MASLD Unveiled: From Fat to Facts in the New Era of Diagnosis and Targeted Therapy

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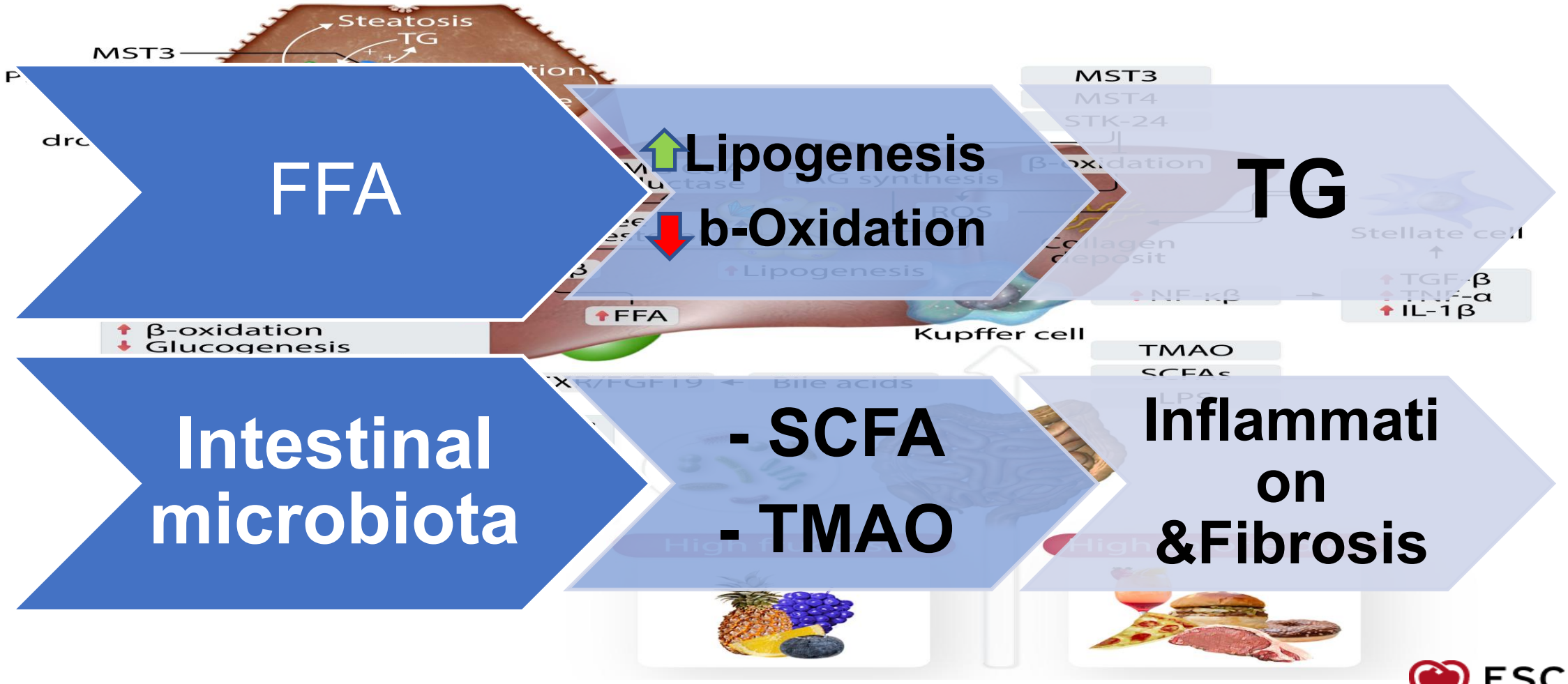
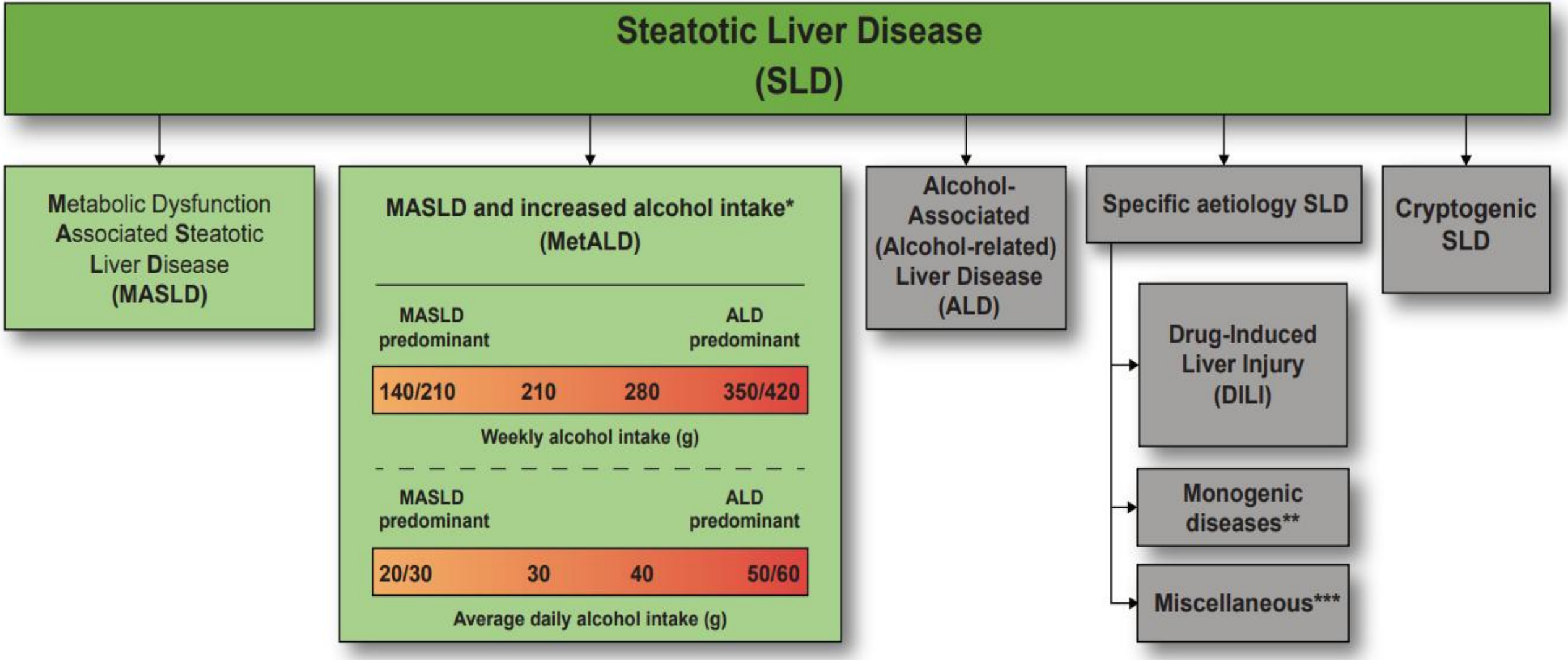
Objectives

