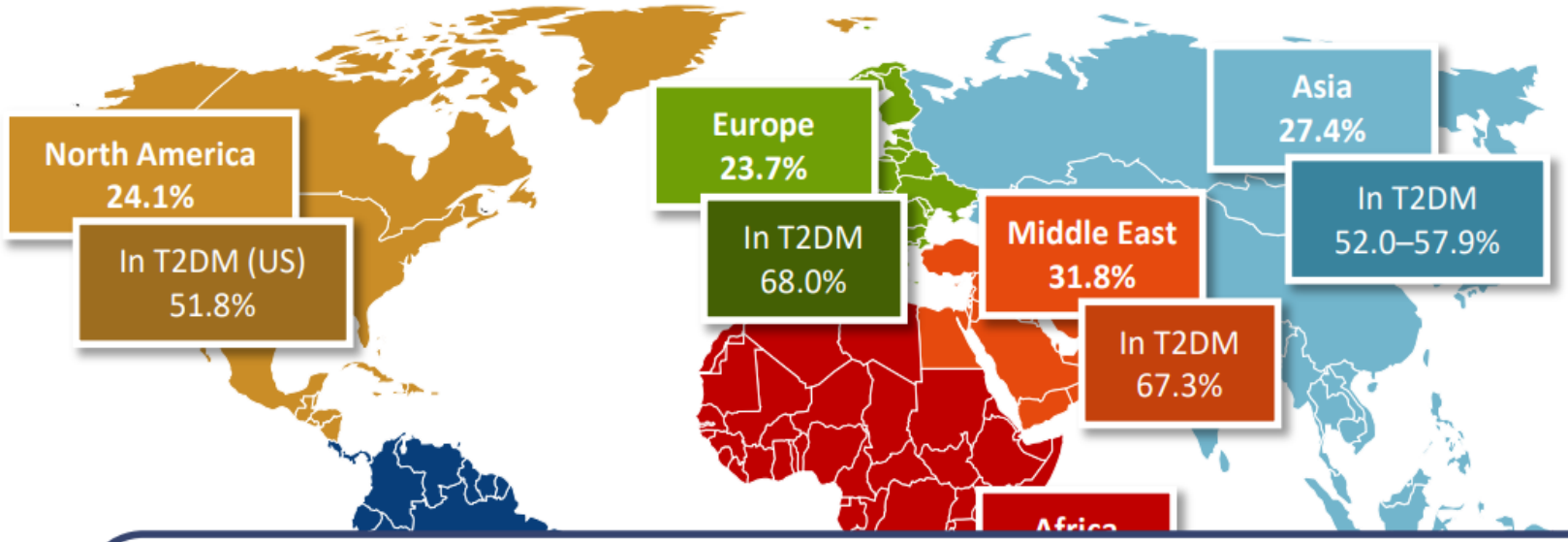
Resmetirom First drug approved by FDA for MASH therapy.

Reza Malekzadeh M.D,AGAF
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Digestive Disease Research Institute
Shariati Hospital
Tehran University of Medical Scienc

MASLD the most common disease of human with one billion adult globally affected

- An estimated 33% of adults and 13% of children and adolescents worldwide have fatty liver disease (MASLD).
- Its more severe form, metabolic dysfunction-associated steatohepatitis (MASH), is estimated to affect around 5%.
- MASH is particularly dangerous when coupled with moderate or advanced fibrosis (stage F2 or higher),

Prevalence of NAFLD and NASH



Worldwide prevalence of NAFLD is 25%

Worldwide prevalence of NAFLD among people with T2DM is 55.5%

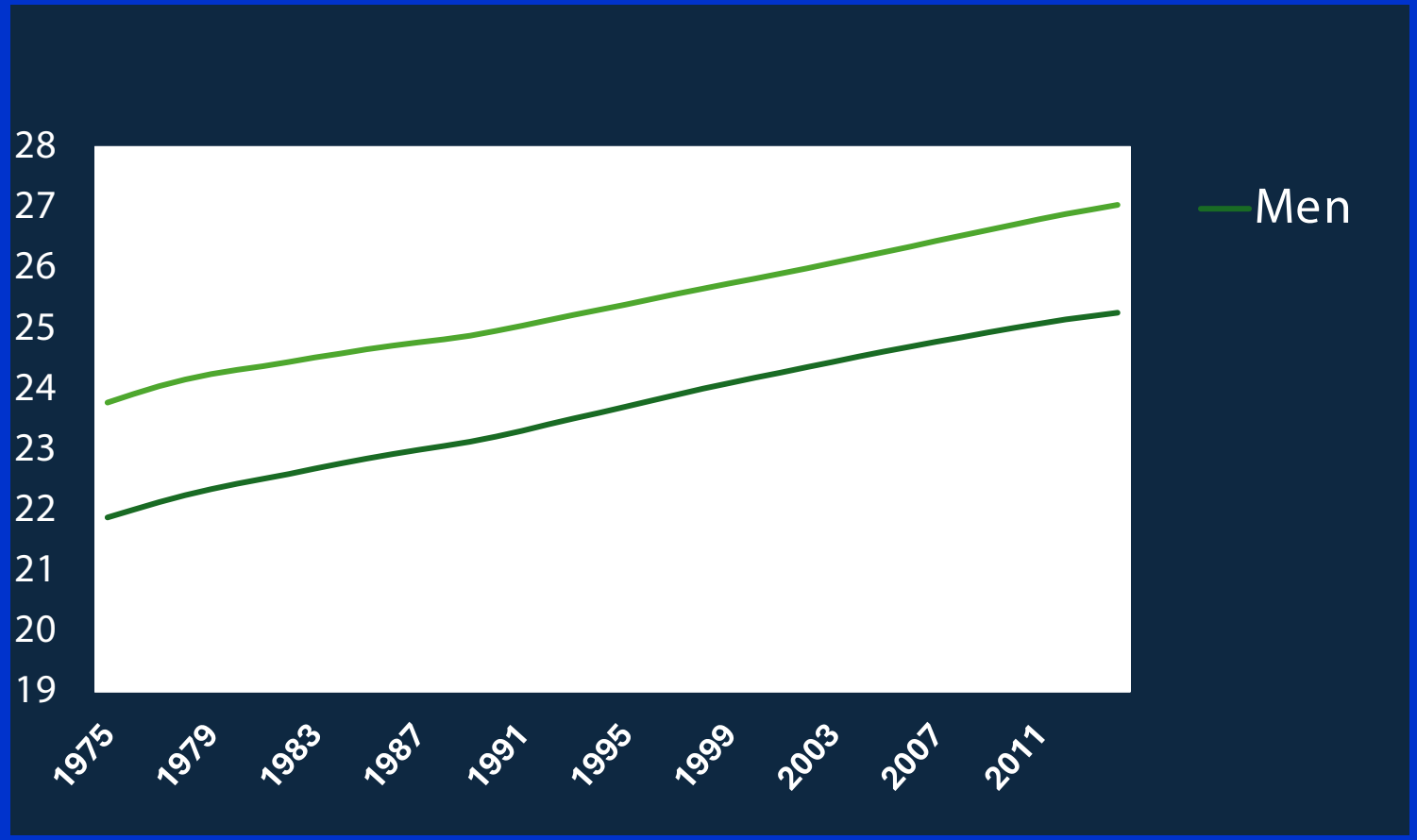
- Prevalence of NASH in general population is between 1.5–6.5%
- Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)
- Prevalence NAFLD in children is 7-10% (highest South America and lowest in Africa)
- Prevalence is higher in Hispanic boys and increases with higher BMI
- The prevalence of NAFLD in the US increased 2.7 fold from the late 1980's to 2010

Younossi ZM et al. *Hepatology*. 2016;64:73–84; Argo CK and Caldwell SH. *Clin Liver Dis*. 2009;13:511–531; Younossi ZM. *J Hepatol*. 2019;70:531–544.

Overeating/Less physical activity : Most common cause

Level of energy intake that exceeds the level of energy expenditure

BMI In Iran during last 40 years



Lancet 2016

Epidemiology

- What is the prevalence of NAFLD in general population?

  30%
- Prevalence of NAFLD in morbid obesity?

  80%
- Prevalence of NAFLD in DM2?

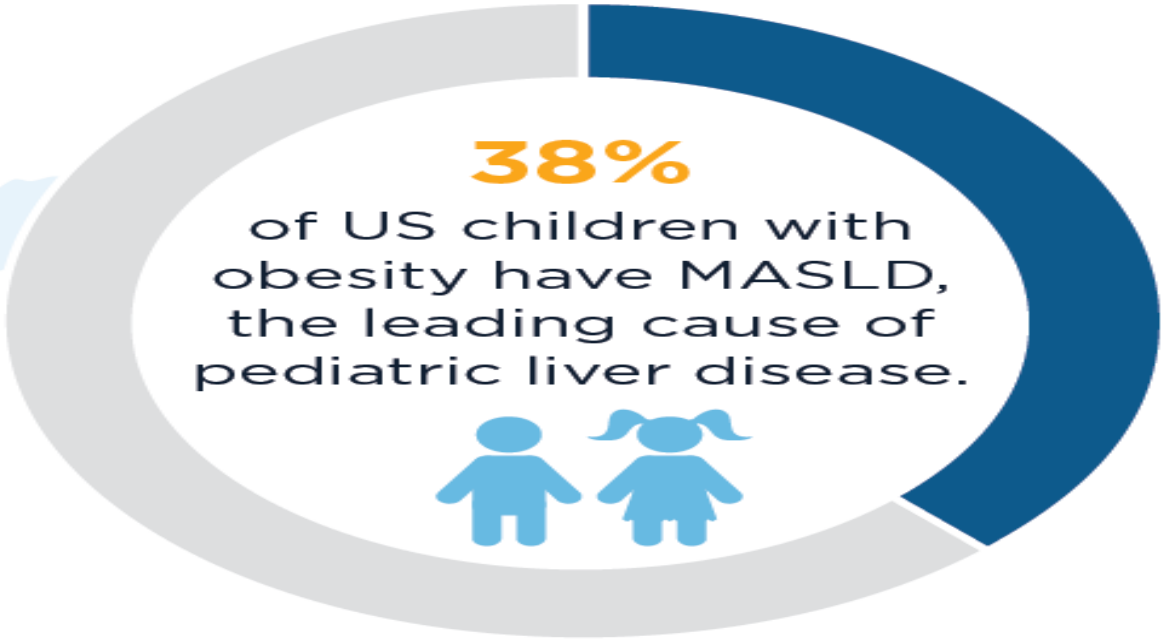
  70%
- Prevalence of NAFLD in hyperlipidemia?

