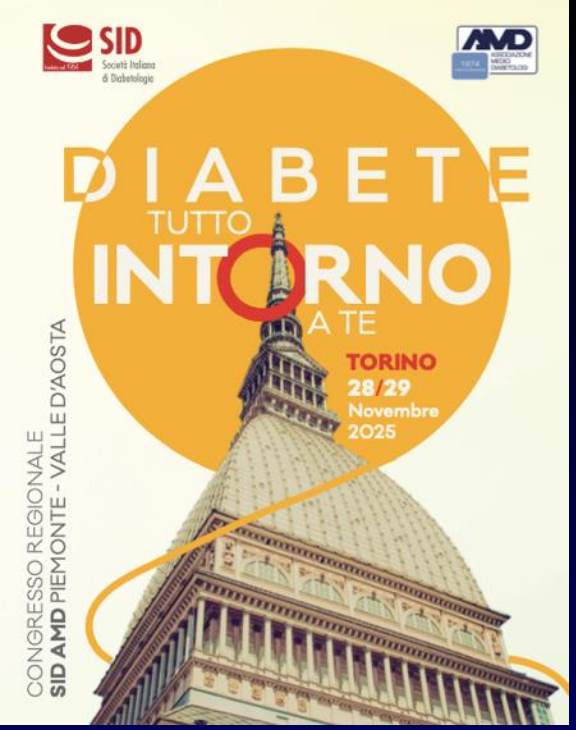


Dal diabetologo all'epatologo e vice-versa

Il ruolo del diabetologo: prevenzione, diagnosi, terapia dietetica e terapia farmacologica sartoriale

Gianluca Perseghin
Department of Medicine and Surgery
Università degli Studi di Milano Bicocca

Department of Medicine and Rehabilitation
Policlinico di Monza, Monza

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

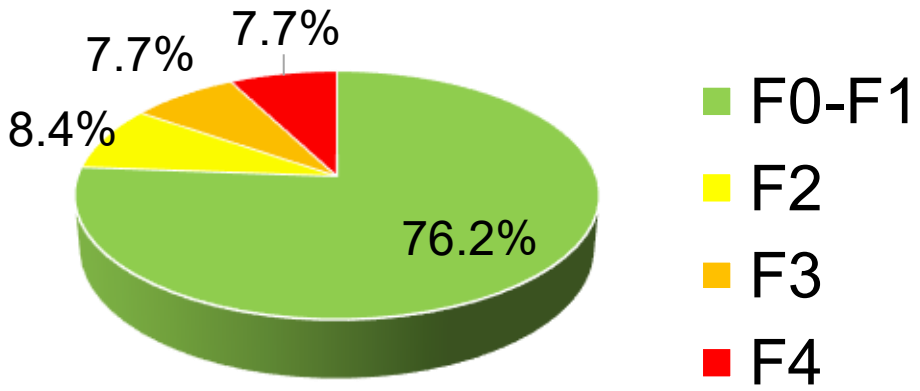
Il ruolo del diabetologo

- Cosa
- Perché
- Come

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

Cosa?
2024, a new era

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.

ADA Standard of Care, Diabetes Care, 2024

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TC-F. Can we use old NAFLD data under the new MASLD definition? J Hepatol 2024;80:e54–e56
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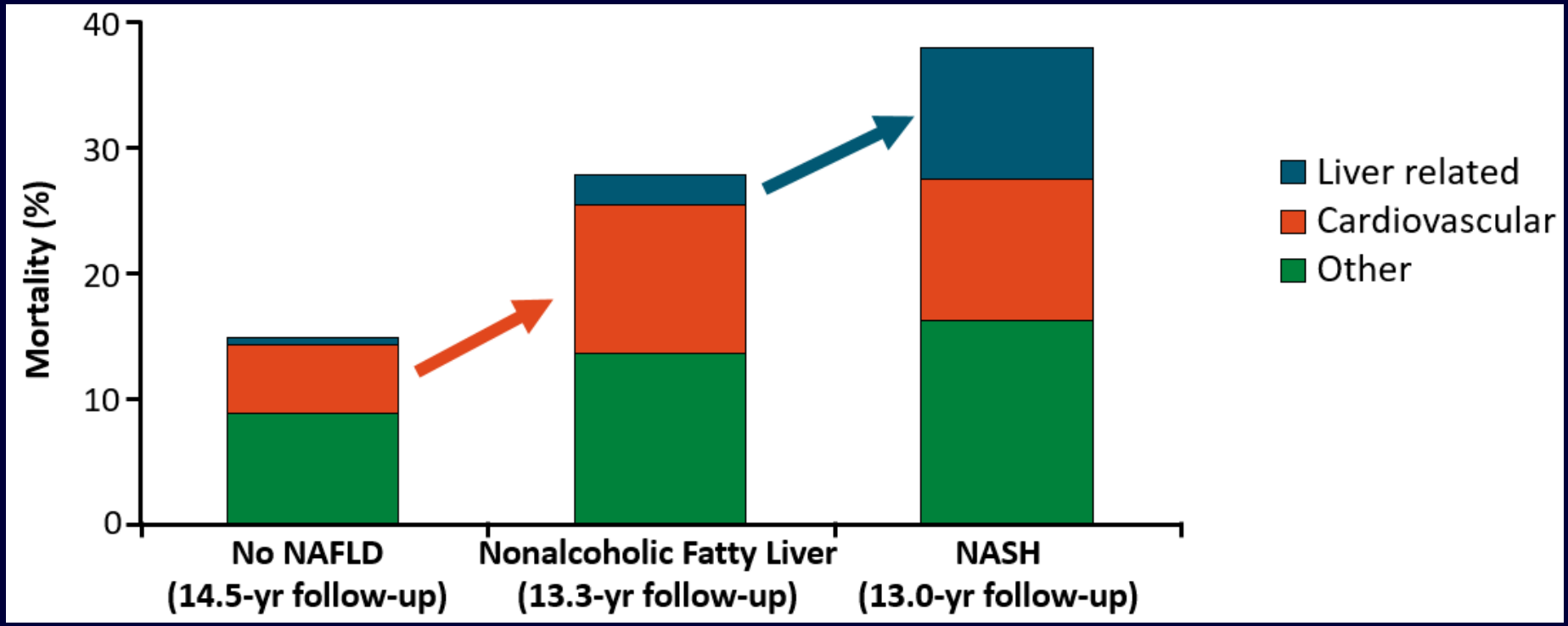
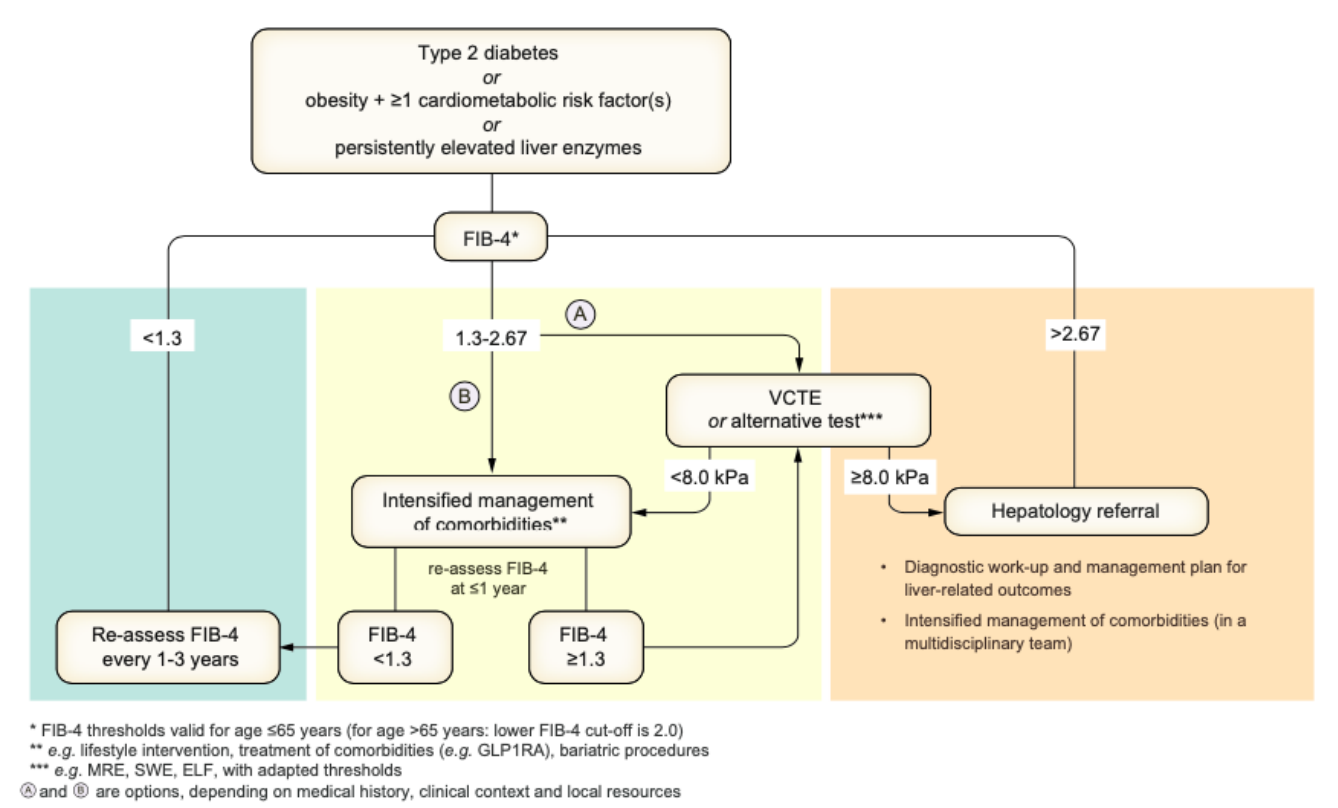
Cusi K et al ADA Consensus MASLD Diabetes Care, 2025

Perché?