- Pathogenesis of the disease
- Epidemiology of Metabolic Dysfunction-Associated SLD (MASLD)
- Noninvasive tests to determine the severity of MASLD
- The current therapeutics for MASLD

The Pathogenesis Of MASLD



Cardiovasc Res, Volume 119, Issue 9, July 2023, Pages 1787–1798, https://doi.org/10.1093/cvr/cvad095

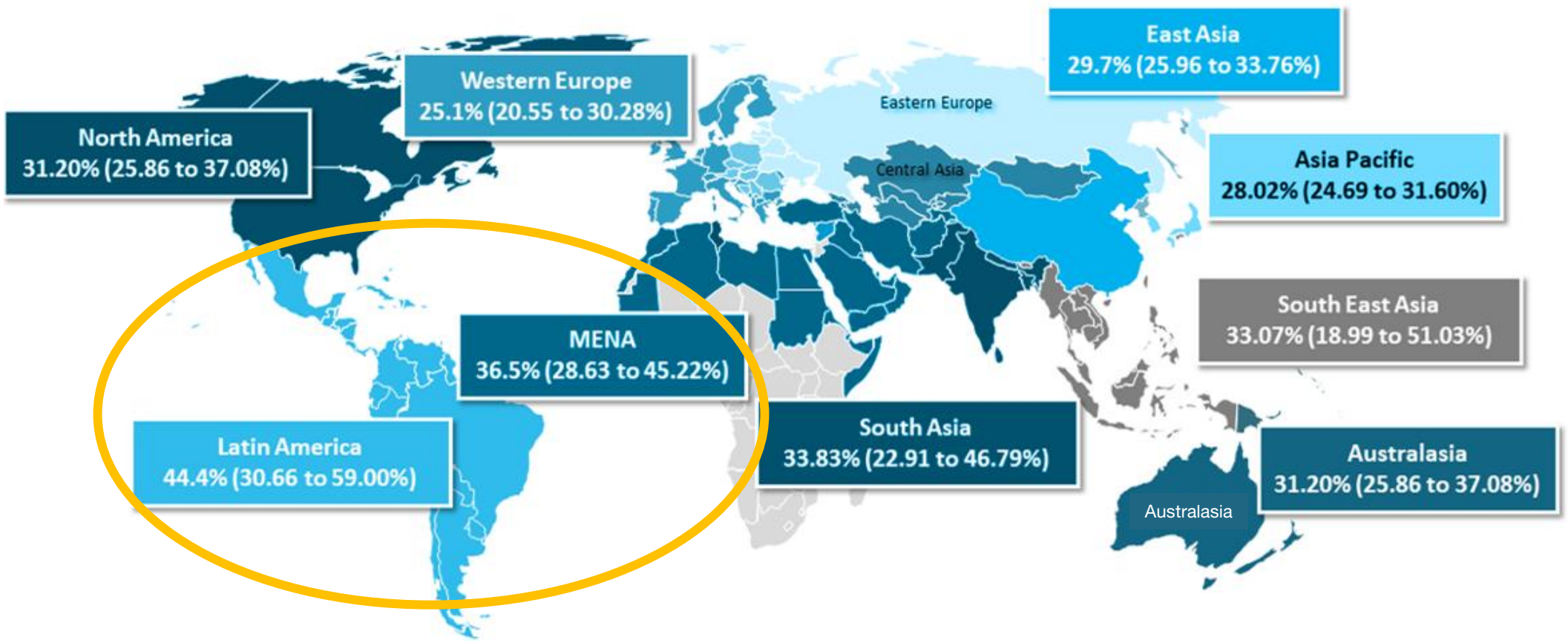


*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

Epidemiology and Disease Burden

The Global Prevalence of MASLD

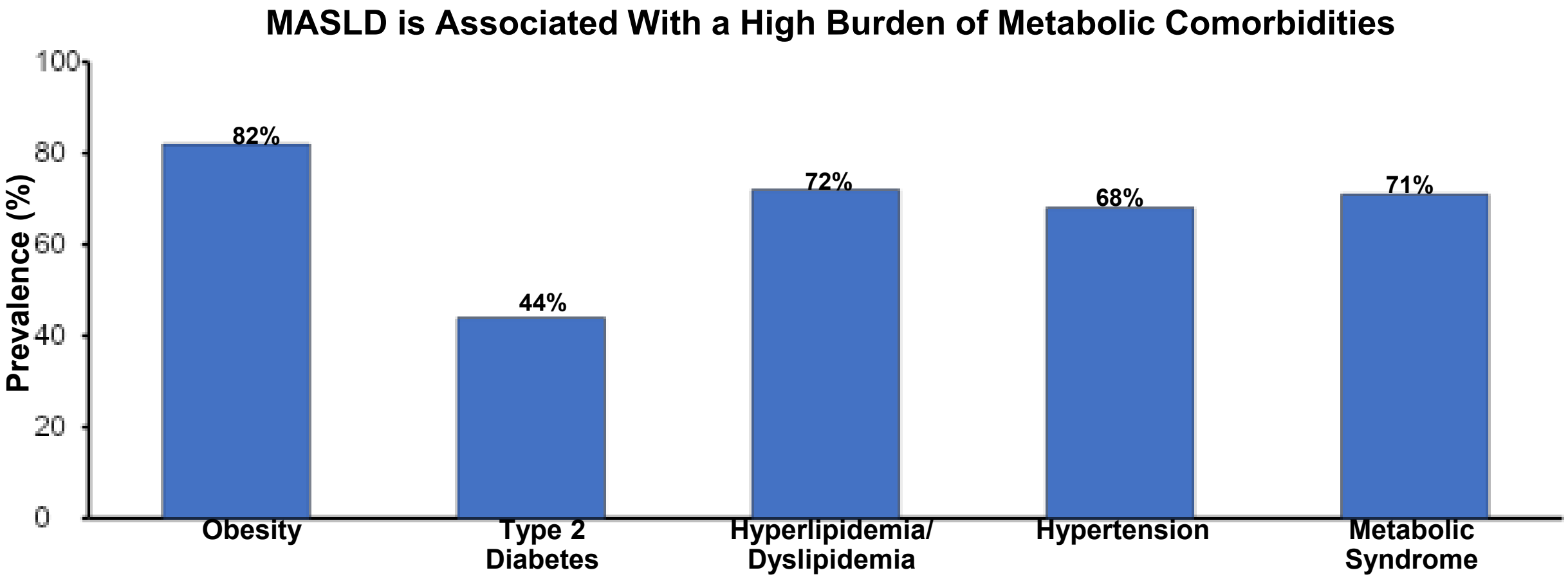
Pooled Prevalence of MASLD: 30.05% (95% confidence interval: 27.88 to 32.32%)



prova℠ EDUCATION

Younossi ZM, et al. *Hepatology.* 2023

Comorbidities Associated With MASLD: Global Prevalence Among MASLD Patients



Younossi ZM, et al. *Hepatology.* 2016;64:73-84.

