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Società Italiana di Diabetologia
Con il patrocinio di
Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento
OMCeO TRENTO
UNIVERSITÀ DI TRENTO
UNIVERSITÀ di VERONA
Facoltà di MEDICINA E CHIRURGIA
CONVEGNO SID
VENETO - TRENTINO ALTO ADIGE
Nuove opportunità terapeutiche e impatto sugli ENDPOINT EPATICI, CARDIOVASCOLARI e RENALI nel DIABETE TIPO 2
4 OTTOBRE 2025
TRENTO, Grand Hotel Trento

Trattamento Farmacologico della MASLD

(Metabolic Dysfunction-Associated Steatotic Liver Disease)

Giovanni Targher

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Convegno SID, Trento 4 ottobre 2025

Dichiarazione di Potenziali Conflitti di Interesse

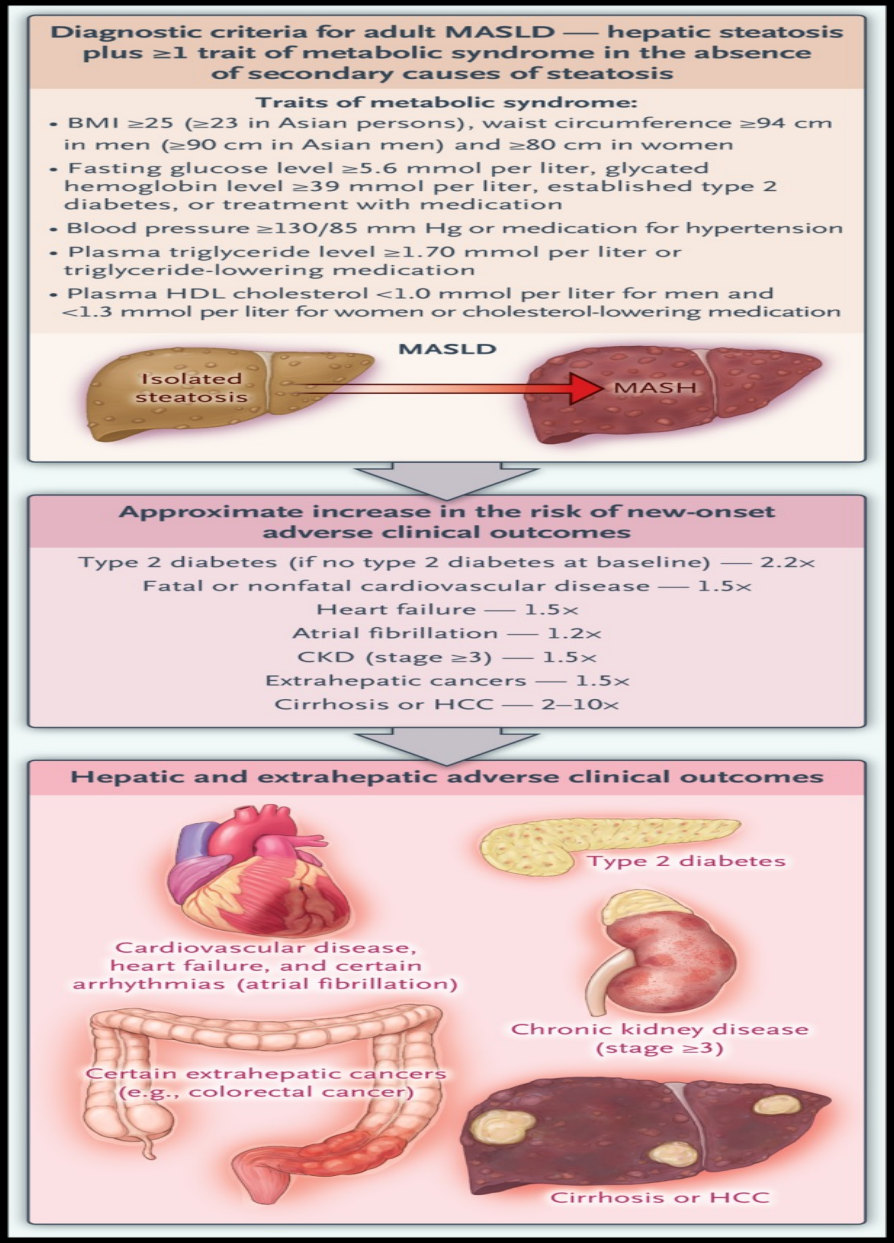
Il sottoscritto **Prof. Giovanni Targher**

ai sensi dell'art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM,

dichiara che di non aver ricevuto negli ultimi due anni compensi e/o finanziamenti da Aziende Farmaceutiche o Diagnostiche.

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

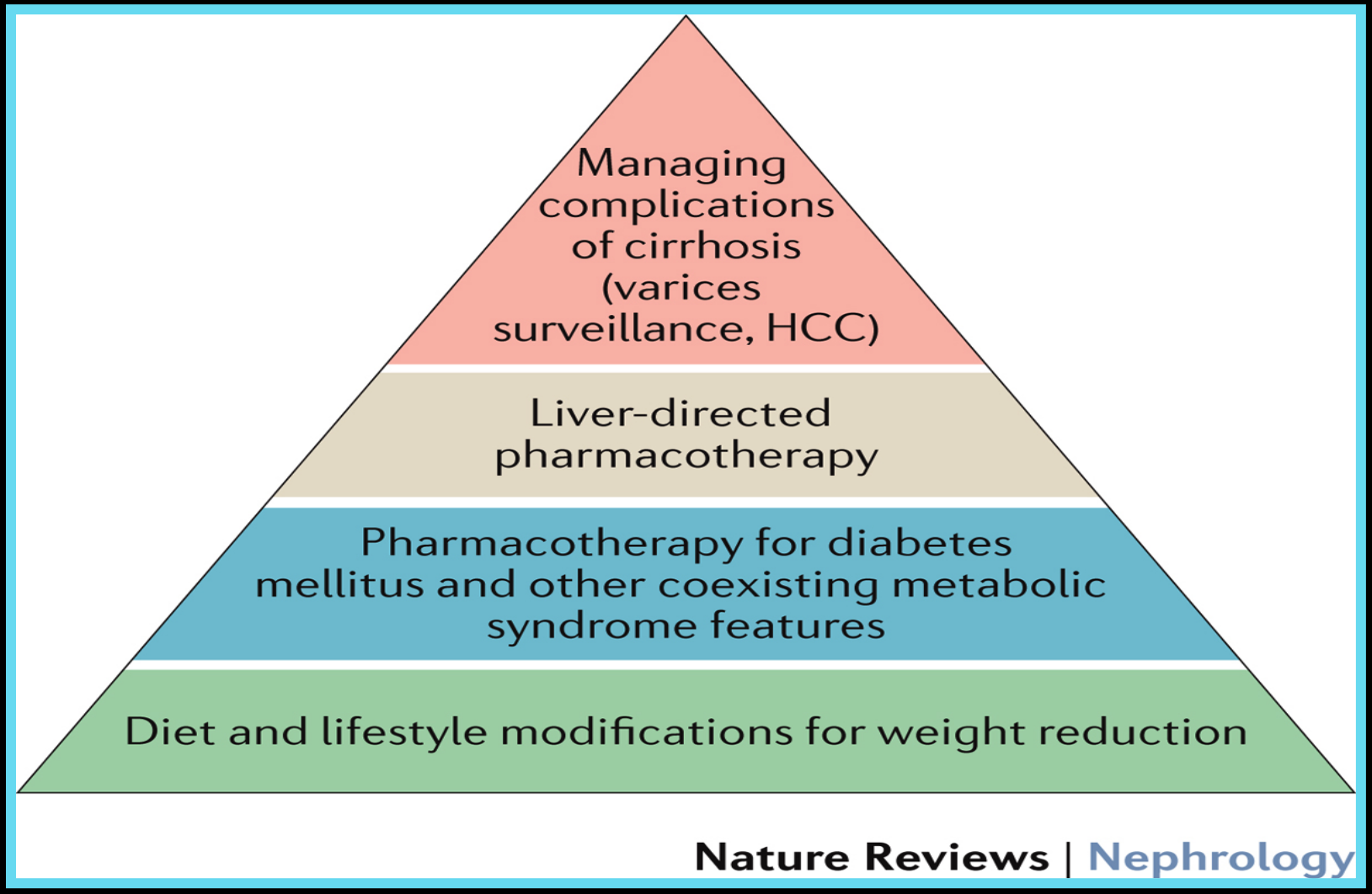
Key Hepatic and Extrahepatic Clinical Outcomes of MASLD



Targher G et al. *N Engl J Med.* 2025; 393: 683-698.

The NEW ENGLAND JOURNAL of MEDICINE

Management and therapeutic strategies for MASLD in patients with T2DM



Targher G, et al. *Nat Rev Nephrol.* 2017; 13: 297-310.

NAFLD Treatment: Impact of Diet and Lifestyle Changes on Liver Histology

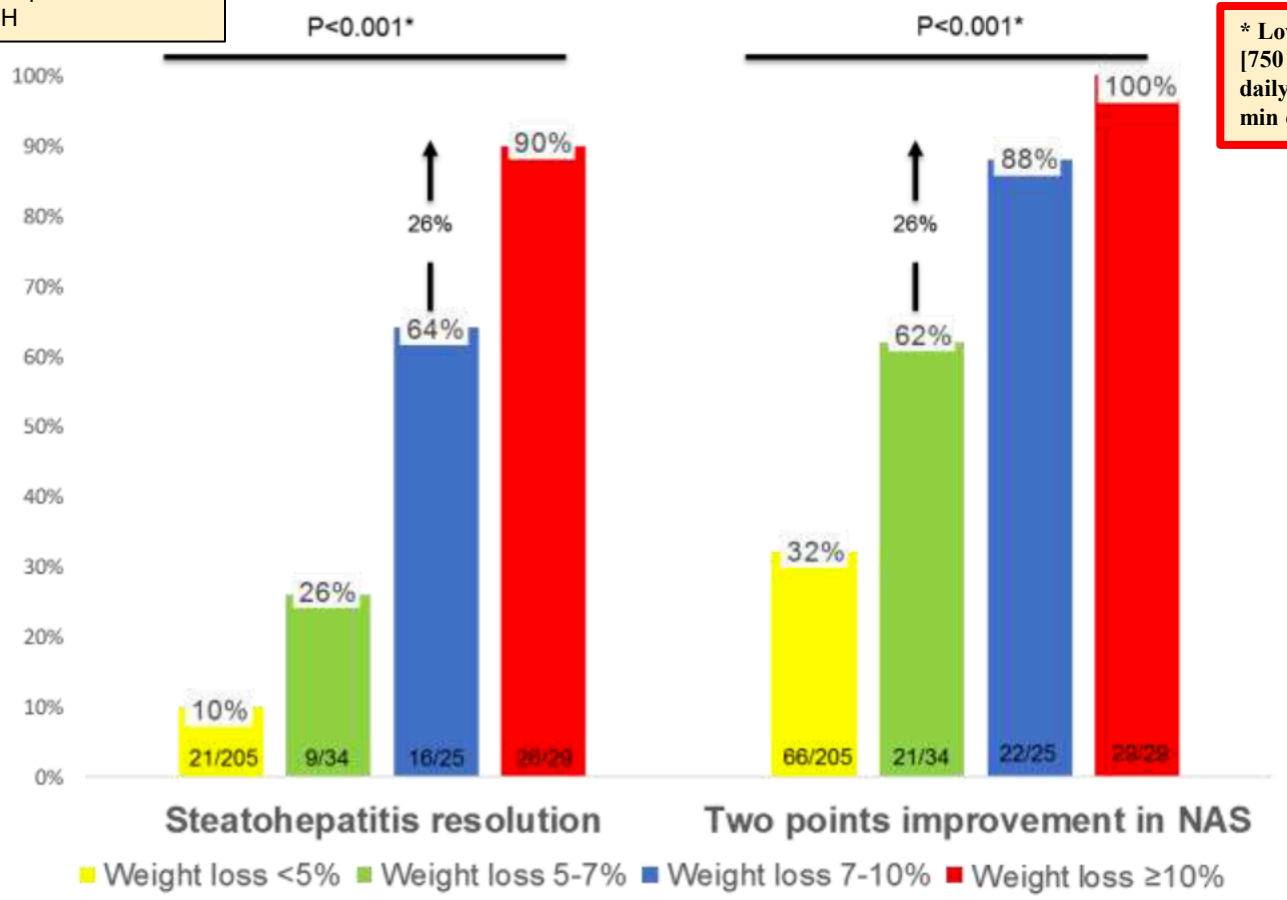
n=293 NASH ± fibrosis

293 overweight or obese patients with biopsy-confirmed MASH

low-fat hypocaloric diet, physical activity*

liver biospy after 52 weeks (n=261)

* Low-fat hypocaloric diet [750 kcal/day less than the daily energy need] and 200 min of weekly walking



Vilar-Gomez E et al. *Gastroenterology*. 2015; 149: 367-378.

