GLP1-RA: "MASH resolution" e "fibrosis improvement" nel diabete mellito tipo 2

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

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

Change in Fatty Liver Disease Nomenclature: "*From NAFLD to MASLD definition*"

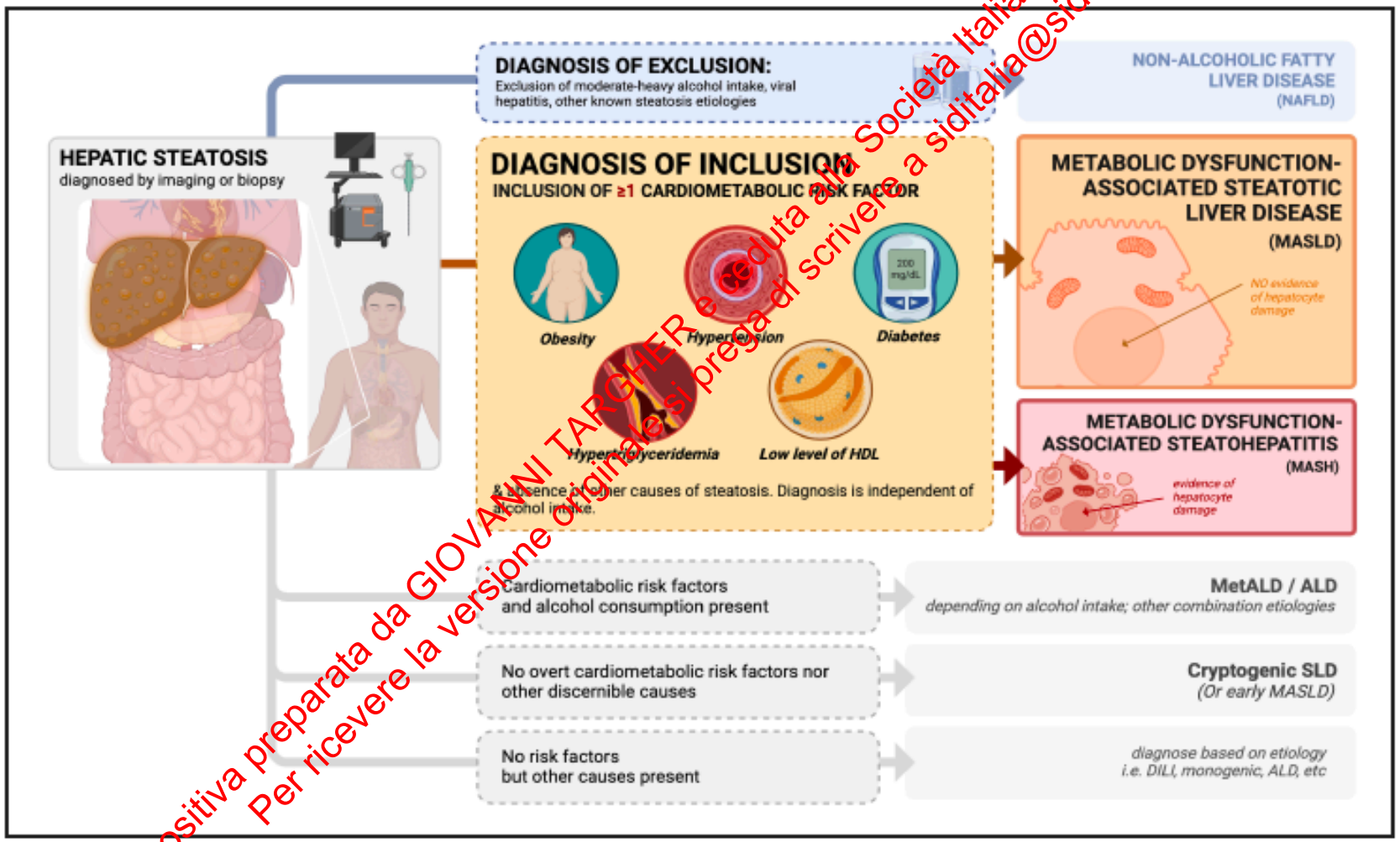
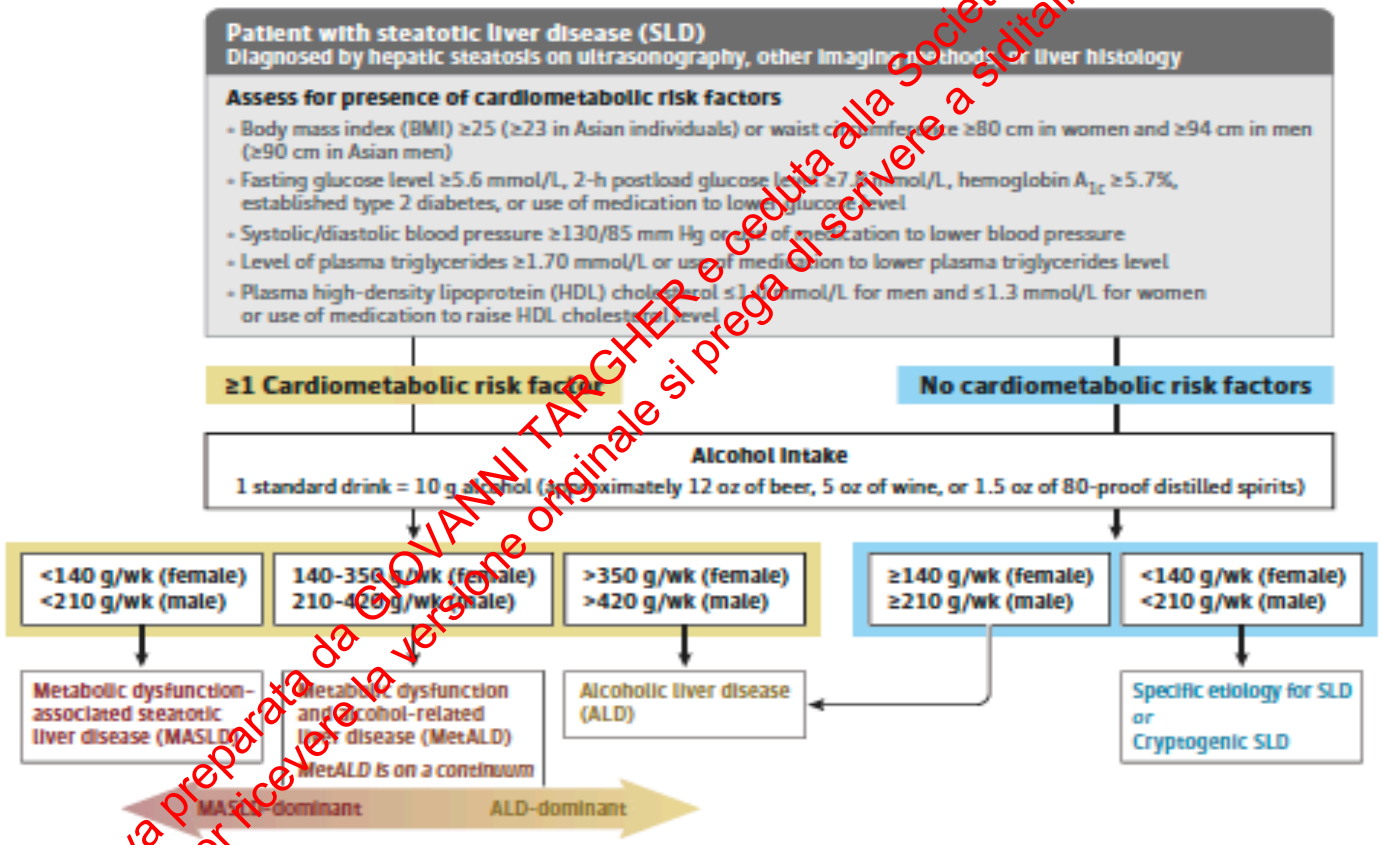


Figure 2. Comparison of the diagnostic criteria for NAFLD and MASLD.