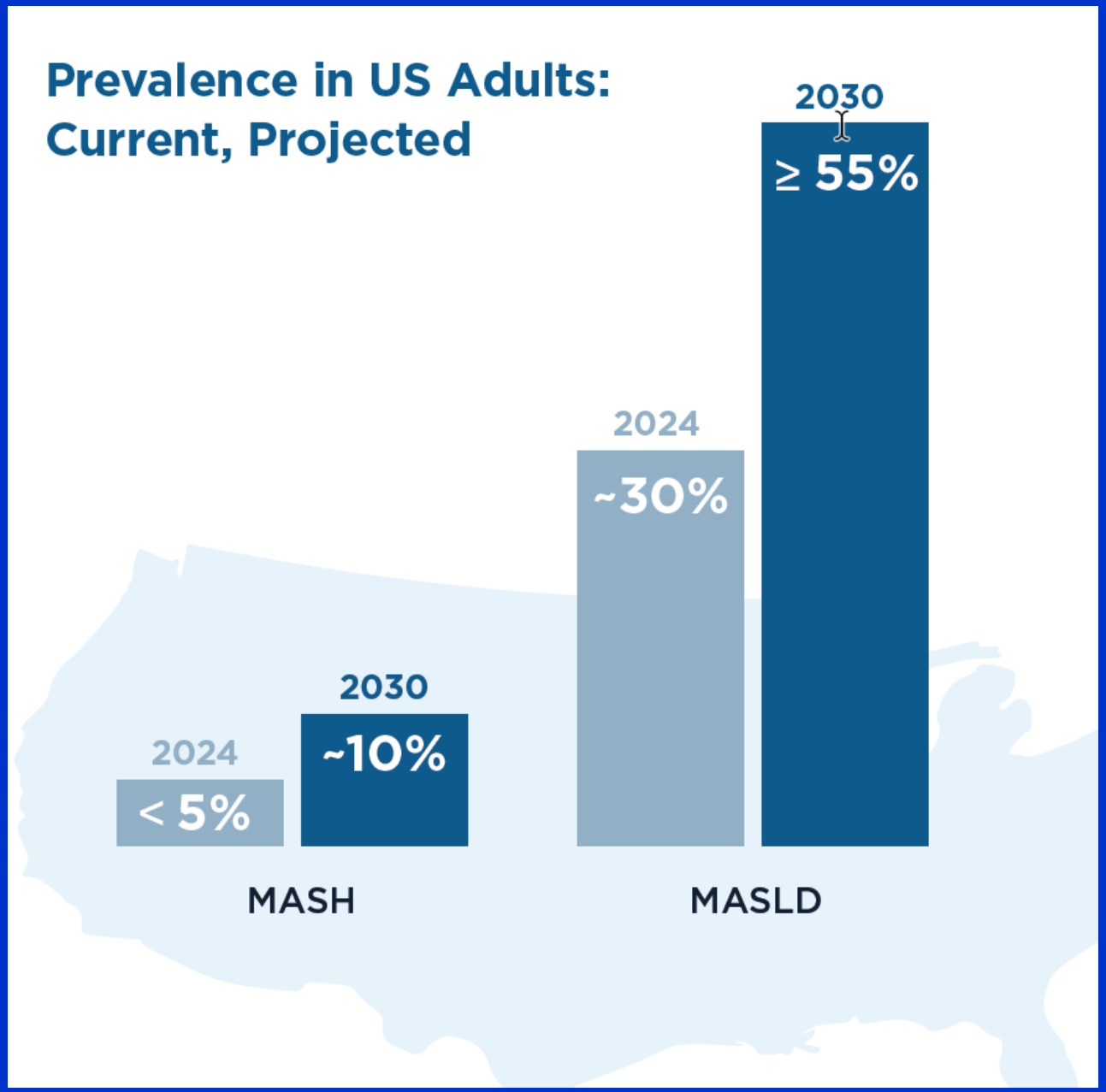
  50%

MASLD/MASH Burden



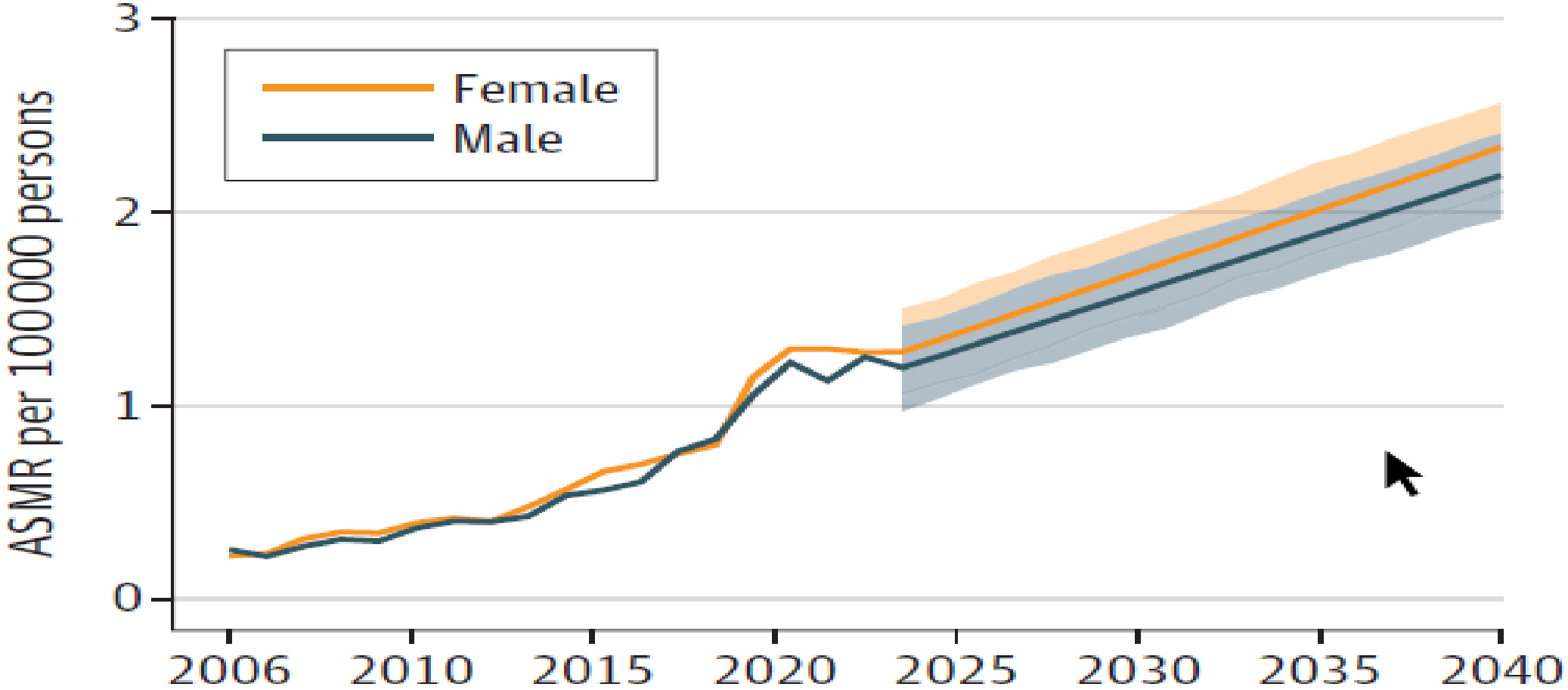
1 billion adults globally are affected by MASLD, the most common liver disorder in the world.





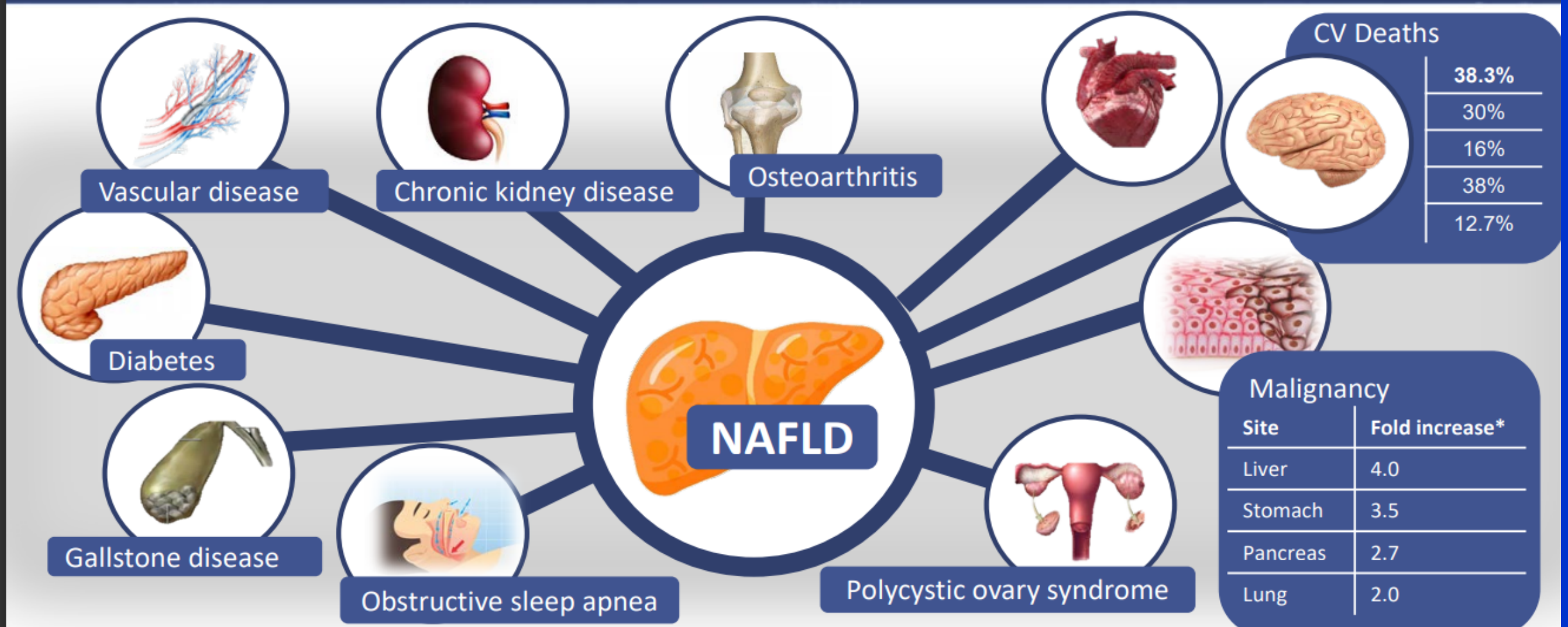
The economic burden of MASLD/MASH in the United States is projected to grow substantially, to over $1 trillion by 2034, highlighting the growing need for improved diagnostic and treatment strategies (and for encouragement of patient lifestyle changes) to effectively manage MASLD and MASH

Mortality Rates (ASMRs) and Projected Values for MDSLD in the United States, 2006-2040