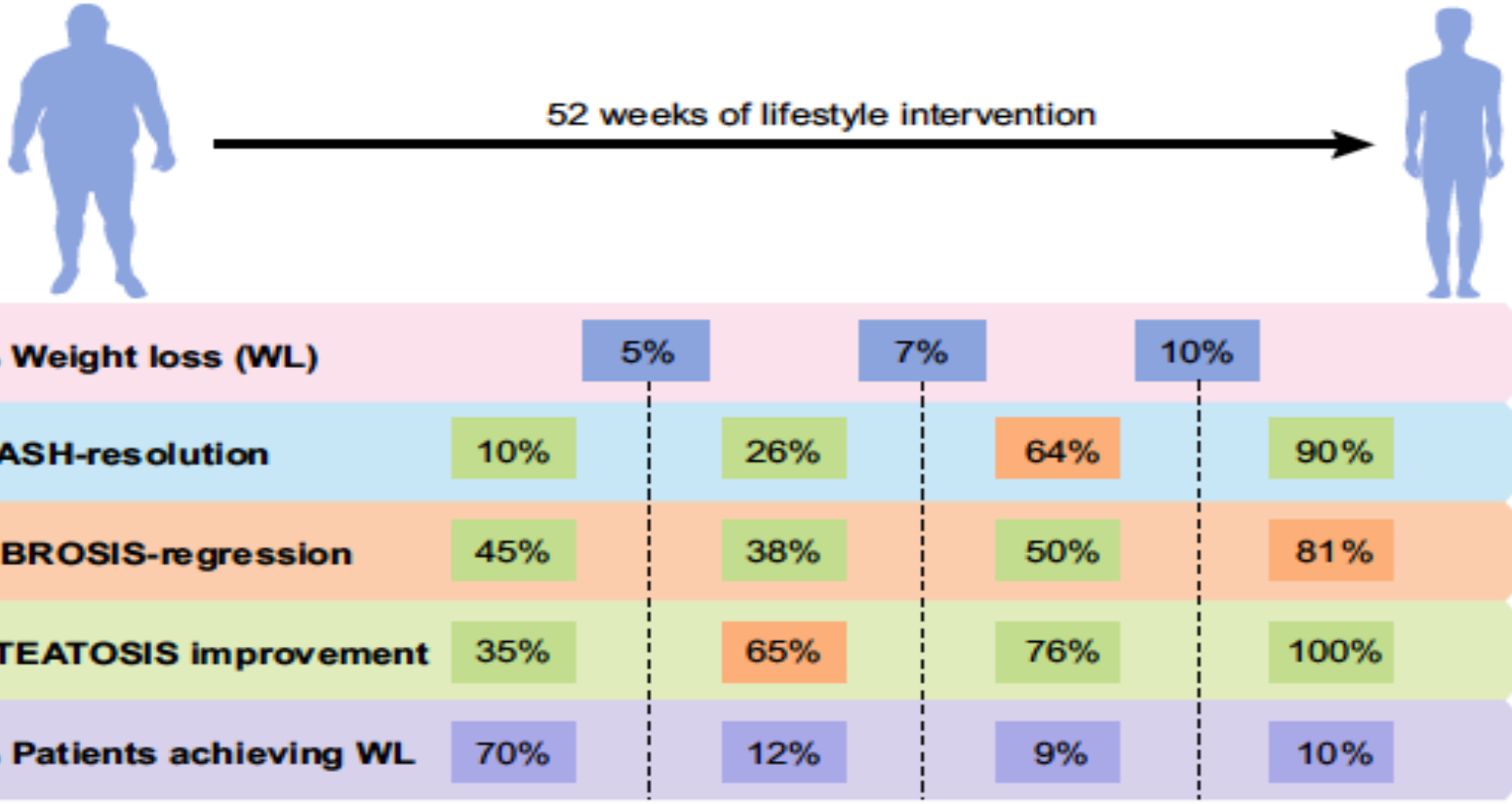
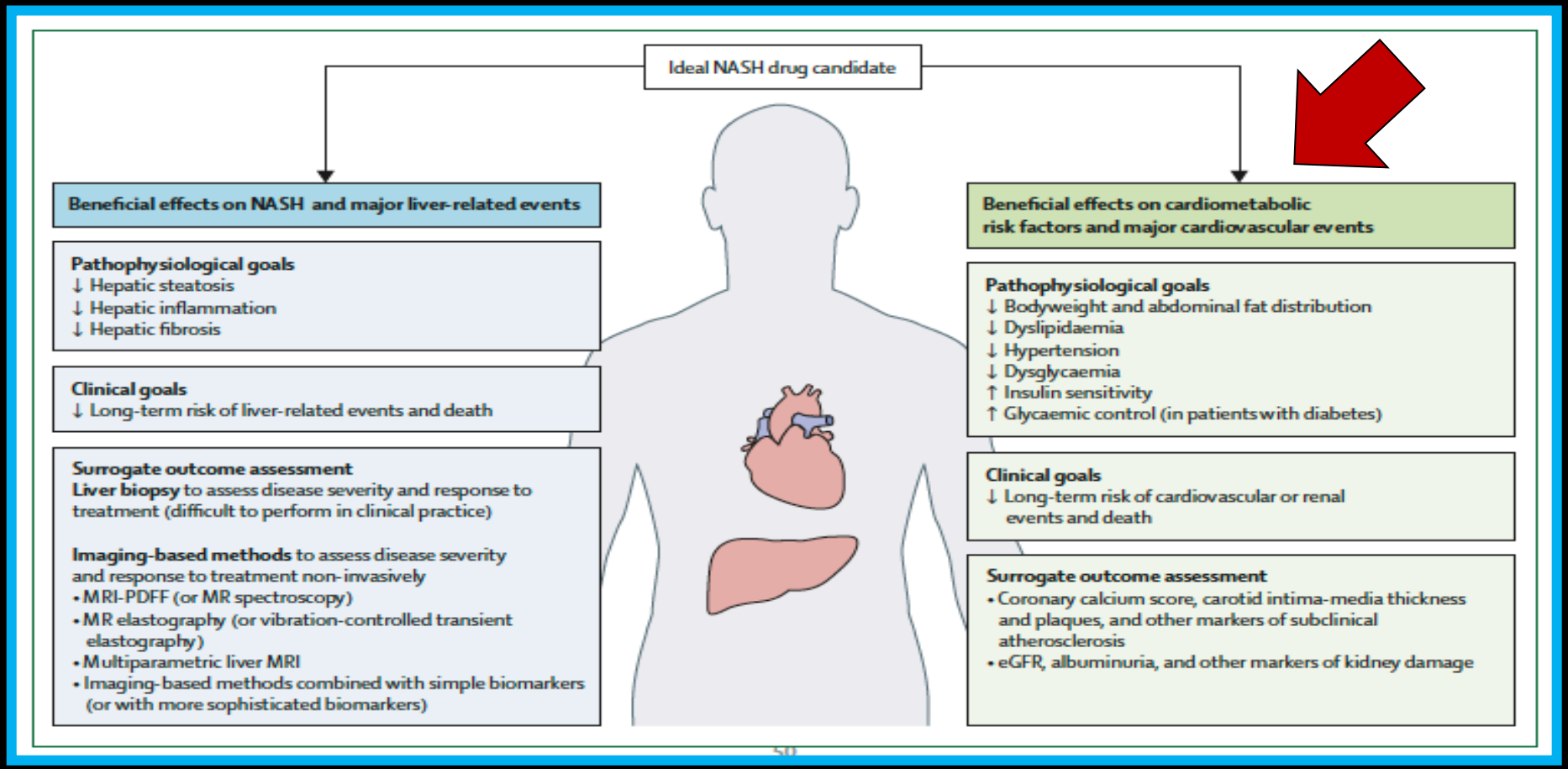


Fig. 3. Probability of reaching NASH resolution, fibrosis regression (at least one stage) and steatosis improvement in patients with NASH under lifestyle intervention according to percentage of weight loss (modified from Vilar-Gomez *et al.*[12]).

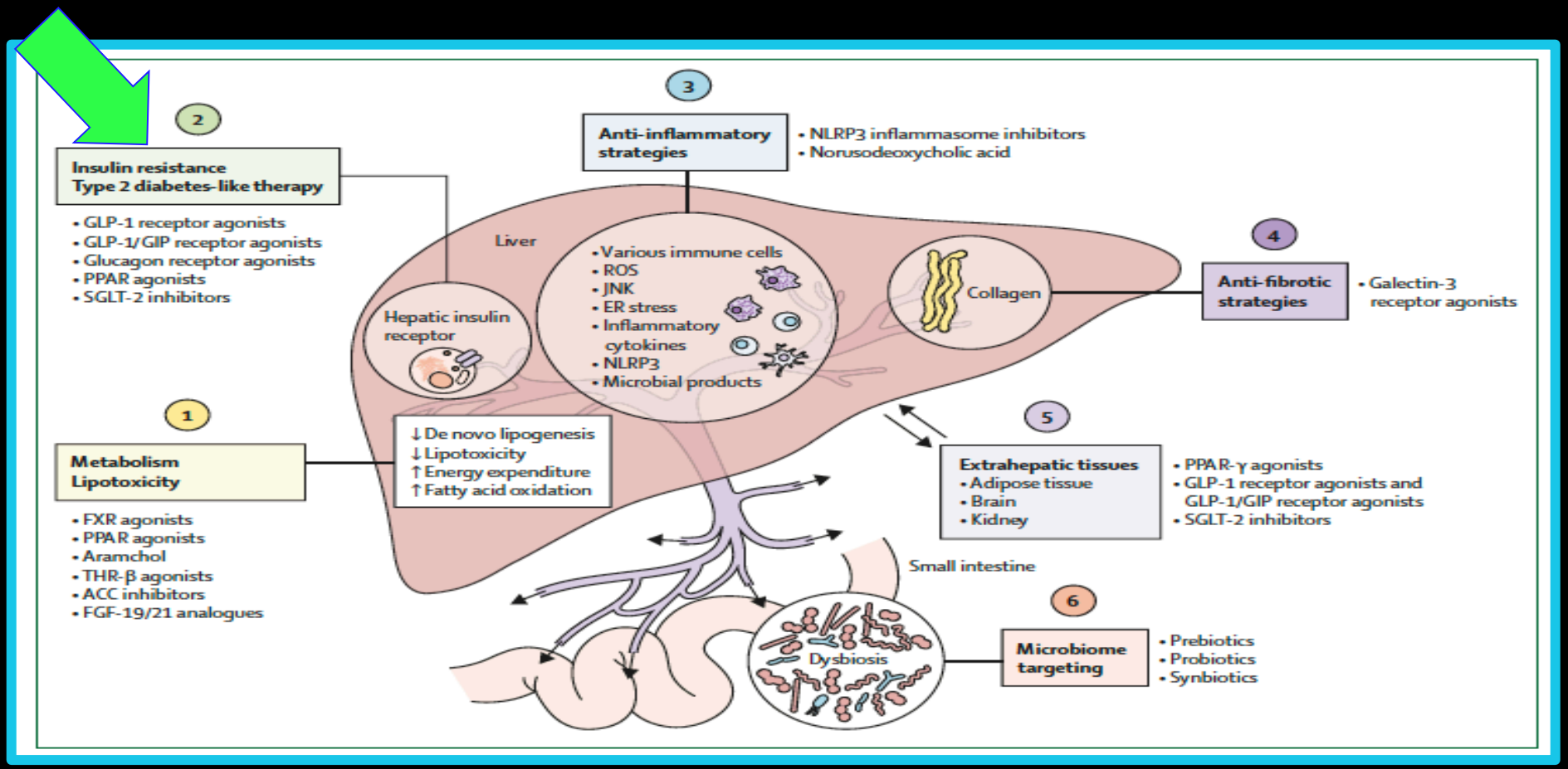
Romero-Gòmez M et al. *J Hepatol*. 2017; 67: 829-846.