Noninvasive Tests for MASH/Fibrosis NITs

NITs To Determine the Stage of Fibrosis

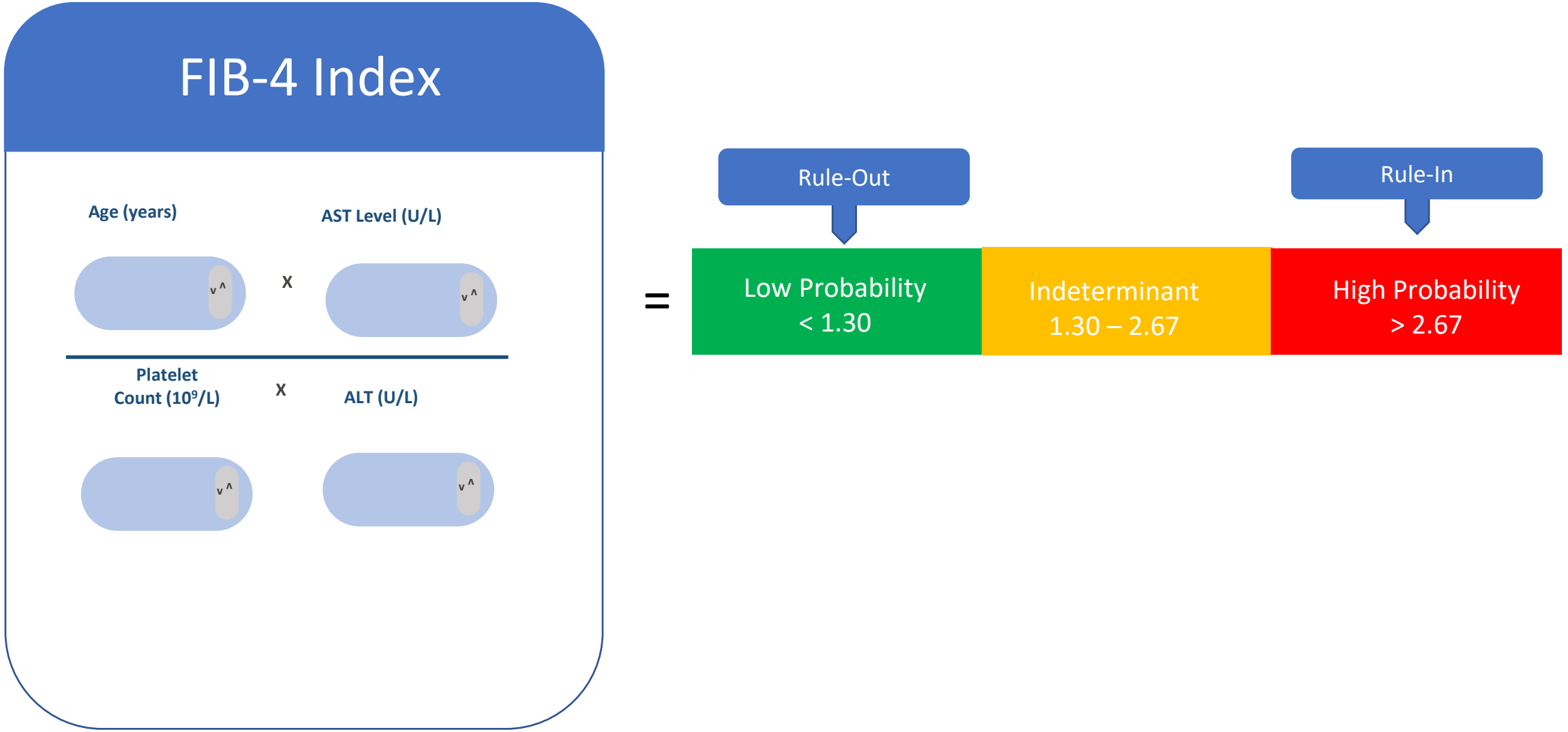
Serologic

- Simple Scores
  - FIB-4 Index
  - NAFLD Fibrosis Score (NFS)
  - AST/ ALT ratio
  - APRI
- Proprietary predictive Scores
  - FibroSURE™, Liver FASt™
  - ELF

Imaging

- Elastography
  - VCTE (Fibroscan)
  - ARFI
  - SWE
  - Velacur
  - Hepatoscope
  - MRE

FIB-4: Identification of Advanced Fibrosis



Limitations of FIB-4 in Certain Populations

T2DM[1]

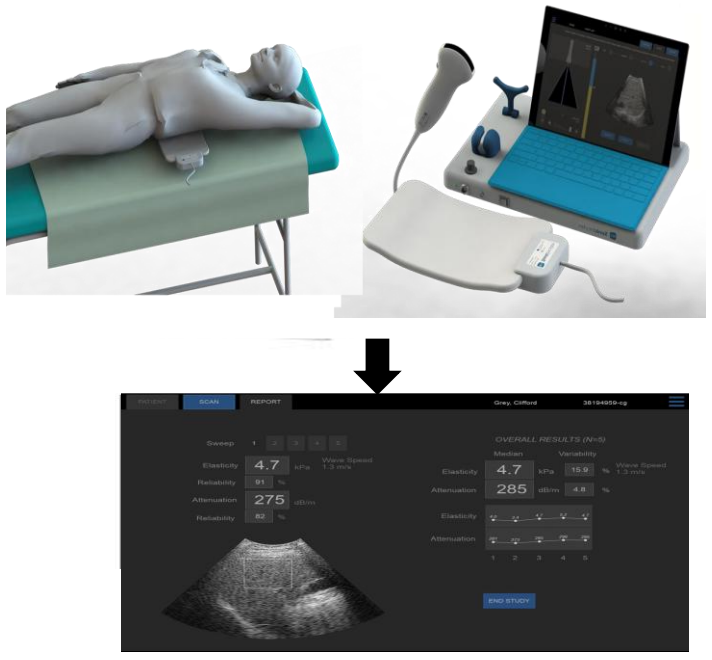
Older patients (≥ 65 y)[2]