NAFLD is Part of A Multisystem Disorder

Non-Liver Related Outcomes of NAFLD

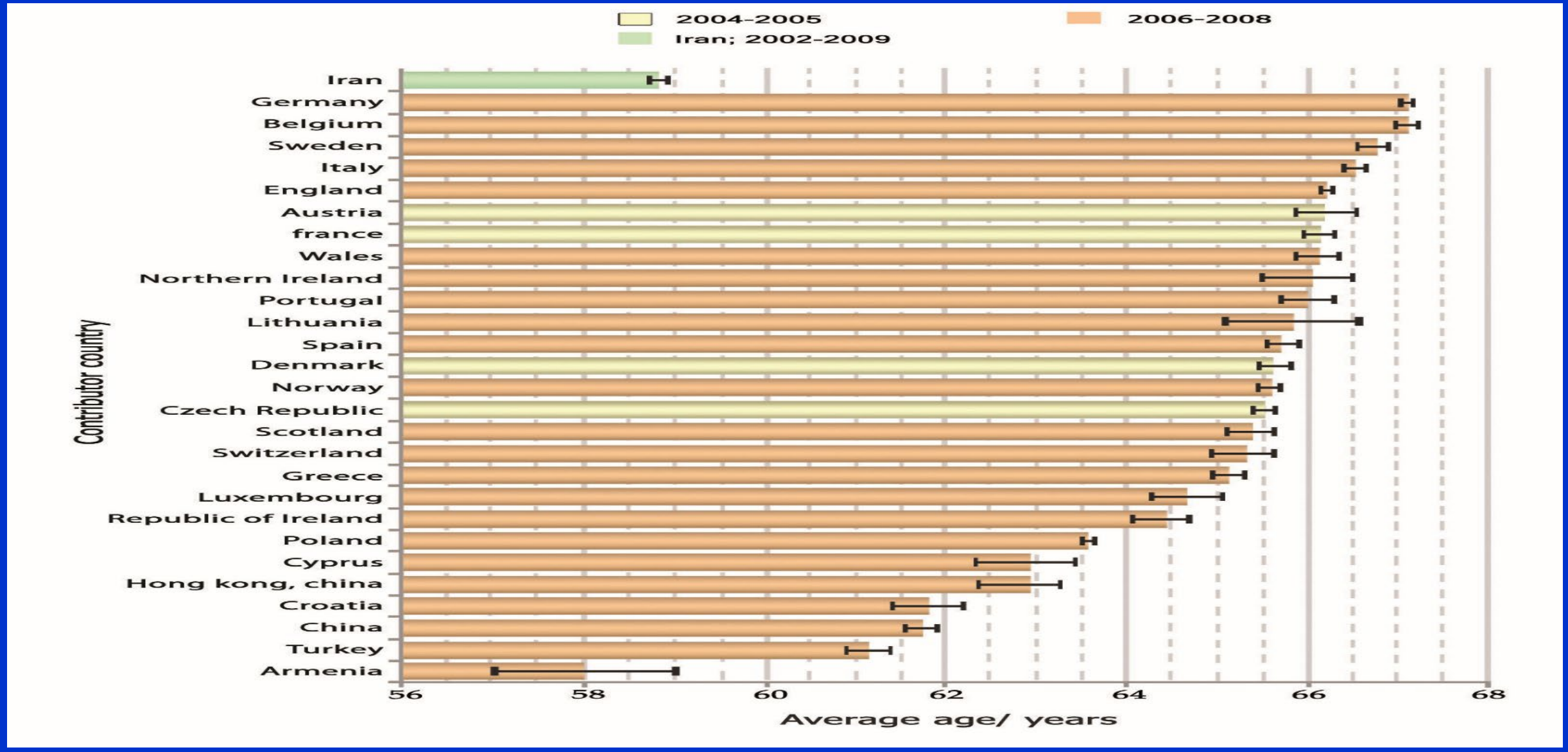


*Fold increase in incidence of malignant cancer diagnosis in patients with NAFLD compared to healthy controls. Angulo P et al. *Gastroenterology*. 2015;149:389–397; Söderberg C et al. *Hepatology*. 2010;51:595–602; Ekstedt M et al. *Hepatology*. 2006;44:865–873; Dam-Larsen S et al. *Scand J Gastroenterol*. 2009;44:1236–1243; Rafiq N et al. *Clin Gastroenterol Hepatol*. 2009;7:234–238; Hicks SB et al. Oral abstract presented at the AASLD Liver Meeting; 31; 11 November 2018; San Francisco, USA.

Major causes of morbidity and mortality of NAFLD sub-phenotypes

NAFL	NASH w/ F0 &F1	NASH with F2 & F3	NASH Cirrhosis
Cardiovascular	Cardiovascular	**Liver disease**	**Liver disease**
Non-hepatic malignancies	Non-hepatic malignancies	Cardiovascular disease	Cardiovascular disease
?Renal disease	Liver disease	Hepatic & non-hepatic malignancies	Hepatic & non-hepatic malignancies
?Cerebrovascular disease	?Renal disease	?Renal	?Renal

Isolated CABG: Average age and contributor country: Tehran Heart Center 2002-2009



Proposed clinical algorithm to identify first-degree relatives at risk of advanced fibrosis using the NFLD Familial Risk Score.

Proband evaluated for NAFLD/fibrosis

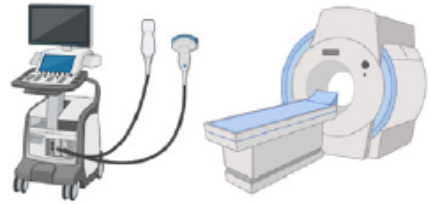


Apply NAFLD Familial Risk Score to first-degree relatives

- **Age** ≥ 50 yrs = 1 point
- **T2DM** = 1 point
- **Obesity** = 2 points
- **Family history*** = 2 points



NAFLD Familial Risk Score ≥ 4 points → **Fibrosis assessment** by non-invasive imaging

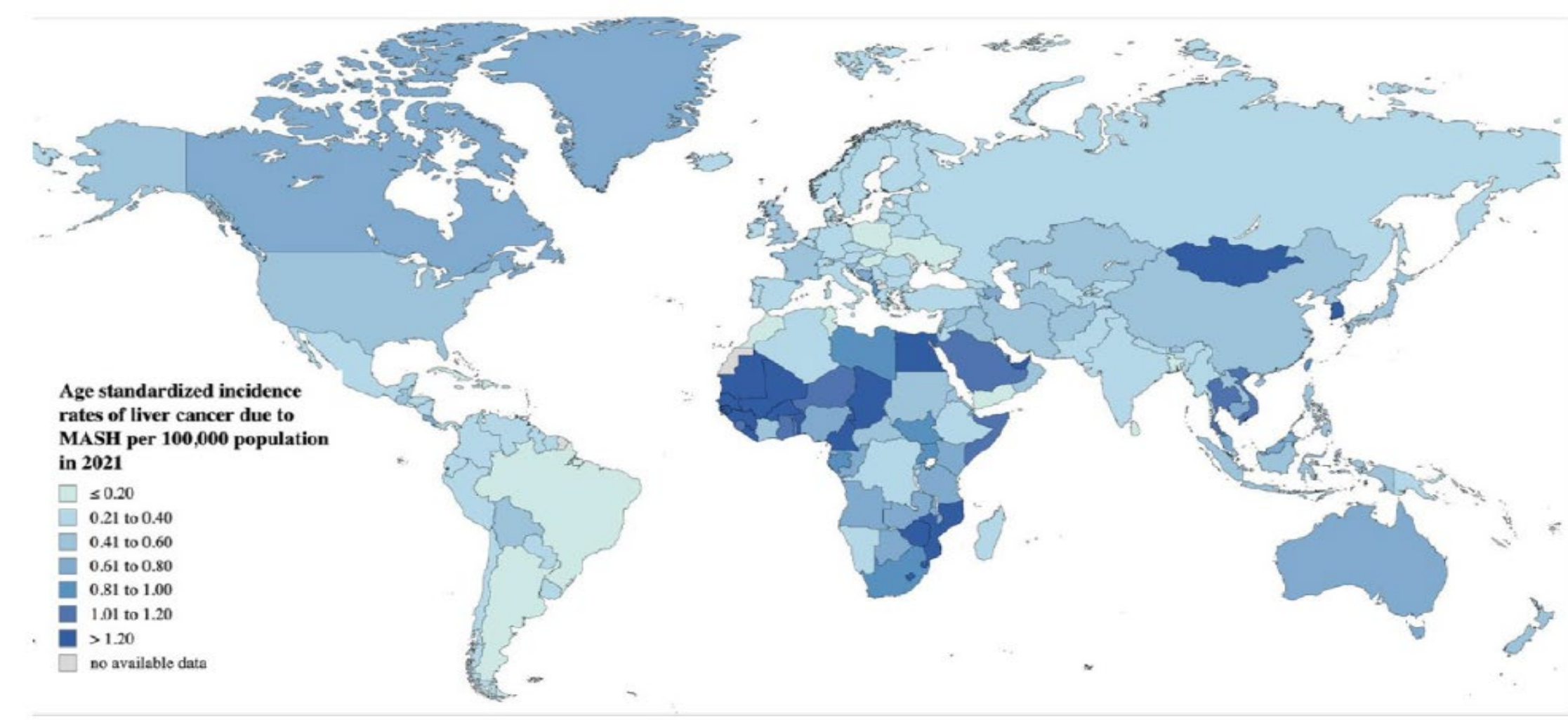


NAFLD Familial Risk Score < 4 points → Risk factor modification

MASLD remains severely underdiagnosed

- Despite its scale and impact, MASLD remains severely underdiagnosed, even in specialist care settings.
- Many individuals remain unaware of their condition until it progresses to cirrhosis or liver cancer.
- This delay in diagnosis often eliminates the opportunity for timely intervention, resulting in poorer outcomes and greater health system costs.

Global Trend of MASH-associated Primary Liver Cancer



New advance in therapy of MASLD in 2024

- Despite global rise in MASLD prevalence , the lack of approved medications was striking.
- Fortunately, during the year 2024 significant advancements have been made in the treatment landscape for MASLD.
- Recent insights into the heterogeneous nature of MASLD have spurred the discovery of novel therapeutic agents and the repurposing of drugs (e.g., semaglutide) available for type 2 diabetes and obesity

Lifestyle modifications like diet and exercise remain the cornerstones of treatment

- Lifestyle modifications like diet and exercise remain the cornerstones of treatment.
- Effective pharmacologic options have been elusive.
- Aspirin and statin was effective in preventing CVD in MASLD
- Numerous phase 3 trials are under way, and more promising therapies will likely become available within the next few years.

In 2024, the FDA conditionally approved resmetirom

- Although this condition is highly under diagnosed, combination therapy may improve outcomes, with greater efficacy for metabolic treatments initiated in the early stages and for liver-targeting drugs initiated in the advanced stages.