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

New Nomenclature for Steatotic Liver Diseases

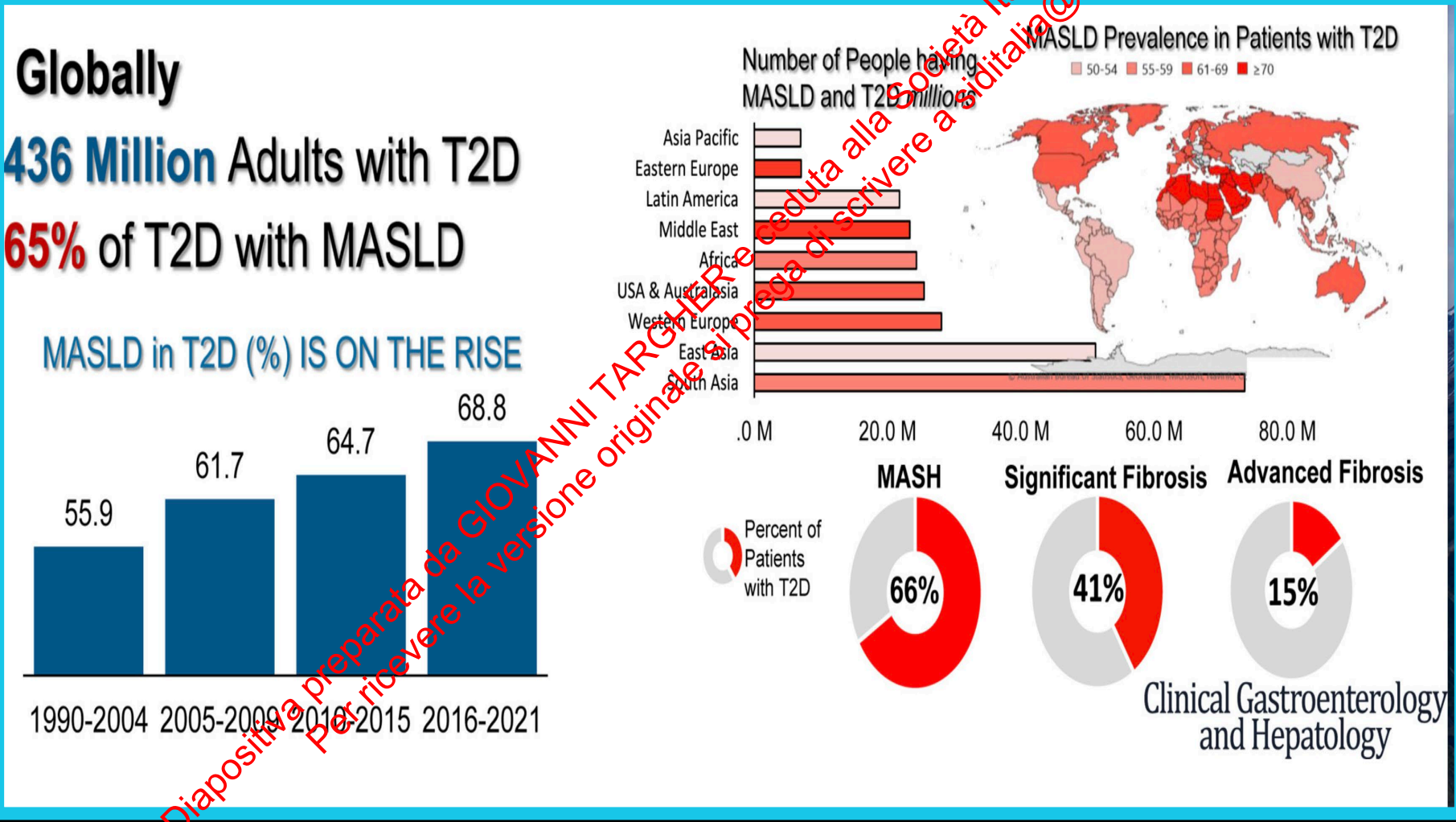
Figure 1. Flowchart Showing the Classification and Subclassification of Steatotic Liver Disease



Tilg H, Petta S, Stefan N, Targher G. *JAMA*. 2026; 335: 163-174.

Global Epidemiology of MASLD and MASH Among Patients With Type 2 Diabetes

Meta-analysis of 123 studies (*N* = 2,224,144 patients with T2DM)



Younossi ZM et al. Clin Gastroenterol Hepatol. 2024; 22: 1999-2010.

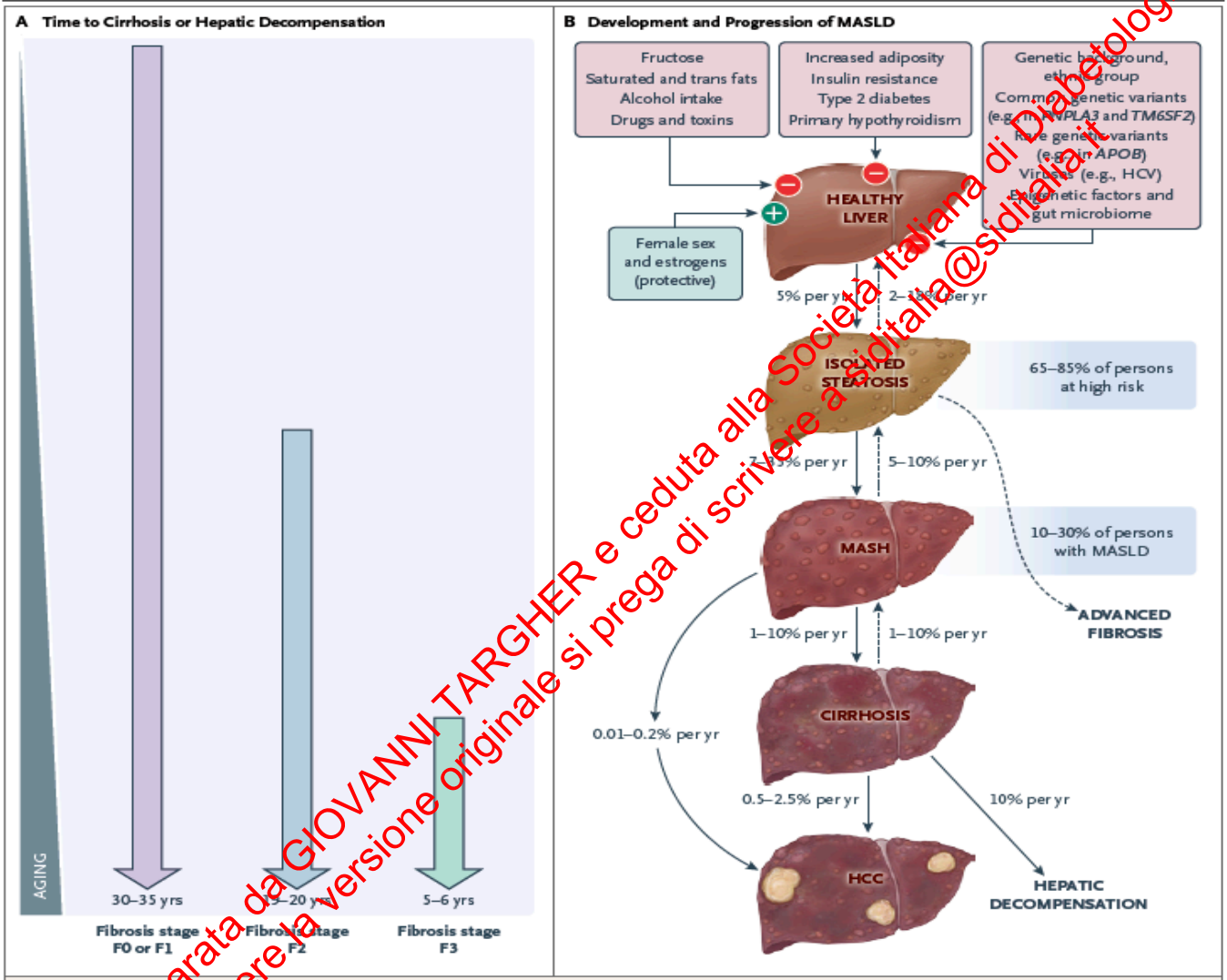


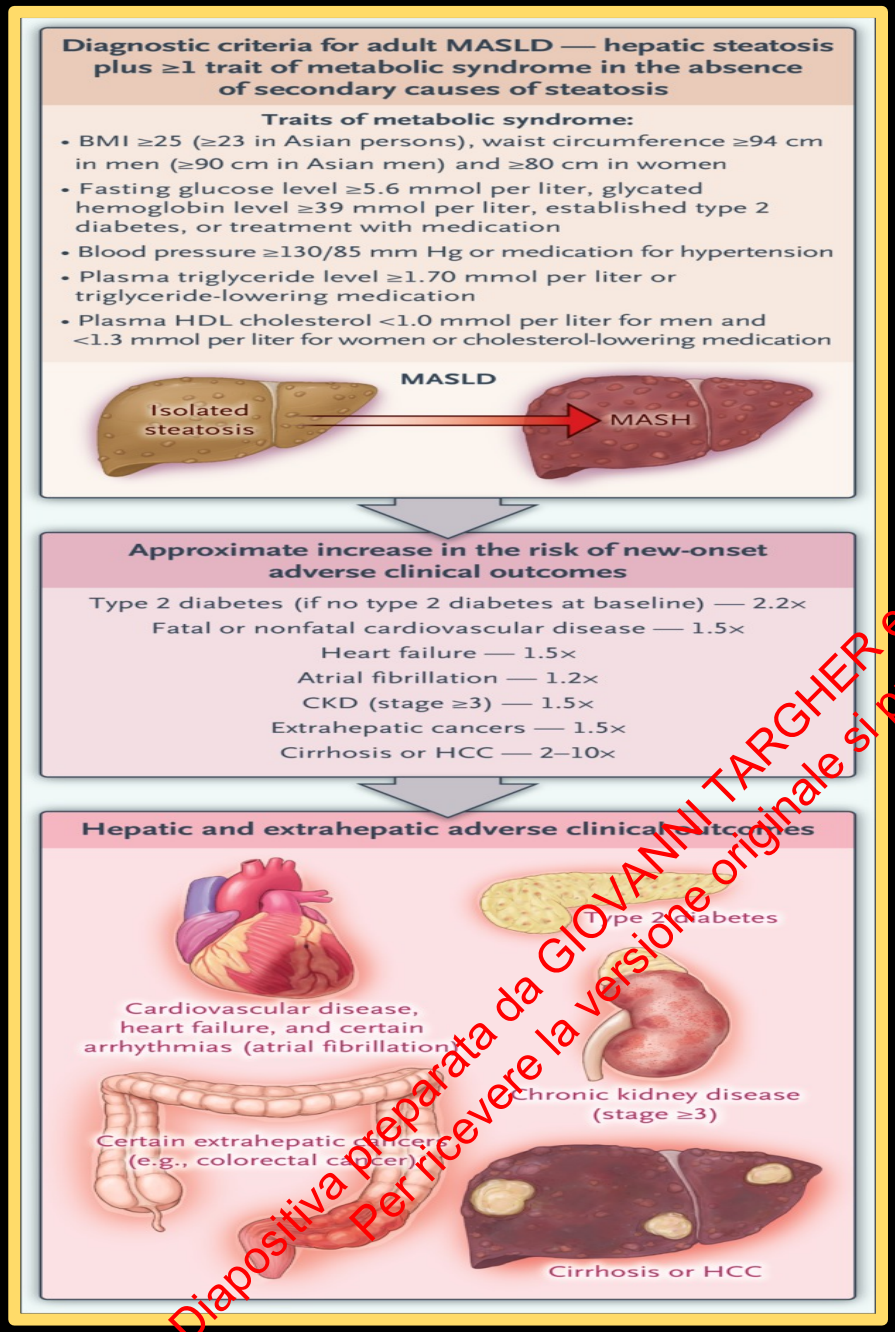
Figure 2. Natural History of Steatotic Liver Disease and MASLD.

