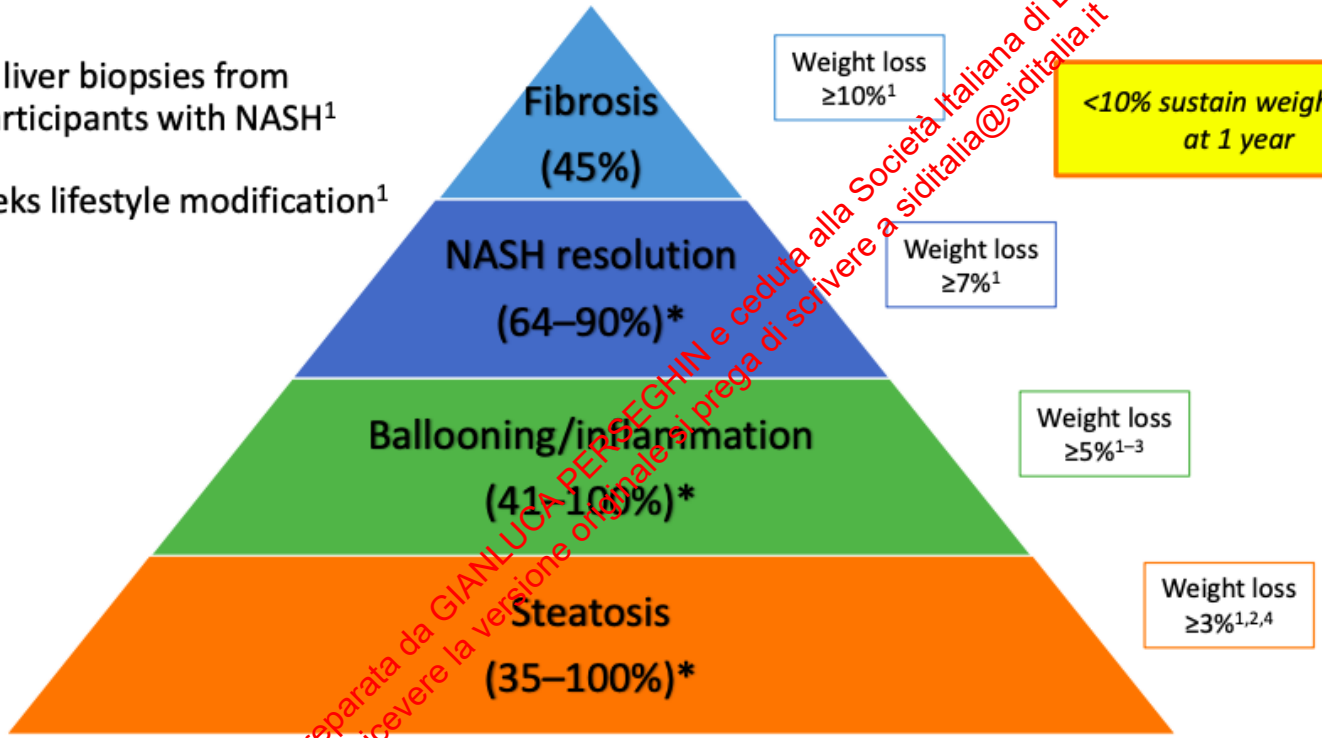
Greater weight loss = better liver health outcomes

*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