- In 2024, the FDA conditionally approved resmetirom a thyroid hormone receptor selective drug, for treating non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced fibrosis.

4 Main Pathways of MASLD Therapies

1- Address the link: MASLD and type 2 diabetes.

2-Reduce liver fat and metabolic stress,

3-Address fibrotic changes

4-Modulate gut-liver axis

Address the link: MASLD and type 2 diabetes

1-Incretins:Semiglutide

2-Thiazolidinedione insulin sensitizers

3- SGLT2 inhibitors

Reduce liver fat and metabolic stress

1- PPAR agonists

2-De novo lipogenesis inhibitors

3-FGF21/19 analogs

4-Bile acid-FXR regulators

Address fibrotic changes

1-Belapectin (galectin 3 inhibitor)

2- Cilofexor (nonsteroidal FXR) + firsocostat (allosteric acetyl CoA carboxylase inhibitor)

3-Antioxidants/chemokines and cytokines regulators

4-Immune modulators

Modulate gut-liver axis

1- Probiotics
2-Fecal microbial transplantation
3-Bariatric surgery
4-IMM-124e
5-Solithromycin

Promising Phase 3 Trials

Drug/Class	Phase 3 Trials	Primary Endpoint: Status Met?	Designation
Resmetirom **THR-β selective agonist**	MAESTRO-NASH	Improvement in liver fibrosis and MASH resolution at week 52: **Yes** *Accelerated FDA approval, March 14, 2024	Non-cirrhotic MASH with moderate to advanced fibrosis
	MAESTRO-NASH Outcomes	Time to first occurrence of all-cause mortality/ liver-related events: **Ongoing**	MASH with compensated cirrhosis (F4)
Efruxifermin **Bivalent Fc-FGF21 analog/ FGF21 analog**	SYNCHRONY-Outcomes	Fibrosis regression without worsening of MASH after 96 weeks of histology-based treatment: **Ongoing**	MASH with compensated cirrhosis (F4)
	SYNCHRONY-Histology	One-stage improvement in fibrosis and resolution of MASH after 52 weeks: **Ongoing**	Pre-cirrhotic MASH (F2/F3)
	SYNCHRONY-Real World	Assess safety and tolerability: **Ongoing**	Noninvasively diagnosed MASH/MASLD
Lanifibranor **Pan-PPAR agonist**	NATiV3	MASH resolution and improvement in fibrosis by ≥ 1 stage: **Ongoing** *Fast Track and BTD from the FDA for MASH, October 12, 2020	Biopsy-proven non-cirrhotic MASH and F2/F3 fibrosis
Pegozafermin **GlycoPEGylated analog of FGF21**	ENLIGHTEN-Fibrosis	≥ 1 point improvement in fibrosis with no worsening of MASH, and MASH resolution with no worsening of fibrosis at 52 weeks: **Ongoing**	Noncirrhotic MASH with fibrosis (F2/F3)
	ENLIGHTEN-Cirrhosis	Regression of fibrosis from F4 to an earlier stage of fibrosis at 24 months: **Ongoing** *FDA BTD for MASH, September 21, 2023	Compensated cirrhosis (F4)
Semaglutide **GLP-1 RA**	ESSENCE	Liver fibrosis improvement and steatohepatitis resolution with no worsening of liver fibrosis at week 72: **Yes**	Type 2 diabetes, obesity, CV risk reduction Noncirrhotic MASH with fibrosis (F2/F3)
Survodutide **Glucagon/GLP-1 RA**	LIVERAGE	Improve MASH/fibrosis at week 52: **Ongoing**	MASH and moderate or advanced fibrosis (F2/F3)
	LIVERAGE-Cirrhosis	4.5 years or time to first occurrence of all-cause mortality/**liver-related** events: **Ongoing** *FDA BTD, October 8, 2024	MASH and compensated cirrhosis (F4)

Resmetirom First drug approved by FDA for MASH therapy.

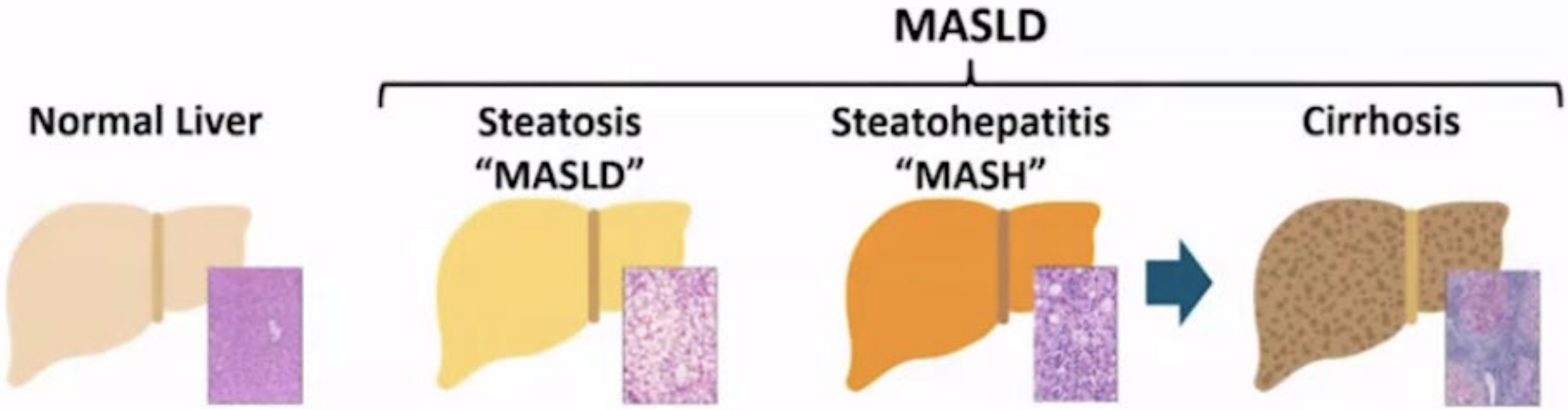
- Food and Drug Administration approval of resmetirom (Rezdiffra) last year, which reduces liver fat by stimulating thyroid hormone receptor beta.
- That was the first medication that got approved with a specific indication to treat MASH.
- Before that, lifestyle measures aimed at weight loss were the only approach.

Efimosfermin another FGF21 analogue

- Another FGF21 analogue efruxifermin which is in phase 3 trials.
- Efimosfermin alfa once-Monthly prescribed for metabolic dysfunction–associated steatohepatitis (MASH) with F2 and F3

  fibrosis significantly improved MASH resolution and fibrosis after 24 weeks.
- Patients received weekly subcutaneous efruxifermin (28 mg or 50 mg) or placebo in a 1:1:1 ratio.
- Liver biopsies were obtained at weeks 36 and 96 and 5/25/25,

Prevalence of MASLD and MASH



Worldwide prevalence:	25%[1]	3%-5%[1]	1%-2% at risk*

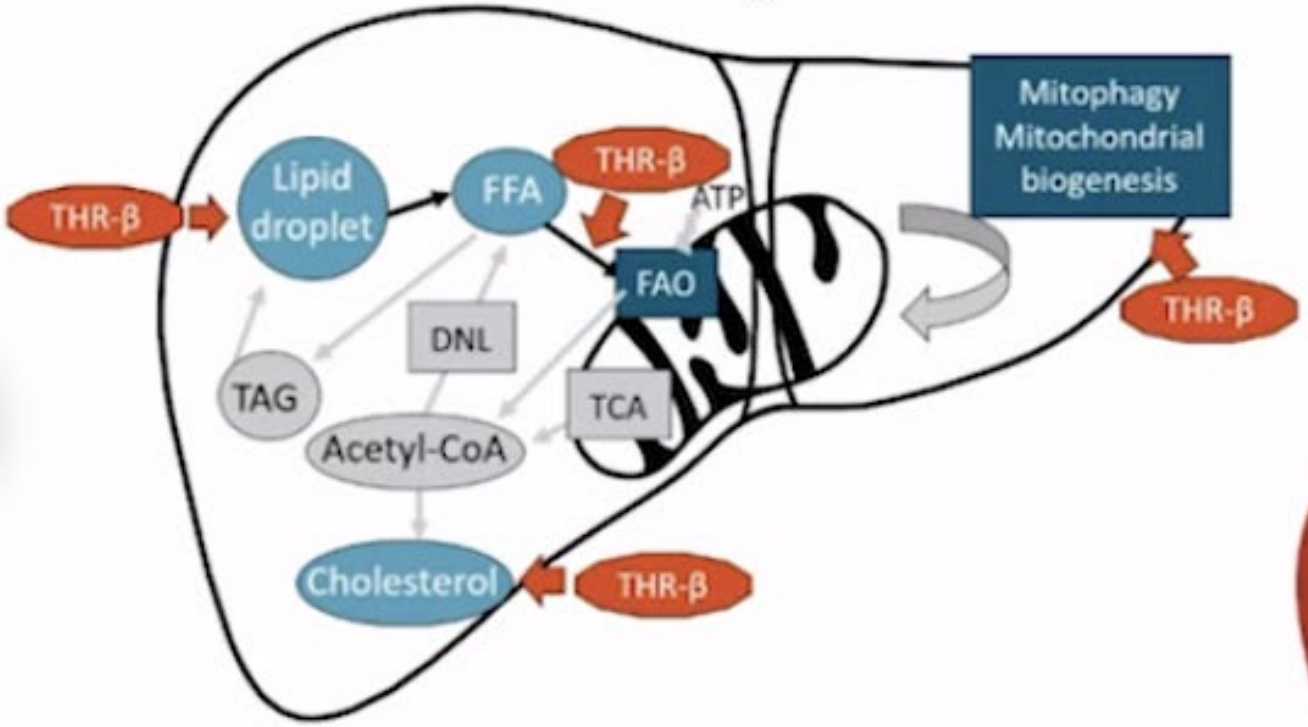
*Based on analysis of NHANES data estimating 1.74% prevalence of MASH with advanced fibrosis.[2]