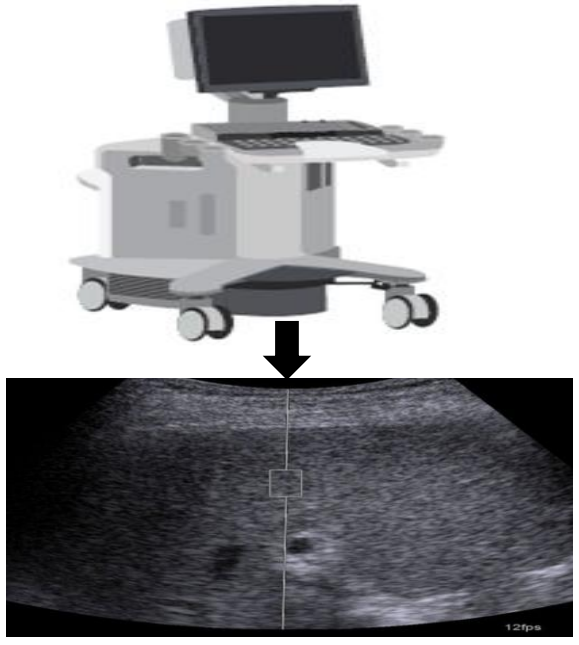
- Higher FIB-4 cut-off value (> 2.0)

Low platelet counts[2]

High alcohol intake[2]

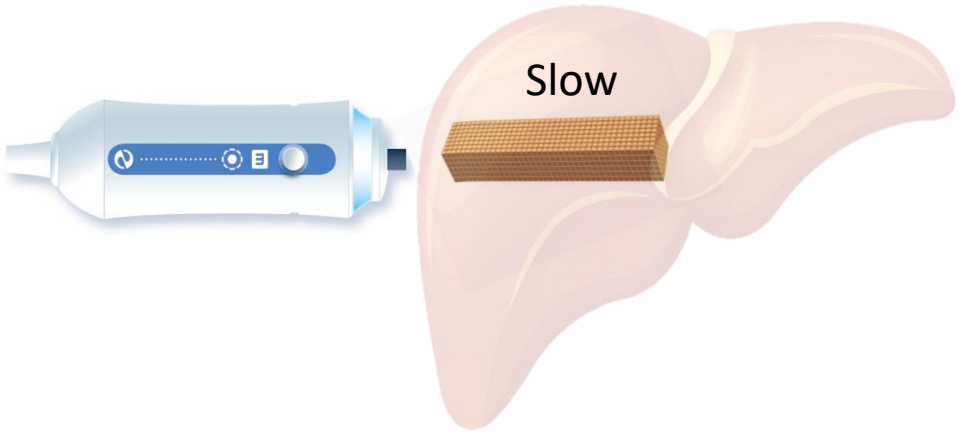
Available US-Based Radiologic Tests

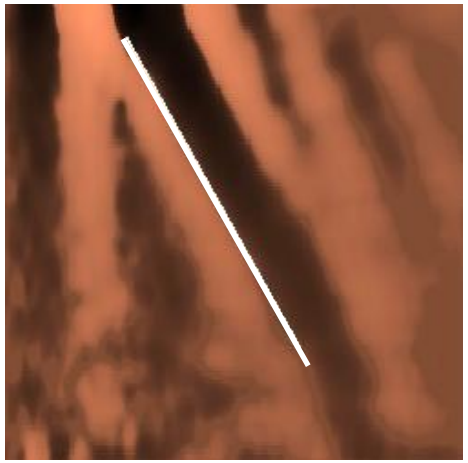




	Transient Elastography (kPa)	Velacur™ (kPa)	ARFI (m/s) – SSW (kPa)
Advantages	- Can be performed in clinic with real-time results	- Can be performed in clinic with real-time results	- Can be integrated into a conventional ultrasound
Disadvantages	- Increased failure rate with obesity - Expensive device - Cutoff values with XL probe are slightly different from M probe	- More time consuming than TE (although time can be reduced significantly with training) - Limited availability - More accurate steatosis grading	- Increased failure rate with obesity - Cutoff values for advanced fibrosis vary significantly

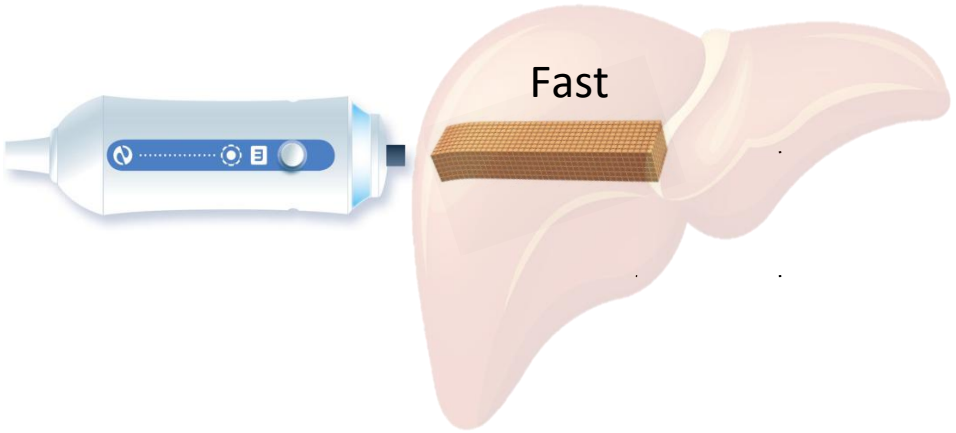
Liver Stiffness Correlates to Fibrosis Level

