CURSO DE AVANCES EN GASTROENTEROLOGÍA
"BUENAS PRÁCTICAS EN GASTROENTEROLOGÍA"

MASLD: Avances en la nomenclatura y el tratamiento

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Conflictos de intereses

- 1.- Estudios clínicos: PI en Chile (PUC) en los siguientes estudios:
    - Native3 (Lanifibranor in NASH, Inventiva)
    - Fortuna trial (ASO PNPLA3 in MASLD)
    - Symphony trial (Efrufixermin in MASH-cirrhosis)
    - LiverAge (Survodutide in MASH, MASH-cirrhosis)

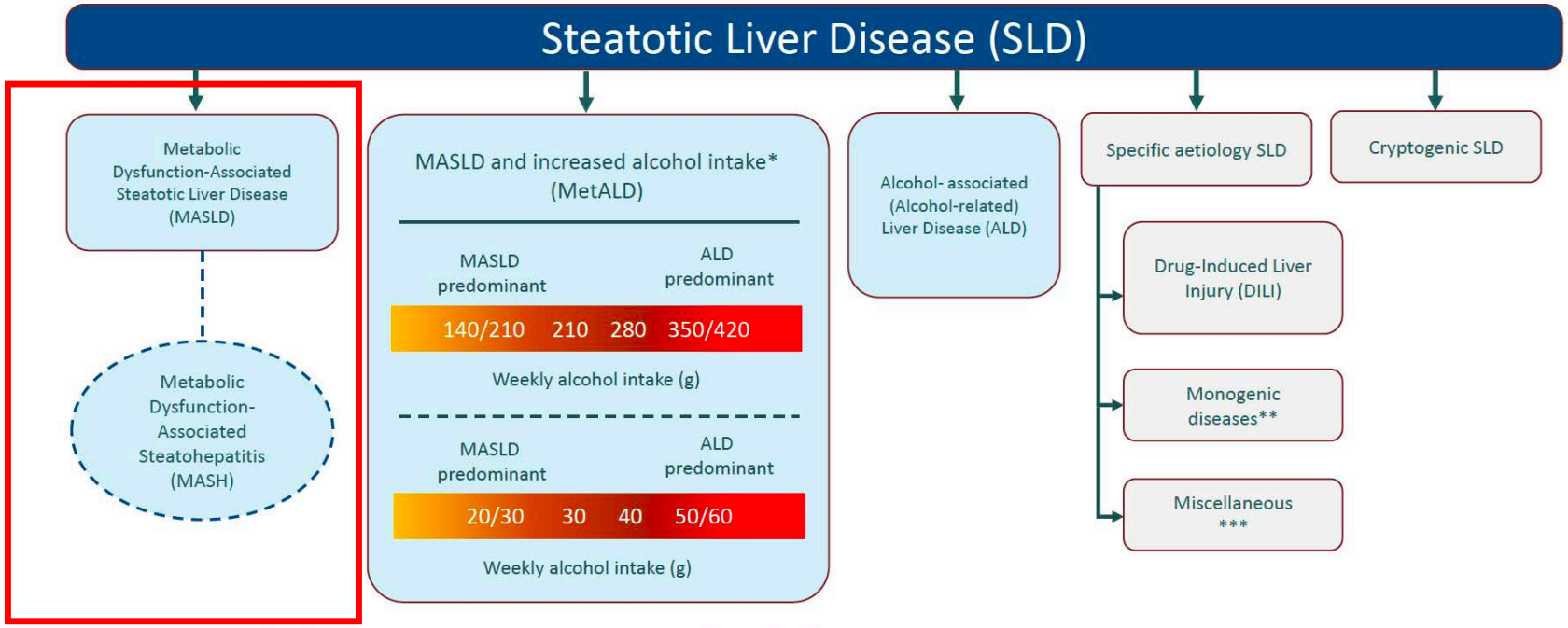
2.- PI FONDECYT Project # 1241450 (ANID, CHILE).

3.- Consultant/speaker/steering committee: Inventiva, Astra Zeneca, Siemens, Novo Nordisk

TOPICOS DE LA PRESENTACION

- De NAFLD a MASLD: cambio de nomenclatura
- Principios terapéuticos
- Farmacoterapia: presente y futura

A paradigm shift: New SLD nomenclature



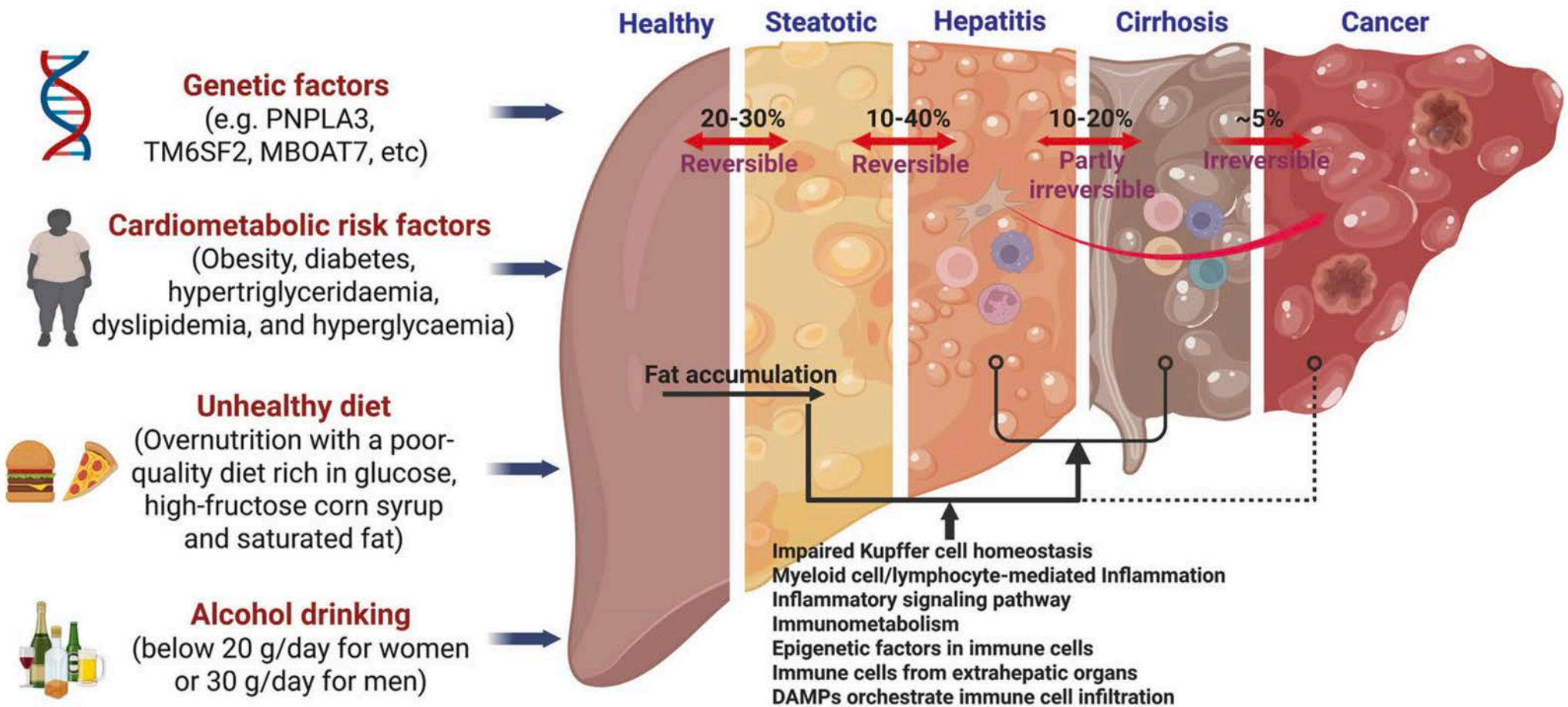
*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)

**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism

***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

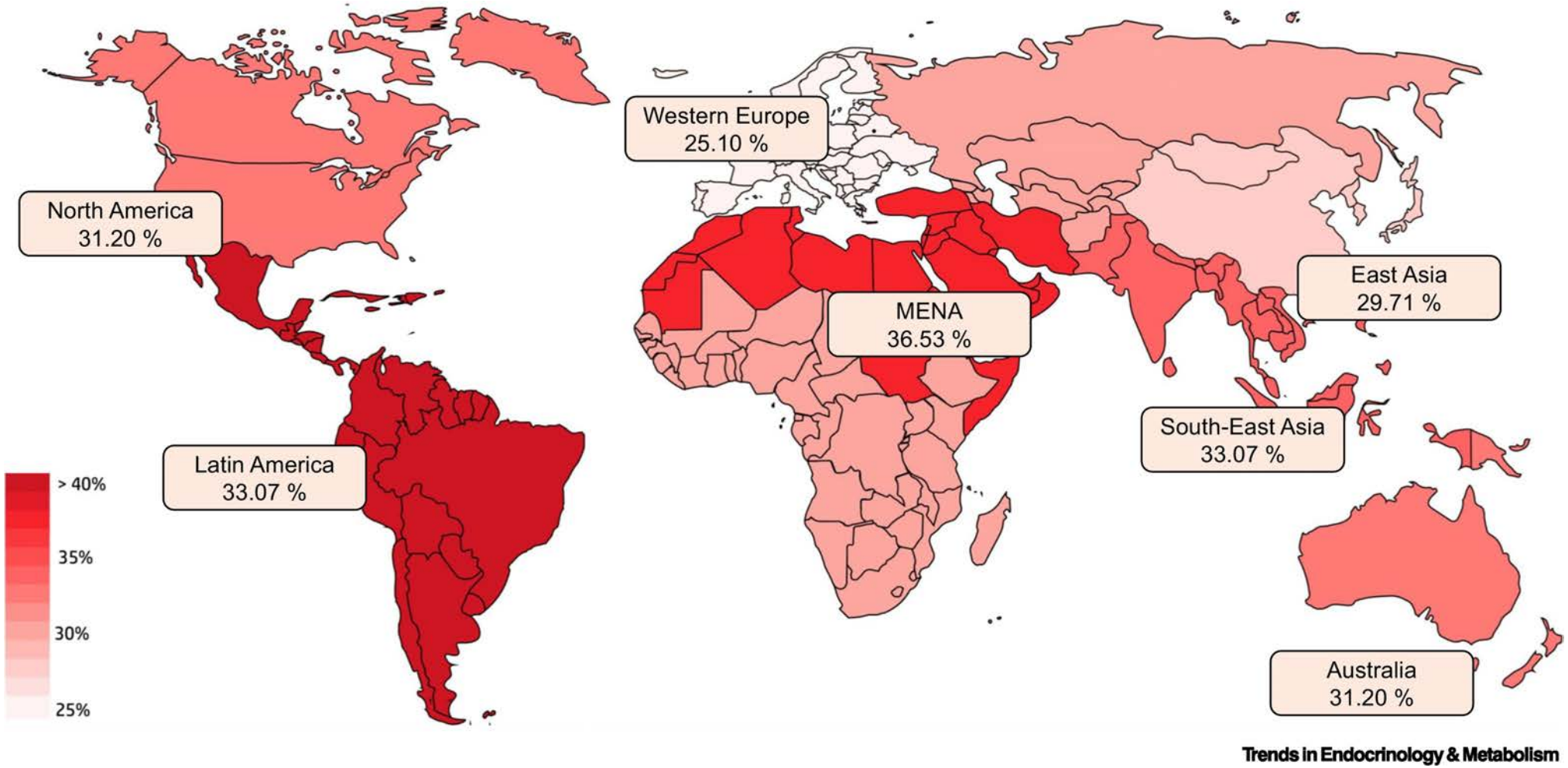
Adapted from Rinella ME, et al. Hepatology 2023