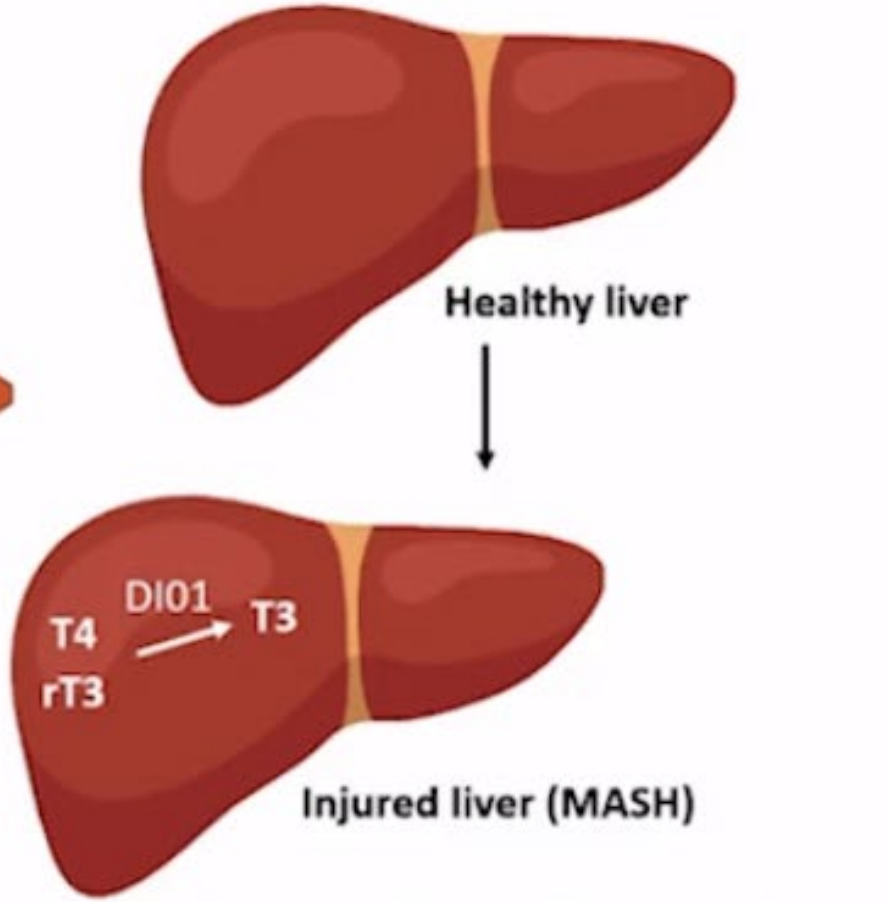
1. Younossi. J Hepatol. 2019;70:351. 2. Kabbany. Am J Gastroenterol. 2017;112:581.

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Resmetirom and the THR-β Pathway





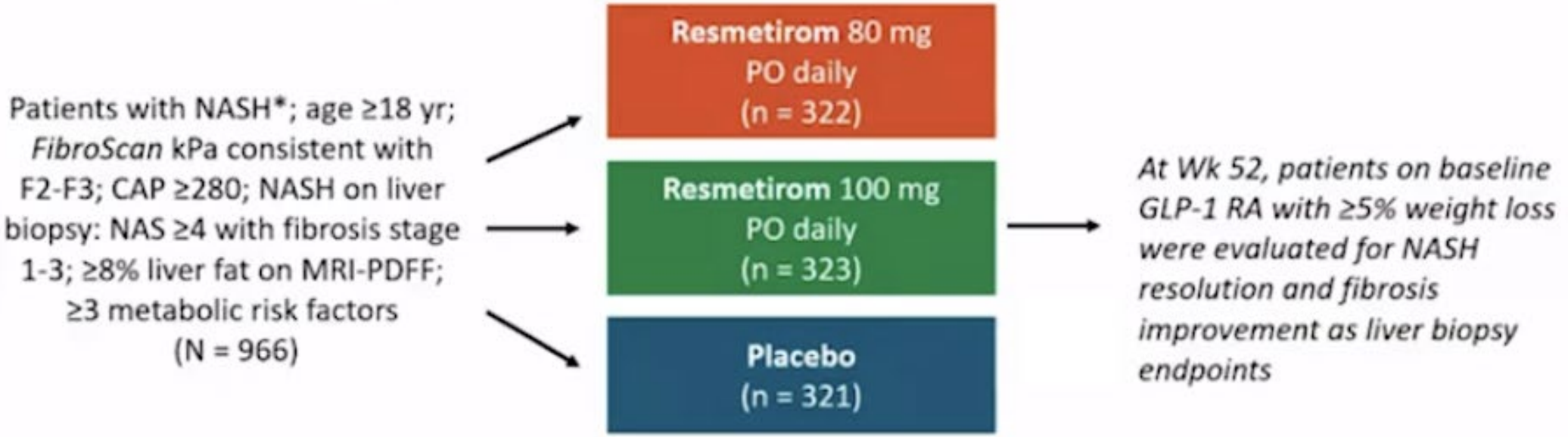
Local *"intrahepatic hypothyroidism"*

Sinha. Nat Rev Endocrinol. 2018;14:259

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MAESTRO-NASH: Study Design

- Multinational, double-blind, placebo-controlled, randomized phase III trial



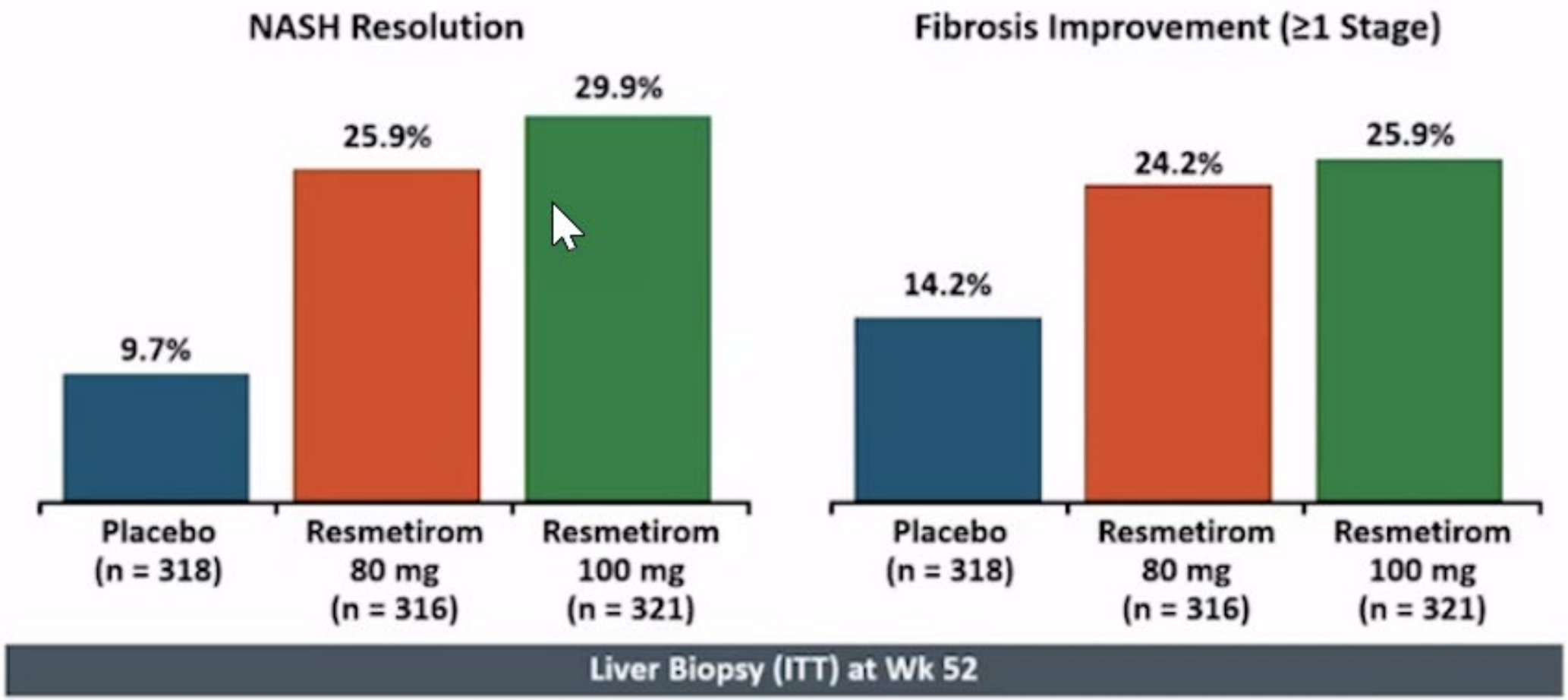
- **Primary endpoints:** NASH resolution at Wk 52, improvement in fibrosis by ≥1 stage with no worsening of NAFLD score
- **Key secondary endpoint:** percent LDL-C change from baseline at Wk 24

*NASH is used instead of MASH to align with the terminology employed in referenced studies

NCT03900429. Harrison. NEJM. 2024;390:497.

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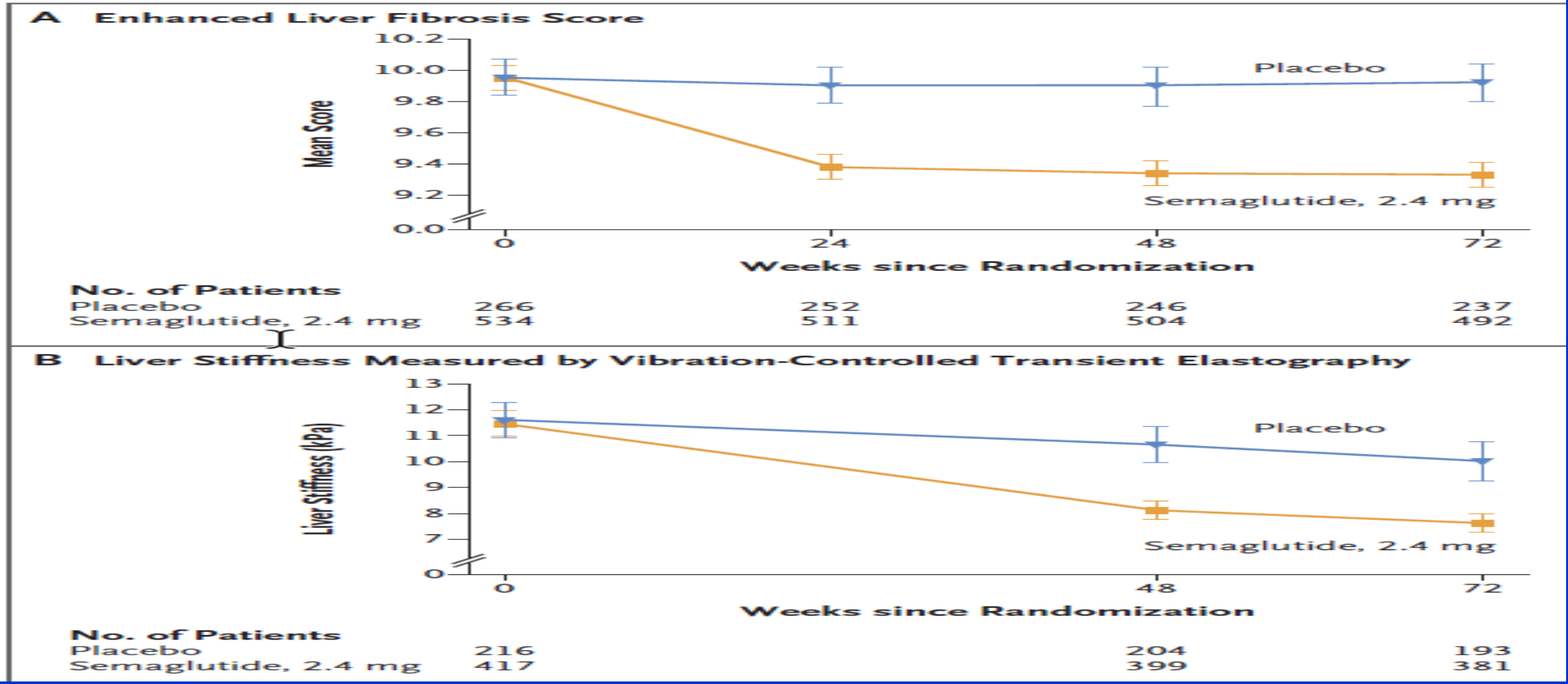
MAESTRO-NASH (Primary Statistical Model)