Bril F et al Endocrinol Metab Clin N Am 2016

Come? Lo screening



EASL–EASD–EASO
J Hepatol, 2024

Life-style intervention

Crucial but difficult task

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

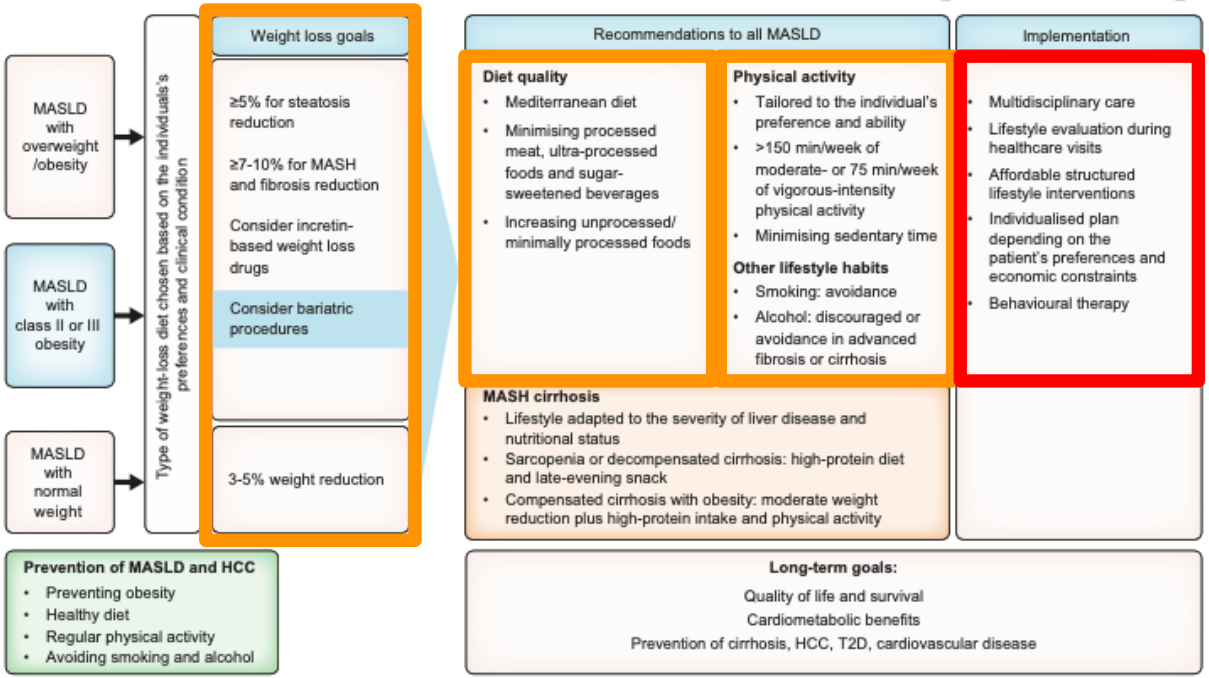


Fig. 3. Lifestyle management algorithm for MASLD. Note: Behavioural therapy includes: self-monitoring, clinicians providing affected individuals with self-efficacy and motivation, setting realistic negotiable goals, and overcoming barriers. Examples of unprocessed/minimally processed foods: vegetables,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

How

Hypocaloric diet

- low-carbohydrate diet
- low-fat diet

appear to be similarly effective in reducing liver lipid content and related biomarkers

EASL/EASD/EASO – J Hepatol, 2024

Mediterranean diet

Why?

- polyphenols
- fiber
- carotenoids
- omega-3 PUFA

Armandi A, Bugianesi E. Eur J Int Med, 2024

Observational studies

the **Mediterranean diet** advocates added value

PREDIMED – N Engl J Med, 2013
corrected and republished 2018

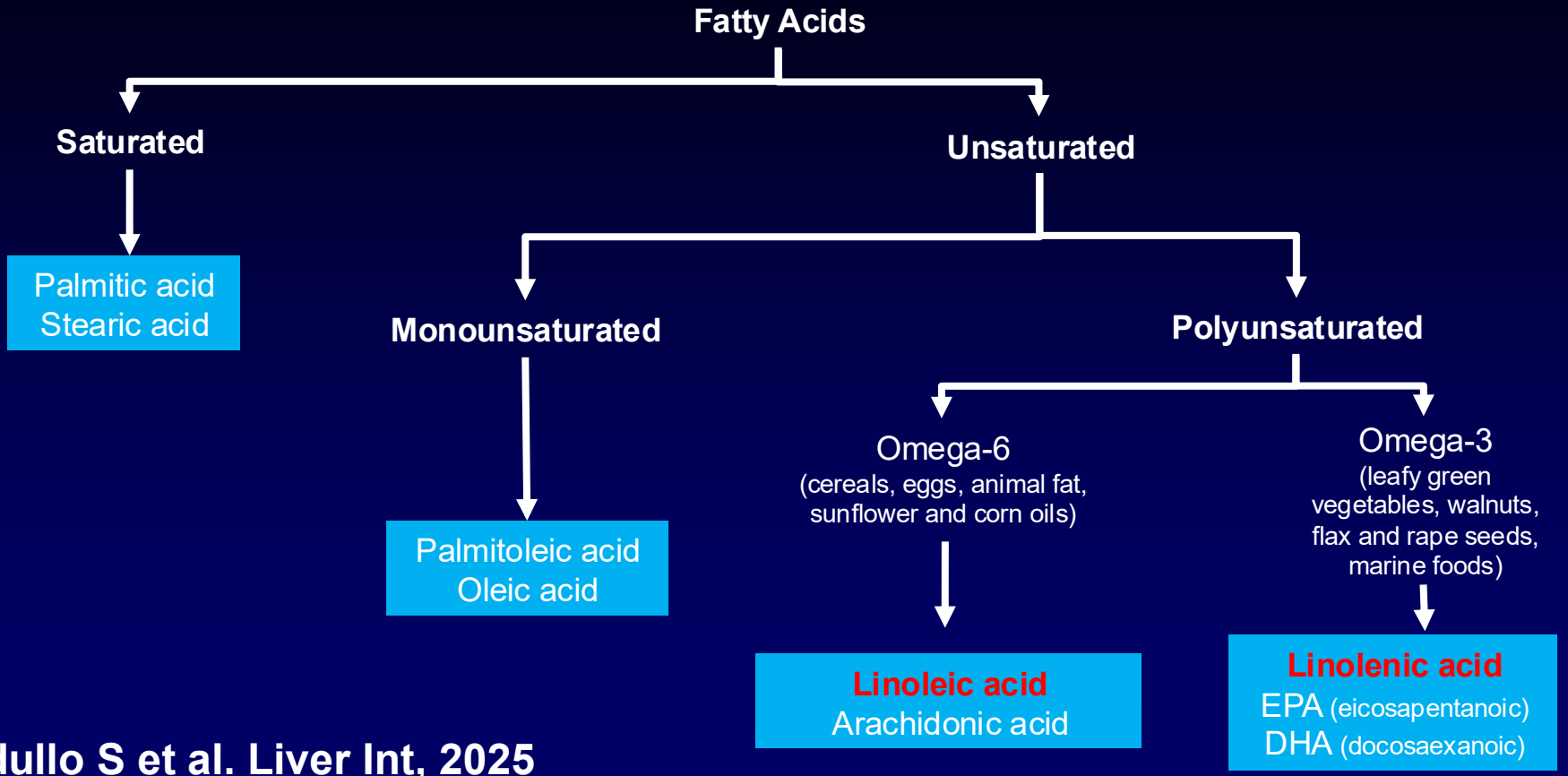
Reduction of

- fructose and refined carbohydrates, especially in soft-drinks (*via* reduction of de-novo lipogenesis),
- saturated fat
- ultra-processed foods
- red and processed meat

all related to MASLD risk (based on epidemiologic association)

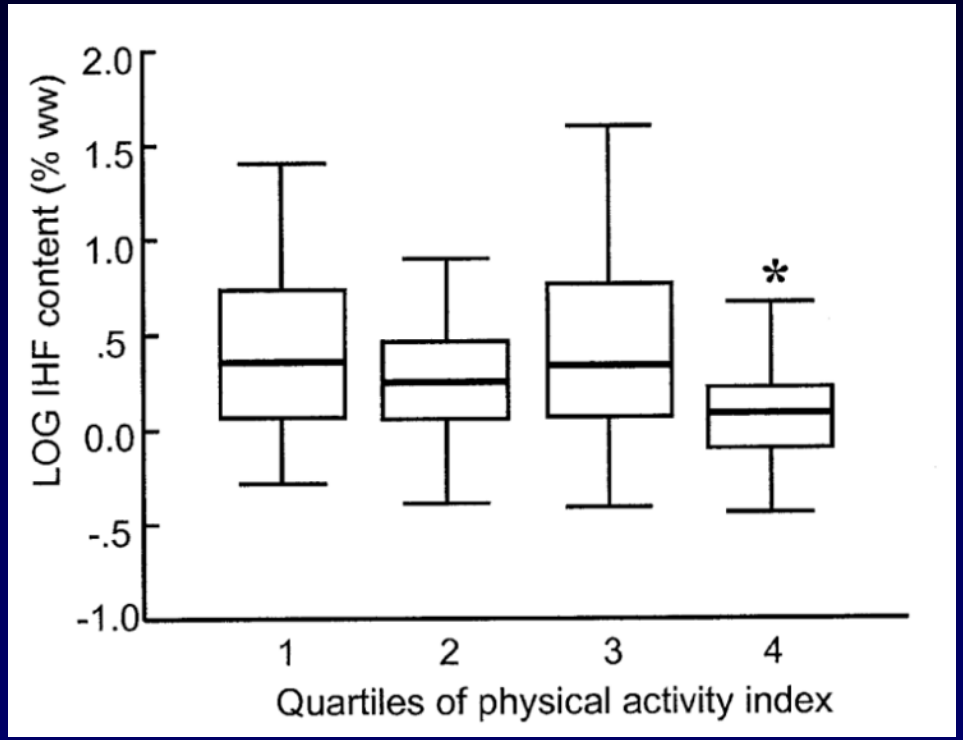
Circulating FA subtypes and MASLD and liver fibrosis

Both esterified and free FAs were measured through GC-MS in the fasting state (≥8 h)



Ciardullo S et al. Liver Int, 2025

Habitual physical activity; retrospective analysis



Based on PAI (physical activity index); self reported questionnaire

- Work
- Leisure time
- Sport

Perseghin G et al Diabetes Care, 2007

Behavior therapy
the Need for a Multi-disciplinary Approach

The favorable effects of lifestyle modifications in MASLD reported in very few studies

But positive results are largely expected

Table 3. Strategies to Engage Patients in Lifestyle Modifications

Communicate empathetically
- Counseling is most effective when a patient feels that physicians understand his/her situation, perspective, and feelings.[62]

Evaluate the pros and cons to change
- Counseling physicians should analyze collaboratively the pros and cons of changing patients' eating and activity habits.[65]
- Change is facilitated by a communication strategy to elicit the person's reasons for and the advantages of change.[66]

Examine the variables maintaining the problematic behavior
- Resistance to change should not be opposed with confrontation, but with a collaborative analysis of the problems that favors the unhealthy behavior.[65]
- In resistant patients, physicians should always think contextually (such as, "What are the reasons for this behavior") and functionally (such as, "What are the consequences of this behavior).[67]

Support self-efficacy
- Self-efficacy refers to a person's belief that he/she is capable of keeping a specific behavior;[68] it plays an important role in achieving health behavior change.[69]
- Initially, self-efficacy is promoted by raising the hope that lifestyle changes can be attained.
- During the program, self-efficacy is promoted by designing an individualized program of eating and physical activity that patients are confident to attain.[16]

Be sensitive to stigma against obese individuals
- Stigma has a negative impact on obese patients' health care experiences and influences their decision to start treatment.[62]
- To reduce stigma, physicians should recognize that obesity is a medical condition not the product of lack of willpower, and treat obese patients with respect and support.[62]

Explain treatment
- The aims, duration, organization procedures and results of lifestyle modification should be detailed using written materials, in order to strengthen the commitments to treatment.[52]
- In reluctant patients it might be helpful to propose treatment as a sort of experiment, with a possible return to the old lifestyle habits in the absence of benefits.[70]