Factors related to insulin resistance and metabolic dysfunction, diet and environmental exposures, and genetic and epigenetic factors are the main drivers of MASLD development and its progression throughout the entire spectrum of liver disease (Panel A). Female sex and hormonal factors can also modulate the development and progression of MASLD (Panel B). Ranges for years for disease progression and percentage of patients are approximations. HCV denotes hepatitis C virus.

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

Key Hepatic and Extrahepatic Clinical Outcomes of MASLD

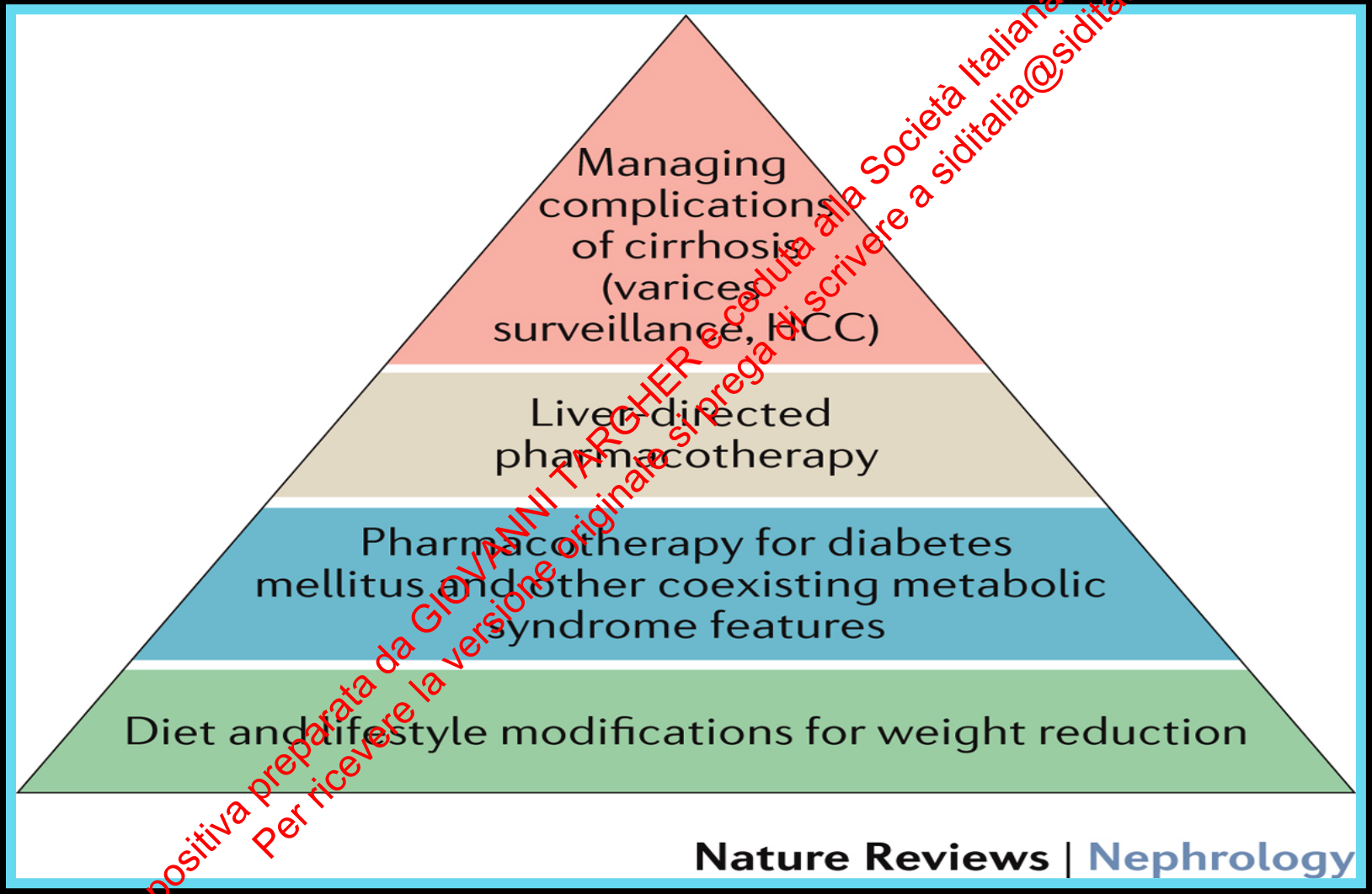
CVD is the leading cause of death in MASLD



The NEW ENGLAND JOURNAL of MEDICINE

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

Management and therapeutic strategies for MASLD in individuals with T2DM



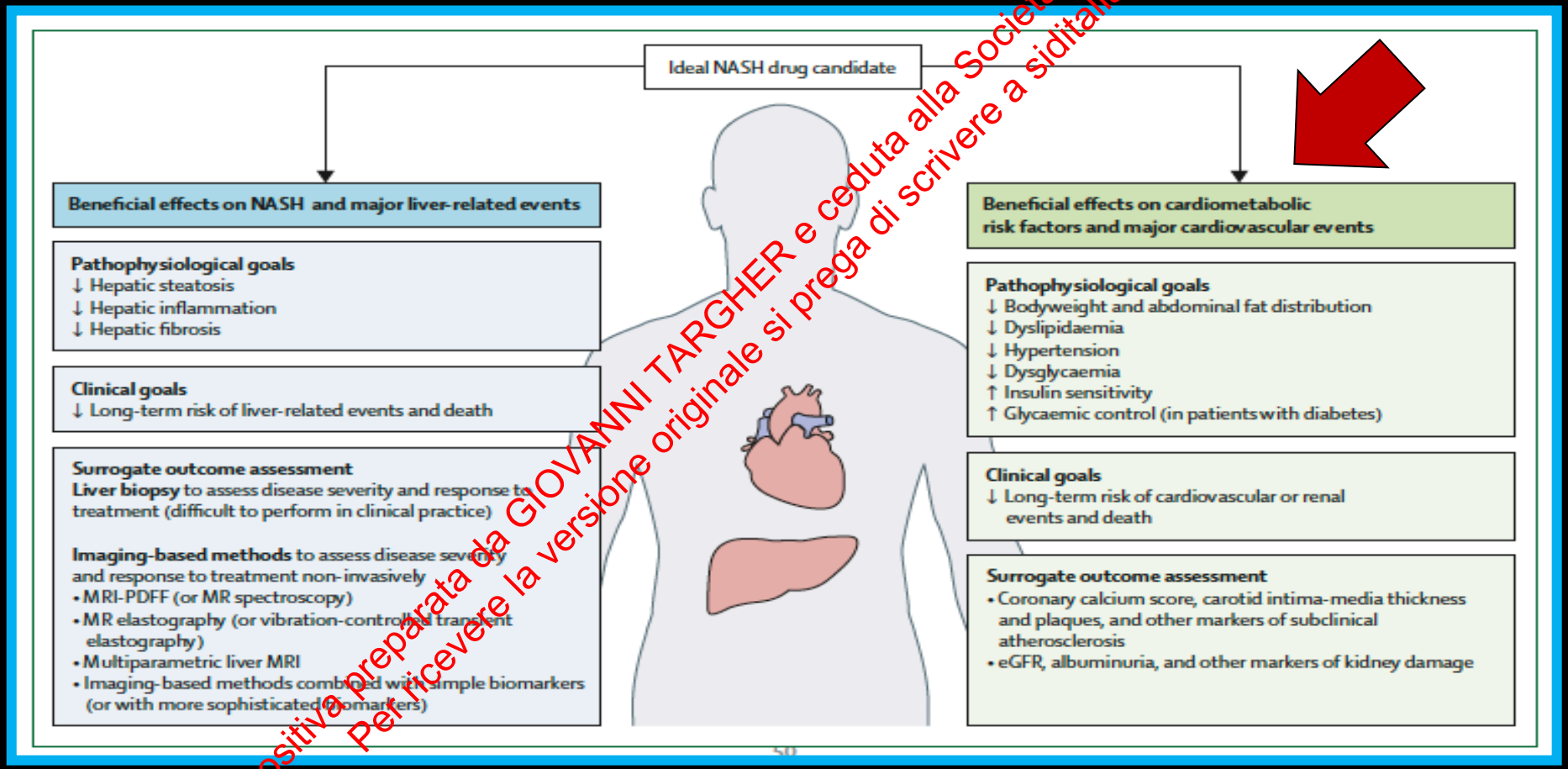
Targher G, et al. *Nat Rev Nephrol.* 2017; 13: 297-310.

Approval of a drug candidate for MASH therapy

- The FDA and EMA currently accept **«MASH resolution without worsening of fibrosis»** *and* **«Fibrosis improvement without worsening of MASH»** as primary histological endpoints for **conditional and accelerated drug approval**.