Effects of an *«ideal»* drug candidate for MASLD/MASH therapy



Tilg H, Byrne CD, Targher G. *Lancet Gastroenterol Hepatol.* 2023; 8: 943-954.

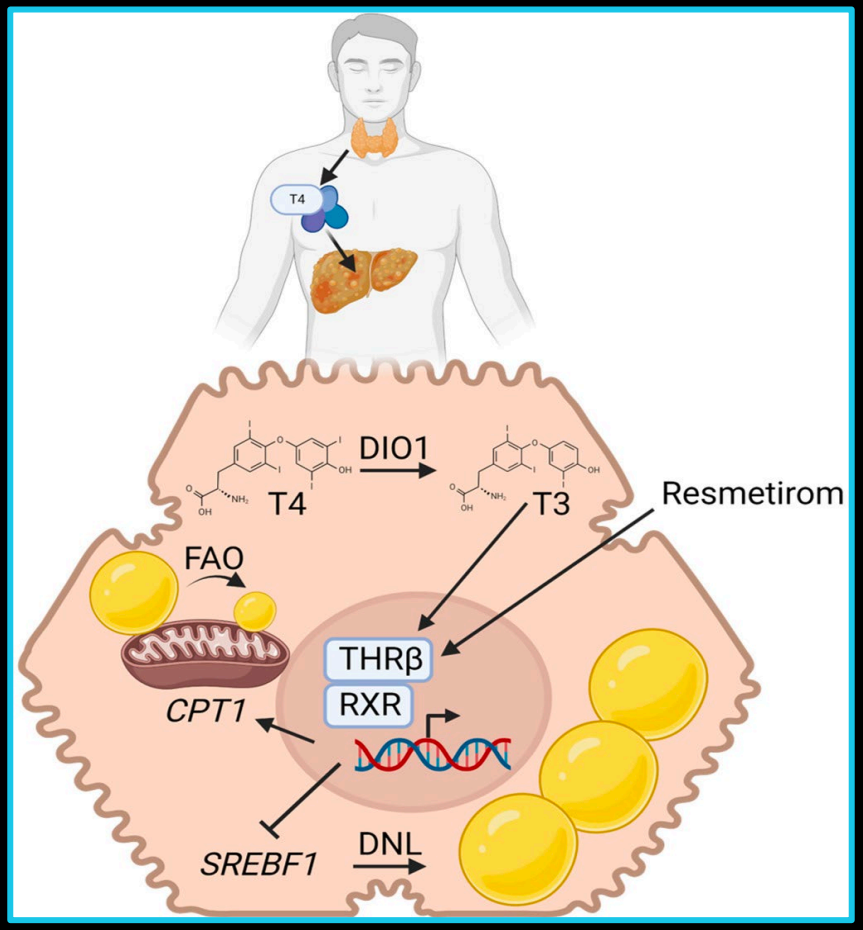
Current «*treatment targets*» based on pathophysiological concepts in MASLD/MASH

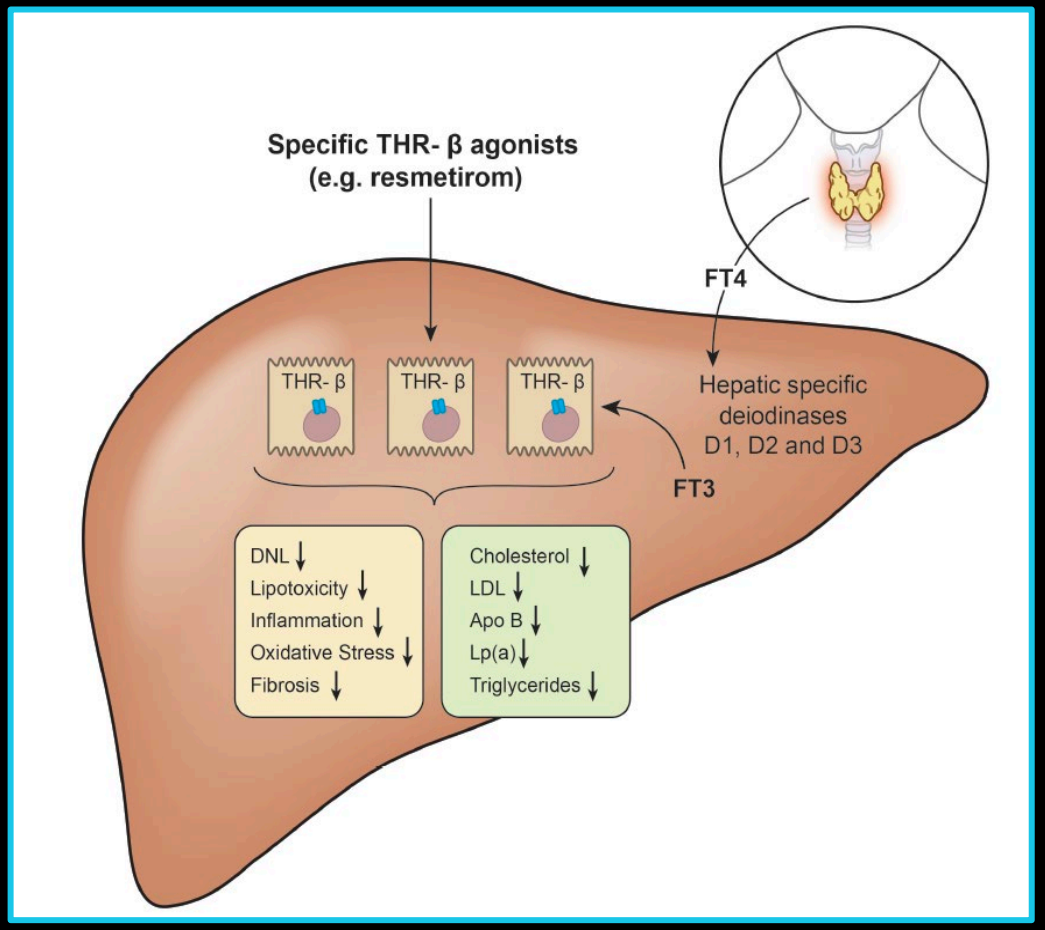


Tilg H, Byrne C, Targher G. *Lancet Gastroenterol Hepatol.* 2023; 8: 943-954.

Resmetirom for MASH and liver fibrosis

1st drug conditionally approved by FDA, 14 March 2024, and by EMA, August 2025





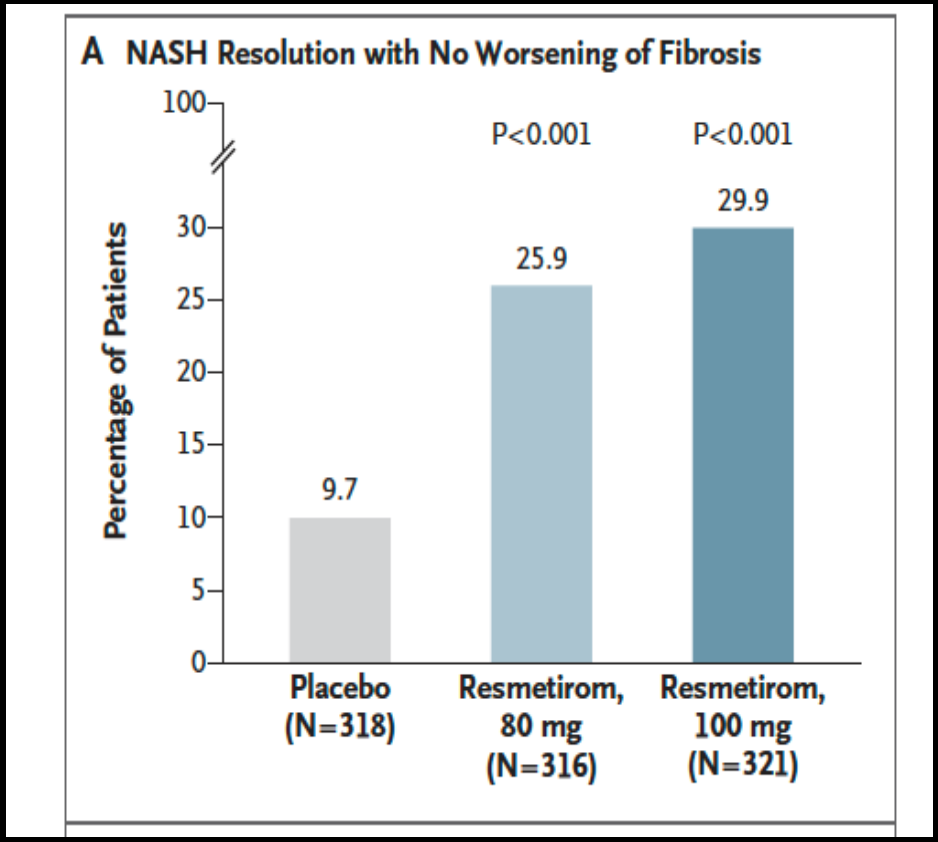
Petta S, Targher G, et al. *Liver Int*. 2024;44:1526-1536.

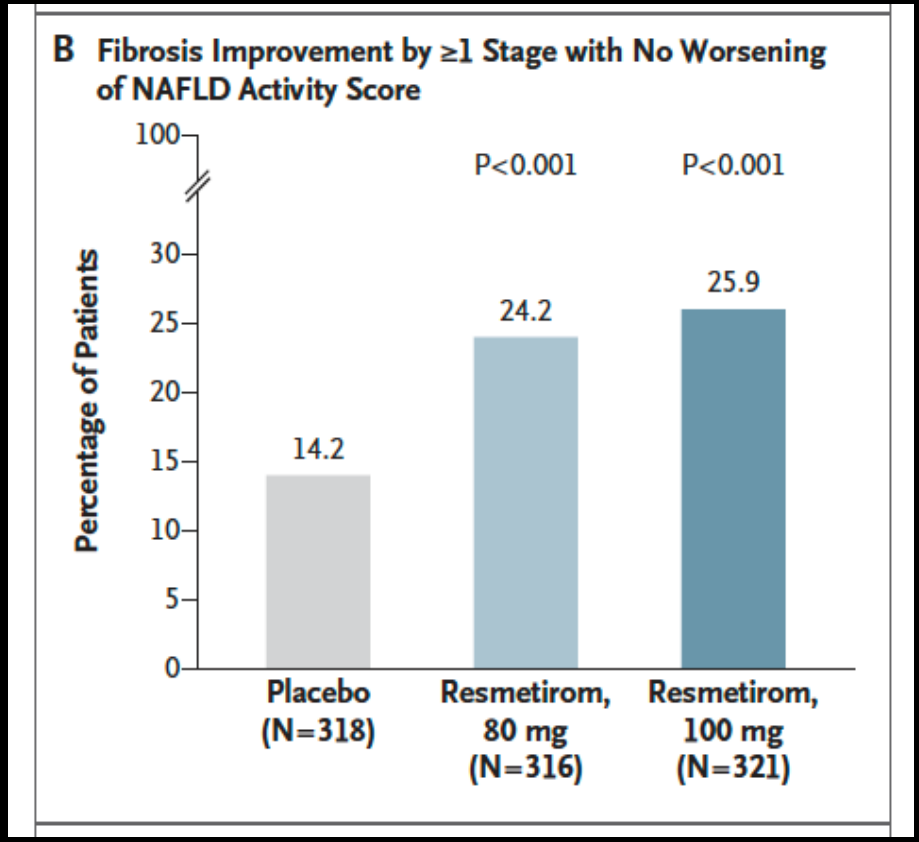
Byrne CD, Targher G, Tilg H. *Gut*. 2024;73:573-581.

Resmetirom for MASH and liver fibrosis

1st drug conditionally approved by FDA, 14 March 2024, and by EMA, 19 August 2025

Phase 3 placebo-controlled MAESTRO-NASH trial: 966 patients with biopsy-proven MASH and moderate-severe liver fibrosis treated for 52 weeks (BMI 35.3 kg/m^2, 65% had T2DM)





Harrison SA et al. *N Engl J Med*. 2024; 390: 497-509.