*†MASH is under the umbrella term, MASLD; *weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male); **e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism; ***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease; HCP, health care professionals. Modified from Rinella, ME et al. Hepatology. 2023. doi: 10.1097/HEP.0000000000000520*



He et al. Cellular & Molecular Immunology 2025

MASLD: a global health threat



Miao et al. Trends in Endocrinology & Metabolism 2024

Research Article
MASLD and Alcohol-Related Liver Diseases

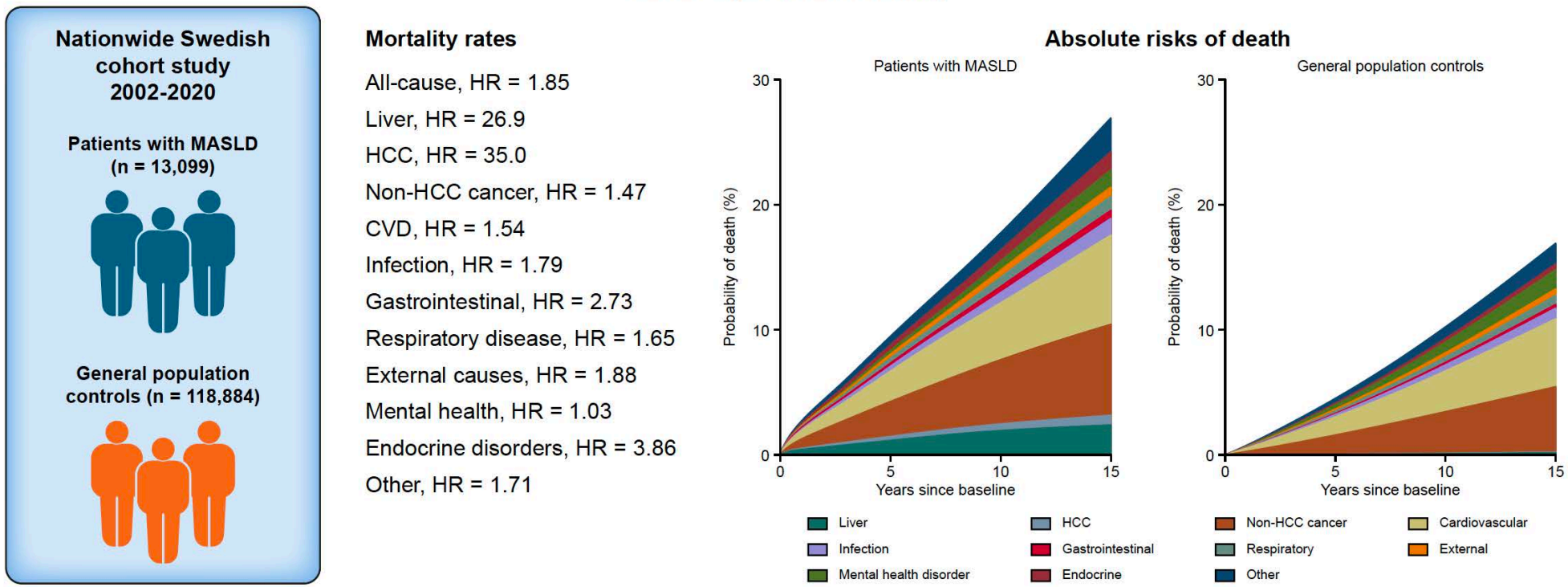
JOURNAL
OF HEPATOLOGY

Cause-specific mortality in 13,099 patients with metabolic dysfunction-associated steatotic liver disease in Sweden