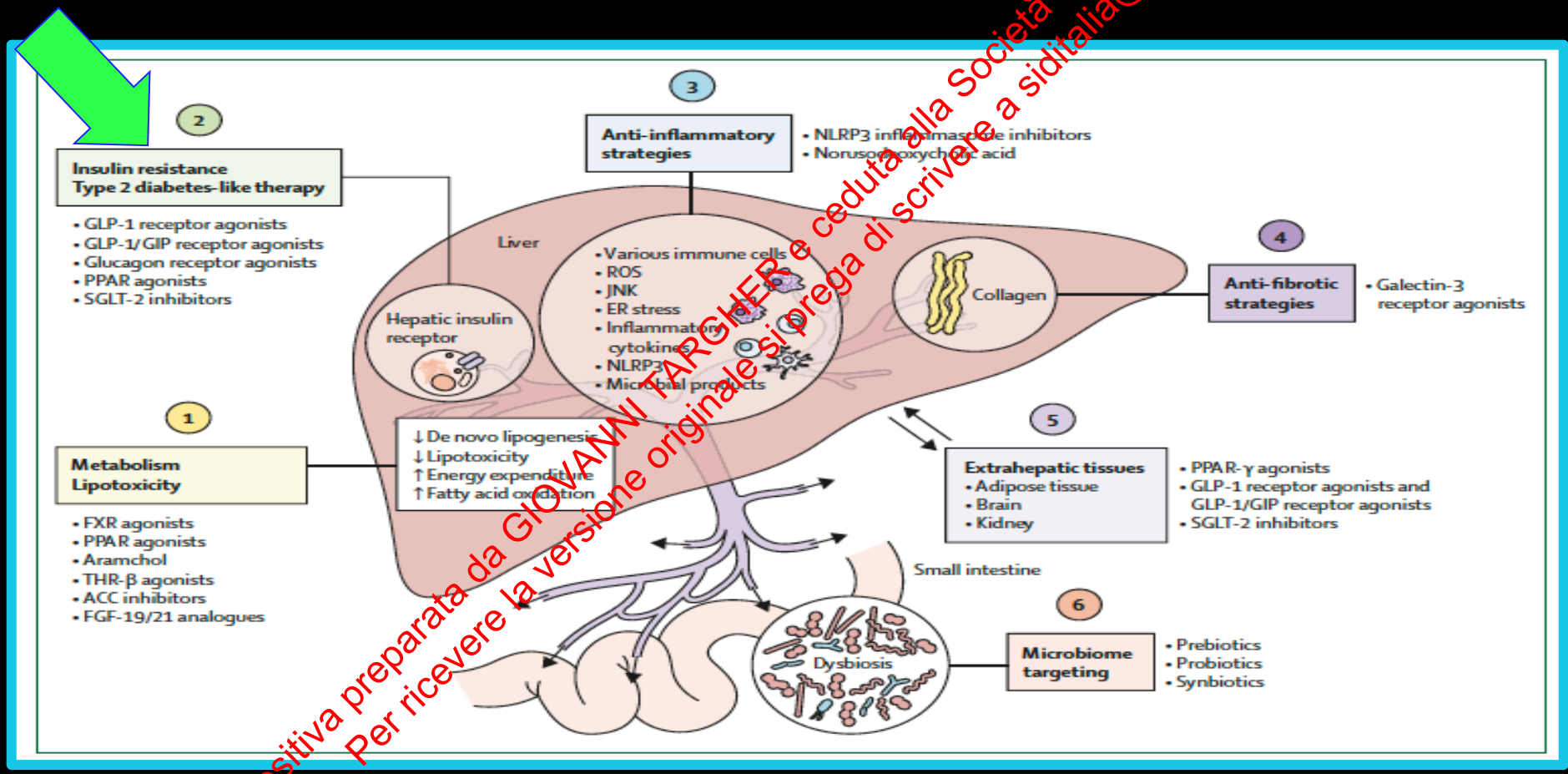
- For **full regulatory approval**, sponsors must ultimately demonstrate long-term clinical benefits, such as risk reductions in major liver-related outcomes (new-onset cirrhosis, hepatic decompensation, HCC, and liver-related deaths).

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



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

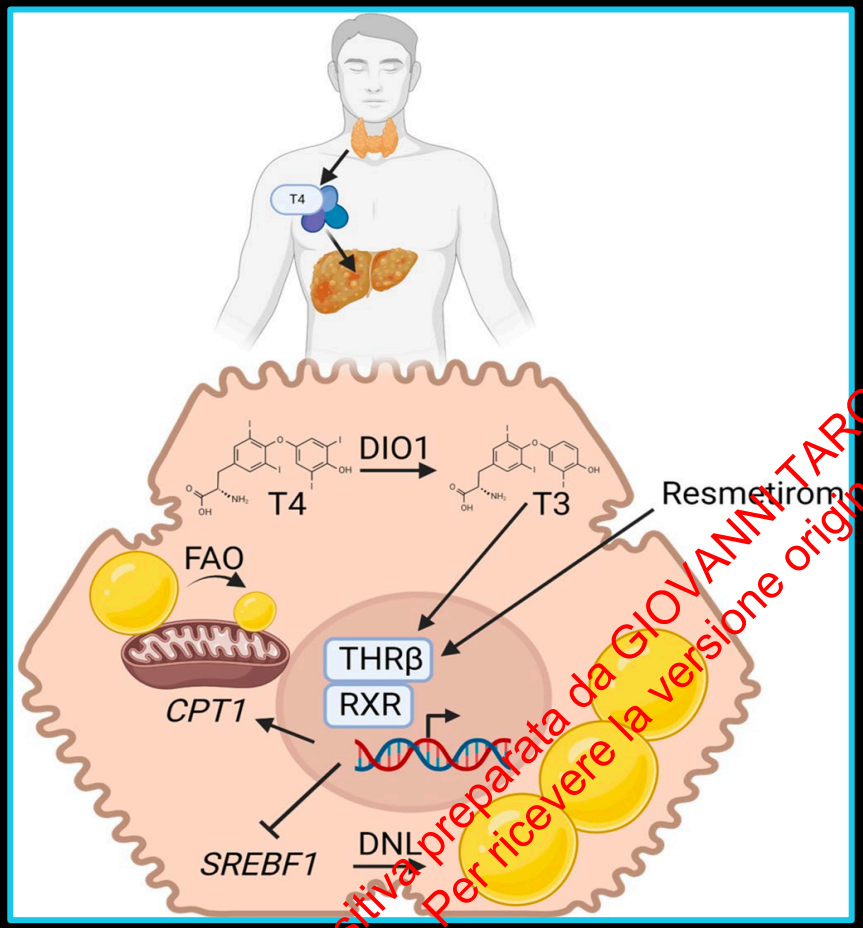
Current «*treatment targets*» based on pathophysiological concepts in MASLD/MASH

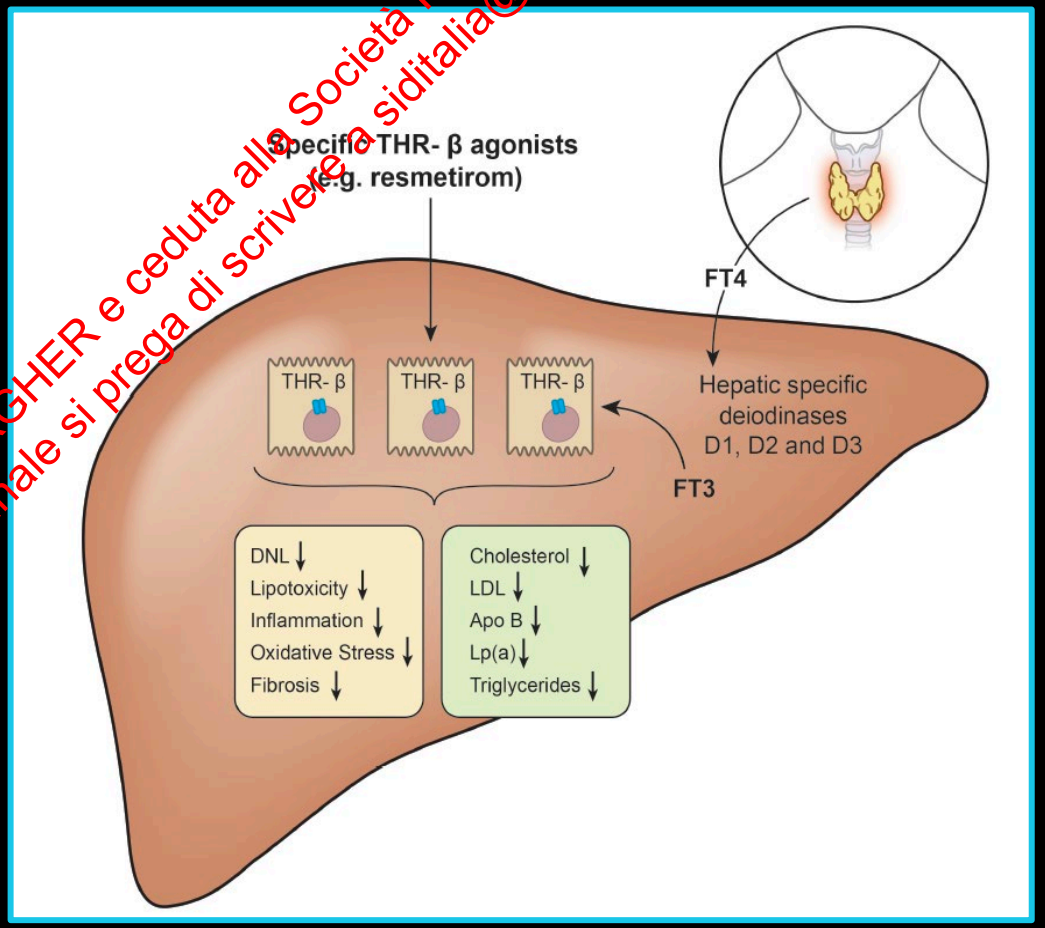


Tilg H, Byrne C, Targher G. *Lancet Gastroenterol Hepatol.* 2023; 8: 943-954.