Resmetirom for MASH and liver fibrosis

(1st drug conditionally approved by FDA, 14 March 2024, and by EMA, 19 August 2025)

Table 3. Key Secondary and Other Secondary End Points (Primary Population).*

Measurement	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)	Difference between Resmetirom, 80 mg, and Placebo (95% CI)†	Difference between Resmetirom, 100 mg, and Placebo (95% CI)†
	least-squares mean percent change from baseline			*percentage points*	
LDL cholesterol level at wk 24‡§	−13.6±1.7	−16.3±1.7	0.1±1.7	−13.7 (−17.5 to −10.0)¶	−16.4 (−20.1 to −12.6)¶
Apolipoprotein B level at wk 24§	−16.8±1.3	−19.8±1.3	0.39±1.3	−17.2 (−20.0 to −14.4)	−20.2 (−22.9 to −17.4)
Triglyceride level at wk 24§‖	−22.7±4.0	−21.7±4.3	−2.6±4.1	−20.1 (−28.3 to −11.8)	−19.1 (−27.8 to −10.3)
Lipoprotein(a) level at wk 24§**	−30.4±3.8	−35.9±4.0	−0.84±3.5	−29.5 (−37.6 to −21.5)	−35.1 (−43.5 to −26.6)
MRI-PDFF at wk 52	−35.4±2.8	−46.6±2.8	−8.7±2.7	−26.7 (−32.9 to −20.6)	−37.9 (−44.2 to −31.7)
Alanine aminotransferase level at wk 48††	−26.6±3.7	−33.2±3.9	−6.9±3.8	−19.7 (−27.7 to −11.6)	−26.3 (−34.5 to −18.1)
Aspartate aminotransferase level at wk 48††	−22.1±3.9	−28.3±3.9	−2.9±3.8	−19.3 (−27.2 to −11.3)	−25.4 (−33.5 to −17.4)
γ-Glutamyltransferase level at wk 48††	−25.0±5.5	−31.9±6.3	3.3±5.2	−28.3 (−37.3 to −19.3)	−35.2 (−45.5 to −25.0)

Harrison SA et al. *N Engl J Med.* 2024; 390: 497-509.
(Phase 3 MAESTRO-NASH trial)

Resmetirom for MASH and liver fibrosis

(1st drug conditionally approved by FDA, 14 March 2024, and by EMA, 19 August 2025)

Table 4. Safety Summary (Primary Population).

Event	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)
	number of patients (percent)		
≥1 Adverse event	296 (91.9)	296 (91.6)	298 (92.8)
Grade 1: mild	73 (22.7)	66 (20.4)	77 (24.0)
Grade 2: moderate	180 (55.9)	183 (56.7)	169 (52.6)
Grade 3 or higher: severe	43 (13.4)	47 (14.6)	52 (16.2)
≥1 Adverse event attributed to resmetirom or placebo*	124 (38.5)	134 (41.5)	88 (27.4)
≥1 Serious adverse event	35 (10.9)	41 (12.7)	37 (11.5)
≥1 Serious adverse event attributed to resmetirom or placebo*	2 (0.6)	0	1 (0.3)
Adverse event leading to trial discontinuation before wk 52†	6 (1.9)	22 (6.8)	7 (2.2)
Adverse event leading to trial discontinuation during entire treatment period†	9 (2.8)	25 (7.7)	11 (3.4)
Fatal adverse event	1 (0.3)	2 (0.6)	1 (0.3)
Major adverse cardiovascular event‡	1 (0.3)	1 (0.3)	1 (0.3)
Other cardiovascular event‡	0	1 (0.3)	3 (0.9)
Adverse events affecting >10% of patients in any group			
Diarrhea	87 (27.0)	108 (33.4)	50 (15.6)
Covid-19	69 (21.4)	54 (16.7)	66 (20.6)
Nausea	71 (22.0)	61 (18.9)	40 (12.5)
Arthralgia	48 (14.9)	35 (10.8)	40 (12.5)
Back pain	35 (10.9)	27 (8.4)	38 (11.8)
Urinary tract infection	33 (10.2)	27 (8.4)	27 (8.4)
Fatigue	33 (10.2)	26 (8.0)	28 (8.7)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)

Harrison SA et al. *N Engl J Med*. 2024; 390: 497-509.
(Phase 3 MAESTRO-NASH trial)

Semaglutide for MASH and liver fibrosis

(drug conditionally approved by FDA, 15 August 2025)

Phase 3 placebo-controlled ESSENCE trial: 800 patients with biopsy-proven MASH and moderate-severe liver fibrosis treated with semagluitide 2.4 mg/week for 72 weeks (BMI 34 kg/m^2, 56% had T2DM)

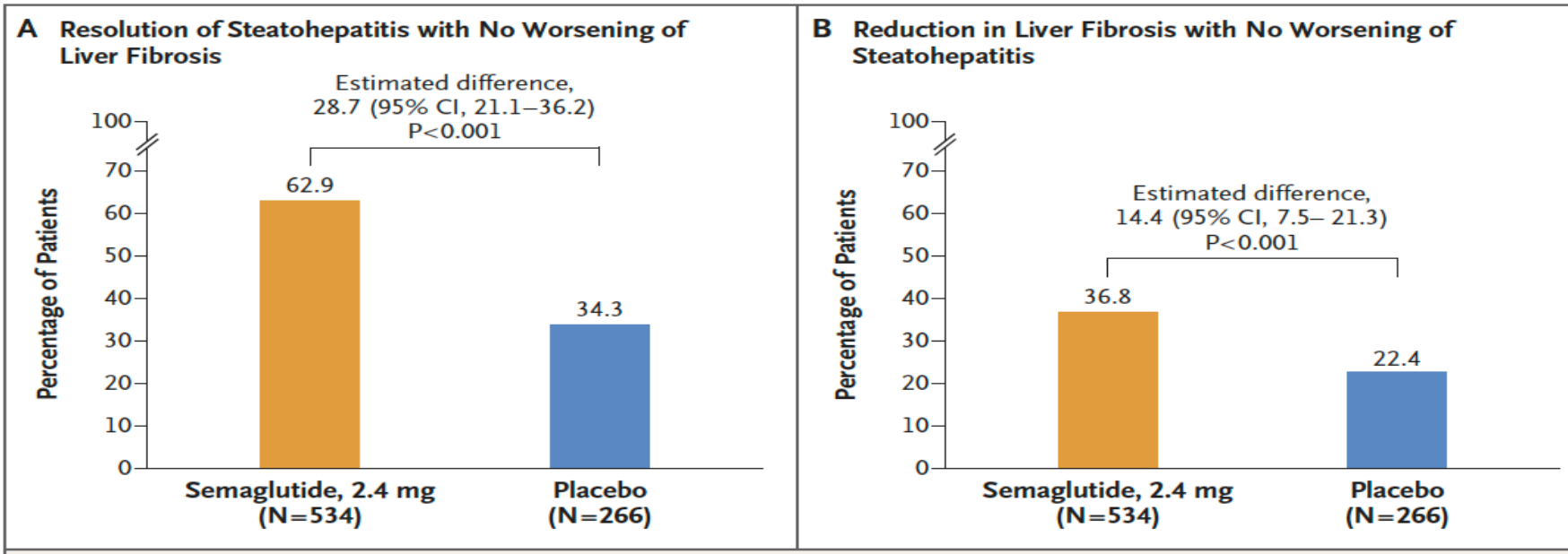


Figure 1. Primary End Points.

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 AJ et al. *N Engl J Med*. 2025; 392: 2089-2099.

Semaglutide for MASH and liver fibrosis

(*drug conditionally approved by FDA, 15 August 2025*)

Table 2. Change in Select Cardiometabolic Features during the Trial Period.*

Measure	Semaglutide, 2.4 mg (N=534)	Placebo (N=266)	Difference between Semaglutide and Placebo at Week 72 (95% CI)
Blood pressure — mm Hg			
Systolic	−5.39	−1.39	−4.00 (−5.93 to −2.07)†
Diastolic	−1.90	0.24	−2.14 (−3.43 to −0.85)†
Glycated hemoglobin — %			
Patients without type 2 diabetes	−0.42	0.11	−0.53 (−0.61 to −0.44)†
Patients with type 2 diabetes	−1.08	0.00	−1.08 (−1.27 to −0.89)†
High-sensitivity C-reactive protein — mg/liter	−53.83	−19.83	−42.41 (−49.75 to −33.98)‡
Triglycerides — mg/dl	−16.77	−0.27	−16.54 (−21.02 to −11.81)‡
Cholesterol — mg/dl			
Total	−6.03	−3.19	−2.93 (−5.60 to −0.19)‡
Low-density lipoprotein	−6.07	−4.11	−2.04 (−6.35 to 2.46)‡
High-density lipoprotein	2.62	−1.95	4.66 (2.12 to 7.26)‡

Sanyal AJ et al. *N Engl J Med*. 2025; 392: 2089-2099.

Semaglutide for MASH and liver fibrosis

(*drug conditionally approved by FDA, 15 August 2025*)