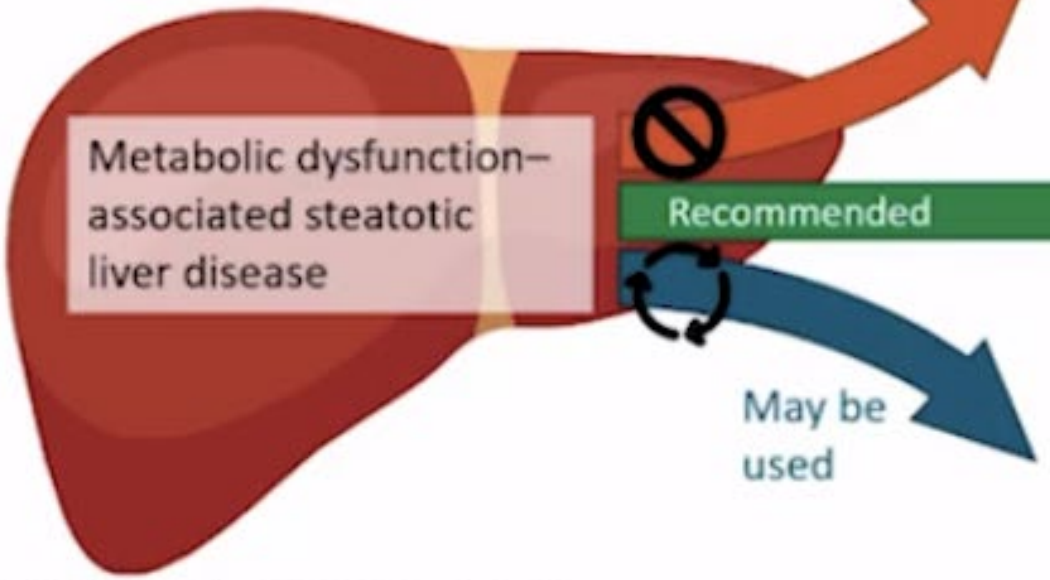
Harrison. NEJM. 2024;390:497.

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ELF Score and Liver Stiffness from Baseline to Week 72.



AASLD 2024 Guidelines on Resmetirom



Not recommended

- Cirrhosis, including LSM via VCTE >20 kPa or MRE >5 kPa
- Concomitant active liver disease
- Excess alcohol use (>20/30 g/day in women/men)
- Active thyroid disease

Recommended

Imaging-based NILDA	VCTE: LSM 8-15 kPa* MRE: LSM 3.1-4.4 kPa*
Liver histology	MASH with F2-F3†

May be used

- Individualized decisions by a specialist experienced in liver fibrosis for:
  - LSM values outside the recommended ranges
  - Other NILDA data consistent with F2-F3‡

*Modified from the AASLD NILDA guidelines.
†Liver biopsy is not routinely recommended for staging of MASH.
‡Imaging-based NILDA is preferred, eg, shear wave elastography (applying local standards for F2-F3) vs enhanced liver fibrosis score (9.2-10.4). The latter range is based on the interquartile range from the MAESTRO trial data; no recommendations are available from the AASLD NILDA guidelines.

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Chen. Hepatology. 2025;81:312.

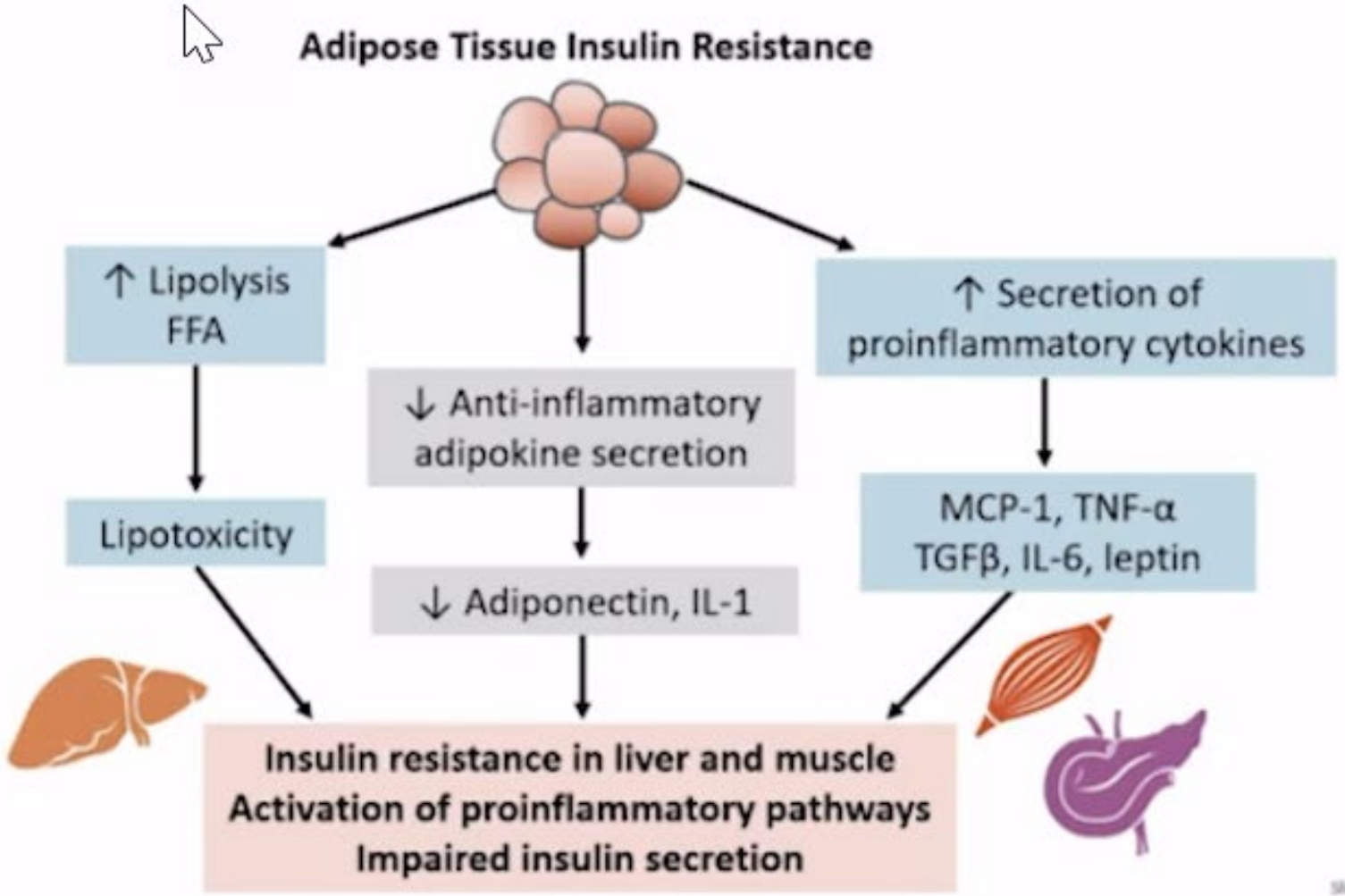
MASH Therapies Conclusions

- First drug approval for MASH 2024
- Multiple drugs in phase III: THR-B, GLP-1 and duals, PPARs, and FGF21s
- Options currently limited for patients with cirrhosis but multiple trials are underway
- The future is bright for our patients

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Semaglutide Improves Severe Liver Disease in Phase 3 Trial

The Pathogenic Relationship Between Diabetes and MASH



Gastaldelli. JHEP Rep. 2019;1:312.

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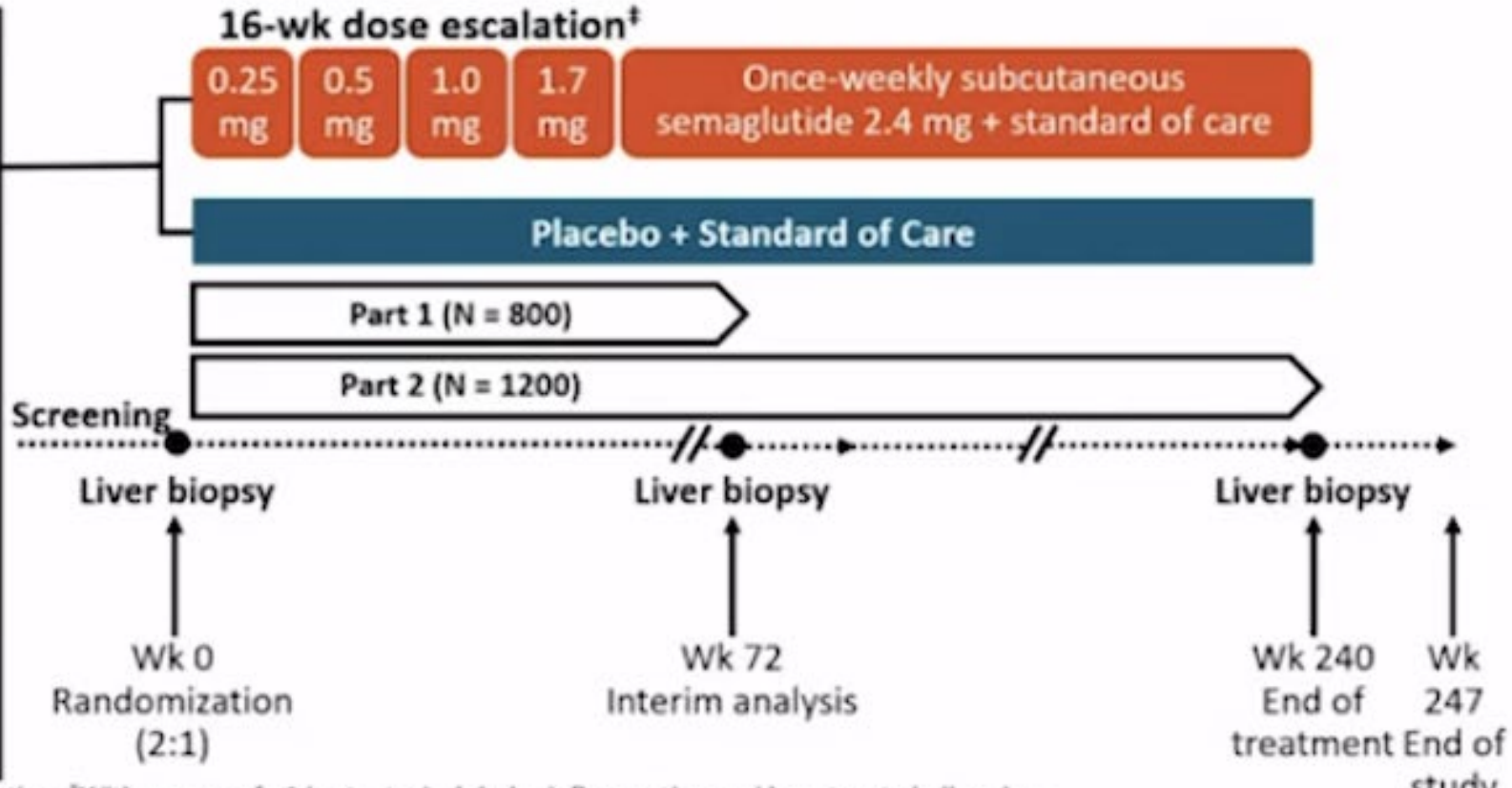
Phase III Essence Trial: Semaglutide in MASH