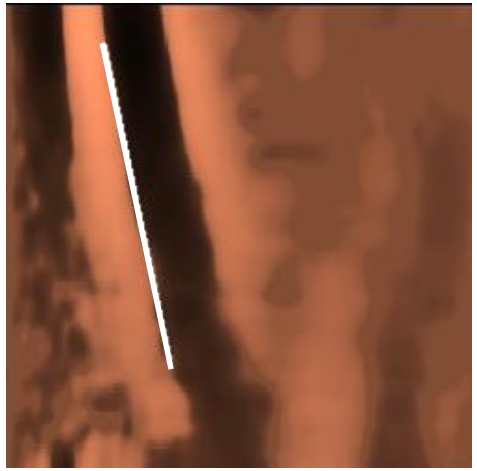




Healthy

- Low Stiffness



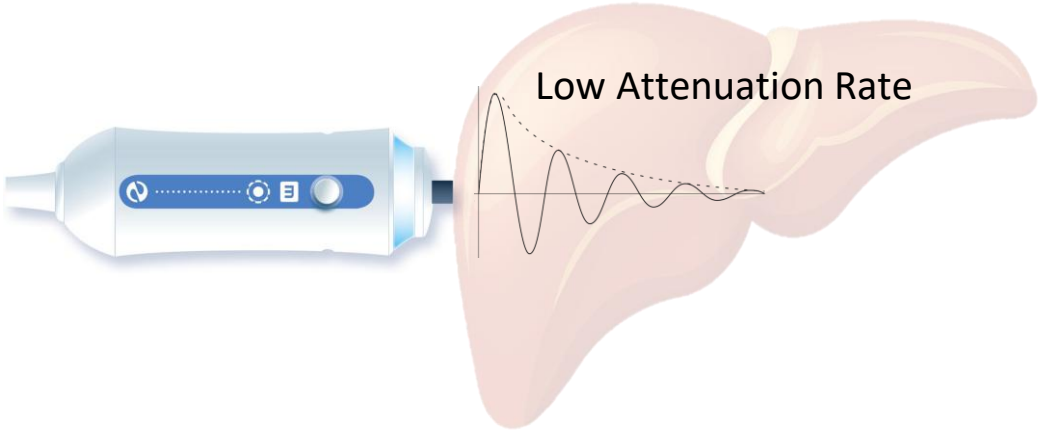


Fibrotic

- High Stiffness

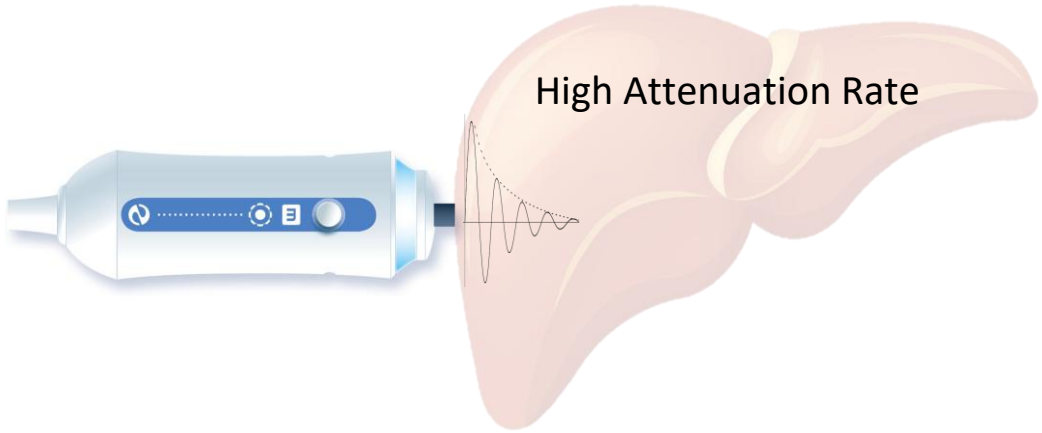
FibroScan VCTE Range: 2.5- 75 kPa

Ultrasound Attenuation Rate Correlates to Steatosis Level



No Steatosis

- Low CAP Value