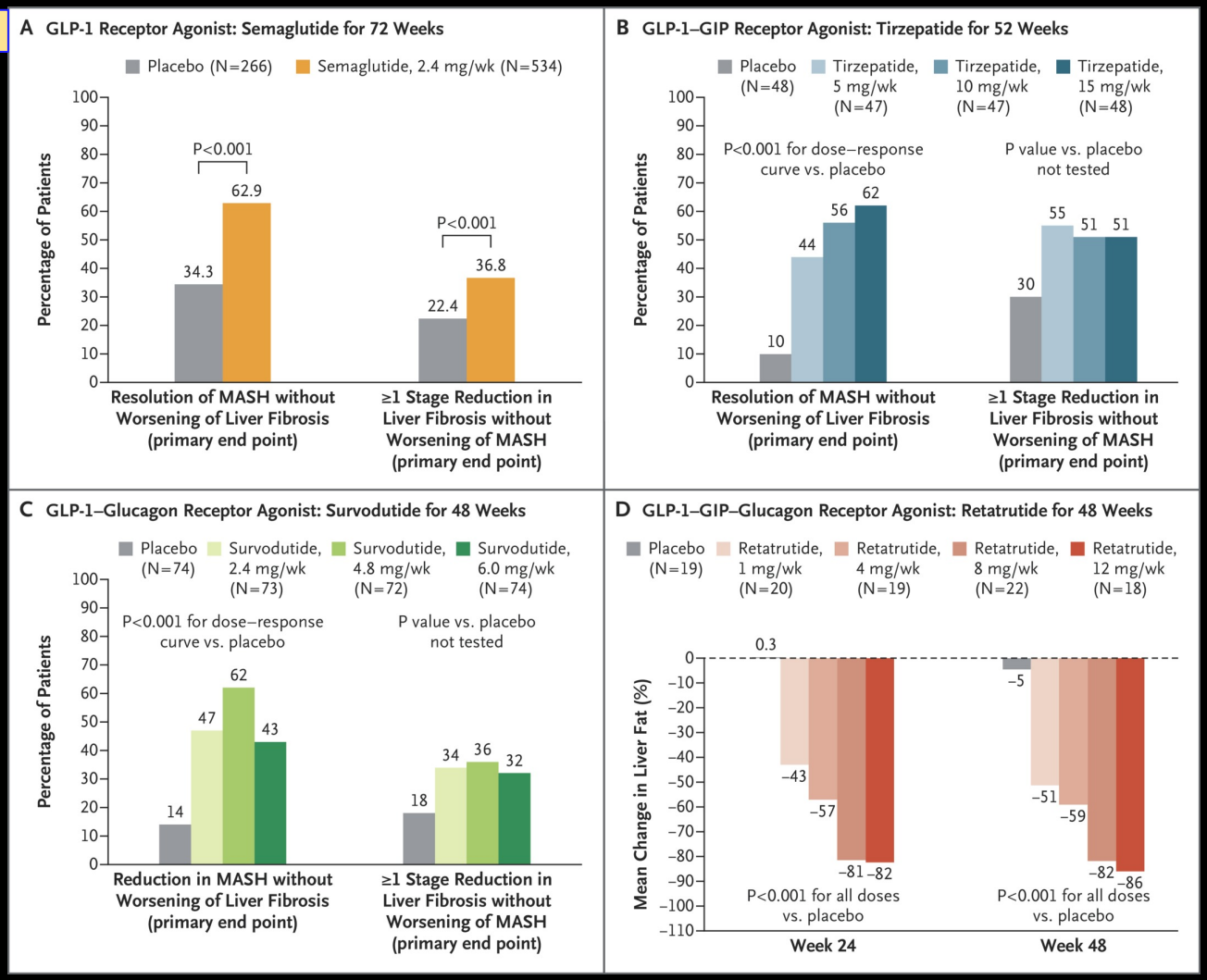
Table 3. Safety Analysis Population.*

Event	Semaglutide, 2.4 mg	Placebo
	number/total number (percent)	
Any adverse event	690/800 (86.2)	315/395 (79.7)
Fatal adverse event	3/800 (0.4)	6/395 (1.5)
Serious adverse event	107/800 (13.4)	53/395 (13.4)
Infection or infestation	22/800 (2.8)	10/395 (2.5)
Gastrointestinal disorder	20/800 (2.5)	6/395 (1.5)
Musculoskeletal or connective-tissue disorder	14/800 (1.8)	6/395 (1.5)
Injury, poisoning, or procedural complication	11/800 (1.4)	5/395 (1.3)
Nervous system disorder	11/800 (1.4)	5/395 (1.3)
Neoplasm†	11/800 (1.4)	8/395 (2.0)
Adverse event leading to trial discontinuation	21/800 (2.6)	13/395 (3.3)
Adverse event affecting ≥10% of patients in either group		
Nausea	290/800 (36.2)	52/395 (13.2)
Diarrhea	215/800 (26.9)	48/395 (12.2)
Constipation	178/800 (22.2)	33/395 (8.4)
Vomiting	149/800 (18.6)	22/395 (5.6)
Coronavirus disease 2019	134/800 (16.8)	74/395 (18.7)
Decreased appetite	112/800 (14.0)	11/395 (2.8)
Adverse event within safety focus area‡		
Gallbladder-related disorder	20/800 (2.5)	6/395 (1.5)
Acute pancreatitis	3/800 (0.4)	2/395 (0.5)
Malignant neoplasm	13/800 (1.6)	9/395 (2.3)
Hypoglycemia		
Patients with type 2 diabetes§	33/446 (7.4)	12/222 (5.4)
Patients without type 2 diabetes	1/354 (0.3)	1/173 (0.6)

Sanyal AJ et al. *N Engl J Med*. 2025; 392: 2089-2099.

Possible Hepatoprotective Effects of GLP-1 Receptor Agonists (Semaglutide 2.4 mg/week) or Other Dual or Triple Incretin–Based Receptor Agonists in Adults with MASLD or MASH and Fibrosis

(Phase 3 ESSENCE trial)



Targher G et al. *N Engl J Med*. 2025; 393: 683-698.

The NEW ENGLAND JOURNAL of MEDICINE

Glucagon-like peptide-1 receptor agonist use is associated with a lower risk of major adverse liver-related outcomes: a meta-analysis of observational cohort studies

Ciro Celsa ,[1,2] Grazia Pennisi,[1] Adele Tulone,[1] Giacinta Ciancimino,[1] Marco Vaccaro,[3] Giuseppe Infantino,[1] Gabriele Di Maria,[4] David J Pinato,[2,5] Giuseppe Cabibbo ,[1] Marco Enea,[4] Alessandro Mantovani ,[6] Herbert Tilg ,[7] Giovanni Targher ,[8,9] Calogero Cammà ,[1] Salvatore Petta [1]

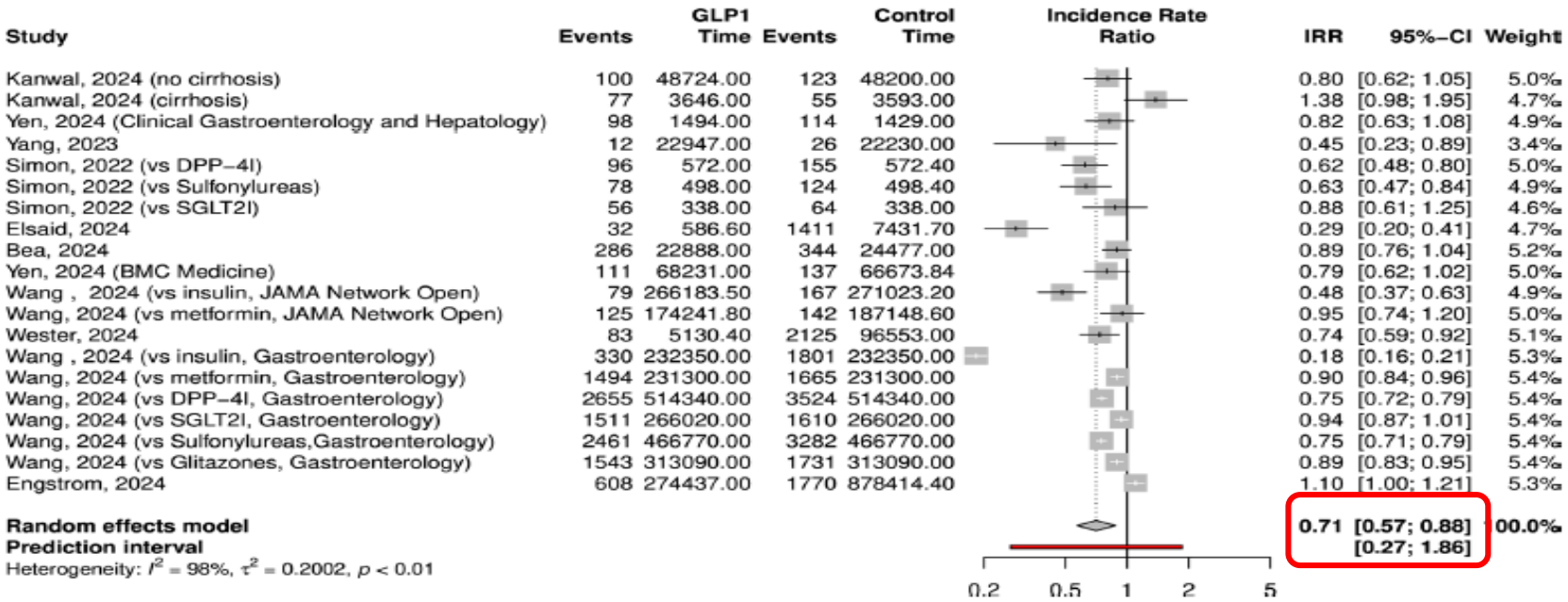
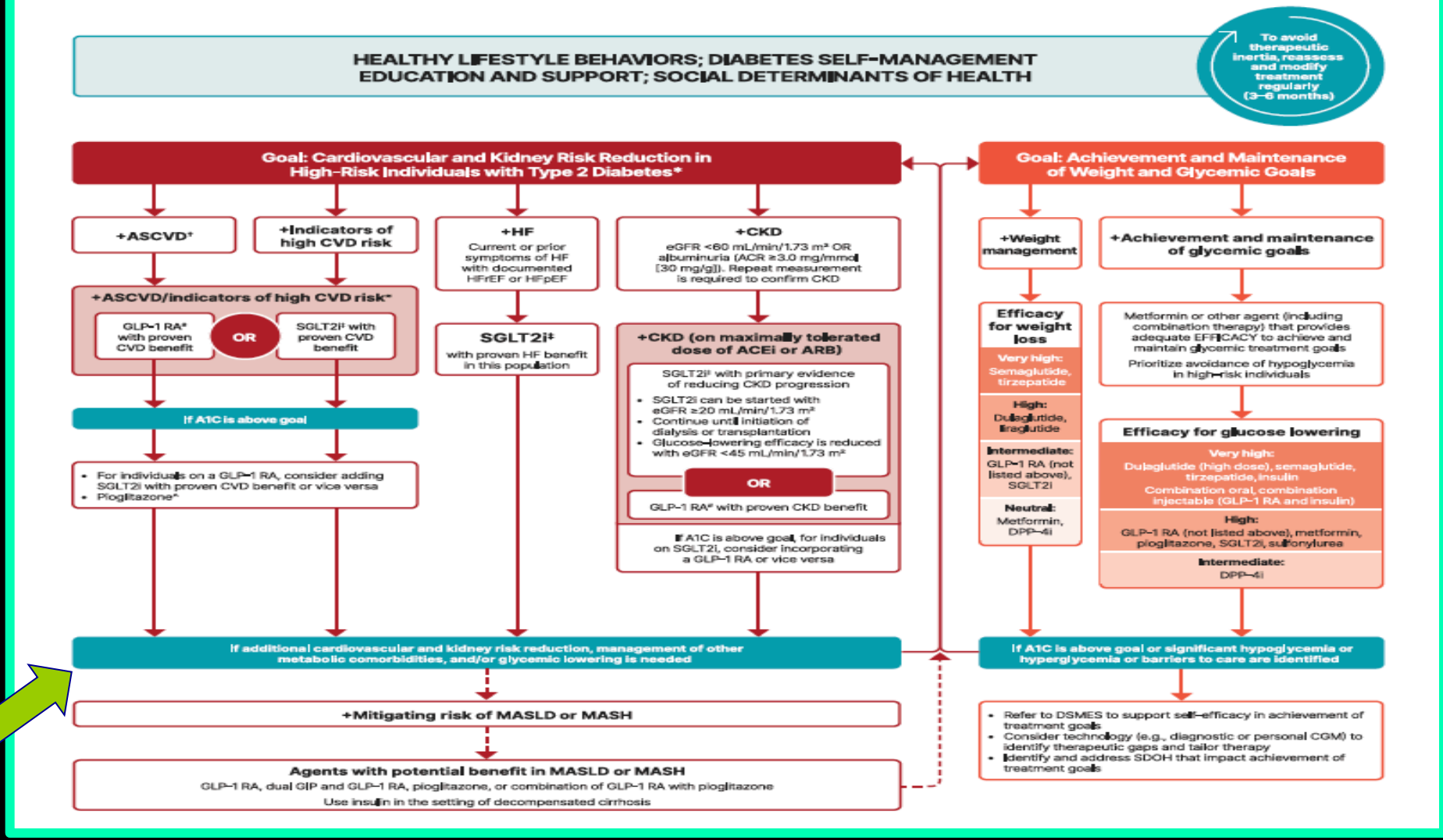


Figure 1 Forest plot and pooled estimates of the long-term effect of GLP-1RA use on the risk of developing major adverse liver-related outcomes (MALOs) (n=11 retrospective cohort studies, including 647 903 GLP-1RA new users and 819 317 GLP-1RA non-users). MALOs were defined as occurrence of hepatic decompensation events, hepatocellular carcinoma and liver-related death. The incidence rate of MALOs was significantly lower in GLP-1RA new users than in non-users (random-effects IRR 0.71, 95% CI 0.57 to 0.88). GLP-1RA, glucagon-like peptide-1 receptor agonists; IRR, incidence rate ratio.

Major adverse liver-related events (MALO): hepatic decompensation events, new-onset HCC, or liver-related deaths

Celsa C et al. *Gut*. 2025; 75: 815-824.