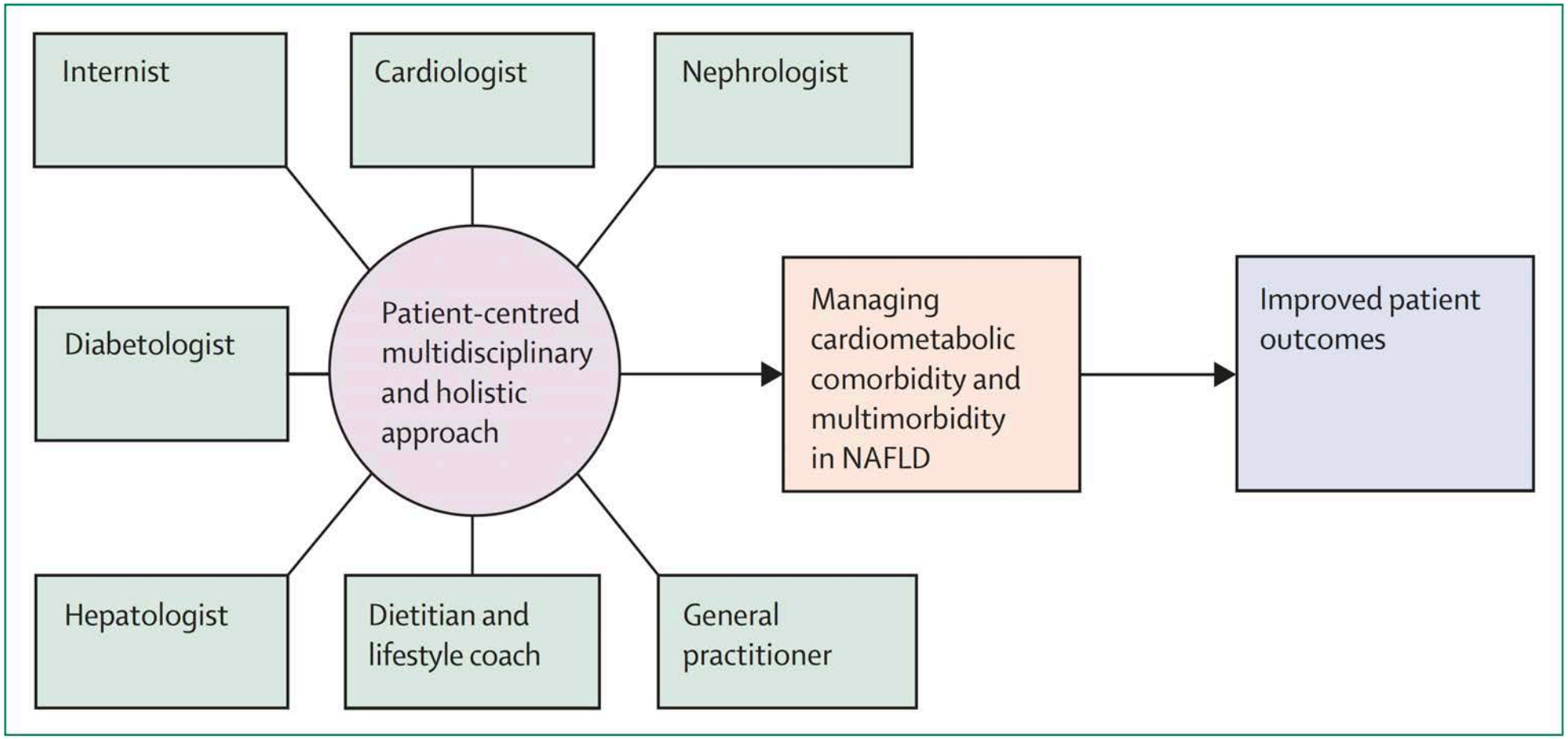
Authors

Gabriel Issa, Ying Shang, Rickard Strandberg, Hannes Hagström, Axel Wester‡

Graphical abstract

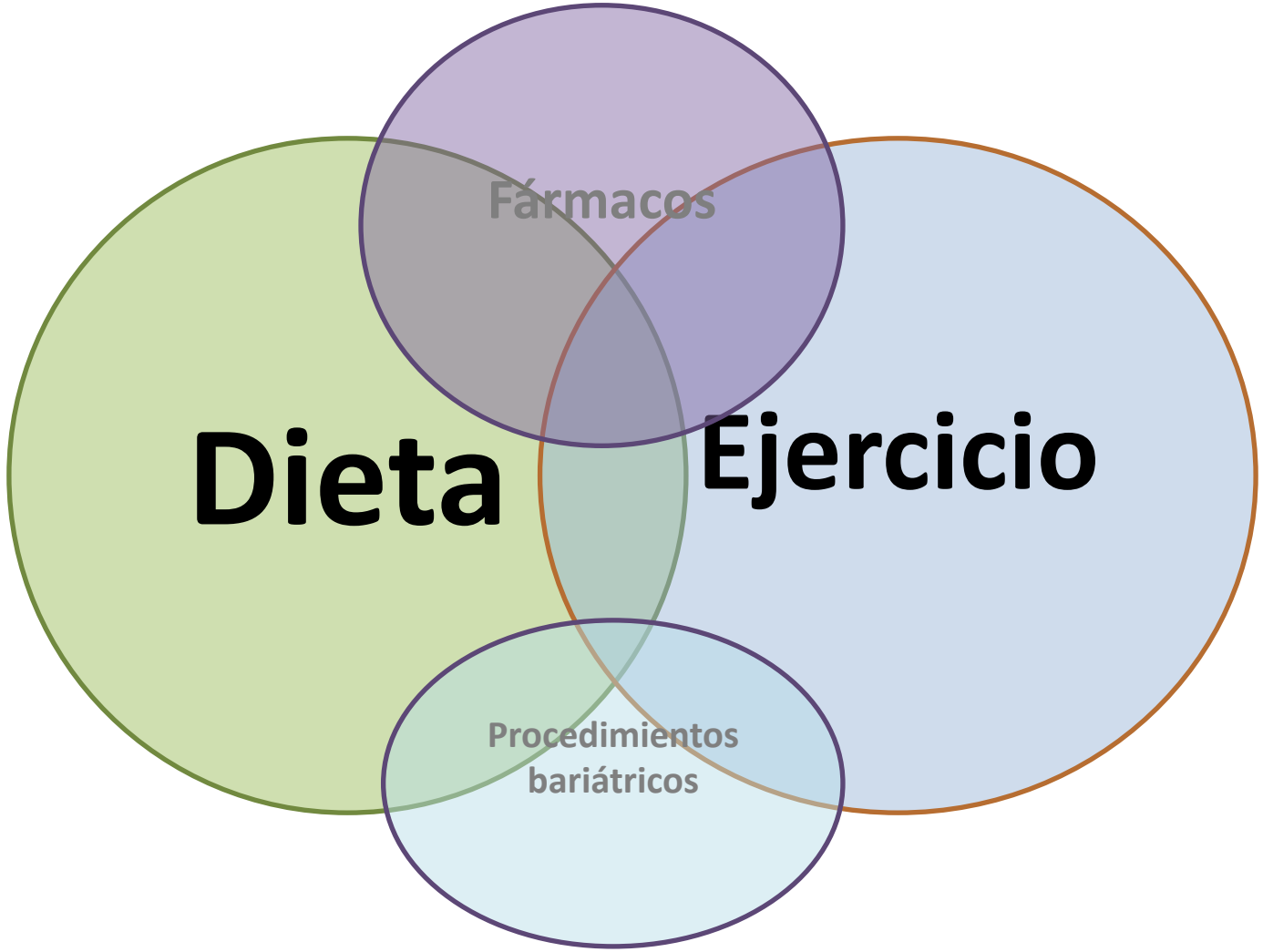


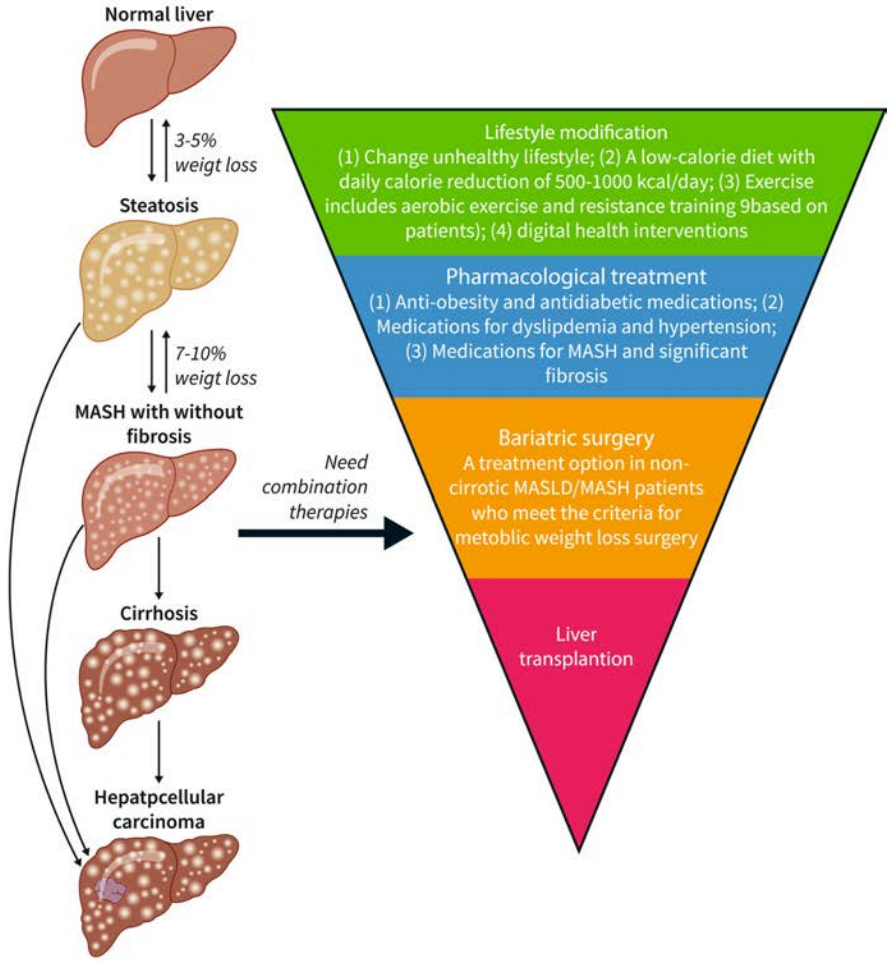
Holistic and personalized treatment in MASLD



Lancet Gastroenterol Hepatol 2021; 6: 578–88

MASLD: Opciones terapéuticas



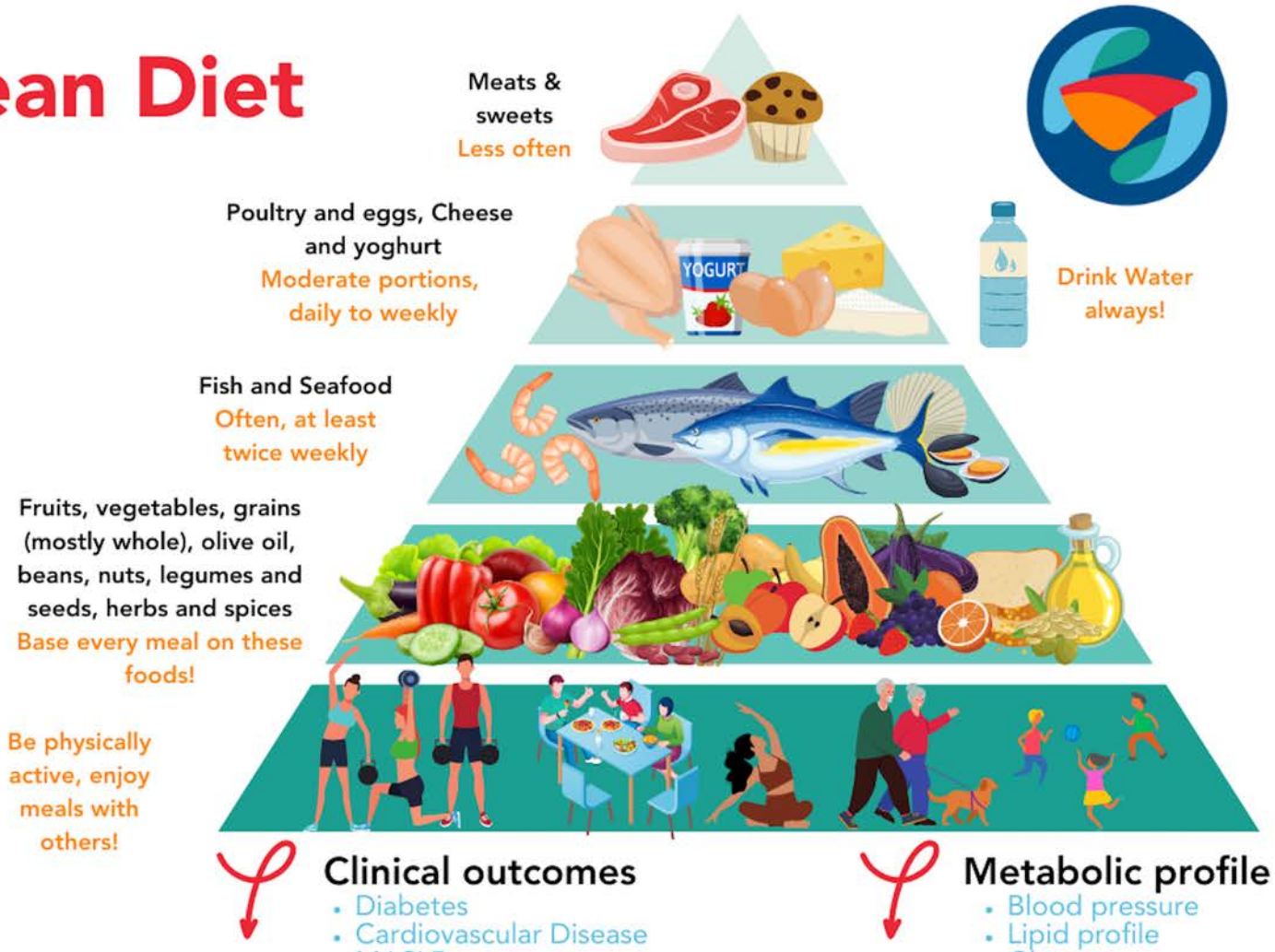


EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) Journal of Hepatology 2024;81:492–542.

The Mediterranean Diet

The Mediterranean diet (MD) is the best diet recommended for managing MASLD (Metabolic dysfunction-associated steatotic liver disease), according to experts from EASL, EASD, and EASO.
Unlike low-fat diets, the Mediterranean diet not only helps with long-term weight loss but also improves liver health and metabolism, even if you don't lose weight.
It is also one of the best diets for preventing Type-2 diabetes and heart disease, as proven by high-quality scientific studies.

Salas-Salvado J., Ann Intern Med 2014
Ryan Mc. Journal of Hepatology 2013
Nordmann AJ., The American Journal of Medicine 2011
Estruch R., N Engl J Med 2013



#worldliverday worldliverday.org

MASLD: diet tips

Minimise

Minimise (or eliminate) these from your diet:


Alcohol


Sugar & HFCS


Sugar sweetened beverages


Saturated fats & red meat


Non-skim dairy


Trans-fat & processed foods


Sodium (<1000 mg per day)


Vegetable seed oils


Simple starches (white rice, white flour, etc.)