Resmetirom for MASH and liver fibrosis

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





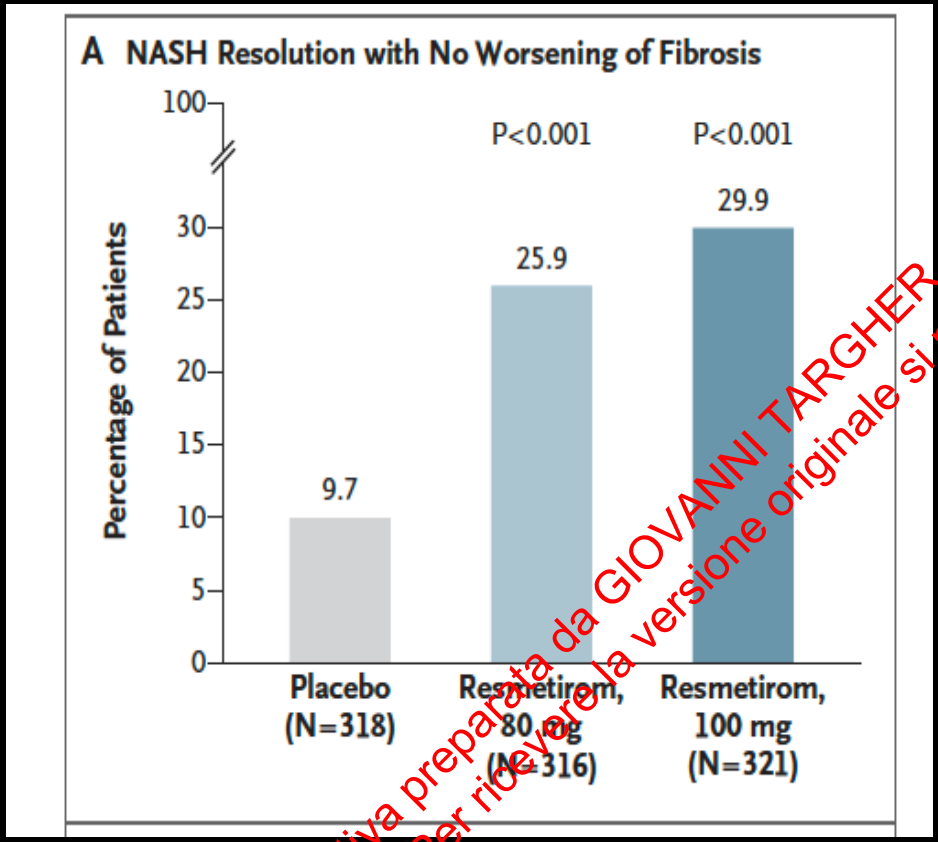
Petta S, Targher G, et al. *Liver Int*. 2024;44:1526-1536.

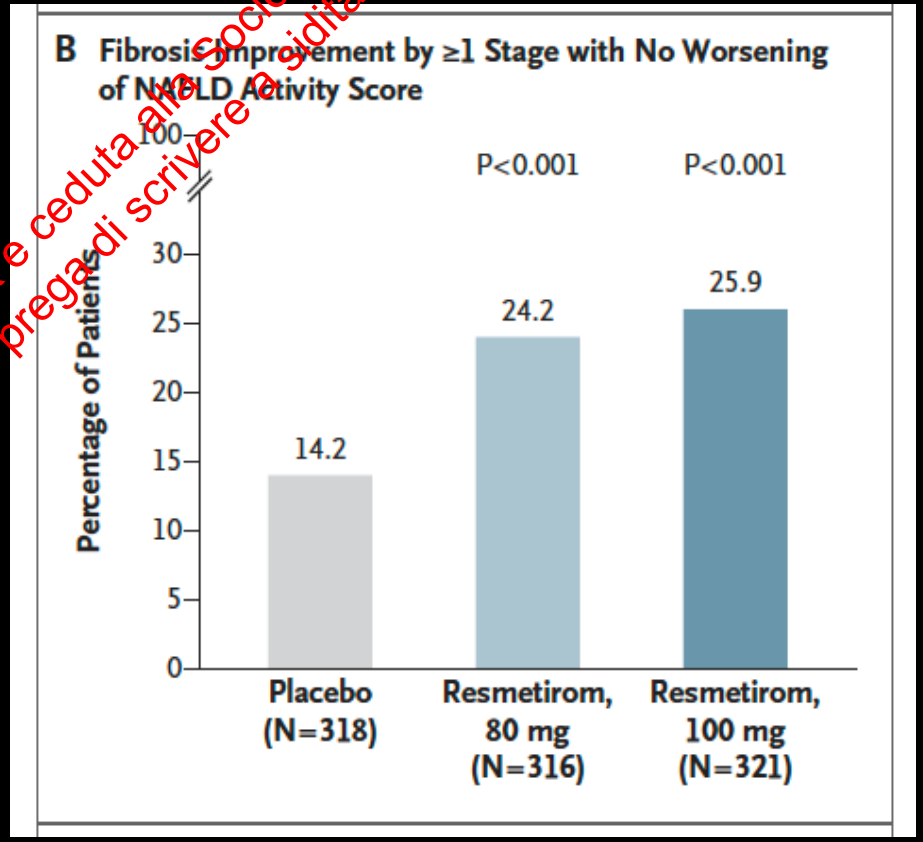
Byrne CD, Targher G, Tilg H. *Gut*. 2024;73:573-581.

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)

Semaglutide for MASH and liver fibrosis

(drug conditionally approved by FDA, 15 August 2025 and by EMA, 30 January 2026)

Phase 3 placebo-controlled ESSENCE trial: 800 patients with biopsy-proven MASH and moderate-severe liver fibrosis (F2-F3 stages) treated with subcutaneous semaglutide 2.4 mg/week for 72 weeks (BMI 34 kg/m^2, 55% had T2DM)

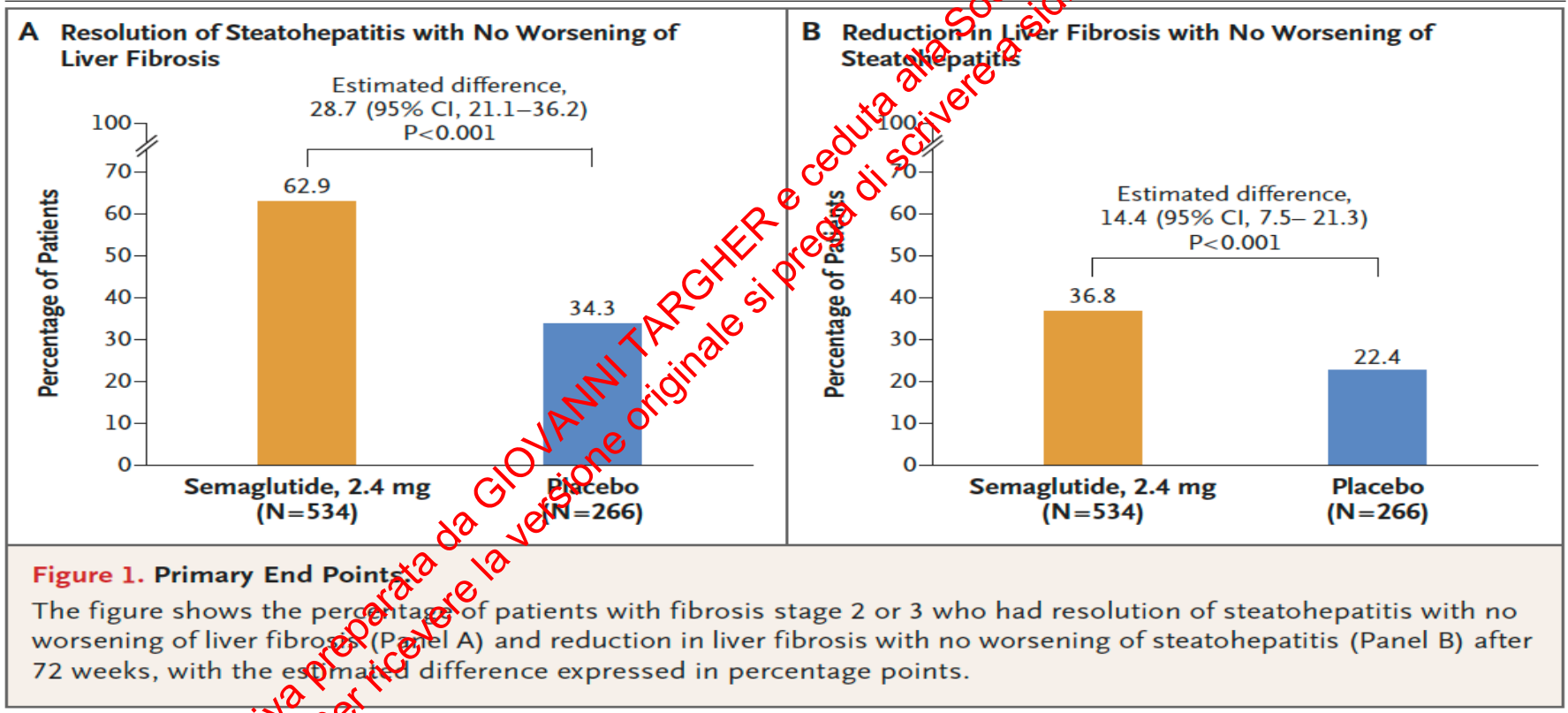


Figure 1. Primary End Points.