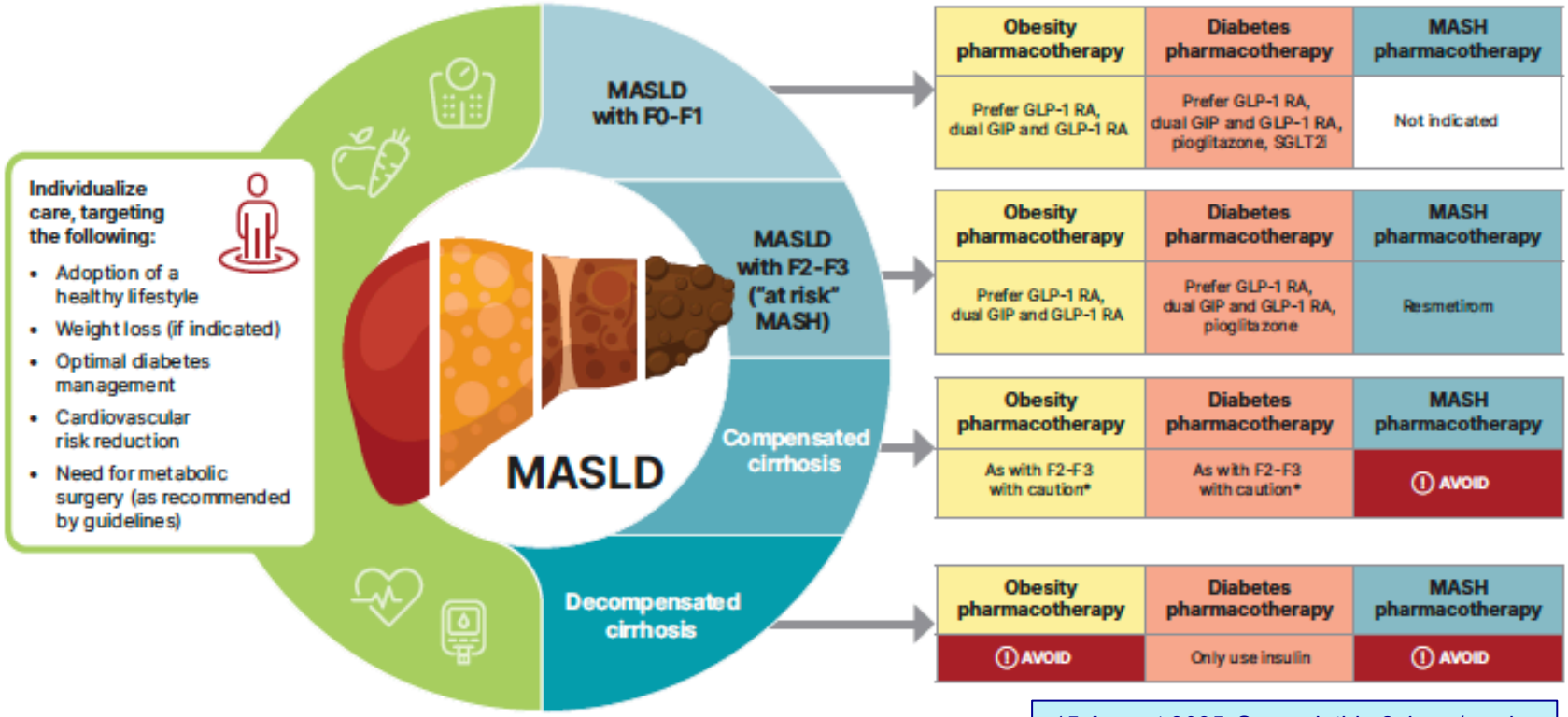
Use of glucose-lowering medications in the management of T2D (& MASLD)



ADA Standard of Care 2025. *Diabetes Care*. 2025; 48: S181-S206.

Treatment algorithm for MASLD in T2D

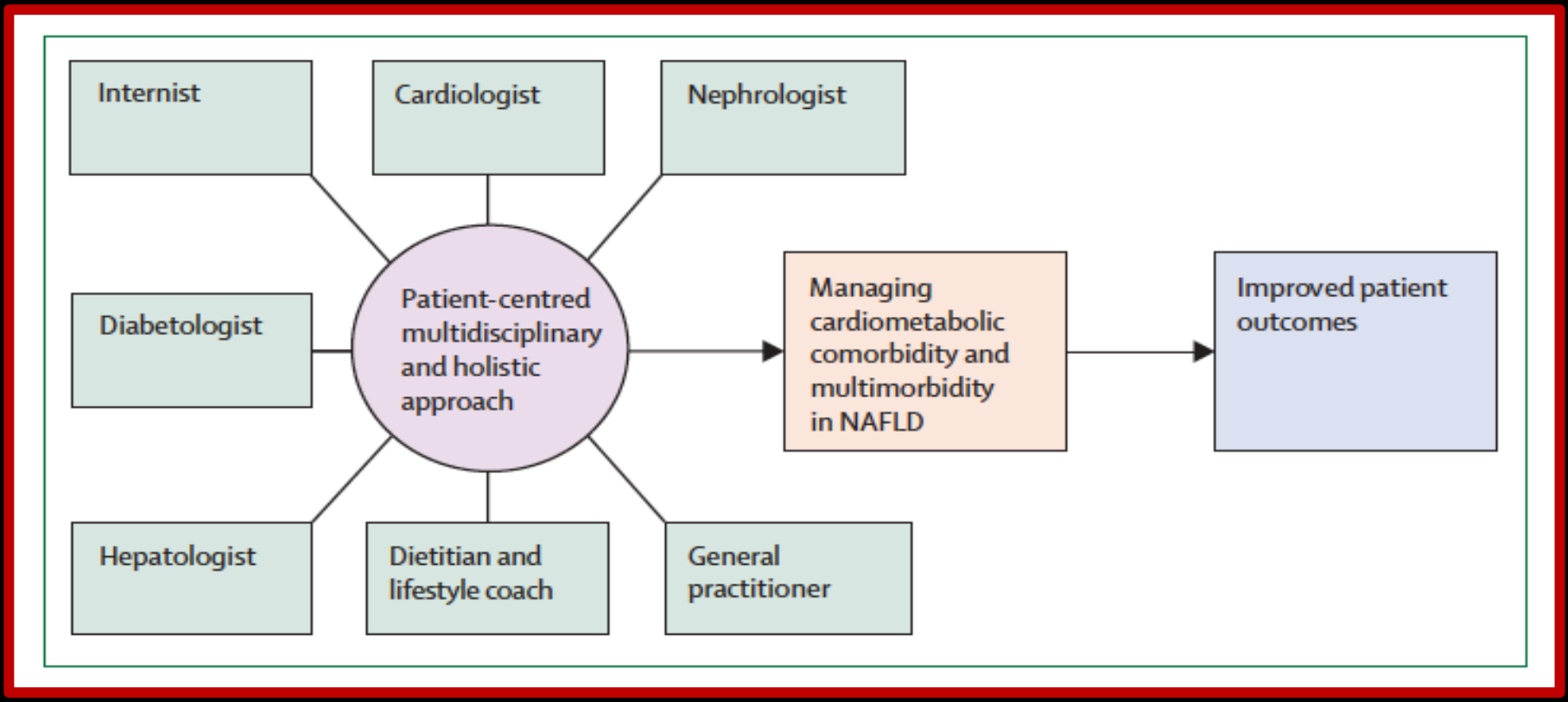
Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) Treatment Algorithm



15 August 2025: Semaglutide 2,4 mg/week (FDA approval for MASH pharmacotherapy)

ADA Standard of Care 2025. *Diabetes Care.* 2025; 48: S59-S85.

Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach



Targher G et al. *Lancet Gastroenterol Hepatol*. 2021; 6: 578-588.

Conclusions

- **A person-centered, multidisciplinary and holistic approach to the treatment of individuals with MASLD, based on a careful evaluation of related cardiovascular-kidney-metabolic risk factors and monitoring for the development of cardiometabolic, renal and liver complications, is warranted.**

- **Clinicians who manage individuals with MASLD (especially those with MASH and significant liver fibrosis) should not only focus on liver disease but also recognize the increased risk of extrahepatic (cardiometabolic) complications and undertake early, aggressive risk factor modifications.**

- **Resmetirom (a liver-directed, thyroid hormone receptor beta agonist) and Semaglutide 2.4 mg/week (a GLP-1 receptor agonist) are the two agents that have now received conditional approval from the FDA and/or EMA for treatment of adults with noncirrhotic MASH and moderate to advanced fibrosis (F2-F3 fibrosis stages).**

- **The possibility of MASLD - *as a «new» chronic diabetic complication* - should be considered as a part of the routine examination of individuals living with T2DM, *in the same way we search for CVD, CKD* or other chronic complications of T2DM.**

STUDIO OSSERVAZIONALE

ITA-MASLD: uno studio per valutare il profilo clinico epidemiologico e l'impatto economico dei pazienti con MASLD e fibrosi del fegato seguiti nei centri di cura multidisciplinari

ITALY	Target Population	Study Design	Data Collection
Nationwide Study	Adults ≥18 years	Prospective	Web-based eCRFs
100+ Clinical Centers	Confirmed MASLD	Multicenter	Standardized protocols
All Regions	Under specialist care	Observational cohort	Quality assurance
Multicenter Network	**Real-world patients**	**Nationwide**	**GDPR compliant**

Primary Objectives

Characterize	Assess	Identify	Generate
Clinical profiles	Comorbidities	Unmet clinical needs	Practice-based evidence
Metabolic markers	Disease severity	Regional variations	Health policy data
Demographics	Management patterns	Care pathways	Resource allocation

Multidisciplinary Alliance

Expected Impact

Informing sustainable MASLD management strategies

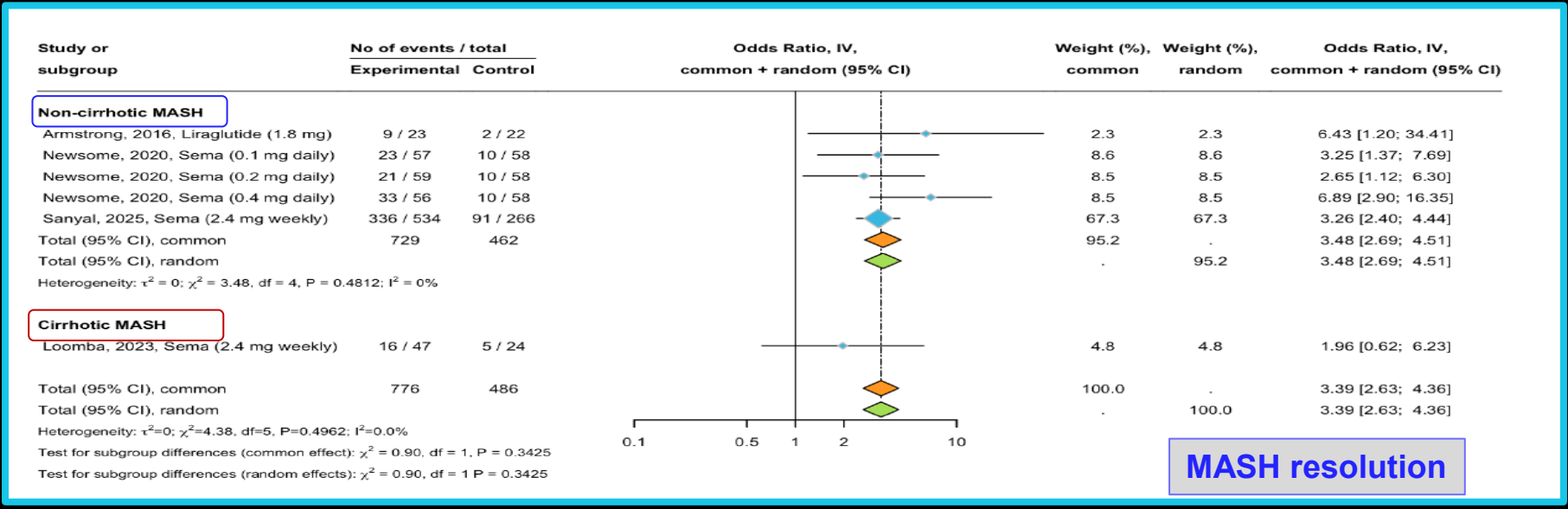
I documenti dello studio sono disponibili al seguente link: https://www.progettopiter.it/studio-ita-masld/

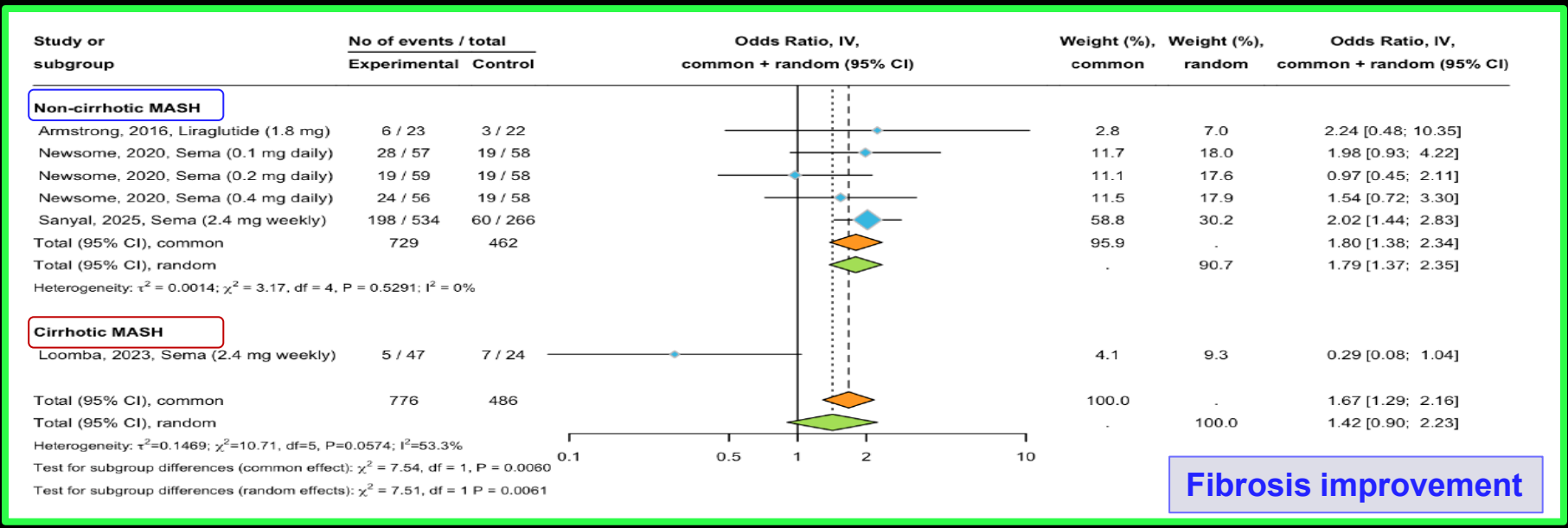
Per aderire allo studio inviare una e-mail all'indirizzo: masld@iss.it