≈

20 years ago

Bellentani S et al
Hepatology, 2008

Diabetes Self-Management Education and Support (DSMES)

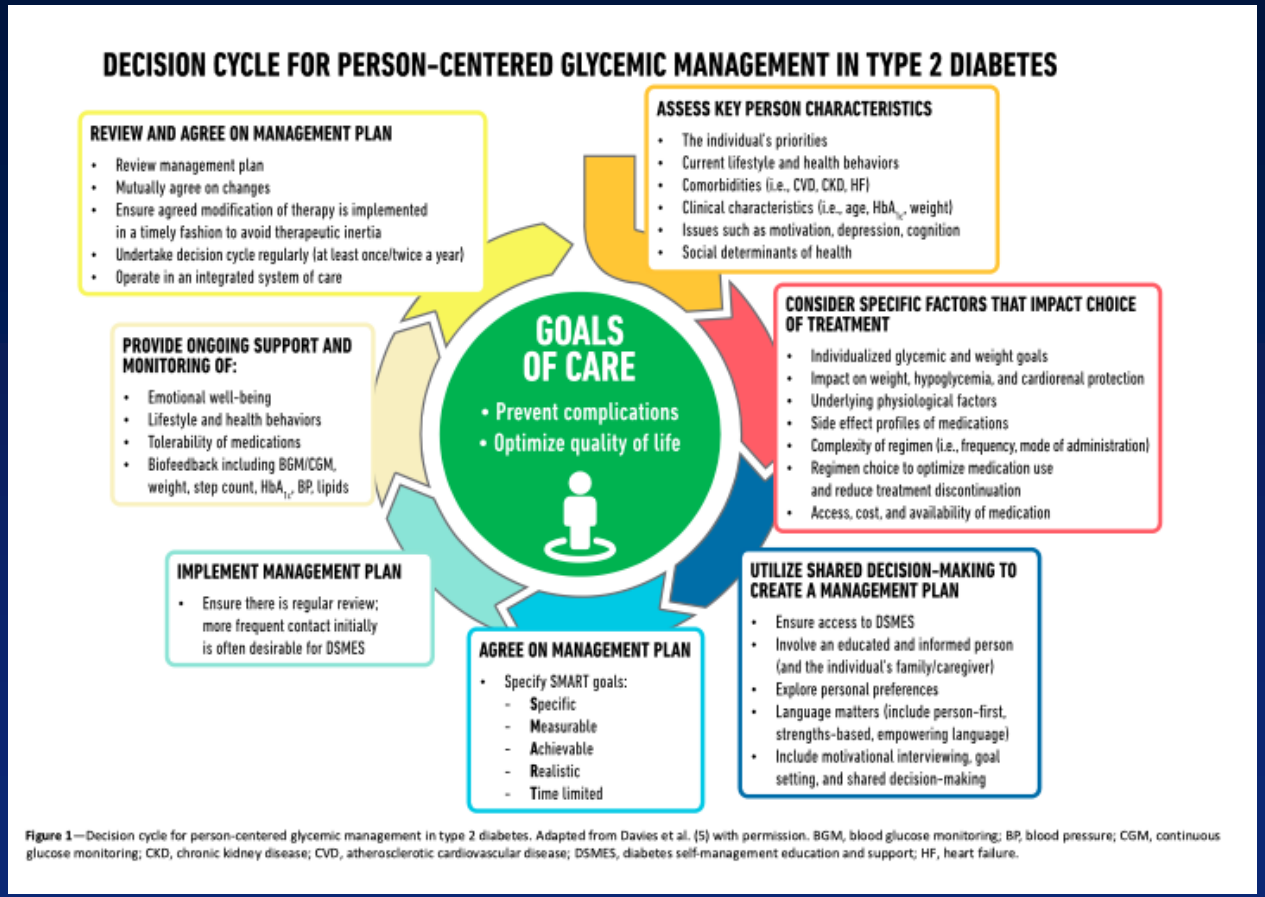


Figure 1—Decision cycle for person-centered glycemic management in type 2 diabetes. Adapted from Davies et al. (5) with permission. BGM, blood glucose monitoring; BP, blood pressure; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CVD, atherosclerotic cardiovascular disease; DSMES, diabetes self-management education and support; HF, heart failure.

Individual sessions

Trained educators

Ongoing Process

- -At onset
- -Annually
- -Onset of complications
- -Transition in life
- -Transition in care

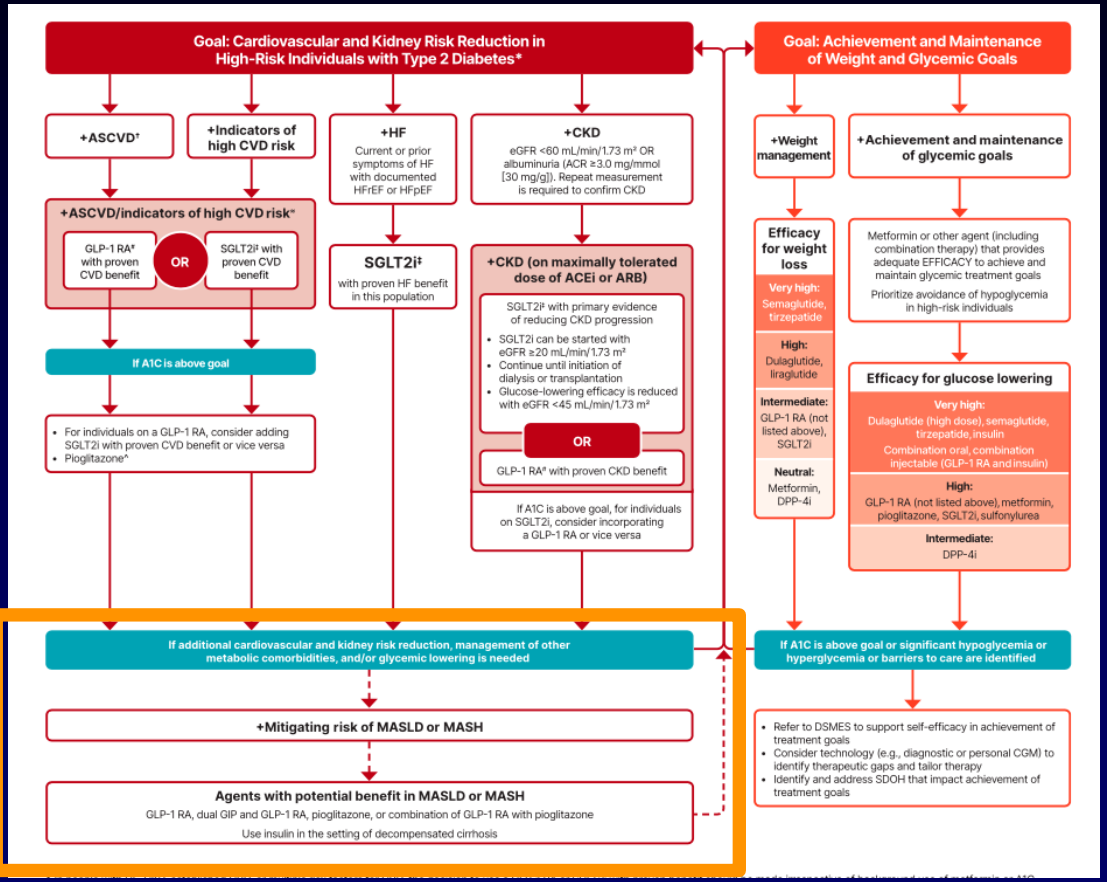
Davies MJ et al
Diabetes Care, 2022

Terapia farmacologica sartoriale

Algoritmo terapeutico ADA 2025

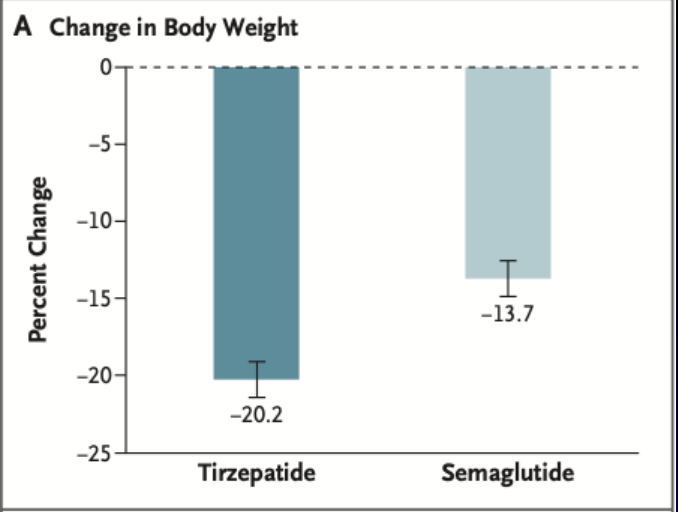
Treat-to-benefit

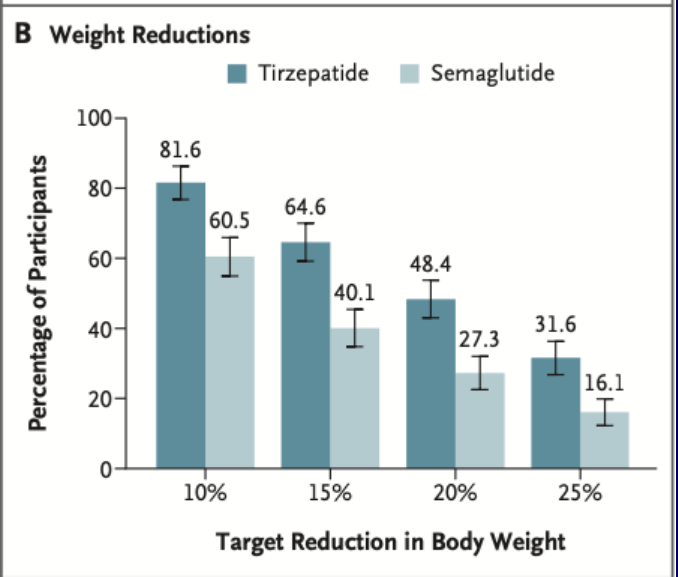
Treat-to-target



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

ADA Standards of Care, Diabetes Care, 2025





No complications

SURMOUNT-5

phase 3b, open-label, controlled trial, adult participants with obesity assigned in a 1:1 ratio to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or the maximum tolerated dose of semaglutide (1.7 mg or 2.4 mg) subcutaneously once weekly

primary end point was the % change in weight from baseline to week 72.