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

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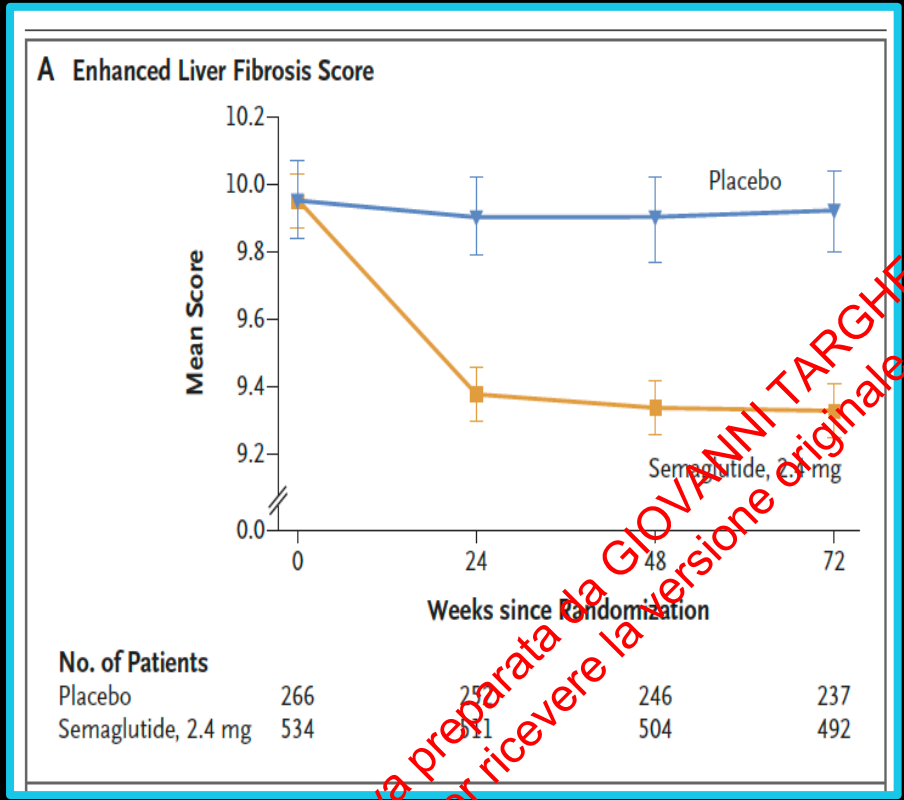
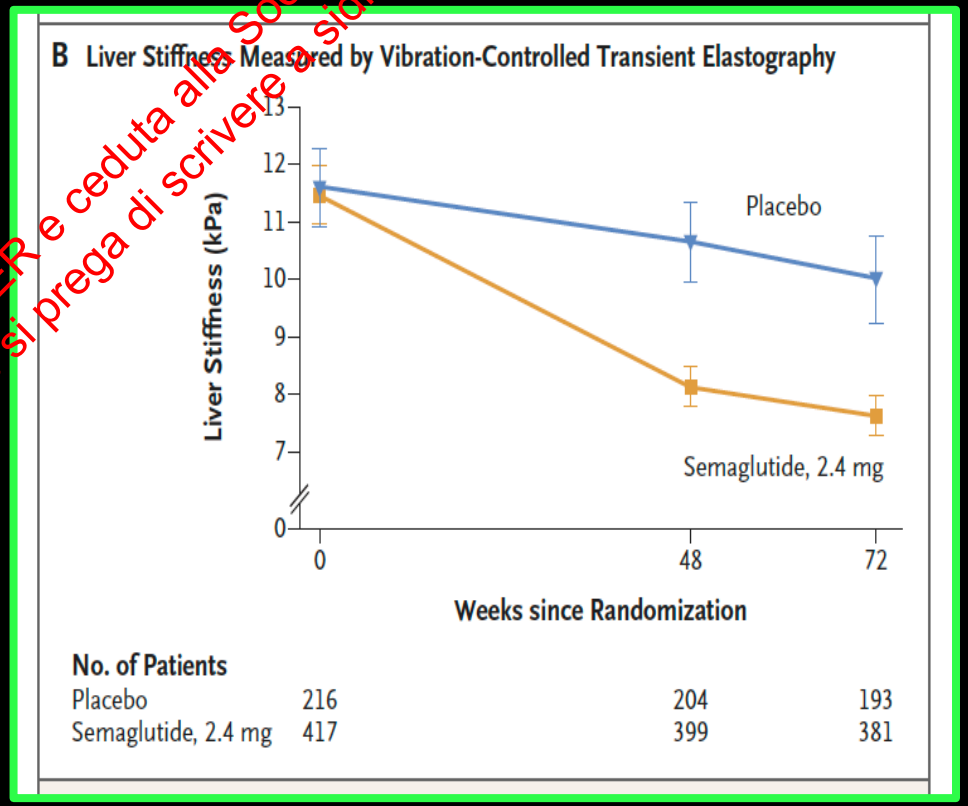




Sanyal AJ et al. *N Engl J Med*. 2025; 392: 2089-2099.

Semaglutide for MASH and liver fibrosis

(drug conditionally approved by FDA, 15 August 2025 and by EMA, 30 January 2026)

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	−0.41	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	−53.80	−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

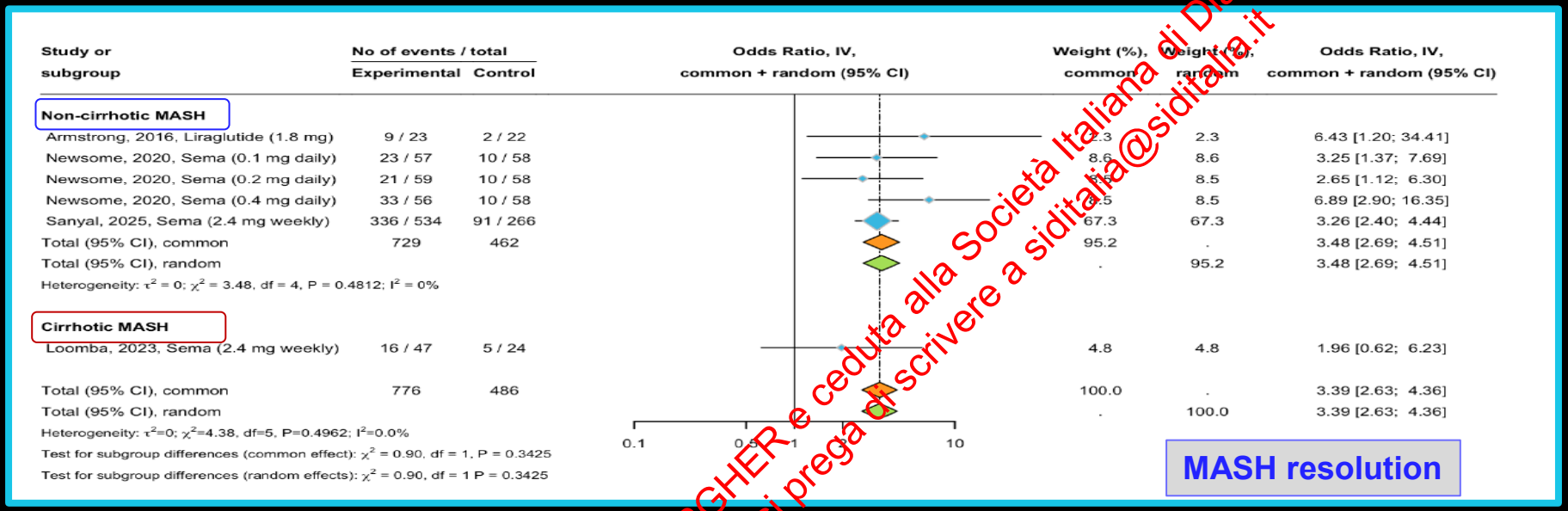
(drug conditionally approved by FDA, 15 August 2025 and by EMA, 30 January 2026)

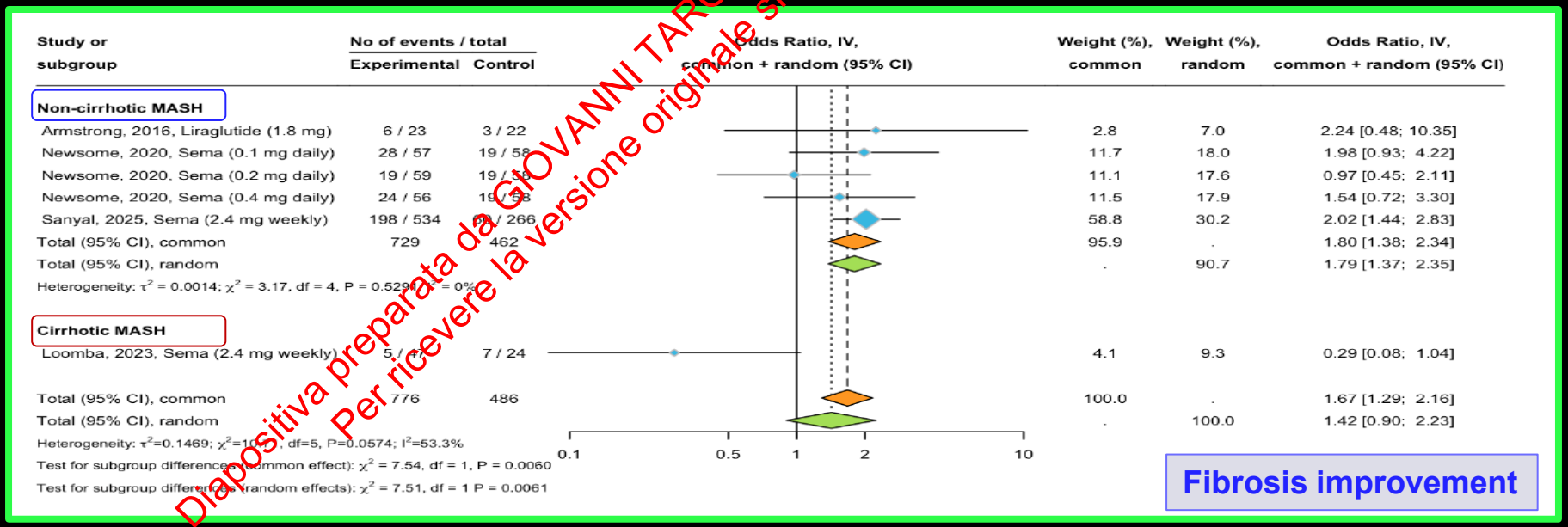
Table 3. Safety Analysis Population.*

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.