Most supplements

Source: Fatty Liver Foundation, Liver Friendly Diet (https://bit.ly/2RePyJr)

Maximise Food Benefit

Maximise (or, for alternative options, moderate) these in your diet:


Unsaturated fats


Non-starchy vegetables


Fruits & berries


Nuts & seeds


Plant protein


Fatty fish & omega-3s


Poultry

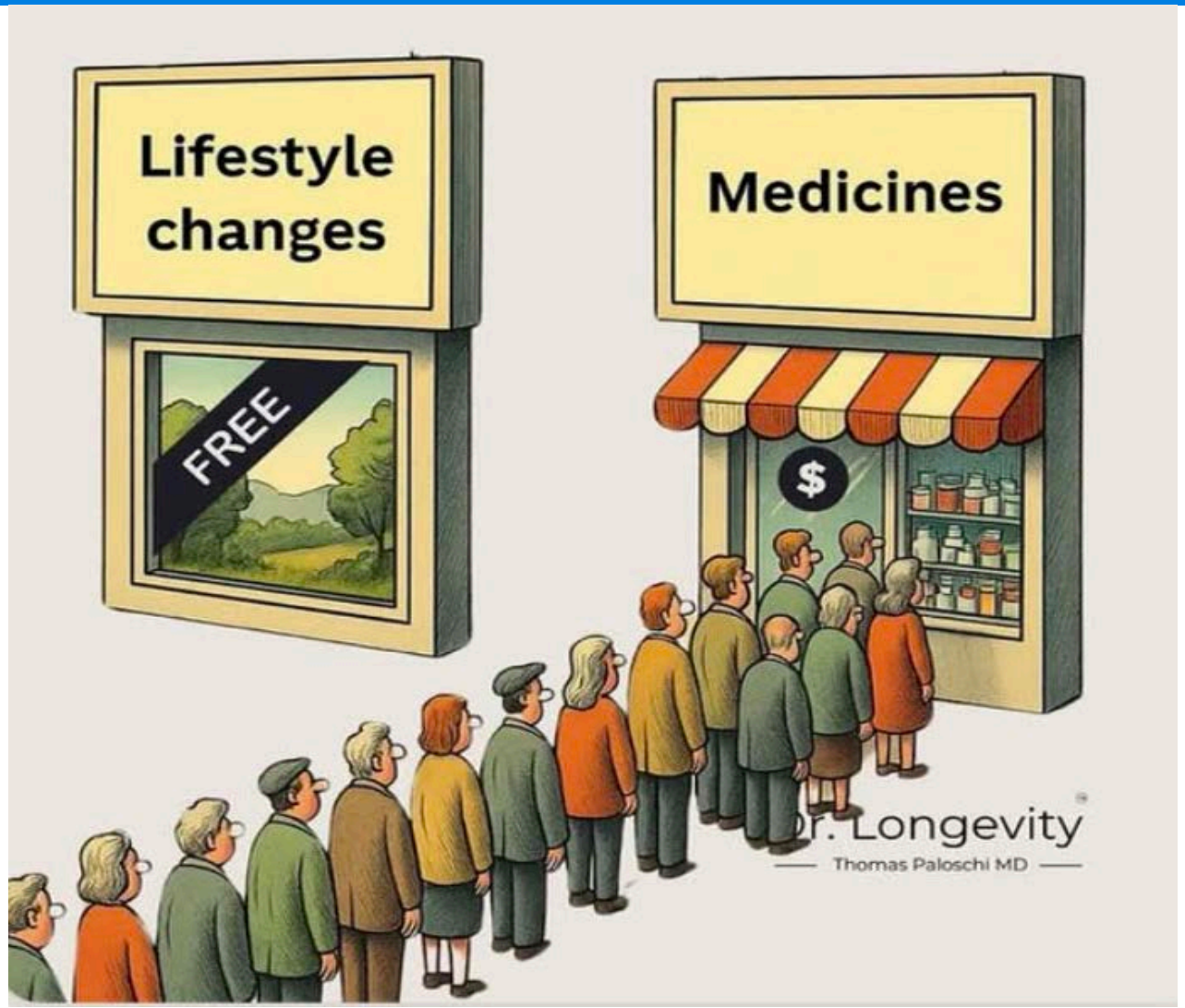

Whole wheat grains

Source: Fatty Liver Foundation, Liver Friendly Diet (https://bit.ly/2RePyJr)

Coffee
in the amount of 3 cups per day has been shown to significantly reduce the incidence of MASLD.

Extra Virgin Olive Oil
has demonstrated beneficial effects on MASLD, such as improving glucose and lipid metabolism and preventing fat build up in the arteries.

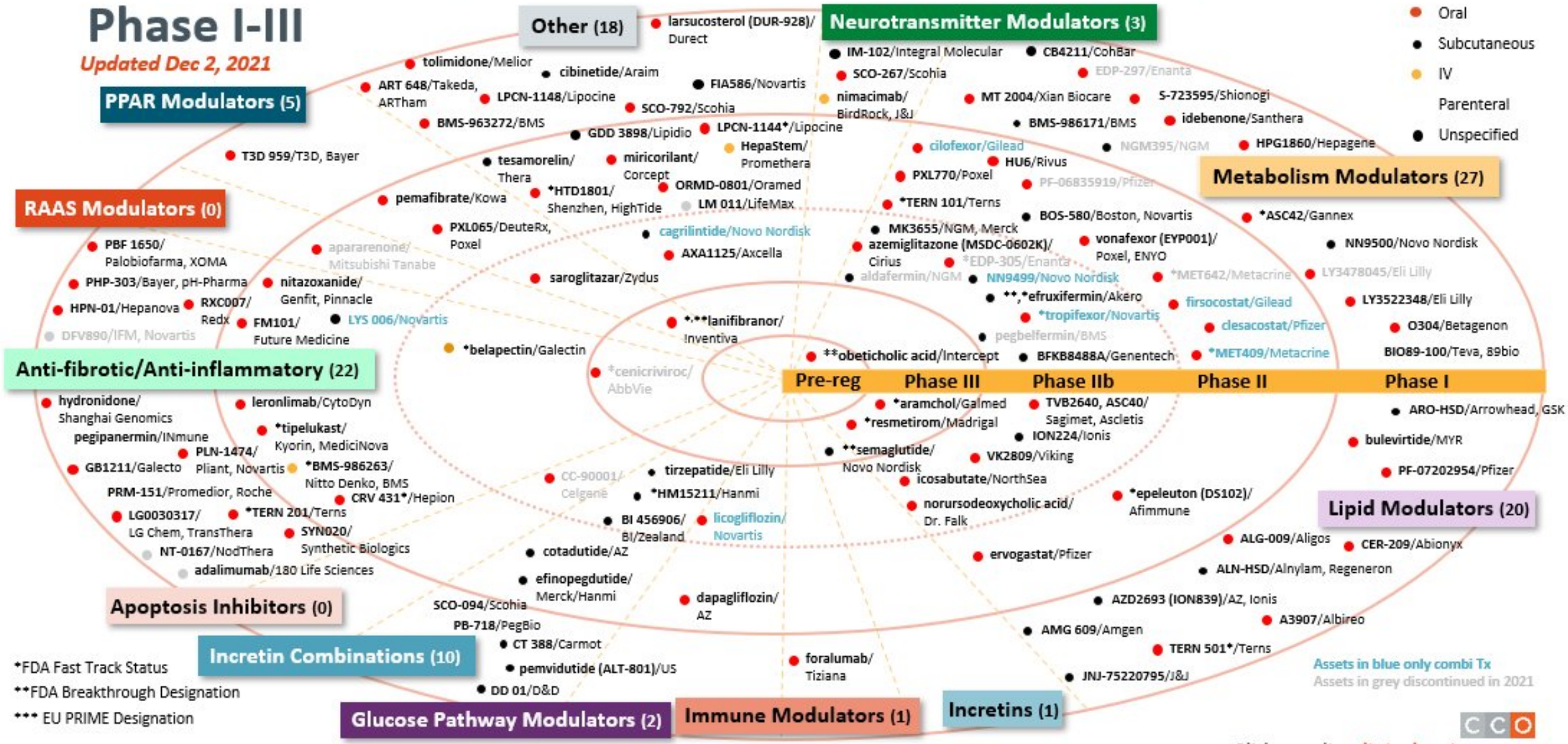
Adherence to lifestyle recommendation is low



Agents in Development for NASH in US, EU, and Japan:

Phase I-III

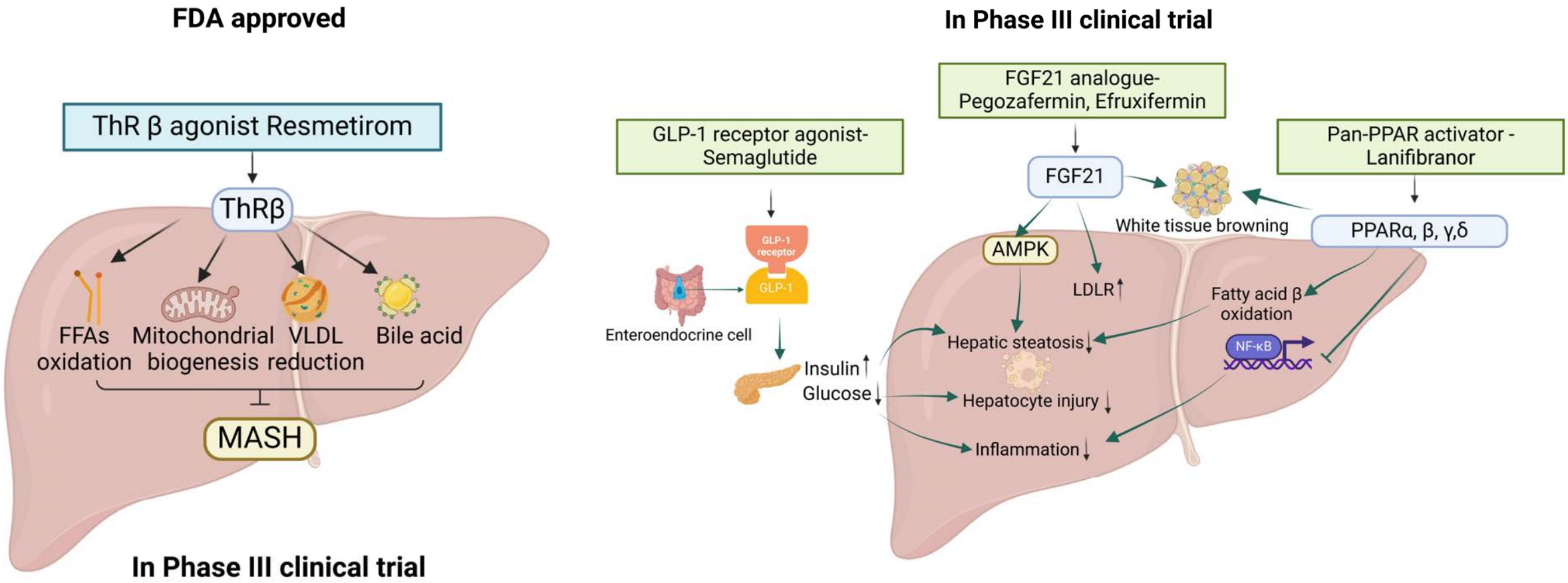
Updated Dec 2, 2021



Courtesy of Nina Brant, PhD

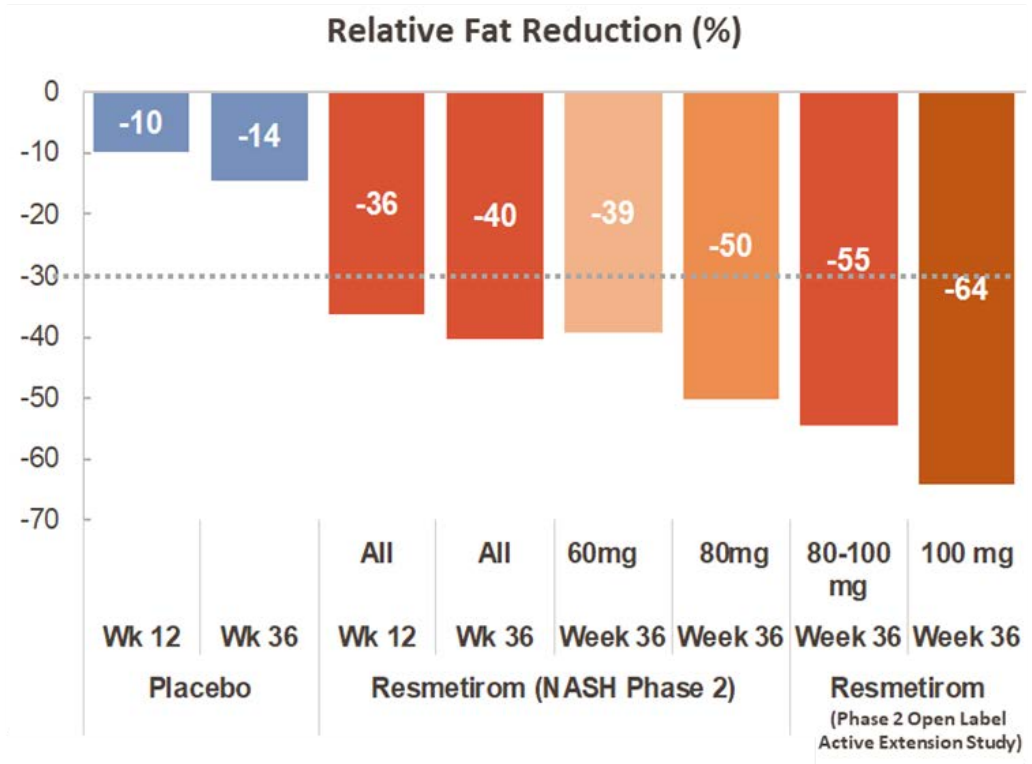
Slide credit: clinicaloptions.com

Pharmacological treatment for MASLD



Pharmacological Reviews 2025;77(2)

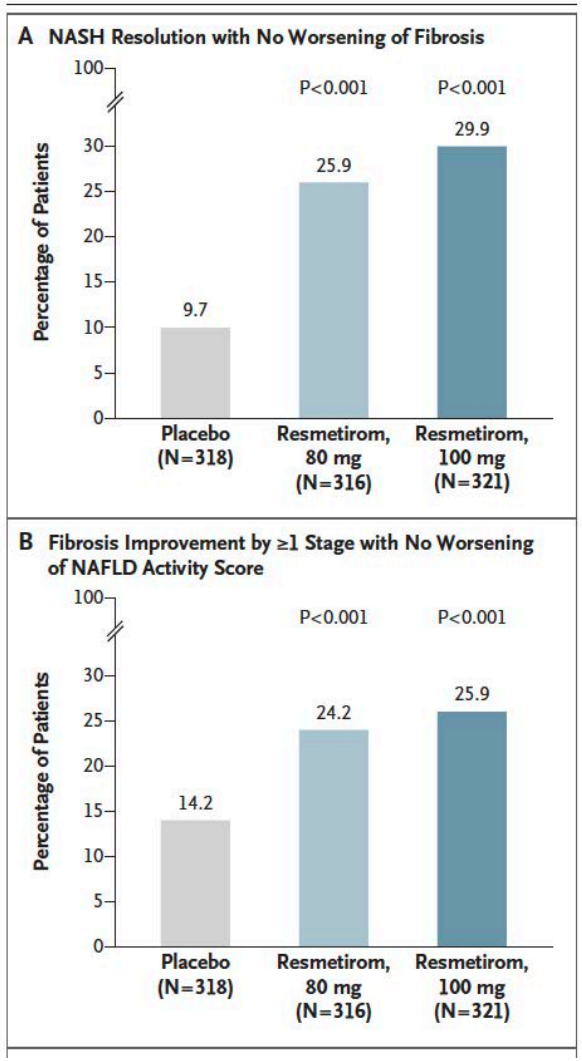
Resmetirom: First MASH drug approved



The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 8, 2024 VOL. 390 NO. 6

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*



N= 966

Glucagon like peptide-1

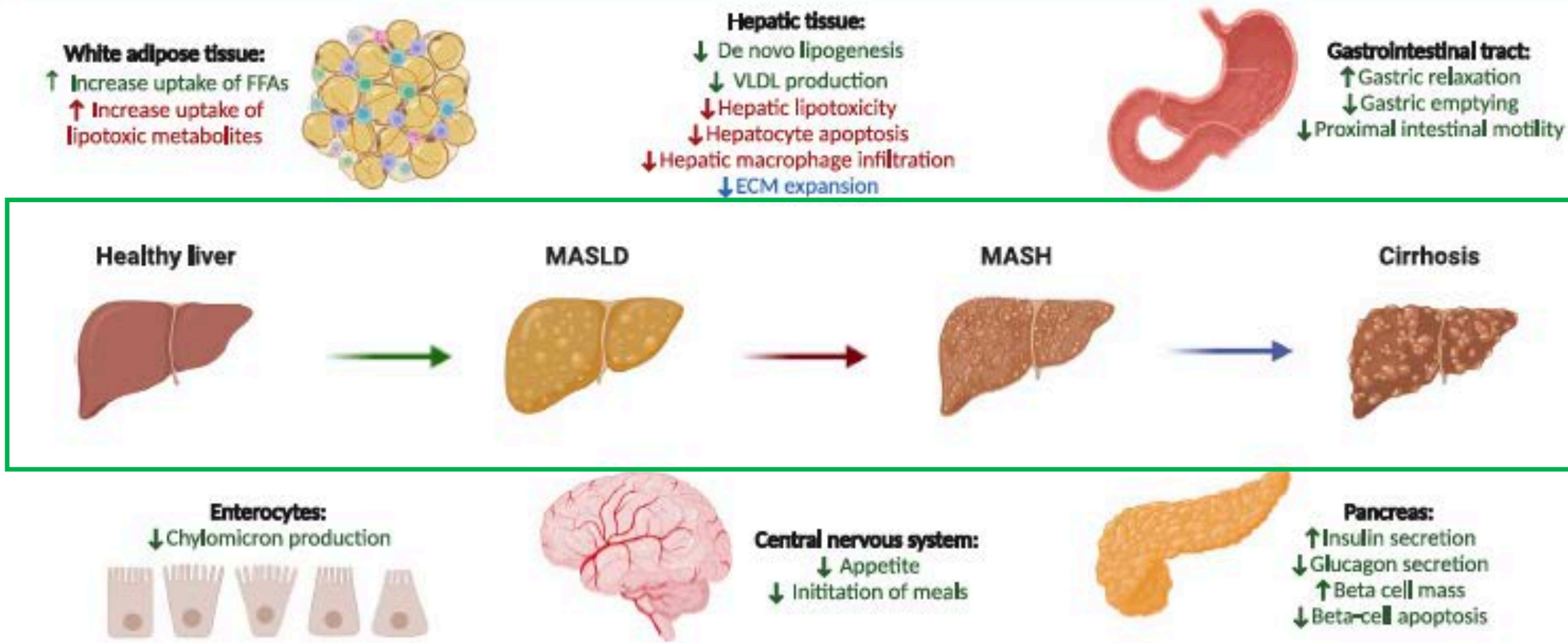


FIGURE 1 | Pathophysiology of receptor glucagon-like peptide 1 agonism. Glucagon-like peptide-1 receptor agonism ameliorates MASLD/MASH at distinct points during pathogenesis. While the predominant actions of enhancing insulin sensitivity and weight loss result in a reduction of hepatic steatosis (green), certain activities mitigate inflammation (red) and fibrosis (blue). ECM = extra-cellular matrix, FFAs = free fatty acids, VLDL = very low-density lipoprotein. Created with BioRender.com.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

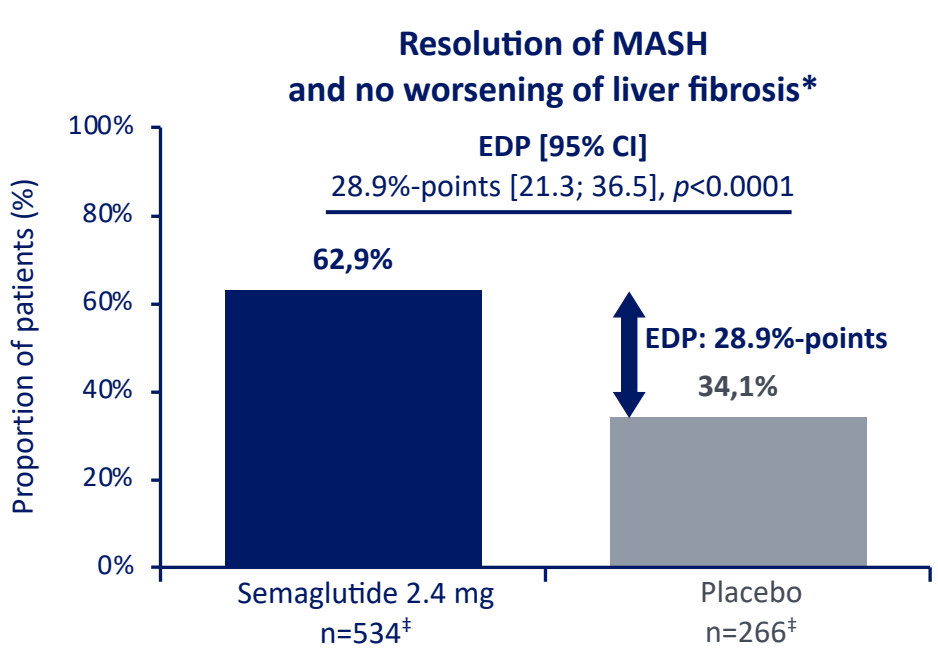
Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis

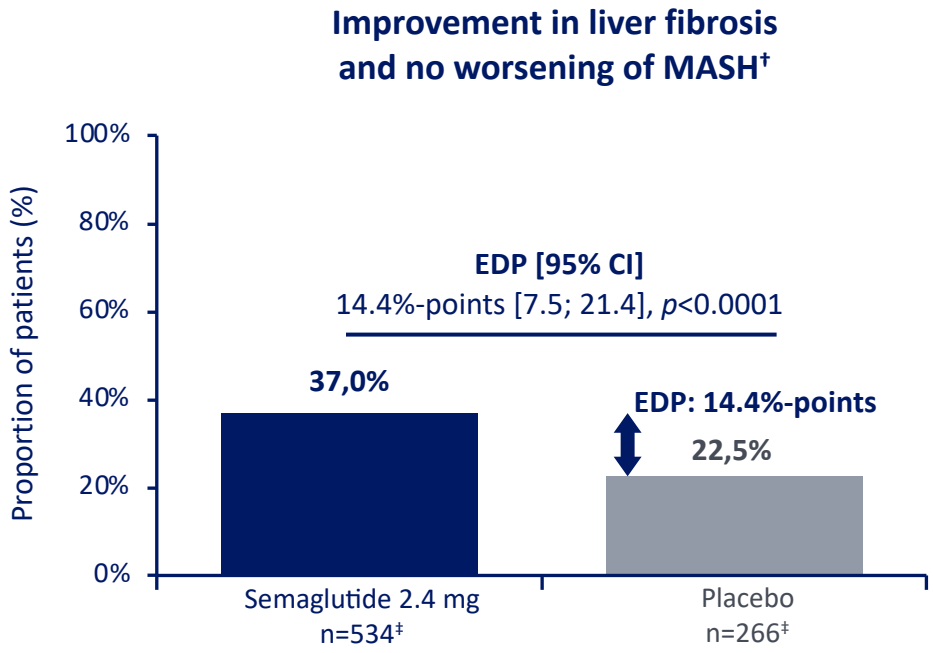
Arun J. Sanyal, M.D.,[1] Philip N. Newsome, M.B., Ch.B., Ph.D.,[2,3] Iris Kliers, M.D.,[4] Laura Harms Østergaard, M.Sc.,[4] Michelle T. Long, M.D.,[4] Mette Skalshøi Kjær, M.D., Ph.D.,[4] Anna M.G. Cali, M.D.,[4] Elisabetta Bugianesi, M.D., Ph.D.,[5] Mary E. Rinella, M.D.,[6] Michael Roden, M.D.,[7-9]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

Steatohepatitis resolution and improvement in liver fibrosis

Proportion of patients at Week 72 (full analysis set)

Primary endpoints





Significantly more patients with MASH F2–F3 treated with semaglutide 2.4 mg achieved **both primary endpoints of MASH resolution (62.9%) and improvement in liver fibrosis (37.0%)** than those treated with placebo **(34.1%, 22.5% respectively)**

*Analysis set: FAS (interim), first 800 randomized subjects. EDP: Estimated difference in responder proportions with 95% confidence interval and two-sided p-value. *Resolution of steatohepatitis is defined as a NAS of 0-1 for inflammation, 0 for ballooning and any value for steatosis according to NASH CRN. No worsening of liver fibrosis is defined as no increase in fibrosis score. Fibrosis is graded on the NASH CRN fibrosis scale from 0-4. †Improvement in fibrosis is defined as >= 1 grade improvement on the NASH CRN fibrosis scale. No worsening of steatohepatitis is defined as no increase from baseline in NAS score for ballooning, inflammation or steatosis. The absolute difference between responder proportions, 95% confidence interval, P value was generated with the use of Cochran-Mantel-Haenszel (CMH) test stratified by baseline diabetes status (medical history) and fibrosis stage (eligibility read). ‡Missing data were handled by reference-based multiple imputation and Rubin's rule based on the Mantel-Haenszel estimator and Sato's estimate of the standard error (reference) were used to aggregate results. CI, confidence interval; EDP, estimated difference in responder proportions; F, fibrosis stage; MASH, metabolic dysfunction associated steatohepatitis; NASH CRN, Non-Alcoholic Steatohepatitis Clinical Research Network. Newsome PN et al. Oral Presentation at American Association for the Study of the Liver The Liver Meeting; Late Breaker 5018; November 19 2024; San Diego, USA.*

ESSENCE: Safety

Any AEs **86.2%** (semaglutide) vs **79.7%** (placebo)

Serious AEs **13.4%** in both groups

Discontinuation due to AEs **2.6%** (semaglutide) vs **3.3%** (placebo)

Most common AEs Gastrointestinal (nausea, diarrhea, constipation, vomiting)

No new or liver-specific safety concerns identified

Sanyal. NEJM. 2025;392:2089.

Selected phase 2 Trials

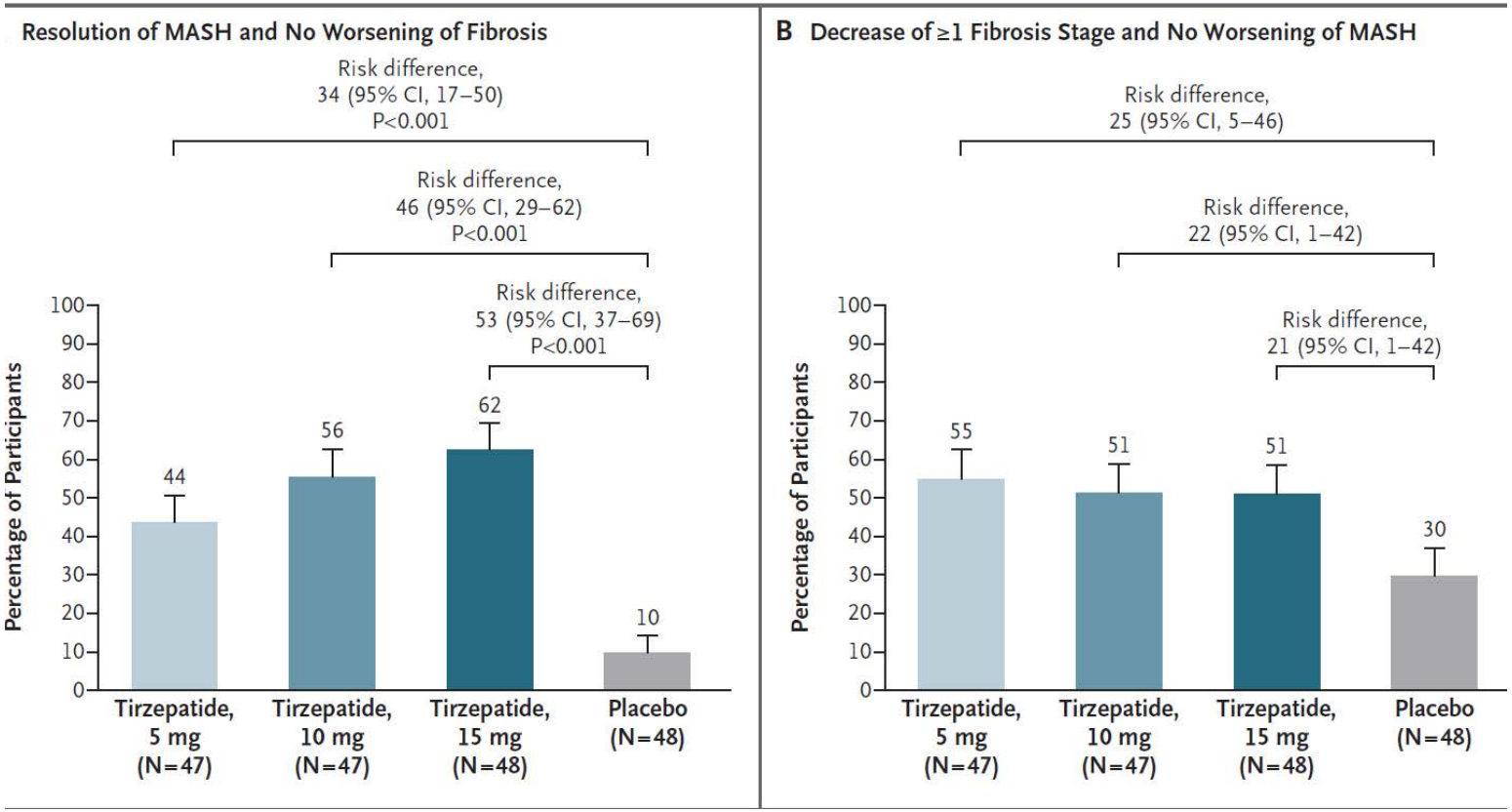
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

- Dual agonism of **GIP*** and **GLP-1**
- 52-week, phase 2 trial, ID administered once weekly
- **190** MASH (F2/F3) patients, biopsy confirmed
- Primary end point was histologic improvement in MASH with no worsening of fibrosis
- A key secondary end point was an improvement of at least one fibrosis stage without worsening of MASH



*glucose-dependent insulinotropic polypeptide4

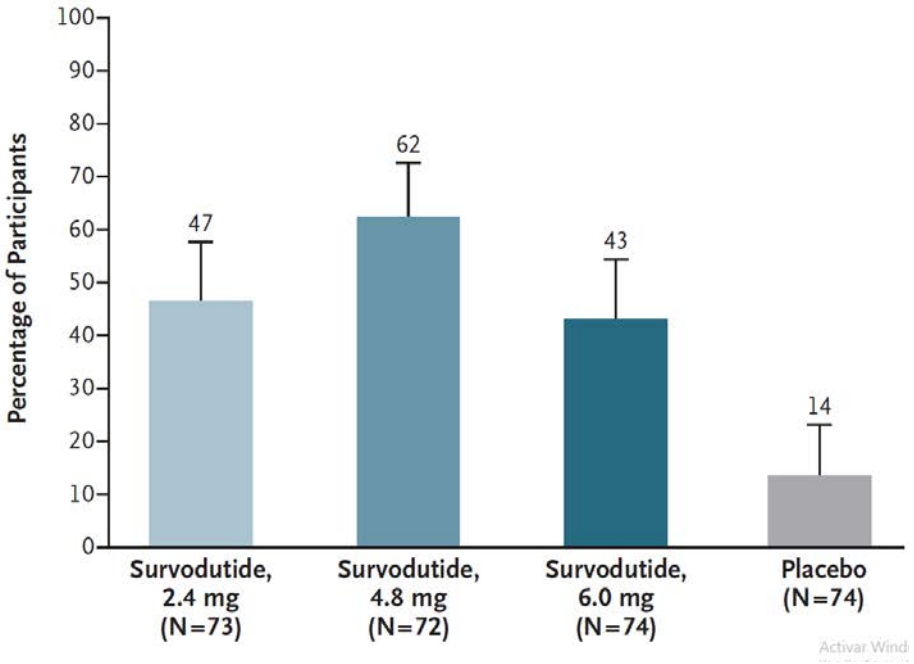
Selected phase 2 Trials

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

- Dual agonism of **glucagon receptor** and **GLP-1**
- 48-week, phase 2 trial, ID Administered once weekly
- **293** MASH (F1 through F3) patients, biopsy confirmed
- Primary end point was histologic improvement in MASH with no worsening of fibrosis
- Secondary end points included a decrease in liver fat content by at least 30% and biopsy-assessed improvement in fibrosis by at least one stage.