Bugianesi E, Buscemi S, Burra P, Calvaruso V, Gastaldelli A, Germani G, Marra F, Masarone M, Miele L, Perseghin G, Persico M, Petta S, Sacco R, Sesti G, Baroni GS, Targher G, Valenti L, Vespasiani-Gentilucci U, Vettor R, Rosato S, Ferrigno L, Buttari B, Mattioli B, Quaranta MG, Kondili LA. ITA-MASLD: A national observational study to characterize the profile of patients with MASLD in specialistic care in Italy. Dig Liver Dis. 2025 Sep 15:S1590-8658(25)01079-5. doi: 10.1016/j.dld.2025.08.092. Epub ahead of print.

Grazie per l'attenzione !

GLP-1RAs improve MASH and liver fibrosis: A meta-analysis of randomized clinical trials





Mantovani A et al. *Liver Int*. 2025;45:e70256.

Semaglutide for MASH and liver fibrosis

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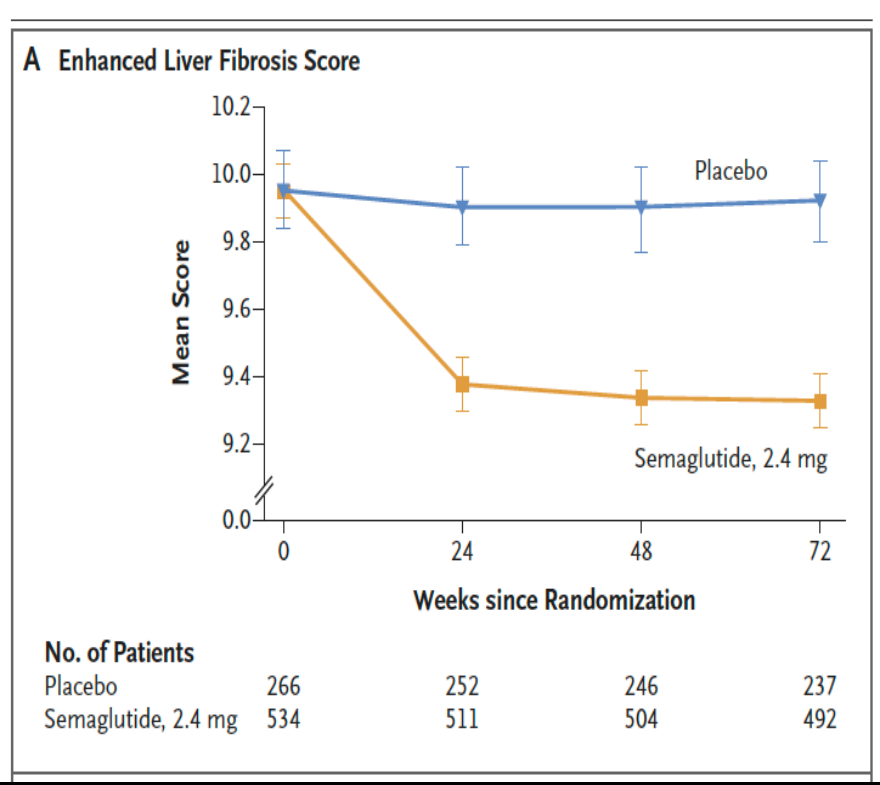
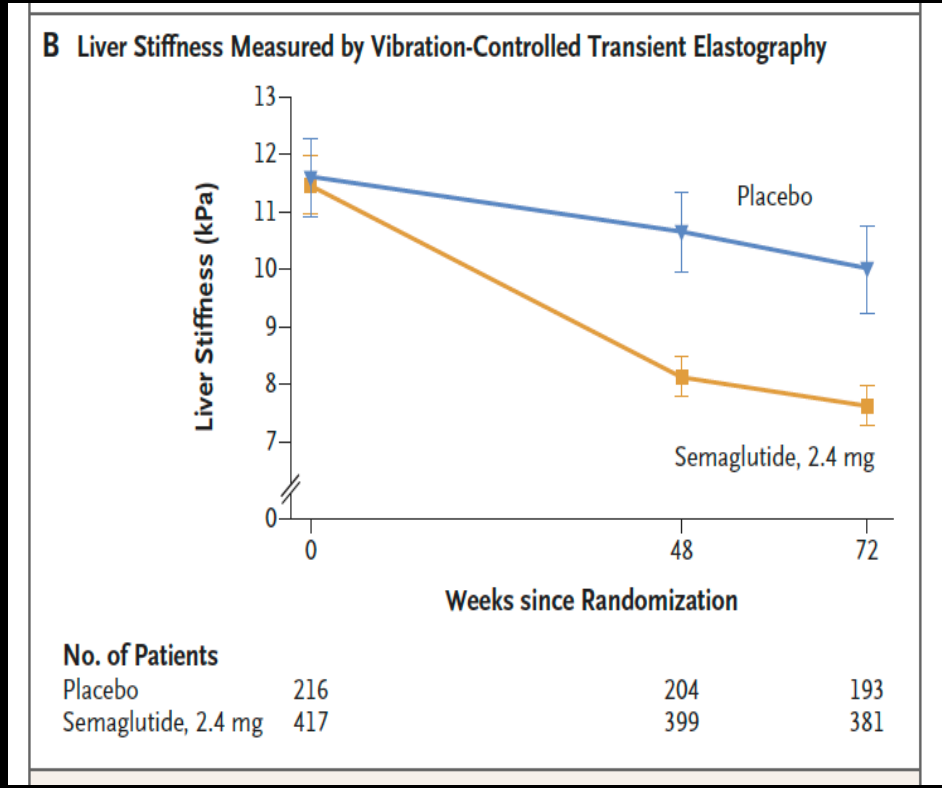




Sanyal AJ et al. *N Engl J Med*. 2025; 392: 2089-2099.

https://doi.org/10.1038/s41591-025-03927-w

Semaglutide targets MASH molecular pathways beyond weight loss

Maurice Michel & Jörn M. Schattenberg

A proteomic study begins to identify the direct and indirect effects of GLP-1 treatment on metabolic dysfunction-associated steatohepatitis (MASH), and reveals insights into treatment-induced changes in liver histology.

Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), has recently demonstrated efficacy in treating fibrosis associated with MASH in the phase 3 ESSENCE trial[1]. This is particularly noteworthy given the lack of GLP-1 receptor expression on hepatocytes, and the lack of fibrosis improvement in the preceding phase 2 study[2] and in a second phase 2 trial in patients with compensated cirrhosis[3]. The academic debate on the weight-dependent and weight-independent benefits of GLP-1RAs in patients with MASH is ongoing, and it has been particularly difficult to study the hepatic compartment, which is influenced by a complex array of metabolic processes (the metabolic 'milieu'). In this issue of *Nature Medicine*, Jara et al.[4] approach this knowledge gap using mediation analyses and proteomic studies, building on data and samples collected in the phase 2 study, an unrelated cohort of tertiary care patients, as well as published data and two mouse models of MASH.

In their classical mediation analysis and natural effect model, Jara et al.[4] estimated that effect sizes attributed directly to weight loss were 82% for improvement in histological steatosis score, 69.3% for MASH resolution, but only 25.1% for fibrosis regression. While modelling approaches are one way to estimate effects sizes, proteomics analyses are a powerful tool to explore protein networks and determine mechanisms. Jara et al.[4] studied the effect of semaglutide exposure on

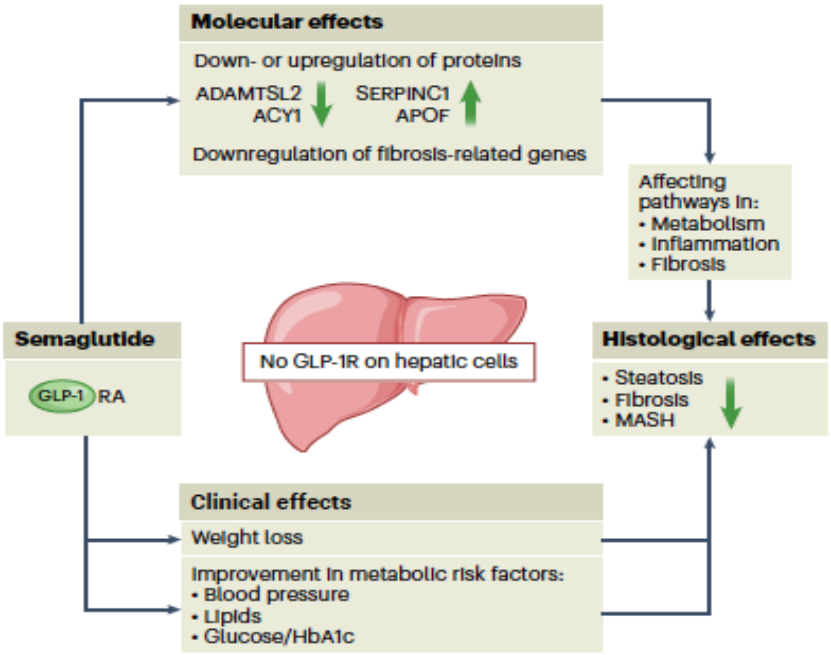
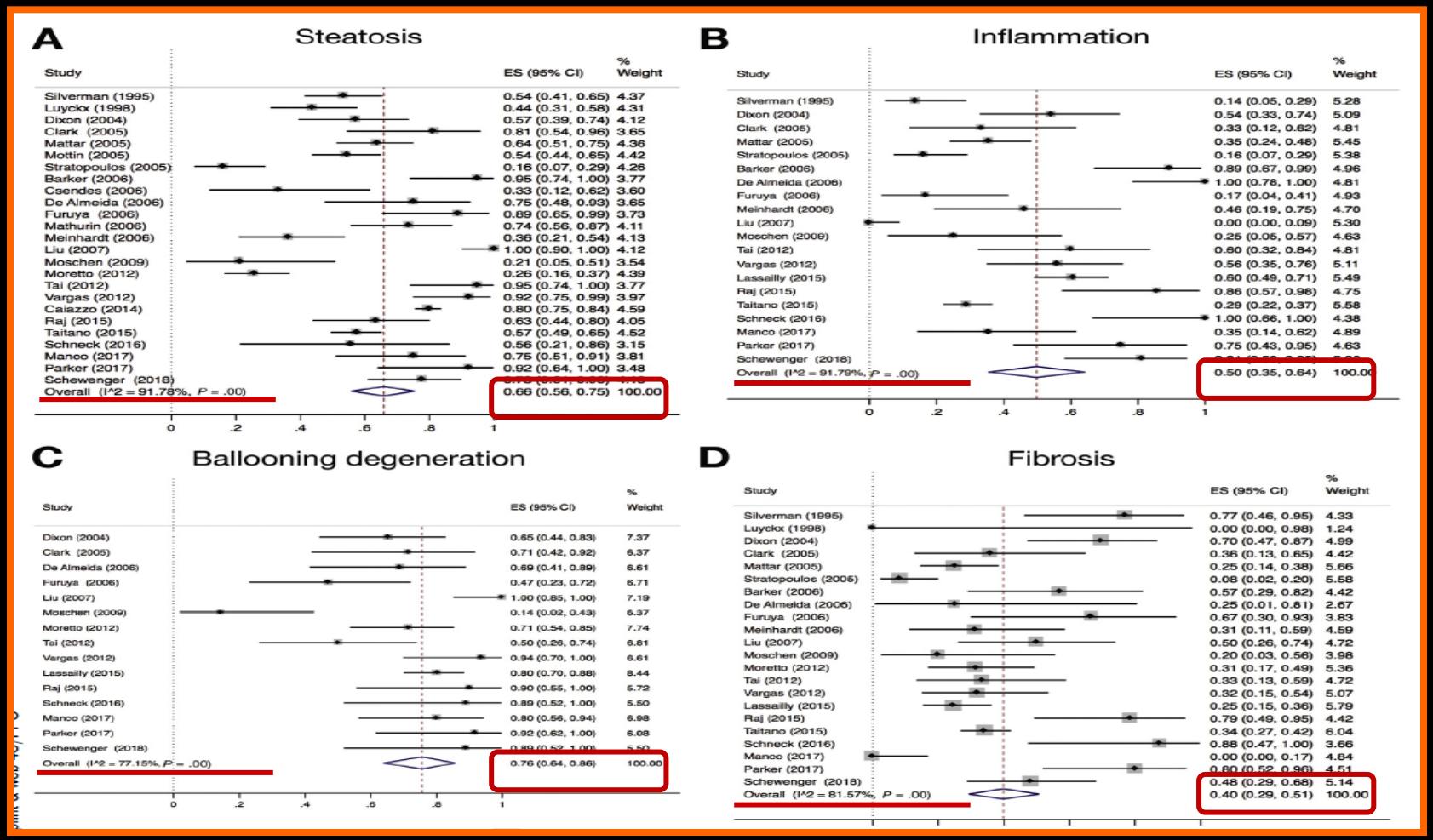