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

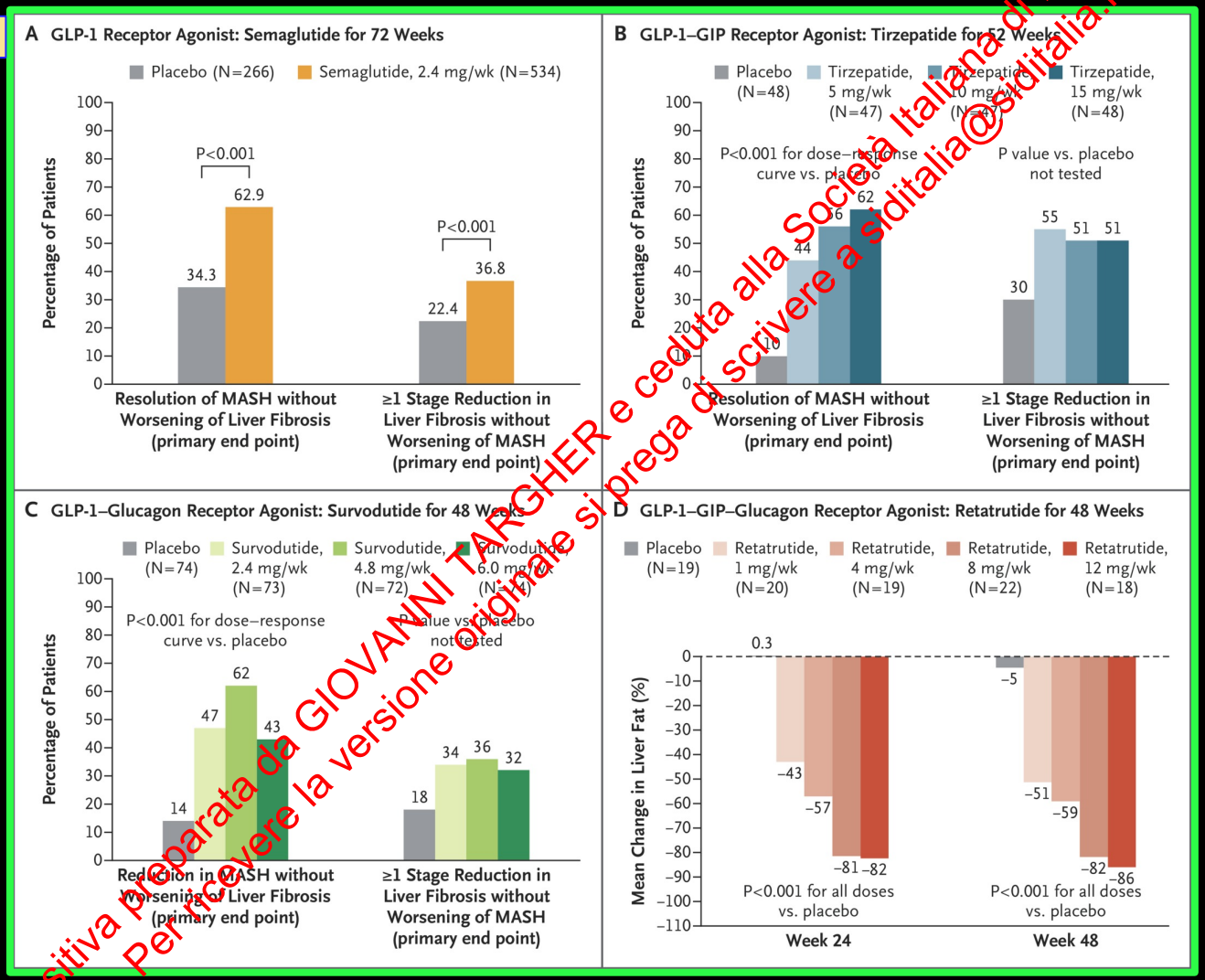




Mantovani A et al. *Liver Int*. 2025;45:e70256.

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.

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 Q. 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]

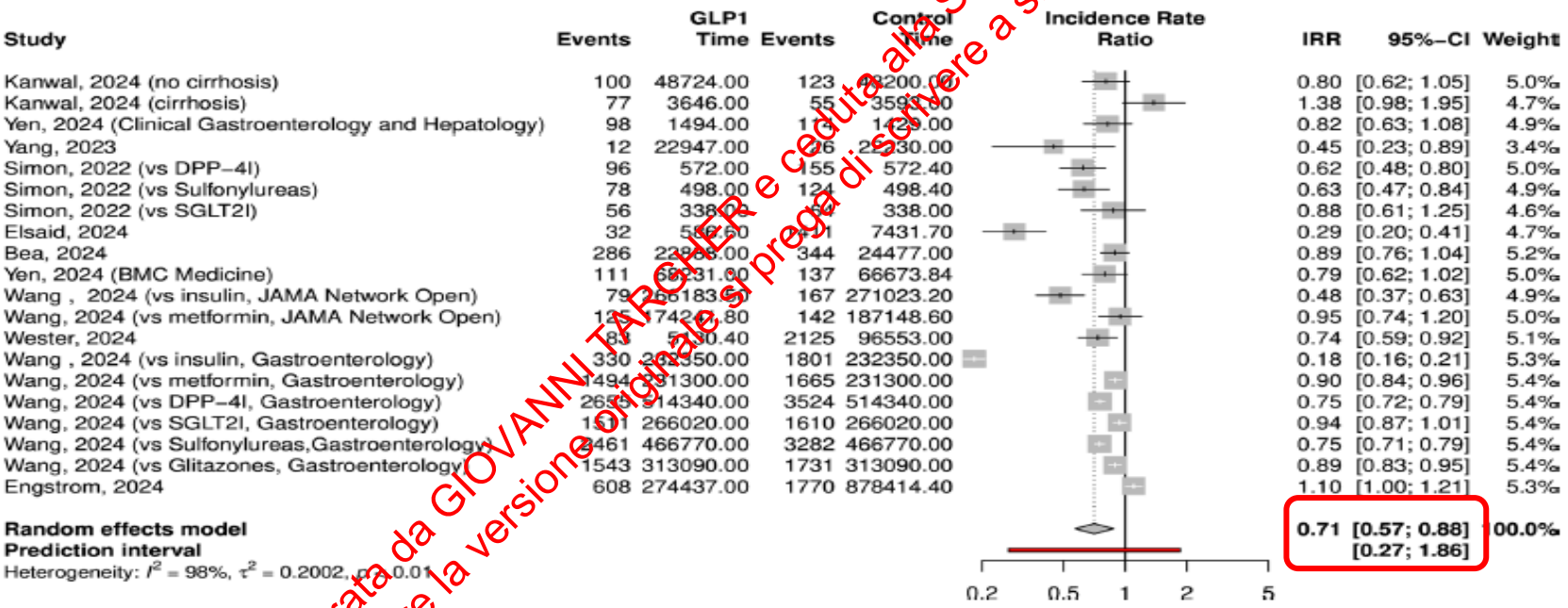
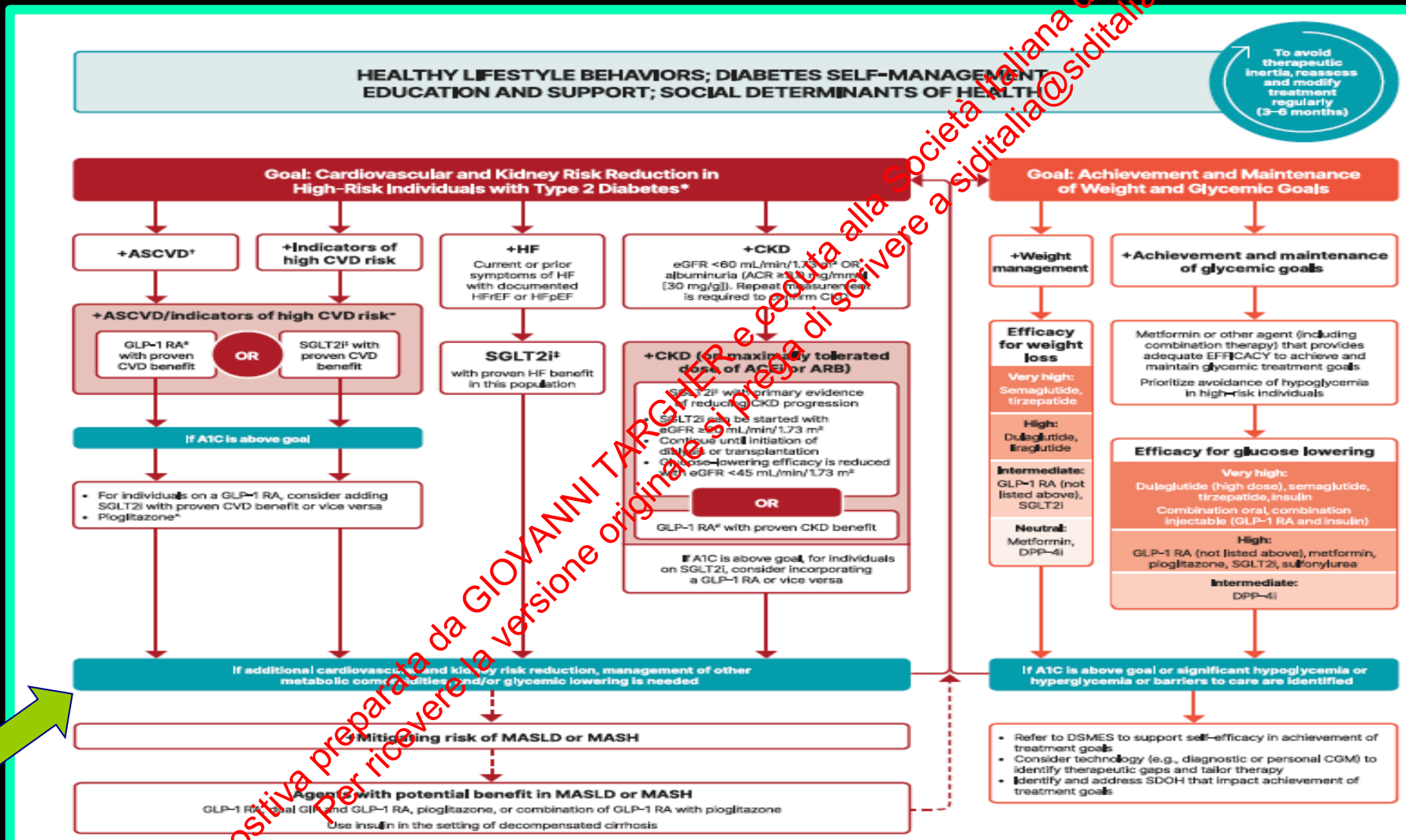