Aronne LJ et al N Engl J Med, 2025

Mechanical Complication: OSAS

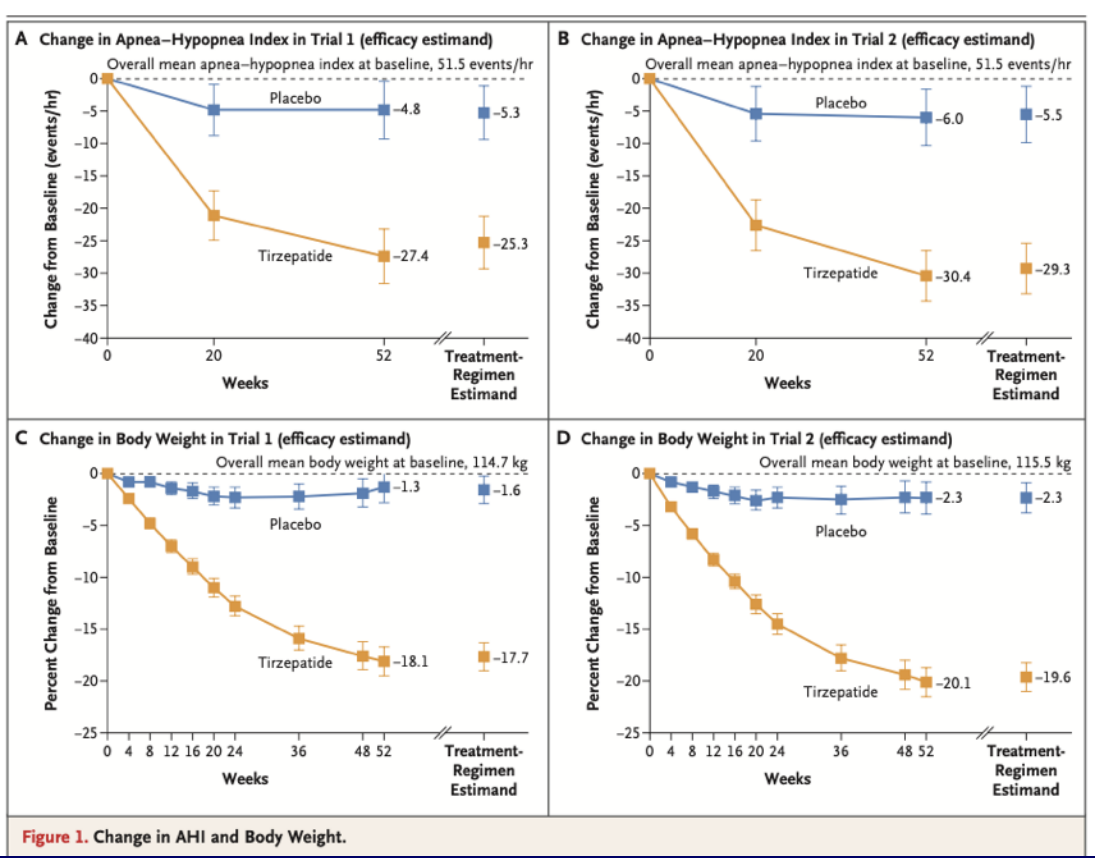


Figure 1. Change in AHI and Body Weight.

SURMOUNT-OSA

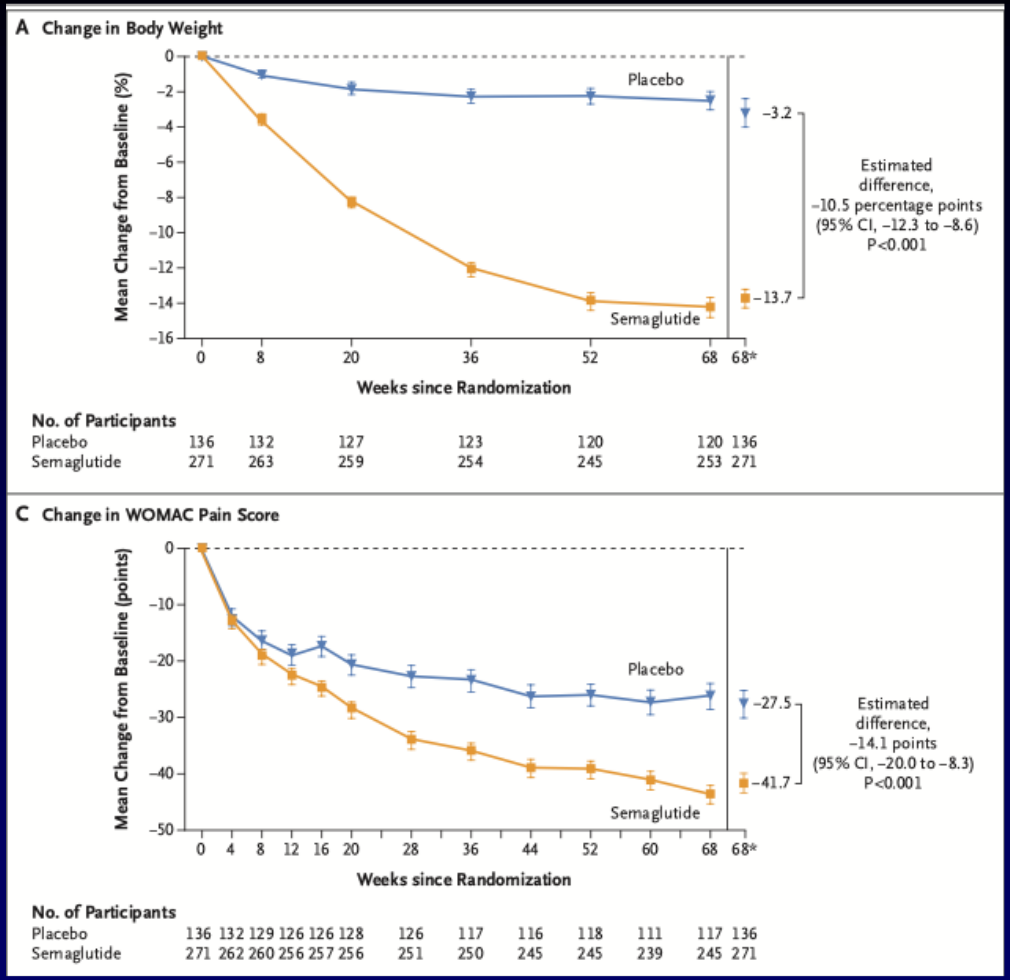
Two phase 3, double-blind, randomized, controlled trials involving adults with moderate-to-severe obstructive sleep apnea and obesity.

- who were not receiving treatment with positive airway pressure (PAP) at baseline
- who were receiving PAP therapy at baseline

maximum tolerated dose of tirzepatide (10 mg or 15 mg) or placebo for 52 weeks.

The **primary end point** was the change in the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) from baseline

Malhotraet A et al N Engl J Med, 2024



Mechanical complication: knee osteoarthritis

STEP-9

68-week, double-blind, randomized, placebo-controlled RCT. Participants with obesity and a clinical and radiologic diagnosis of moderate knee osteoarthritis with at least moderate pain were randomly assigned,

The primary end points were the percentage change in body weight and the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score

A key confirmatory secondary end point was the physical-function score on the 36-Item Short Form Health Survey (SF-36), version 2

Bliddal H et al N Engl J Med, 2024

Sick fat complication: prediabetes

STEP-10

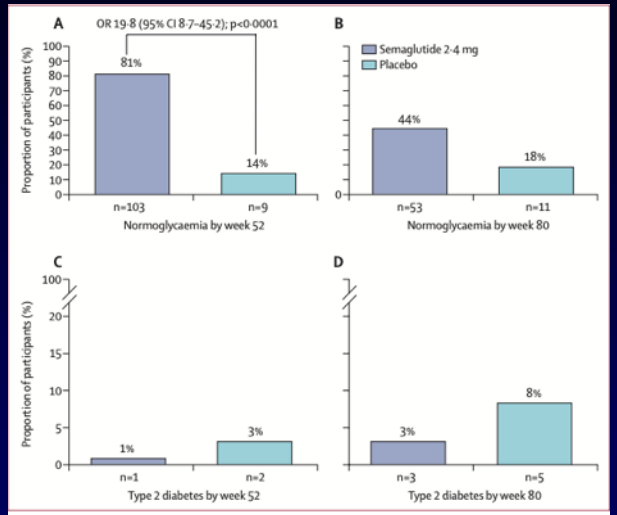
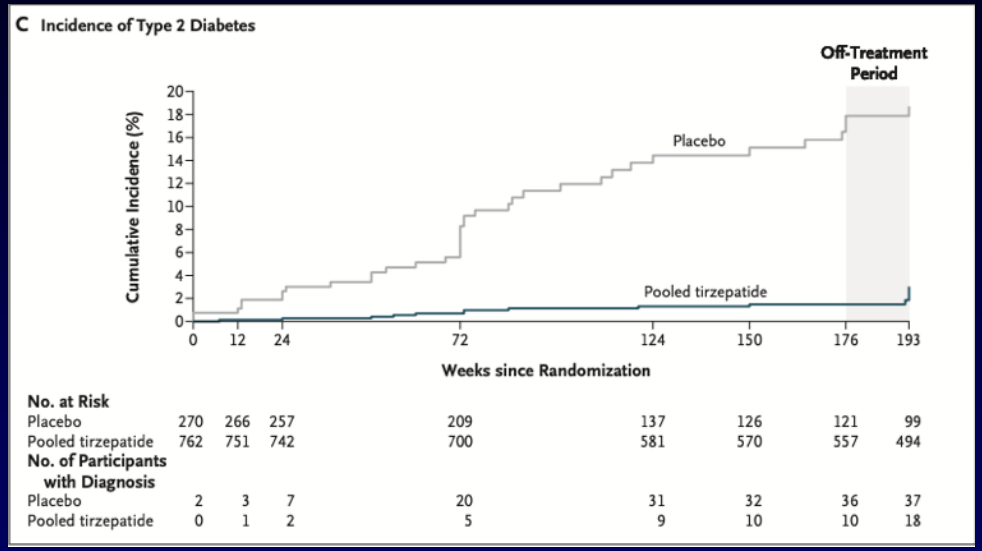


Figure 3: **Proportion of participants who reverted to normoglycaemia or progressed to type 2 diabetes with semaglutide 2·4 mg versus placebo in the full analysis set during the in-trial observation period**
Observed proportions of participants who reverted to normoglycaemia (HbA_{1c} <6·0% [<42 mmol/mol] and FPG <5·5 mmol/L) at week 52 (A; OR is for the treatment policy estimand) and week 80 (B). Observed proportions of who progressed to type 2 diabetes (HbA_{1c} ≥6·5% [≥48 mmol/mol] or FPG ≥7·0 mmol/L, verified with a repeated blood sample within 4 weeks from baseline) at week 52 (C) and week 80 (D). OR for panel A is for the treatment policy estimand. FPG=fasting plasma glucose. OR=odds ratio.