Additional findings

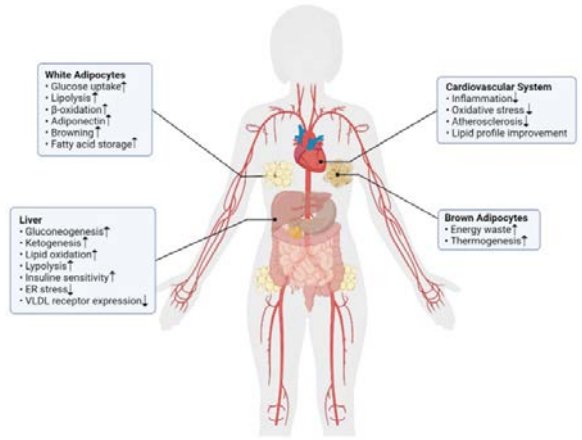
- Improvement in fibrosis (34% survodutide 6.0-mg group vs. 22% placebo group)
- Trial discontinuation due to adverse events occurred in 20% of participants (gastrointestinal events)
- No unexpected safety issues were identified

Sanyal AJ et al. NEJM June 7, 2024

The NEW ENGLAND JOURNAL of MEDICINE

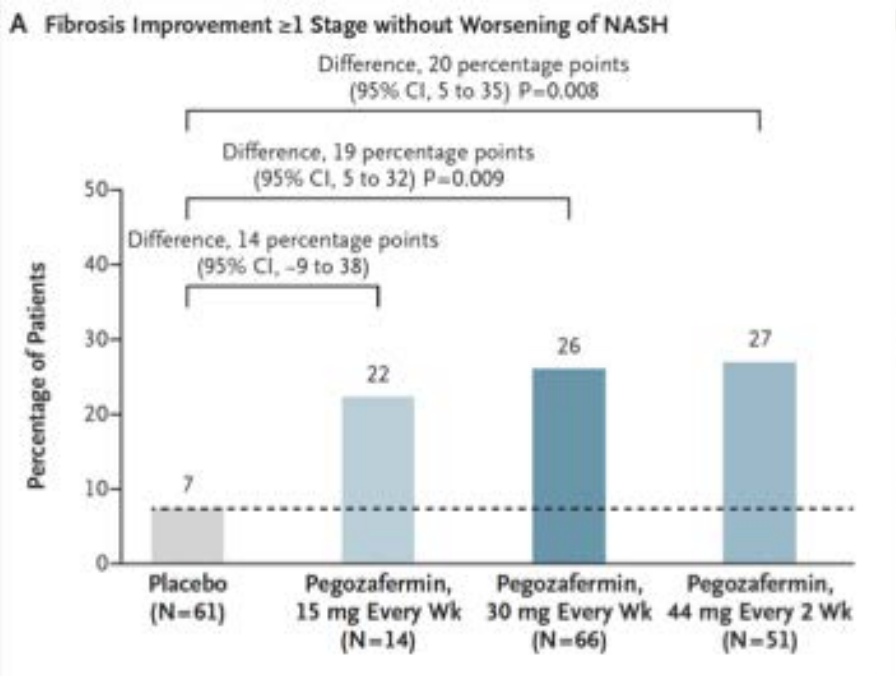
ORIGINAL ARTICLE

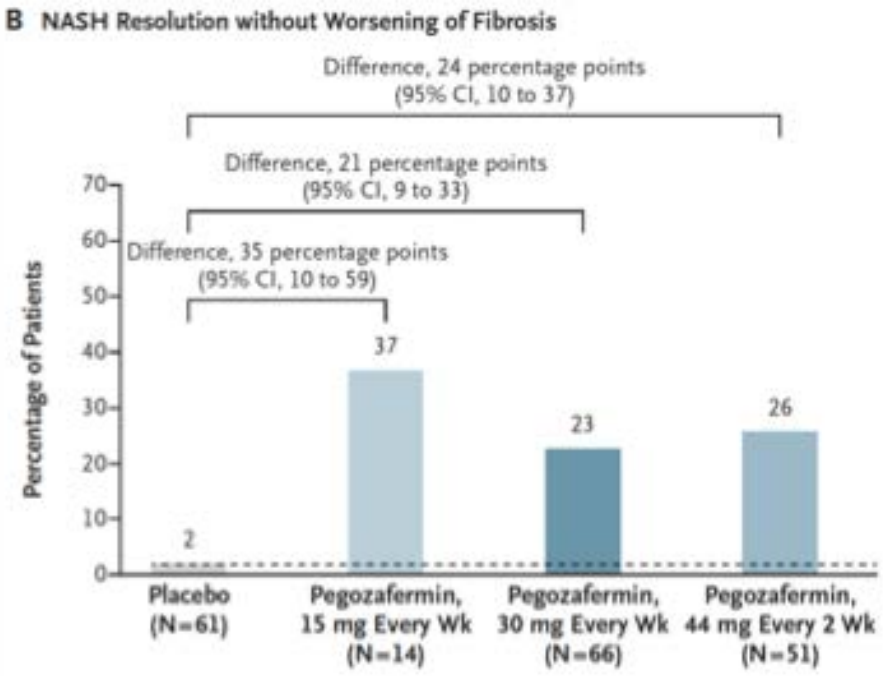
Randomized, Controlled Trial of the FGF21 Analogue Pegozafermin in NASH



Phase 2b: **22**2 pts randomized to 4 groups

Pegozafermin Treatment Led to a Significant Improvement on Primary Endpoints at Week 24

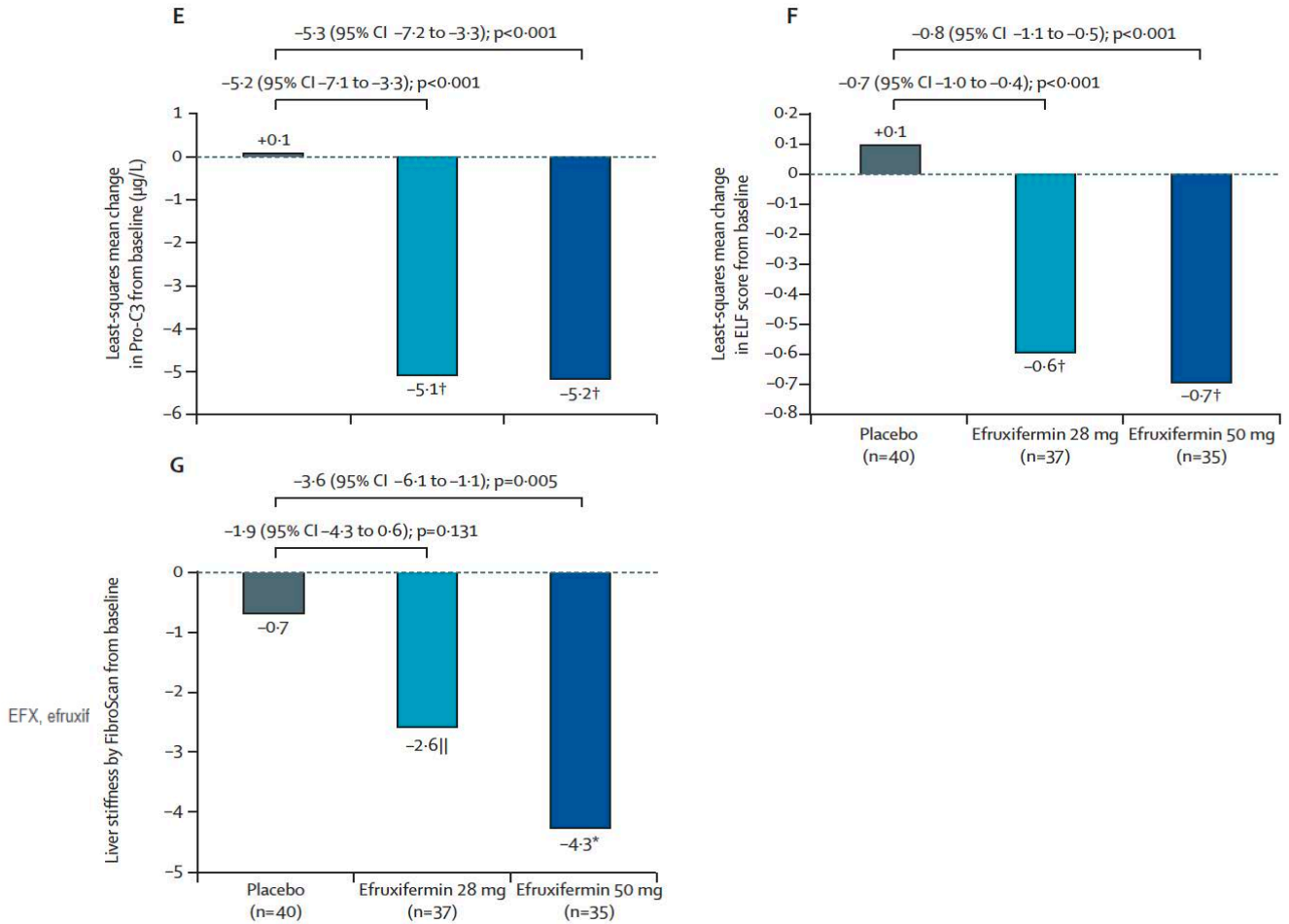




Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial

*Stephen A Harrison, Juan P Frias, Guy Neff, Gary A Abrams, K Jean Lucas, William Sanchez, Sudhanshu Gogia, Muhammed Y Sheikh, Cynthia Behling, Pierre Bedossa, Lan Shao, Doreen Chan, Erica Fong, Brittany de Temple, Reshma Shringarpure, Erik J Tillman, Timothy Rolph, Andrew Cheng, Kitty Yale, for the HARMONY Study Group**

This phase 2b study showed that 24 weeks of efruxifermin treatment produced significant regression of fibrosis and resolution of steatohepatitis in patients with NASH.
The results from this study reproduced the results of hepatic fat normalisation and the reductions in markers of liver injury and fibrosis reported from our phase 2a studies.
The combination of improvements in liver and whole-body metabolic health, including enhanced insulin sensitivity, better glycaemic control, and improved lipid profile and modest weight loss, appears unique to NASH therapeutic agents in late-stage development.