Key inclusion criteria

- Age ≥18 yr
- Histologic 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-1 RAs or unstable use of other glucose-lowering, lipid-lowering or weight loss medications within 90 days prior to screening

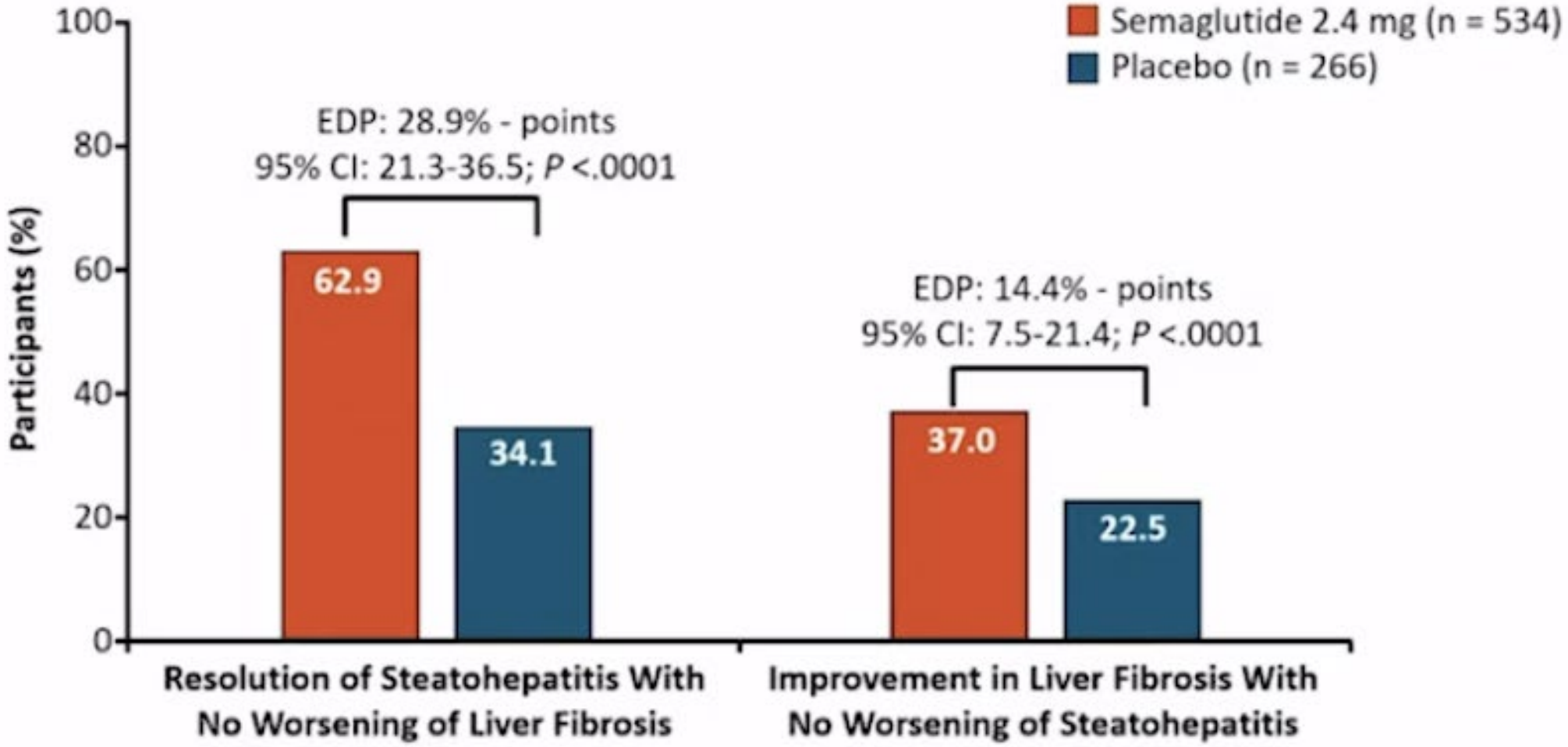


*According to NASH Clinical Research Network classification. †With a score of >1 in steatosis, lobular inflammation and hepatocyte ballooning, based on central pathologist evaluation. ‡Uptitration every 4 wk. One or more dose steps can be prolonged or the dose lowered if the actual dose is not tolerated. If the designated target dose of once-weekly subcutaneous semaglutide 2.4 mg is not tolerated, patients may stay at a lower dose level.

NCT04822181. Newsome. Aliment Pharmacol Ther. 2024;60:1525. Newsome. AASLD 2024. Abstr 5018.

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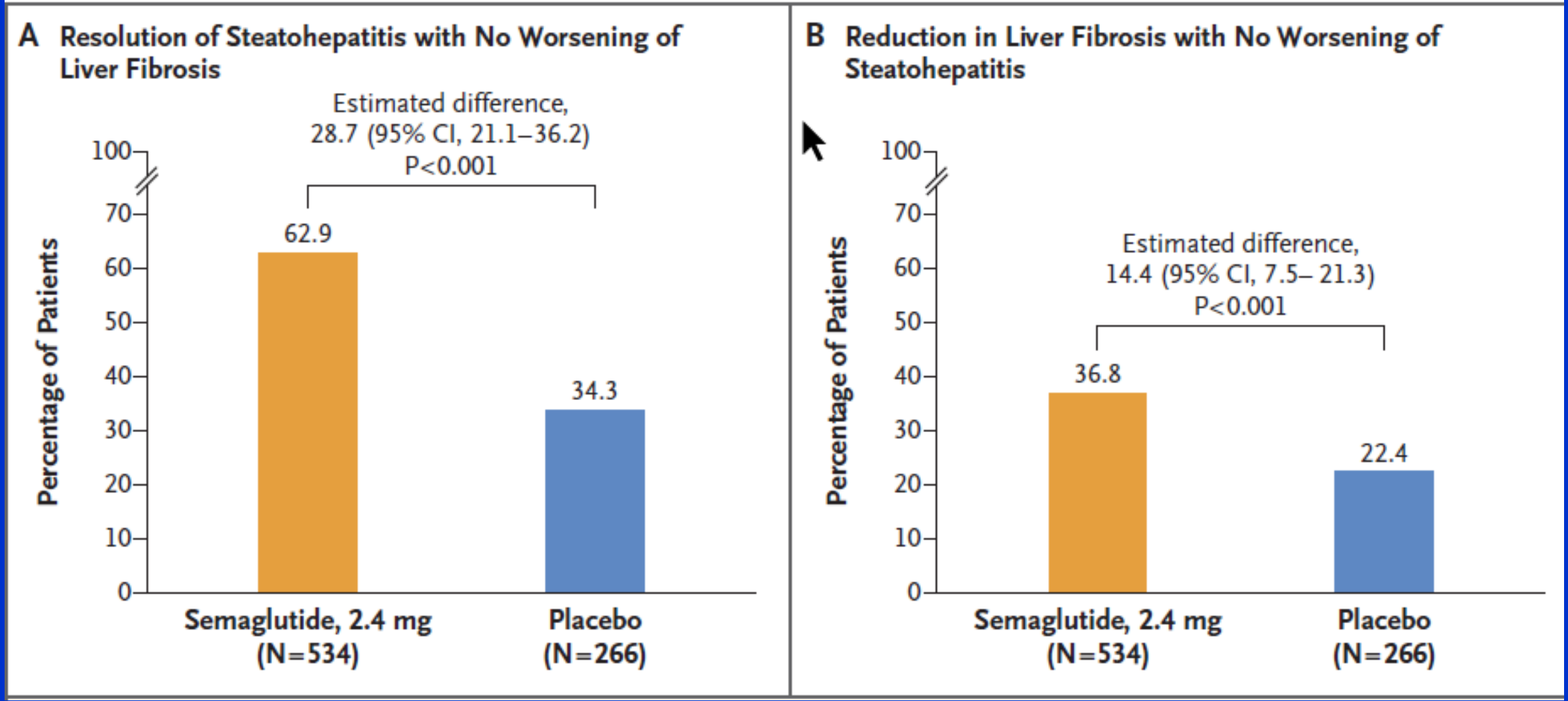
Primary Endpoints (ITT Population)



Newsome. AASLD 2024. Abstr 5018.c

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Phase 3 Trial of Semaglutide in MASLD Primary End Points.