Figure 1 Forest plot and pooled estimates of the long-term effect of GLP-1RA use on the risk of developing major adverse liver-related outcomes (MALOs) (n=11 retrospective cohort studies, including 647 903 GLP-1RA new users and 819 317 GLP-1RA non-users). MALOs were defined as occurrence of hepatic decompensation 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, new-onset HCC, or liver-related death.

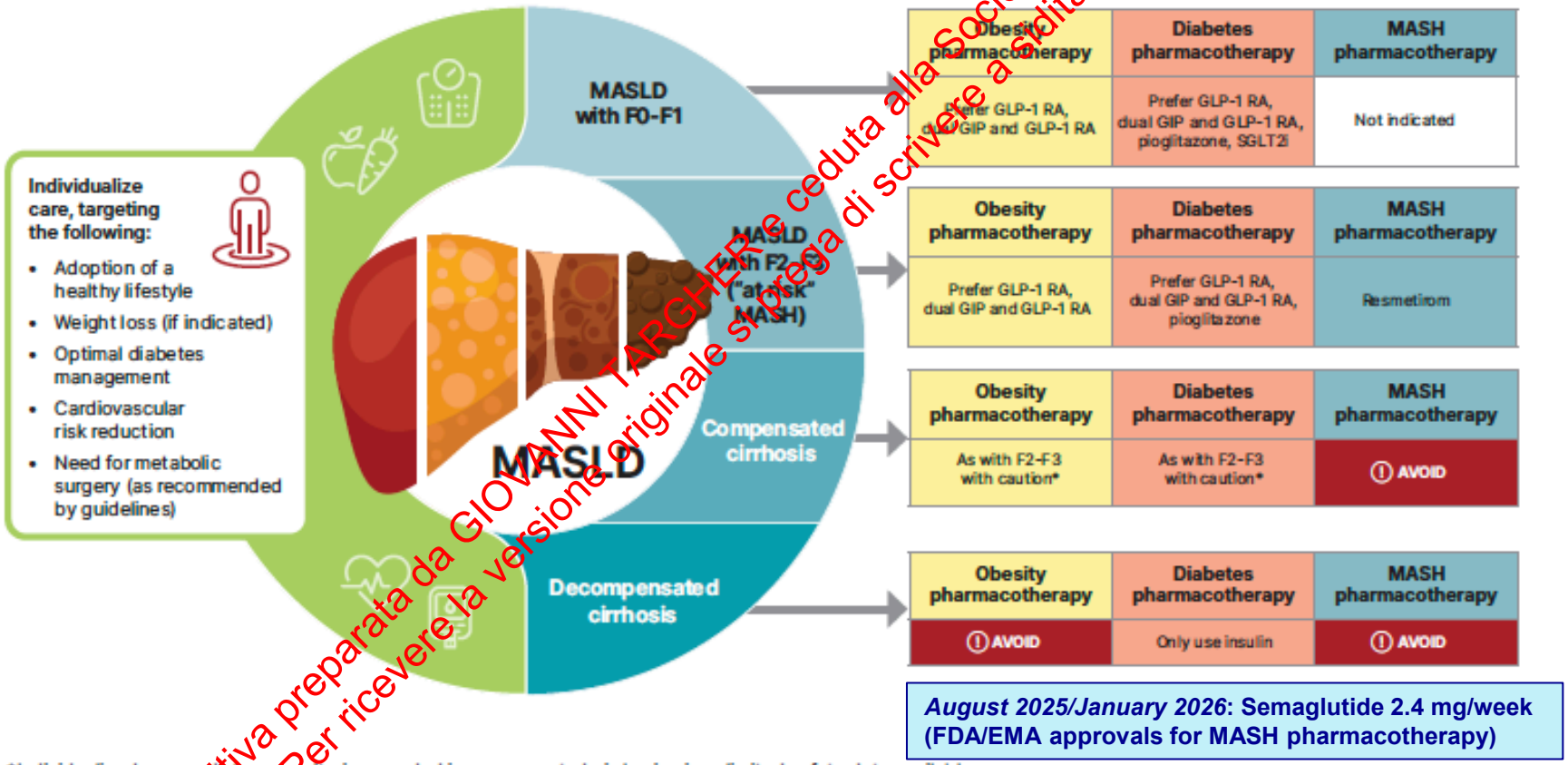
Celsa C et al. *Gut*. 2025; 75: 815-824.

Use of glucose-lowering medications in the management of T2DM (& MASLD)



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

Treatment algorithm for MASLD in T2DM



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

Grazie per l'attenzione!

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

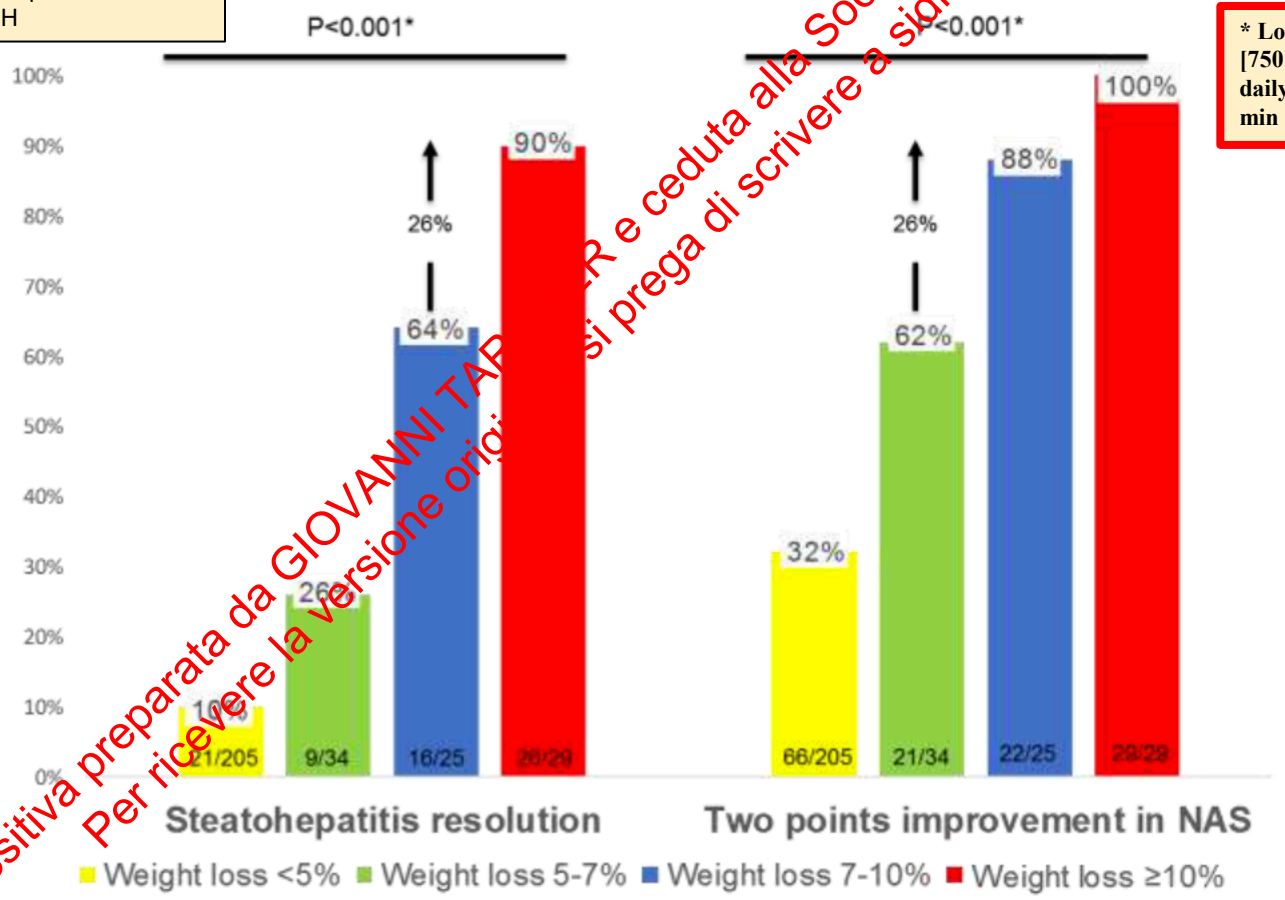
n=293 NASH ± fibrosis

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.

52 weeks of lifestyle intervention

% Weight loss (WL)	5%	7%	10%
NASH-resolution	10%	26%	64%	90%
FIBROSIS-regression	45%	38%	50%	81%
STEATOSIS improvement	35%	65%	76%	100%
% Patients achieving WL	7%	12%	9%	10%

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.