Fig. 1 | The many indirect effects of semaglutide in MASH with fibrosis. Semaglutide works through several mechanisms that affect the liver, despite the absence of GLP-1 receptors on hepatocytes. The study by Jara et al.[4] revealed mechanistic insights into how semaglutide alters molecular pathways involved in metabolism, inflammation and fibrosis in individuals with MASH. Although most of these mechanisms are strongly associated with weight loss, some exert their effects independently of weight changes – particularly in relation to fibrosis. These molecular mechanisms enhance and synergize with the clinical effects of semaglutide to improve steatosis, MASH and fibrosis.

Jara M, et al. *Nat Med*. 2025 Jul 21. doi: 10.1038/s41591-025-03799-0.

Complete Resolution of Nonalcoholic Fatty Liver Disease After Bariatric Surgery: A Systematic Review and Meta-Analysis



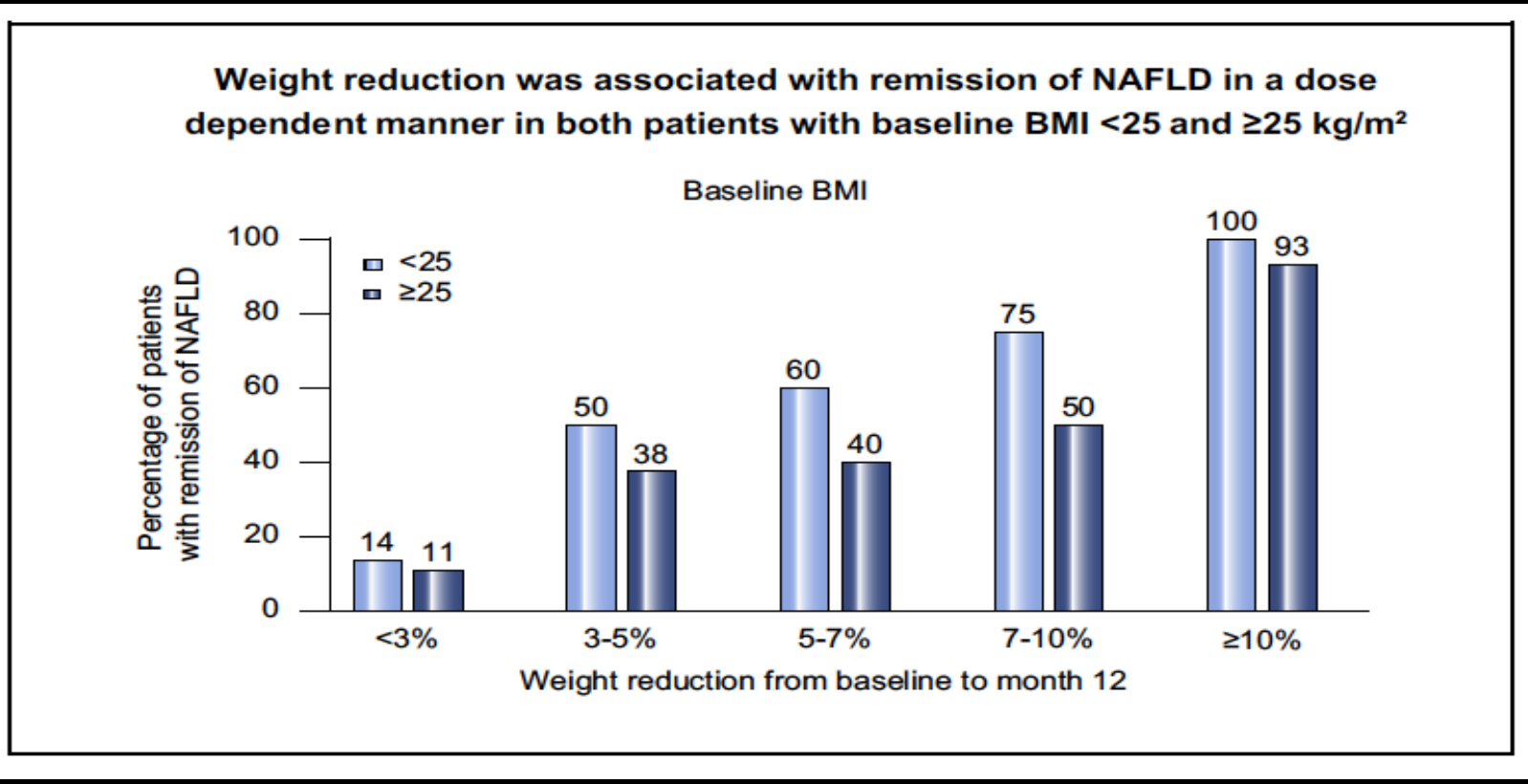
N = 32 cohort studies, including 3,093 patients with severe obesity and biopsy-proven MASLD

Lee Y et al. *Clin Gastroenterol Hepatol*. 2019; 17: 1040-60.

Beneficial effects of lifestyle intervention in both obese and non-obese patients with NAFLD

RCT trial: Effect of 12-month lifestyle intervention programme (diet + regular exercise) *vs*. standard care on **remission of NAFLD** (liver fat <5% as measured by MR spectroscopy) in 154 Chinese adults with NAFLD

More patients in the intervention group (n=77) achieved remission of NAFLD compared to control group (n=77), *regardless* of baseline BMI (non-obese: 67% *vs*.18%, $p<0.001$; obese: 61% *vs*. 21%, $p<0.001$)



Wong VW et al. *J Hepatol*. 2018; 69: 1349-1356.

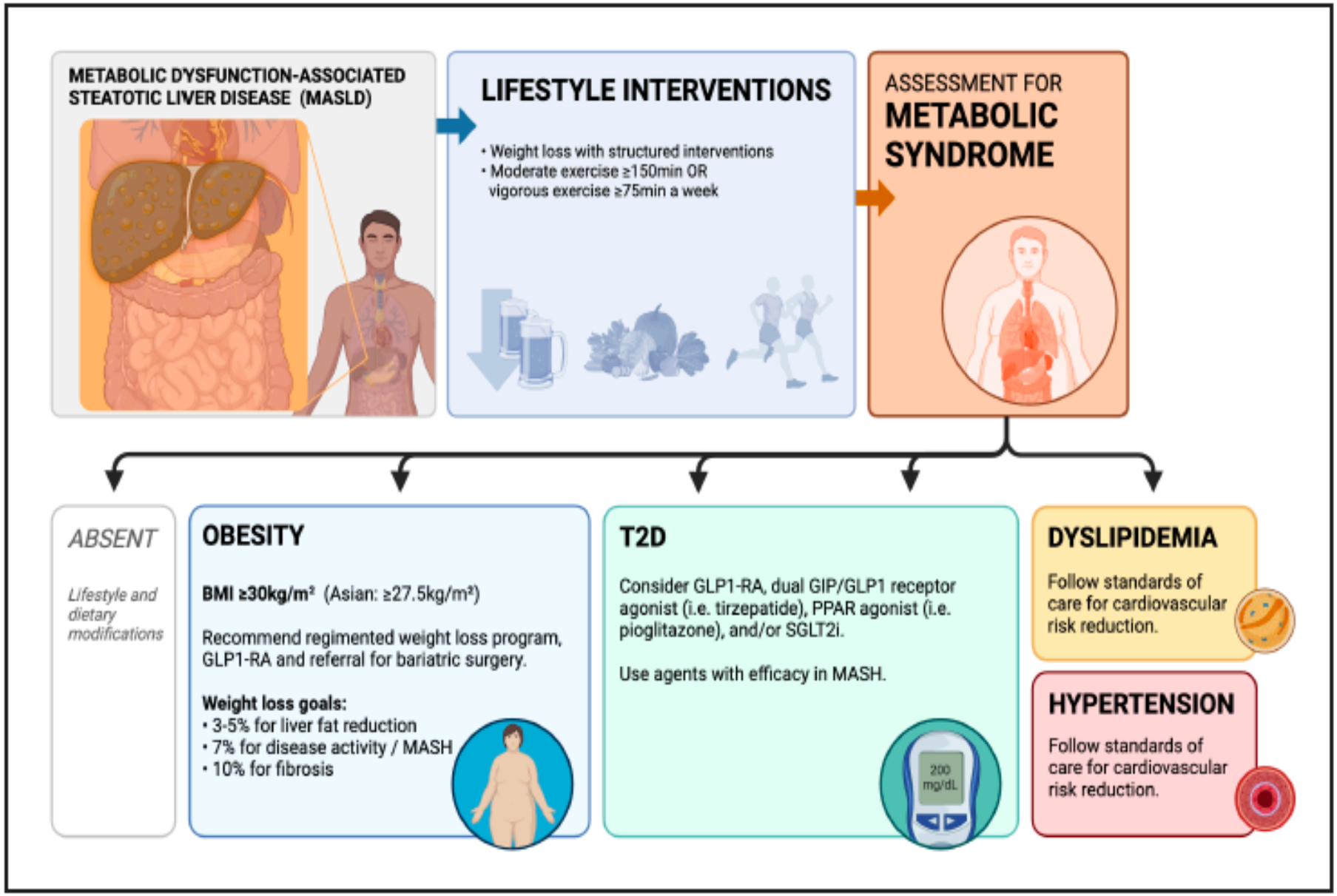


Figure 5. Treatment strategies for patients with MASLD.

Chew NWS et al. *Circulation*. 2025; 151: 98-119.

SGLT2 Inhibitor Use and Liver-Related Events: A Meta-analysis

Methods:

- Eight cohort studies
- n=626,104 with T2DM

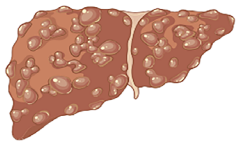
Rx

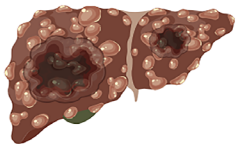
- n=228,298 SGLT2 inhibitor new users
- n=397,806 other DM medication new users

Outcomes: SGLT2 Inhibitors vs. Other Diabetes Medication

Major Adverse Liver Outcomes

HR 0.83
(95% CI 0.72-0.95)





Liver-Related Death

HR 0.64
(95% CI 0.50-0.82)

Conclusions: SGLT2 inhibitor use was associated with significant risk reduction in major adverse liver outcomes in comparison with use of DPP-4 inhibitors, metformin, or pioglitazone but not GLP-1 receptor agonists.

DM, diabetes mellitus; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HR, hazard ratio; SGLT2, sodium–glucose cotransporter 2.

Mantovani A et al. *Diabetes Care*. 2025;48:1042-1052.