1% vs 3%
OR 19.8; 95% CI 8.7 to 45.2; p<0.0001

McGovan B et al Lancet Diabetol Endocrinol, 2024

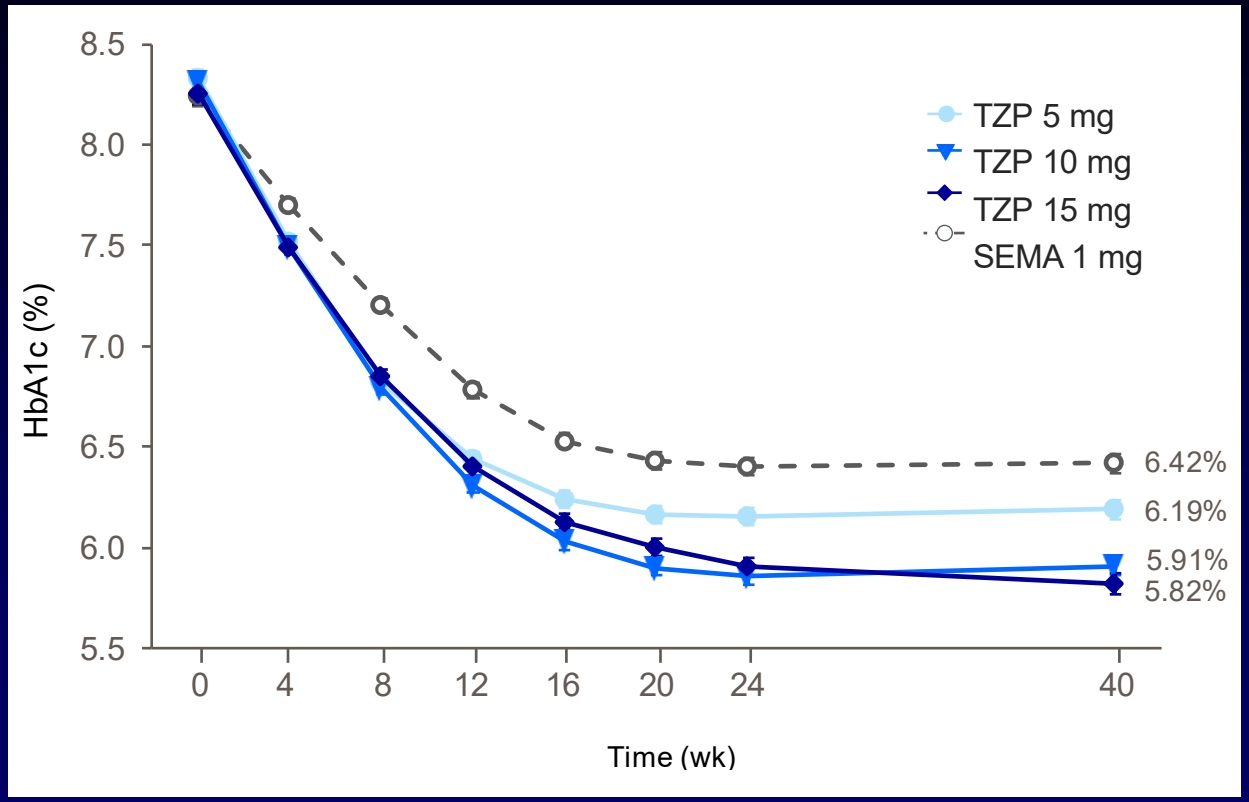
SURMOUNT-1



1.3% vs. 13.3%
HR 0.07; 95% CI: 0.0-0.1; P<0.001

Jastreboff AM et al N Engl J Med, 2024

Sick fat complication: T2DM



SURPASS-2

Frias JP et al N Engl J Med, 2021

Sick fat complication: CVD

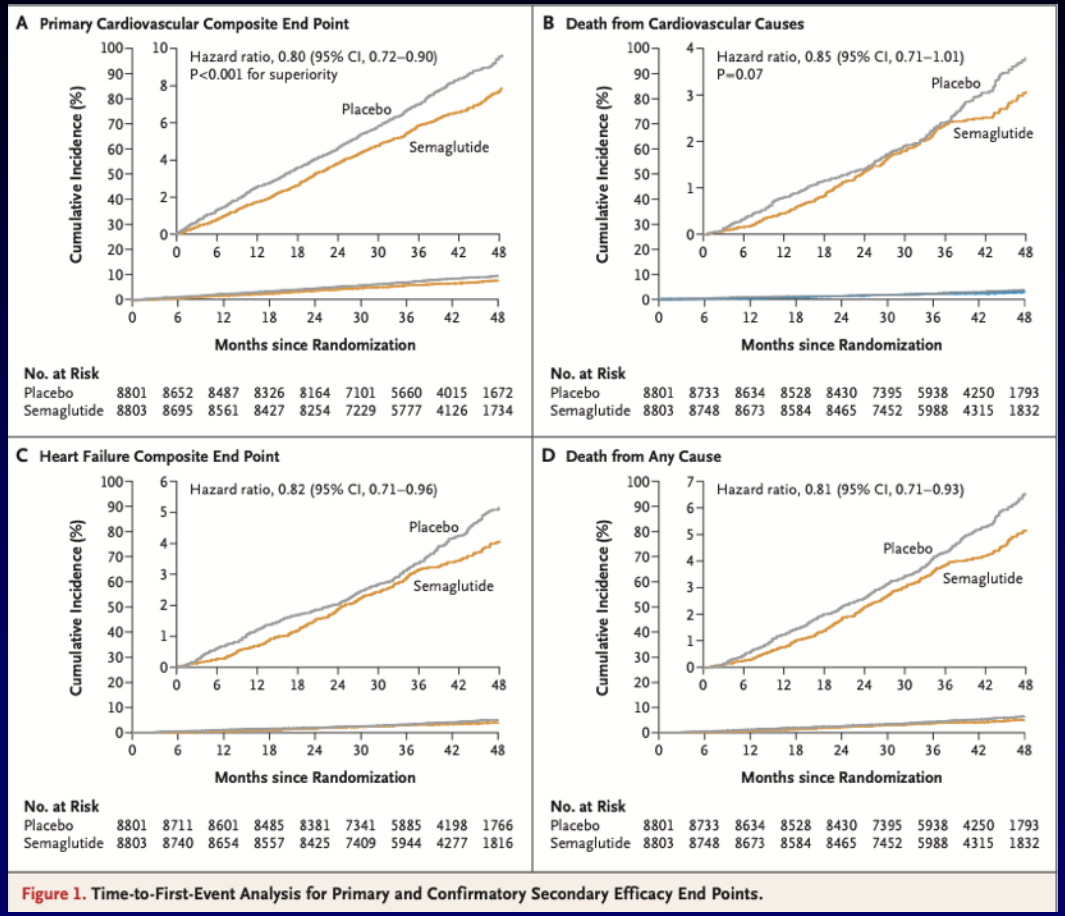


Figure 1. Time-to-First-Event Analysis for Primary and Confirmatory Secondary Efficacy End Points.

SELECT

multicenter, double-blind, placebo-controlled RCT event-driven for superiority

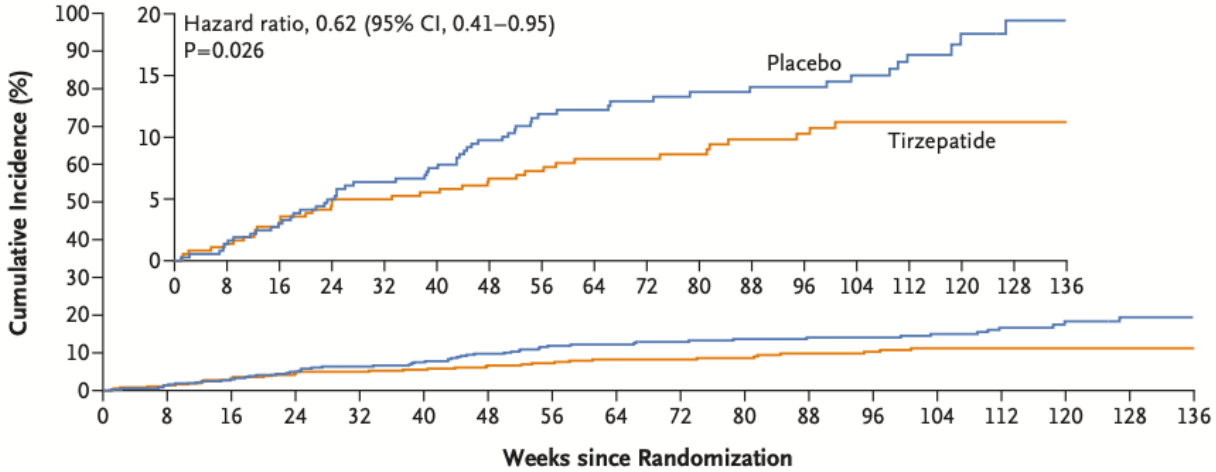
45 years of age or older who had pre-existing CVD and BMI>27 kg/m^2 without diabetes

semaglutide at a dose of 2.4 mg or placebo

The primary end point was composite of death from CVD, nonfatal myocardial infarction, or nonfatal stroke in a time-to-first-event analysis.

Lincoff AM et al N Engl J Med, 2023

Sick fat complication: heart failure



No. at Risk																		
Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45
Tirzepatide	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46

Figure 1. Composite of Death from Cardiovascular Causes or a Worsening Heart-Failure Event.

Shown is the cumulative incidence of death from cardiovascular causes or a worsening heart-failure event (the composite primary end point), assessed in a time-to-first-event analysis, among 364 patients who received tirzepatide and 367 patients who received placebo. The inset shows the same data on an expanded y axis.

SUMMIT

double-blind, randomized RCT
731 patients with HF, and FE: 50%, and BMI > 30 kg/m2

The two primary end points

- composite of CVD death or a worsening heart-failure
- change from baseline to 52 weeks in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS)

Packer M et al N Engl J Med, 2025

Sick fat complication: MASLD-MASH

ESSENCE

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

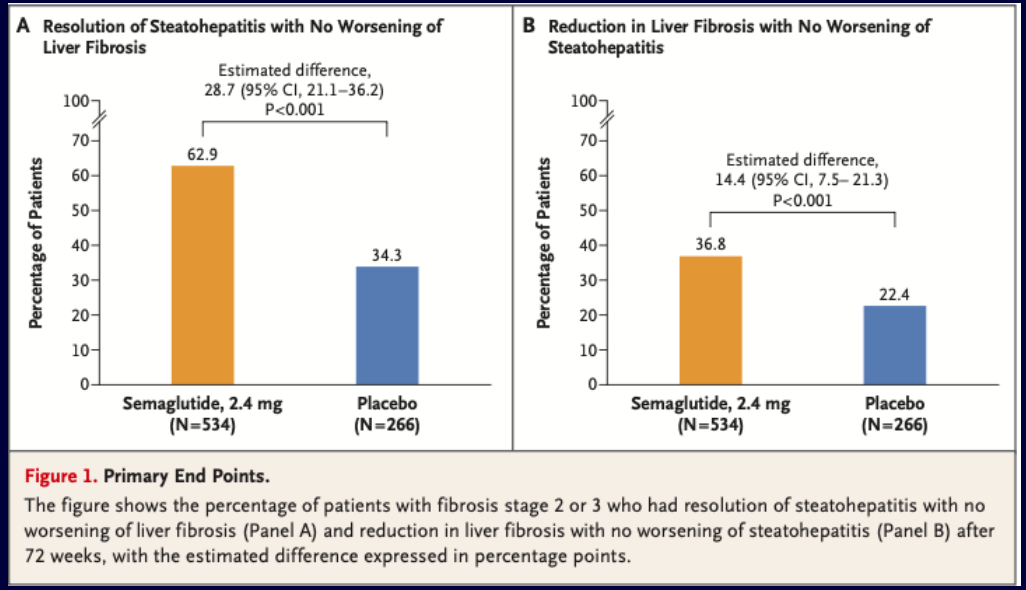
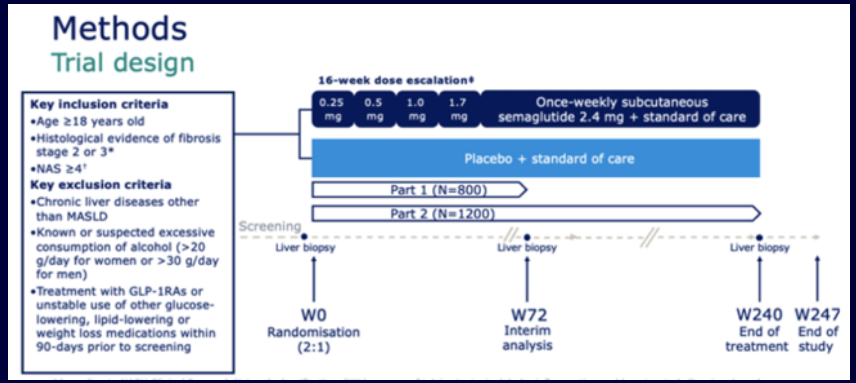