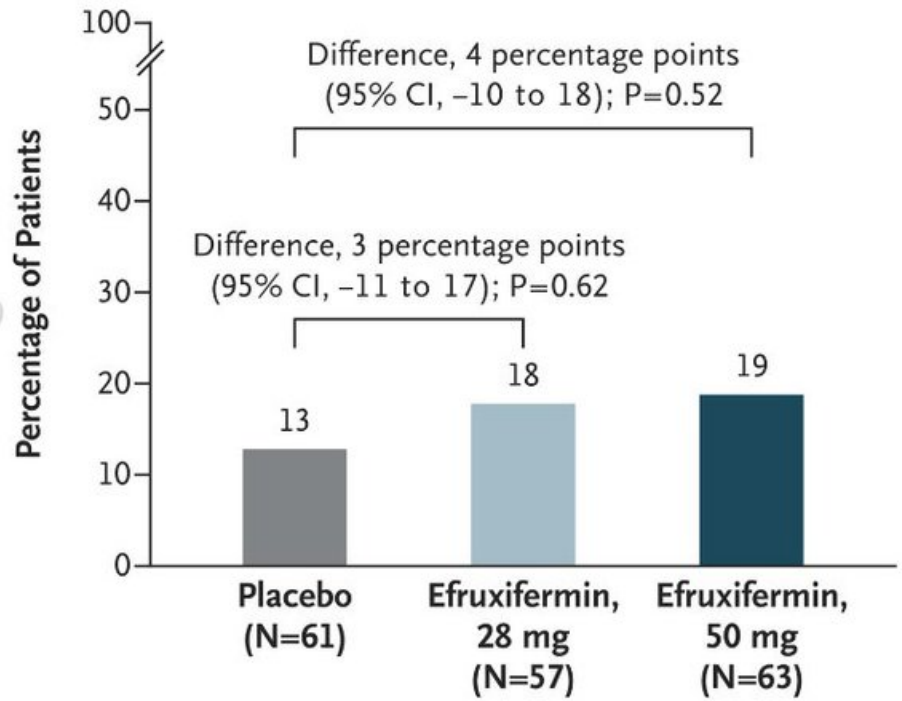
Lancet Gastroenterol Hepatol 2023;8:1080-1093

ORIGINAL ARTICLE

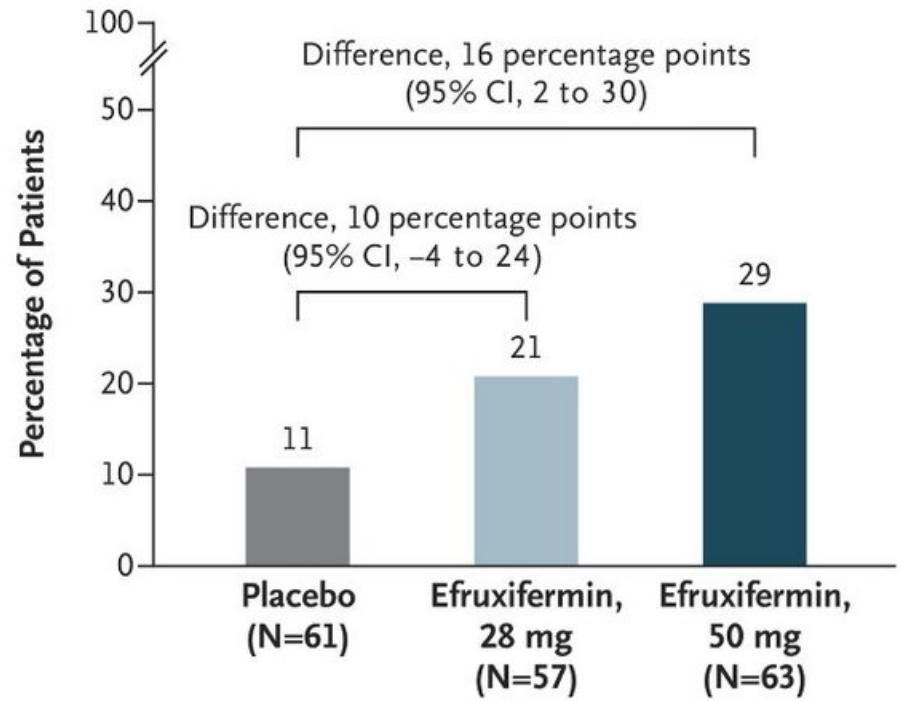
Efruxifermin in Compensated Liver Cirrhosis Caused by MASH

Mazen Noureddin, M.D.,[1,2] Mary E. Rinella, M.D.,[3] Naga P. Chalasani, M.D.,[4]
Guy W. Neff, M.D.,[5] K. Jean Lucas, M.D.,[6] Manuel E. Rodriguez, M.D.,[7]
Madhavi Rudraraju, M.D.,[8] Rashmee Patil, M.D.,[8] Cynthia Behling, M.D., Ph.D.,[9]
Mark Burch, Ph.D.,[10] Doreen C. Chan, Ph.D.,[10] Erik J. Tillman, Ph.D.,[10]
Arian Zari, B.S.,[10] Brittany de Temple, B.S.,[10] Reshma Shringarpure, Ph.D.,[10]
Meena Jain, M.B., B.Chir., Ph.D.,[10] Timothy Rolph, D.Phil.,[10]
Andrew Cheng, M.D., Ph.D.,[10] and Kitty Yale, B.S.[10]

A **Reduction in Fibrosis of ≥1 Stage without MASH Worsening at Week 36**



B **Reduction in Fibrosis of ≥1 Stage without MASH Worsening at Week 96**



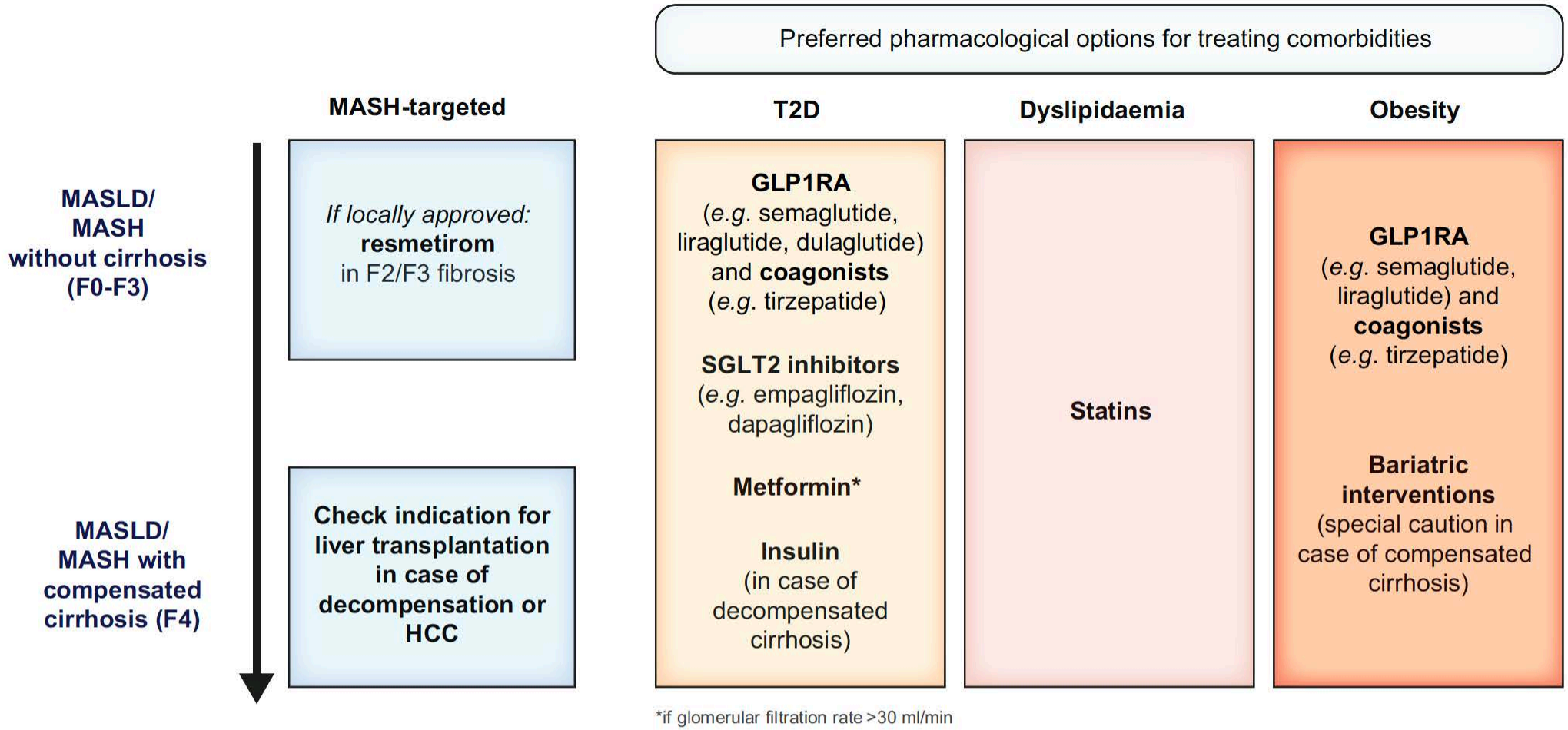


Fig. 4. Treatment recommendations beyond lifestyle modification in MASLD/MASH. The recommended choice of pharmacological treatment options in individuals with MASLD/MASH is dependent on comorbidities and stage of disease. GLP1RA, glucagon-like peptide 1 receptor agonist; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

Mensajes finales

- ✓ MASLD es una enfermedad multisistémica y necesita un enfoque de equipo multidisciplinario (MDT).
- ✓ Las intervenciones en el estilo de vida son la piedra angular del tratamiento.
- ✓ Los **tiromiméticos** (Resmetirom), **agonistas de GLP-1** (i.e, Semaglutida) y compuestos relacionados, **agonistas de PPAR** y agonistas de **FGF21,** son los agentes más prometedores.
- ✓ Los enfoques combinatorios diseñados racionalmente (es decir, personalizados) son el siguiente paso lógico.

Invitación próximos eventos

medicina.uc.cl

Gracias por su atención

Marco Arrese
Departamento de Gastroenterología
Facultad de Medicina
P. Universidad Católica de Chile

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marrese@uc.cl

FONDECYT
Fondo Nacional de Desarrollo Científico y Tecnológico