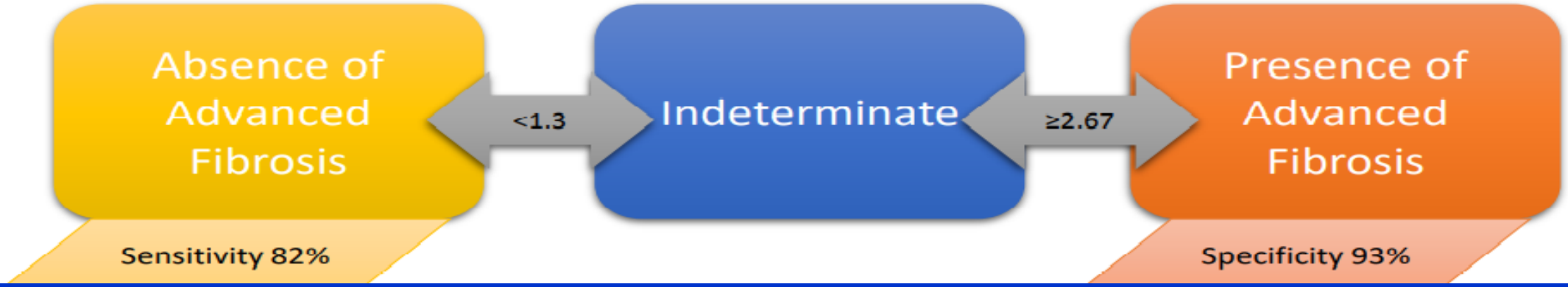


Liver fibrosis tests, non-commercial blood-based,

Name	Components (or formulas if available)	Rule-out cut-off*	Tested in ALD?	Tested in MASLD?	Appropriate for community testing?
Non-patented, blood-based tests					
APRI	(AST levels IU/L/AST upper limit of normal IU/L) x 100/platelet count 10^9/L).	<0.50	+	+	Extensively tested in community cohorts, but has many false positives[71] Formula freely available.
$CLivD_{GGT}$ $CLivD_{non\text{-}GGT}$	Alcohol intake, waist-hip ratio, smoking, diabetes, sex, age, GGT **see formula in the footer	$<-0.258_{GGT}$ $<-0.412_{non\text{-}GGT}$	+	+	Needs further validation, but developed and validated in community cohorts. Cannot be incorporated in laboratory systems. Half of the population may test positive[96,97] Formula freely available.
FIB-4	Age (years) x AST levels UI/L)/(Platelet count 10^9/L x √ALT levels IU/L)	<1.30 for patients <65 years-old <2.0 for patients ≥65 years-old	+	+	Extensively tested in community cohorts, recommended by international guidelines, but has been reported to have almost one third (28%) of false positives[46,98] Formula freely available. Adjusted for patients ≥65 years[99]
Forns score	7.811 - 3.131 x ln [platelet count 10^9/L]+ 0.781 x ln [GGT levels IU/L] + 3.467 x ln [age] – 0.014 [cholesterol levels (mg/dl)]	<4.2	+	+	Little evidence from community cohorts, mostly focused on detection of liver fibrosis due to viral hepatitis[100] Formula freely available.
LiverRisk score	AST, ALT, fasting glucose, GGT, cholesterol, platelet count, sex, age***	<10	-	-	Needs independent validation, but developed and validated in community cohorts[73] Formula is copyright protected, but the score can be calculated for free on liverriskscore.com
NFS	-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glucose/diabetes (yes = 1, no = 0)	<-1.455	+	+	Extensively tested in community cohorts, but has almost one third (29%) of false positives, and cannot be incorporated in laboratory systems[46,99] Formula freely available.

FIB-4

- Can be calculated in the office with easily available variables
  - Age, platelet count, ALT, AST
- Useful in identifying patients with a higher likelihood of F3 or F4
- AUROC 0.78 (95% CI: 0.78-0.78)



Anstee QM, Lawitz EJ, Alkhouri N, et al. Noninvasive Tests Accurately Identify Advanced Fibrosis due to NASH: Baseline Data From the STELLAR Trials. Hepatology. 2019;70(5):1521-1530.

https://nafldscore.com/

NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

Age (years)

BMI (kg/m^2)

IGF/diabetes

AST

ALT

Platelets ($x10^9/l$)

Albumin (g/l)

calculate score

BMI: body mass index
IGF: impaired fasting glucose

JAMA Internal Medicine | Original Investigation

Statin Use and Risk of Hepatocellular Carcinoma and Liver Fibrosis in Chronic Liver Disease

Jonggi Choi, MD, PhD; Vy H. Nguyen, BA; Eric Przybyszewski, MD; Jiunn Song, MD; Allison Carroll, MD; Megan Michta, MPH; Erik Almazan, MD; Tracey G. Simon, MD, MPH; Raymond T. Chung, MD

IMPORTANCE Statins may lower the risk of hepatocellular carcinoma (HCC) by mitigating liver fibrosis progression.

OBJECTIVE To evaluate the association between statin use and the risk of HCC and hepatic decompensation, with an emphasis on liver fibrosis progression, among adult patients with chronic liver disease (CLD).

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from the Research Patient Data Registry from 2000 to 2023 on patients 40 years or older with CLD and a baseline Fibrosis-4 (FIB-4) score of 1.3 or higher. Participants were grouped into statin users and nonusers. Data analysis was conducted from August 5, 2024, to January 3, 2025.

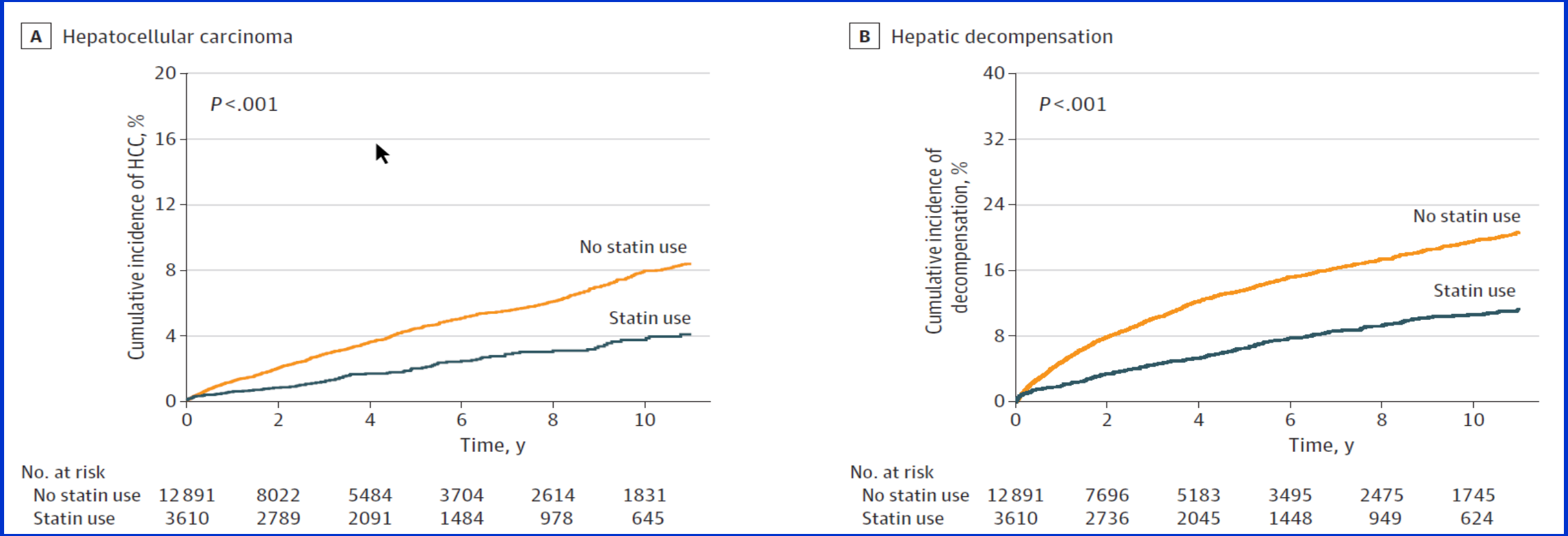
EXPOSURES Statin use.

MAIN OUTCOMES AND MEASURES Outcomes included 10-year cumulative incidence of HCC and hepatic decompensation as well as transitions in liver fibrosis risk categories based on FIB-4 scores. Statin use was defined as exposure to a cumulative defined daily dose (cDDD)
of 30 or more. Fibrosis progression was assessed through FIB-4 group transitions (low, intermediate, and high) over time. Outcomes were analyzed using adjusted subhazard ratio (aSHR) and trends in serial FIB-4 scores.

RESULTS The analysis included 16 501 participants (mean [SD] age, 59.7 [11.0] years; 6750 females [40.9%] and 9751 males [59.1%]) with CLD, including 3610 statin users and 12 891 nonusers. Statin users exhibited a significantly lower 10-year cumulative incidence of HCC (3.8% vs 8.0.%; risk difference, −4.2%; 95% CI, −5.3 to −3.1%) and hepatic decompensation (10.6% vs 19.5%; risk difference, −9.0%; 95% CI, −10.6 to −7.3) compared with nonusers. The aSHR was 0.67 (95% CI, 0.59 to 0.76) for HCC and 0.78 (95% CI, 0.67 to 0.91) for hepatic

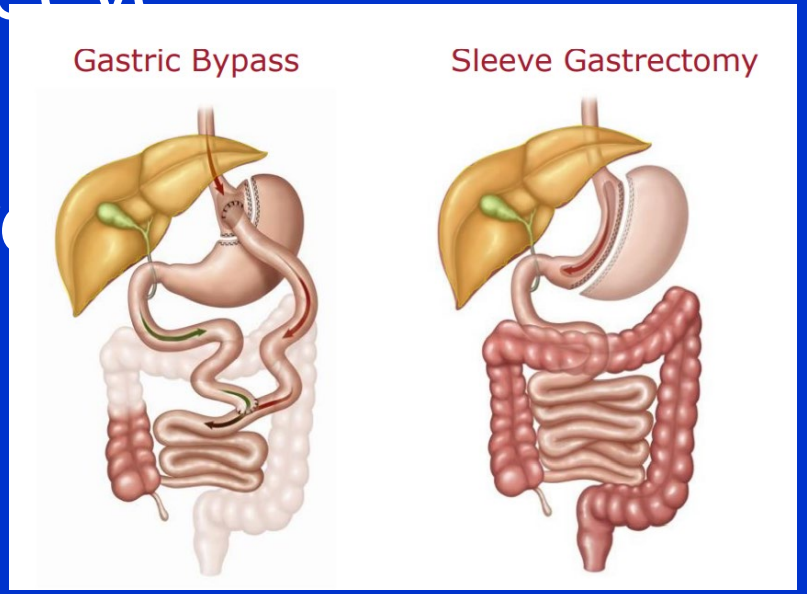
Supplemental content

Cumulative Incidence of Hepatocellular Carcinoma (HCC) and Hepatic Decompensation Among Statin Users and Nonusers



Bariatric Surgery Improves Several Aspects of NAFLD

- Subjects: 65 adults with advanced NASH (F3-4 or NAS 3-4) and perioperative and follow-up liver biopsies (from 868 who had undergone bariatric surgery)
- Intervention: gastric bypass (53) or sleeve gastrectomy (12)
- Average time to follow-up biopsy - 6 y
- Average weight loss 23%
- Average change in NAS Score -3.12



MASLD Research Priority

- An estimated 38% of adults and 13% of children and adolescents worldwide have fatty liver disease.
- Using a Delphi methodology, over two rounds a multidisciplinary panel (n = 288) from 94 countries reviewed and ranked fatty liver disease research priorities.
- Across rounds, consensus increased in all domains.
- The final research agenda comprises 28 priorities that can catalyse the global health community's efforts to advance and accelerate responses to this widespread and fast-growing public health threat.

A research agenda for turning the tide on fatty liver disease