Figure 1. Primary End Points.
The figure shows the percentage of patients with fibrosis stage 2 or 3 who had resolution of steatohepatitis with no worsening of liver fibrosis (Panel A) and reduction in liver fibrosis with no worsening of steatohepatitis (Panel B) after 72 weeks, with the estimated difference expressed in percentage points.

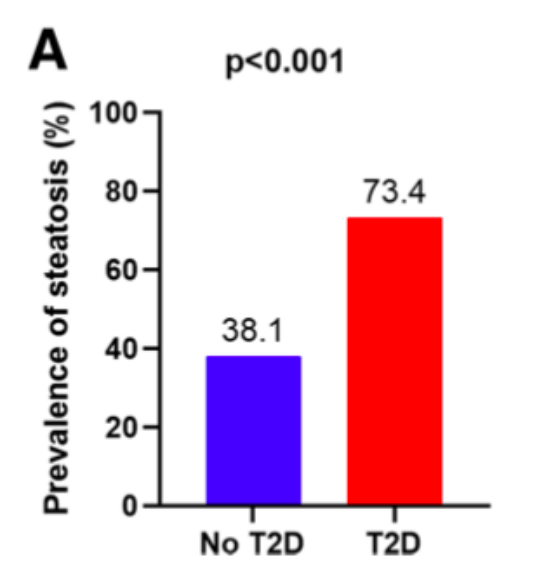


Sanyal A et al N Engl J Med, 2025

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

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

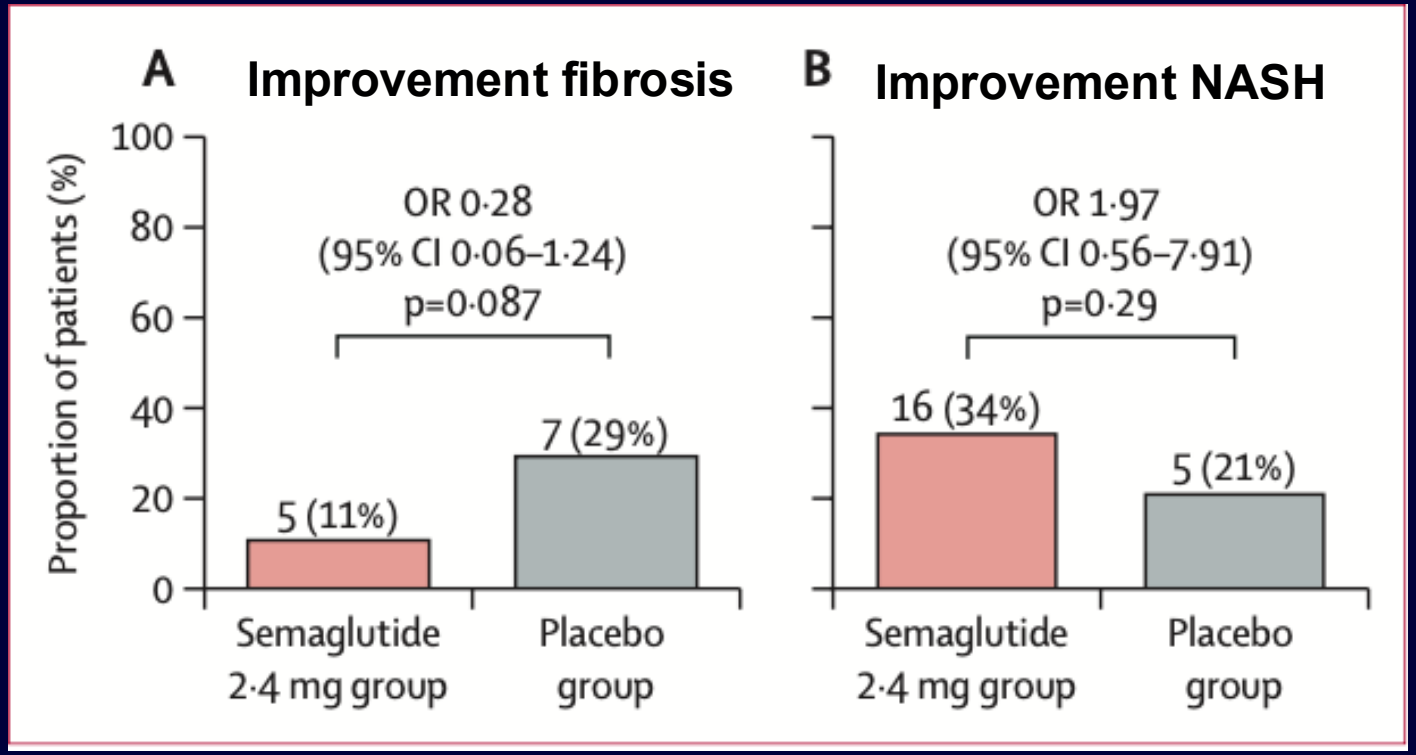
Ciardullo S et al. Diabetes Care, 2024



MASLD/MASH

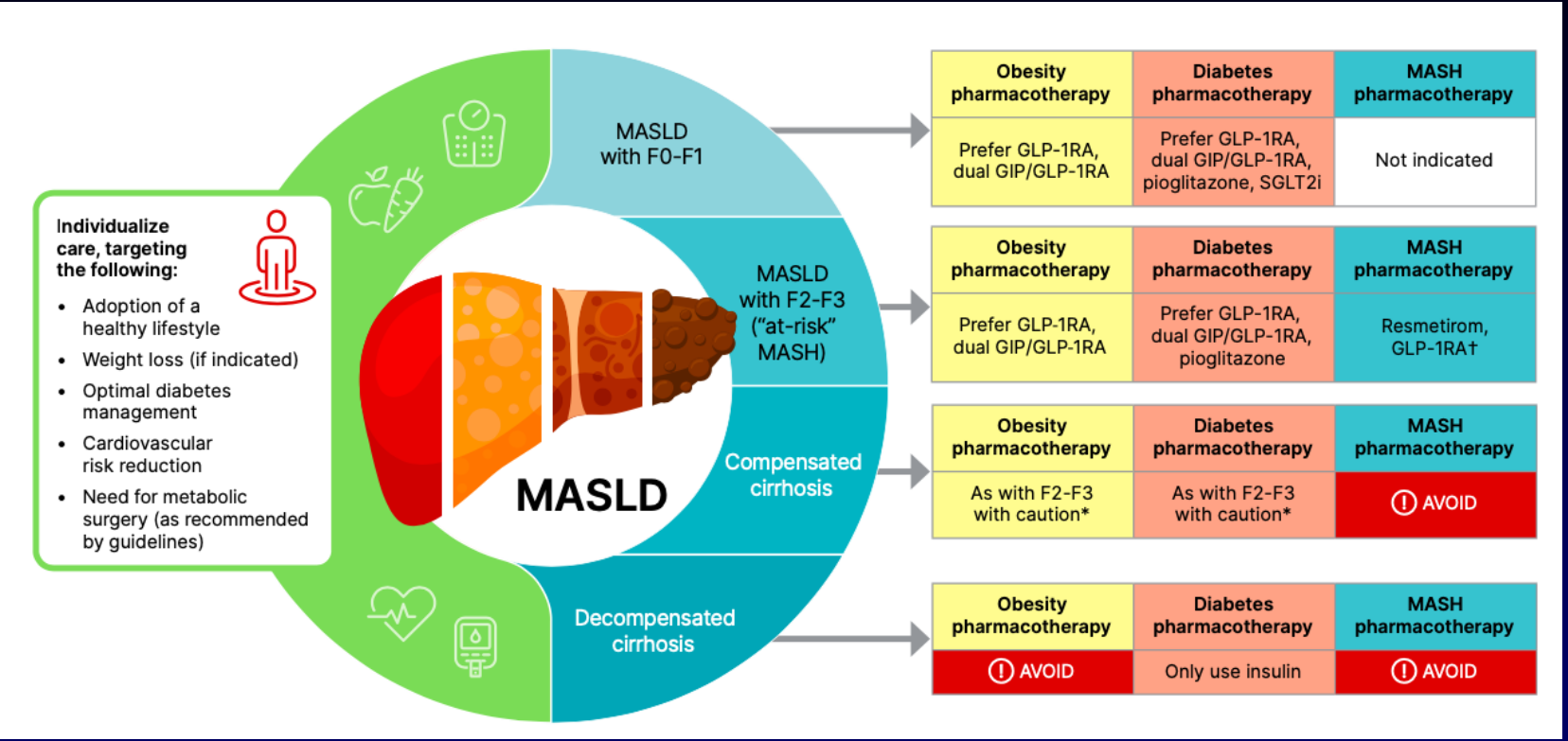
GLP1-RA in compensated cirrhosis (F4) - Semaglutide