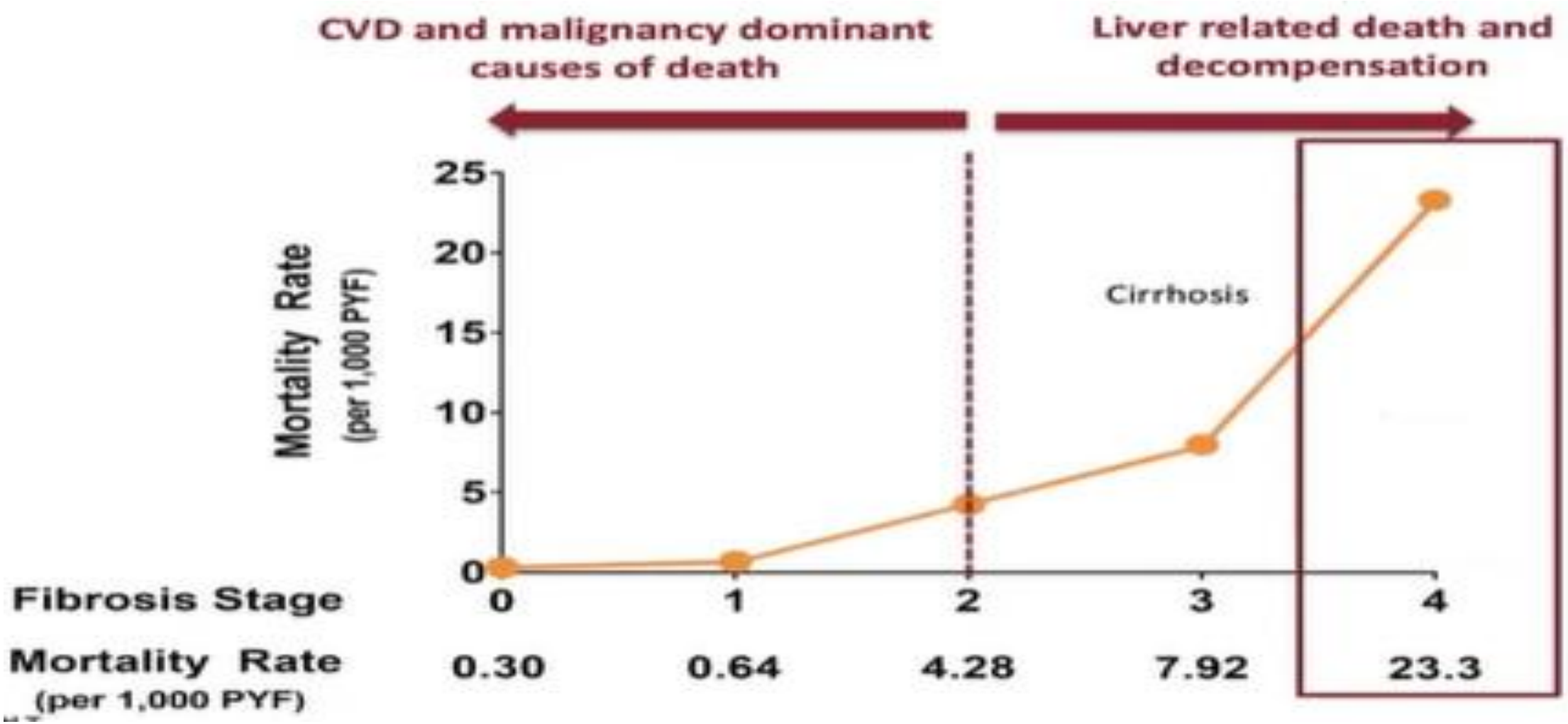
Elevated Steatosis

- High CAP Value

The Controlled Attenuation Parameter (CAP): A novel Tool for the Non-invasive Evaluation of Steatosis Using FibroScan; Sasso, Beaugrand, De Ledinghen et al;. Clin Res Hepatology Gastroenterol, 2012. 36(1): p. 13-20.