Phase 2:
71 patients
48 weeks

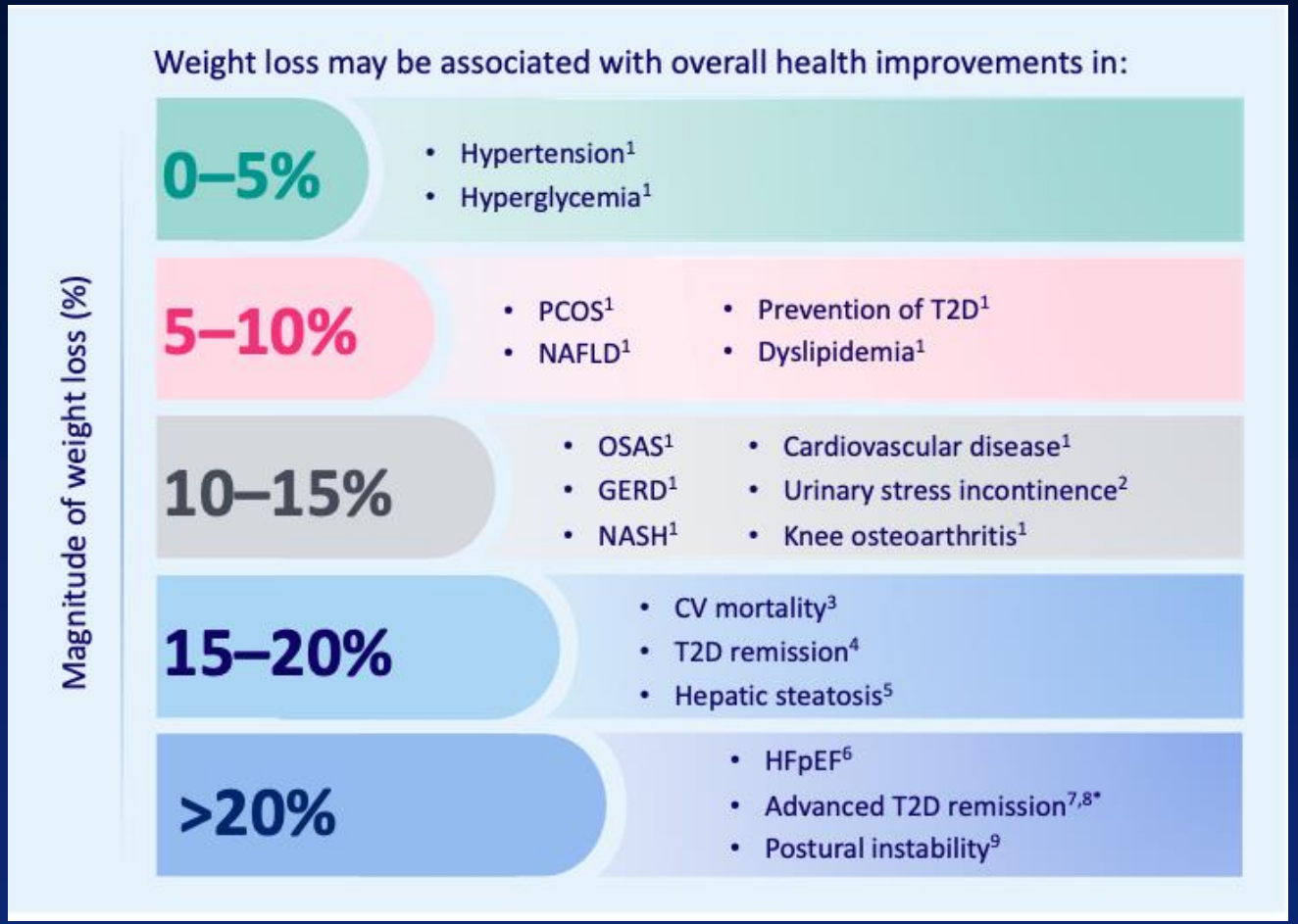


Loomba R et al, Lancet Diabetes Endocrinol, 2023

Anti metabolic & anti fibrotic therapy



Cusi K et al ADA Consensus MASLD Diabetes Care, 2025



Bariatric surgery
GLP1 & GLP1/GIP-RA

Look Ahead
DiRECT

evidences suggesting that

Greater weight loss = better liver health outcomes

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Lucia Mastria

Clinical Psychology
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Adm Office
Anna Maria Costa
Monica Cambiaghi

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Giovanna Castoldi

Gastroenterologia
Pietro Invernizzi
Marco Carbone

Department of Statistics
UNIMIB (Motive Project PRIN2017)
Federico Rea
Matteo Compagnoni
Laura Savarè
Giovanni Corrao

Hypertension Unit
UNIMIB
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Giuseppe Mancia

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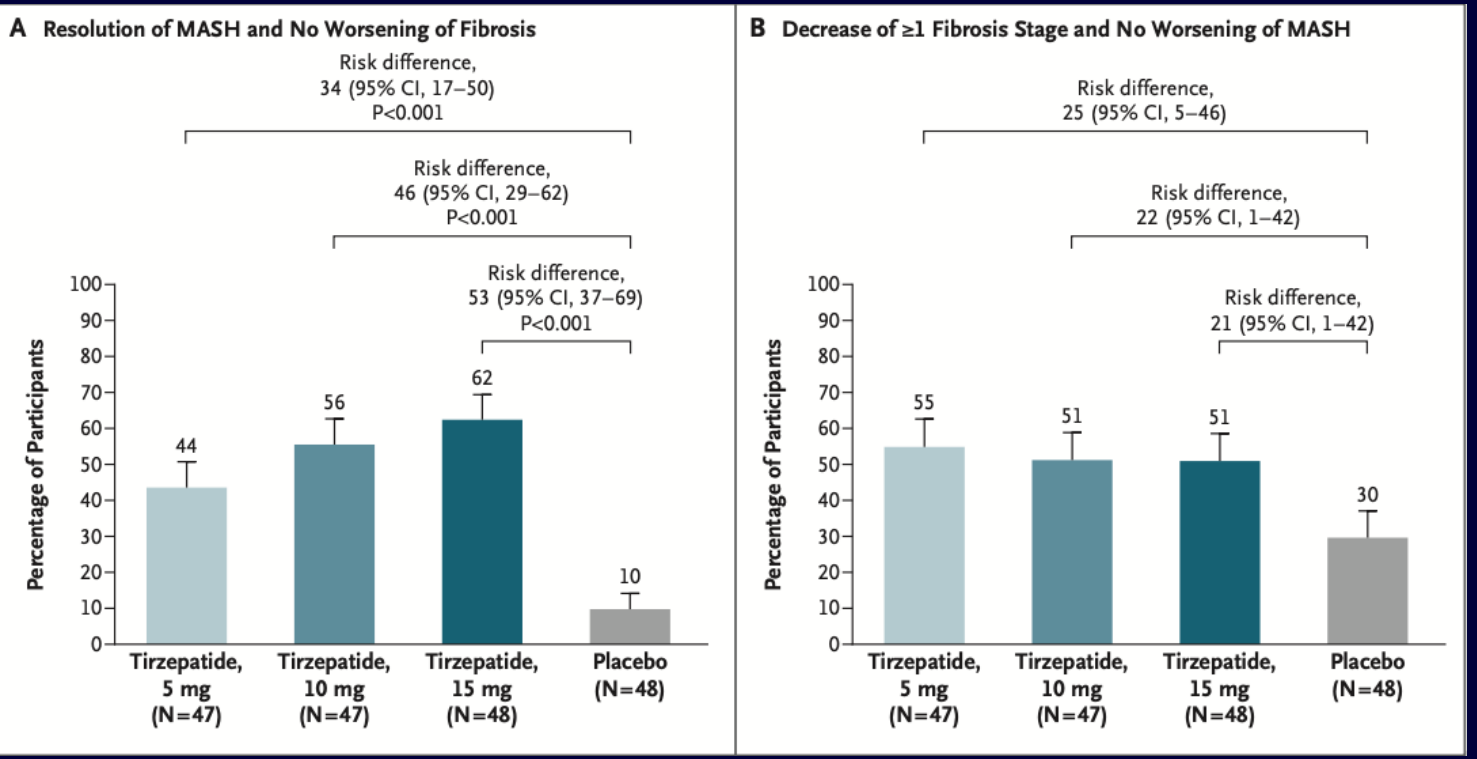
Stefano Volpato (UNIFE)
Angelo Scuteri (UNICA)

UNIVR
Alessandro Mantovani
Giovanni Targher

Dual-agonists

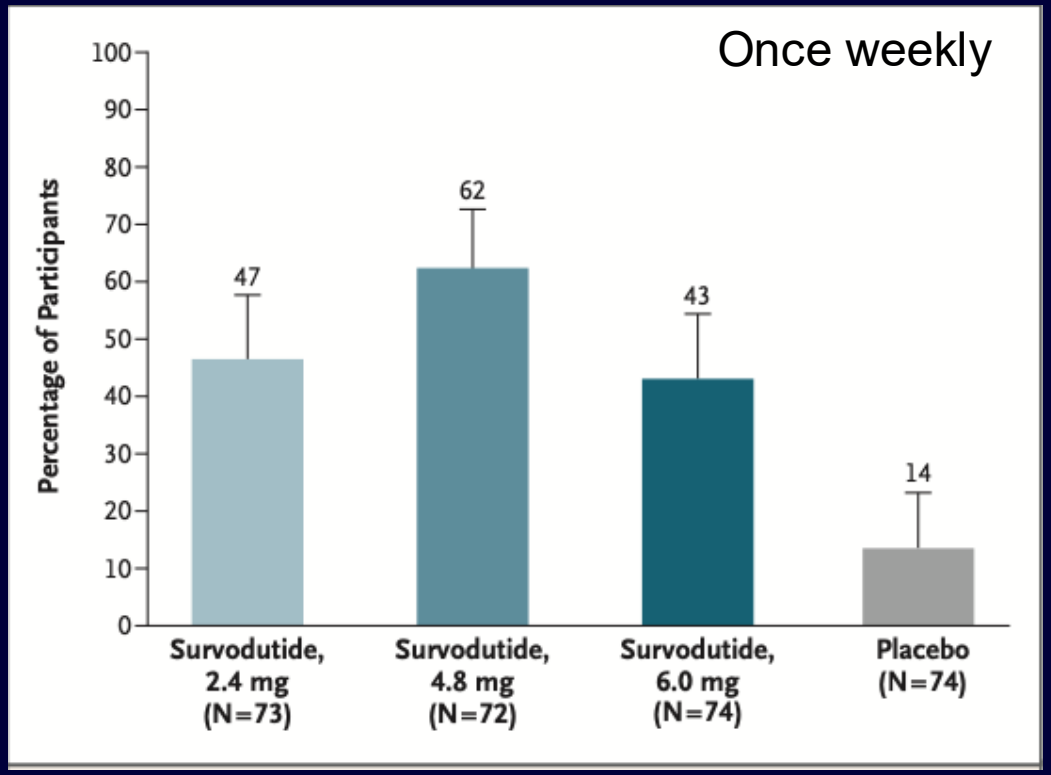
GLP1/GIP RA: Tirzepatide



Phase 2:
190 pats
54 weeks

Loomba R et al, N Engl J Med, 2024

GLP1/Glucagon RA: Survodutide

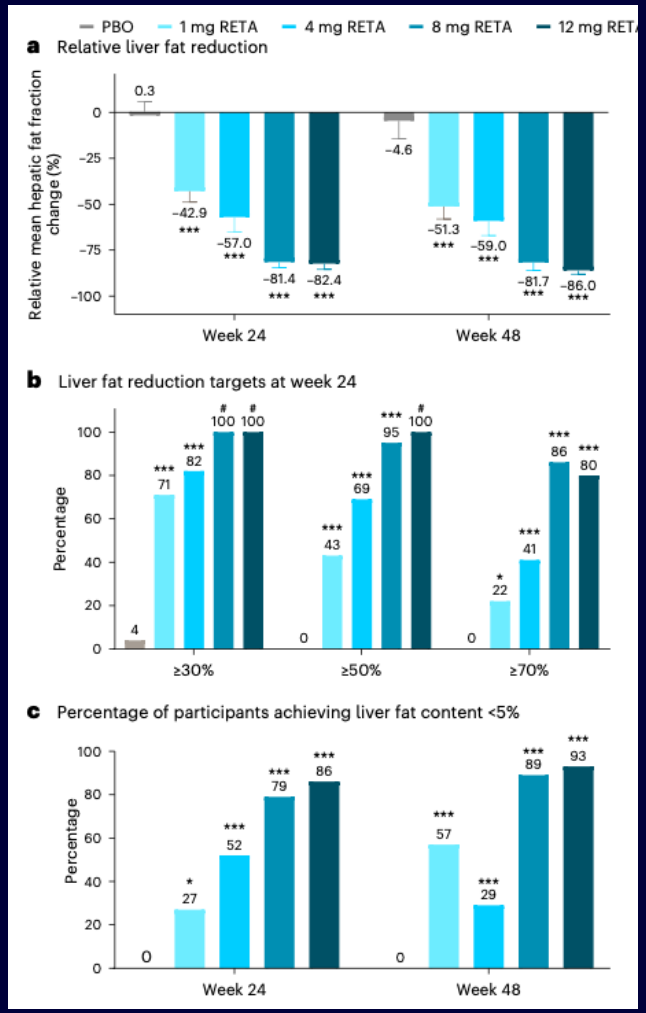


Phase-2, 48 weeks
Histologic improvement in MASH, with no worsening of fibrosis

Sanyal AJ et al, N Engl J Med, 2024

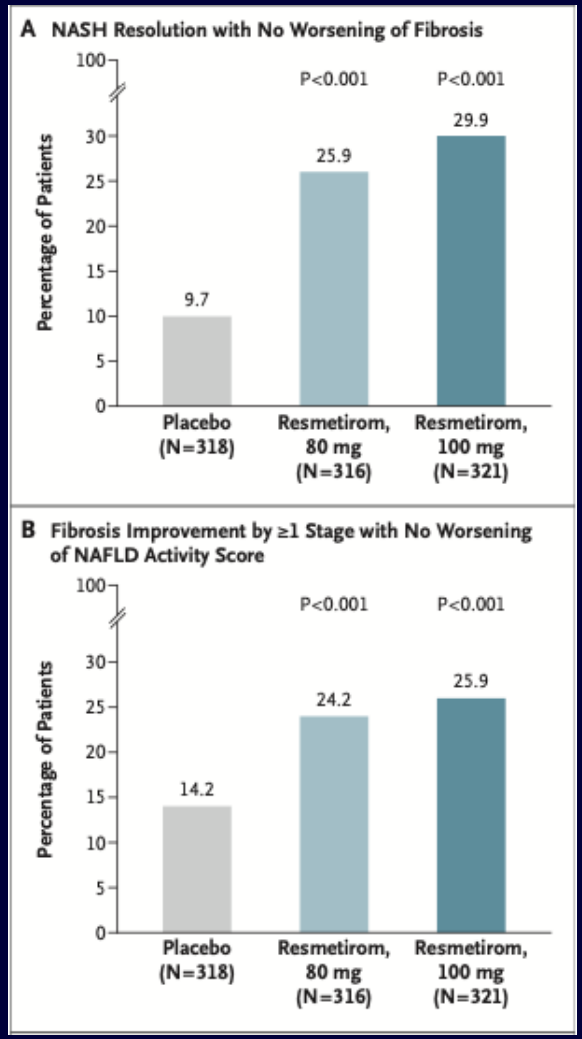
Triple-agonists

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

Clinical Practice Guidelines

JOURNAL
OF HEPATOLOGY

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

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO)

Life-style intervention
5 Questions + 1

Journal of Hepatology, September 2024; 81: 492–542

Q1

In adults with MASLD,
what is the efficacy of dietary and behavioural therapy-induced weight loss on

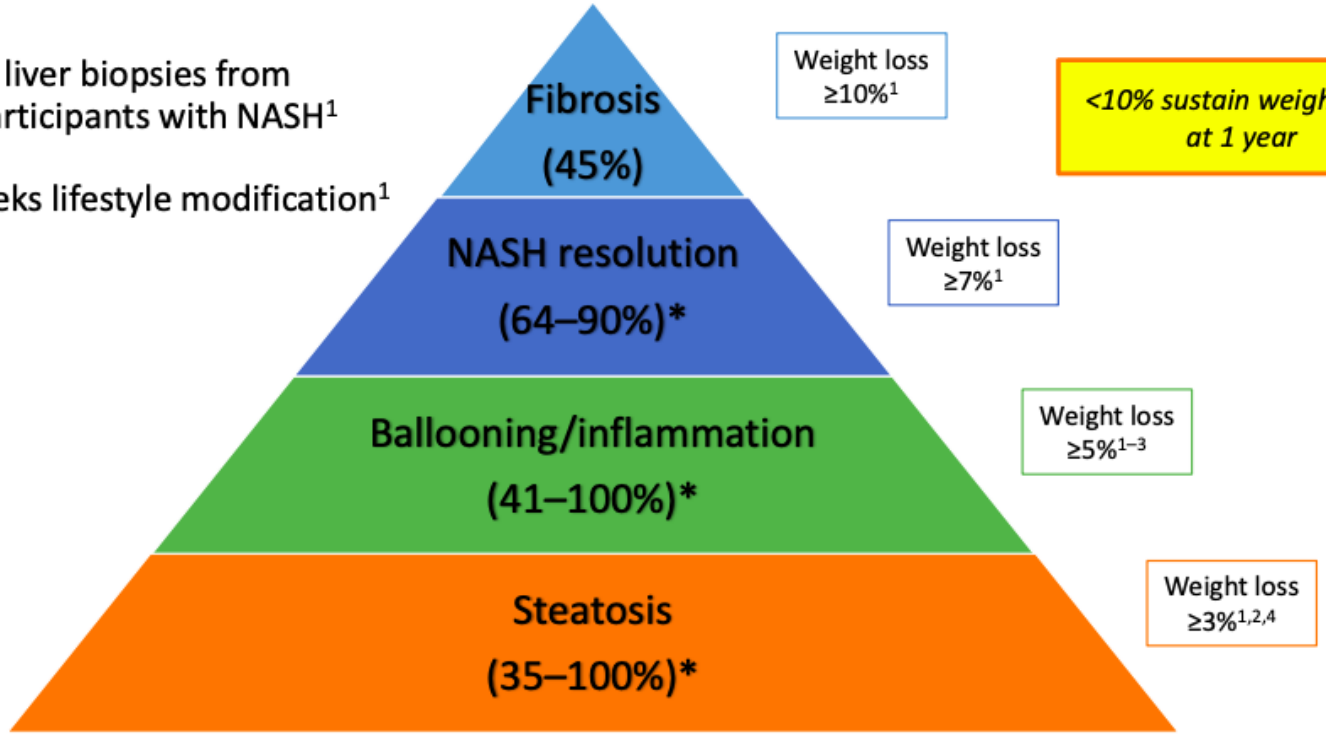
- histologically
- non-invasively assessed liver damage/fibrosis
- liver related outcomes

compared with no intervention?

EASL/EASD/EASO – J Hepatol, 2024

Lifestyle Modification and Histology in NAFLD

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



Vilar-Gomez E et al Gastroenterology, 2015

Limitations

- Short duration of intervention

- Lack of hard liver-related outcomes

In a Cochrane systematic review of RCTs in people with MASLD, with follow-up periods of 2–24 months, data were sparse regarding the effects of lifestyle interventions on any clinical outcome (death, liver-related complications, and liver cancer)

- Time-restricted eating: very little evidence for a beneficial effect vs. regular caloric restriction on hepatic lipid content in individuals with MASLD

EASL/EASD/EASO – J Hepatol, 2024

Q2

In adults with MASLD
is changing diet quality effective in reducing

- histologically
- non-invasively assessed liver damage/fibrosis
- liver-related outcomes

compared with no intervention?

EASL/EASD/EASO – J Hepatol, 2024

Q3

In adults with MASLD
are physical activity and exercise effective at reducing

- histologically
- non-invasively assessed liver damage/fibrosis
- liver-related outcomes compared

with no intervention?

EASL/EASD/EASO – J Hepatol, 2024

RCTs

- aerobic training
- resistance training
- high-intensity interval training
- combinations

With varying frequency and length of sessions and intensities

Effective for steatosis reduction
No data for individuals with fibrosis

EASL/EASD/EASO – J Hepatol, 2024

Q4

In adults with MASLD who are normal weight
are diet and exercise interventions effective in reducing

- histologically
- non-invasively assessed liver damage/fibrosis
- liver related outcomes

in comparison with no intervention?

EASL/EASD/EASO – J Hepatol, 2024

Few, but interesting data

In an RCT of a 12-month lifestyle intervention programme, a 3-5% weight reduction led to remission of MASLD (1H-MRS) among 50% of the individuals without obesity.

Individuals defined as non-obese were more likely than individuals with obesity to maintain weight reduction and normal liver enzymes over long-term (6-year) follow-up

In a large cohort study that included 2,383 normal-weight adults with MASLD, weight reduction over a median follow-up of 3 years was associated with MASLD resolution (measured by abdominal ultrasound) in a dose-dependent manner

Wong VW et al, J Hepatol 2018
Sinn DH et al, Eur J Gastroenterol Hepatol 2021

Q5

In adults with MASLD, are nutraceuticals (food supplements, herbal products, gut microbiota-modifying agents) effective to reduce

- Histologically
- non-invasively assessed liver damage/fibrosis
- liver-related outcomes compared

with no intervention?

EASL/EASD/EASO – J Hepatol, 2024

Observational

Microbiome-centred therapies such as engineered bacteria, postbiotics, and phages have mainly been tested in preclinical models

Coffee consumption – caffeinated or not – has been shown to have a protective association with MASLD (fibrosis > steatosis) in several observational studies of varying quality

Q6 - End-stage liver disease?

Malnutrition and sarcopenia (a progressive decline in skeletal muscle mass and function) are prevalent, especially if MASH-related

Intervention

- high-calorie (35 kcal/kg of body weight/day)
- protein-rich (1.2–1.5 g/kg of body weight/day rich in BCAA)
- snack late evening (to prevent muscle breakdown during prolonged overnight fasting)

- nutritional status and sarcopenia
- hepatic encephalopathy
- survival
- QoL

EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol, 2019

Critical topics

- Cultural
- Infrastructures
- Value

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Clinical Psychology
Simonetta Sarro

Data Manager
Guido Lattuada

Adm Office
Anna Maria Costa
Monica Cambiaghi

H San Gerardo
Giovanna Castoldi

Gastroenterologia
Pietro Invernizzi
Marco Carbone

Department of Statistics
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Federico Rea
Matteo Compagnoni
Laura Savarè
Giovanni Corrao

Hypertension Unit
UNIMIB
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