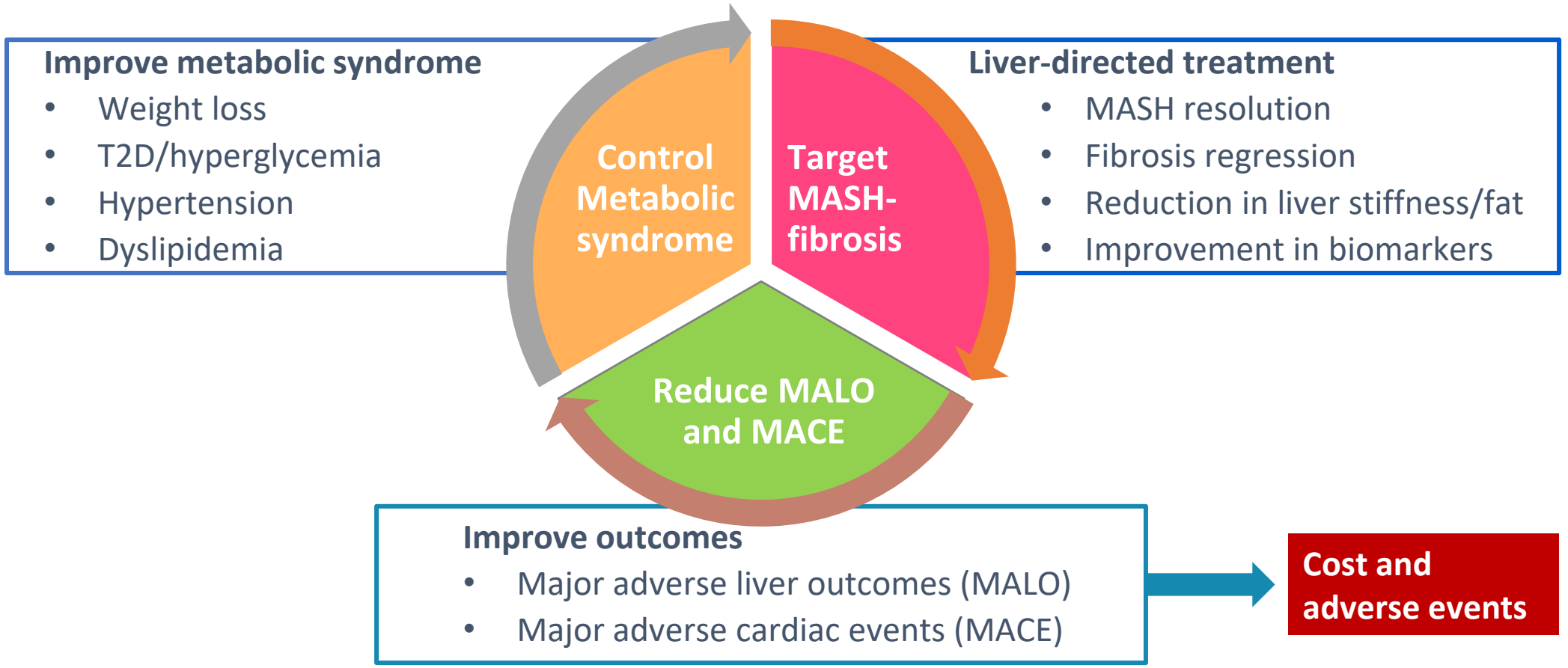
Current Treatments for MASH

Liver Fibrosis & Mortality

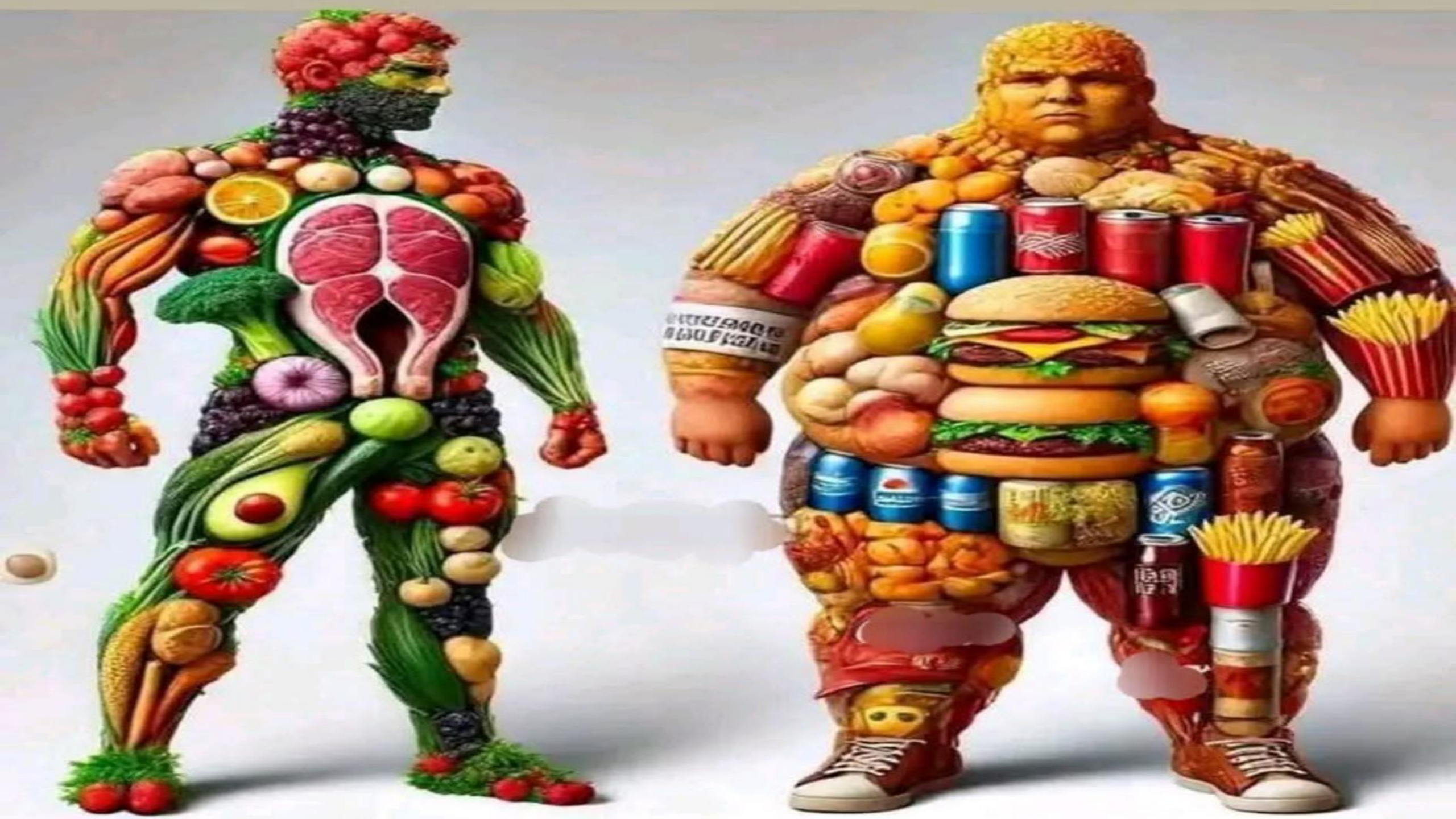


Dulai, et al. Hepatology 2017

The Goals for MASH management



MACE, major adverse cardiac events; MALO, major adverse liver outcomes; MetS, metabolic syndrome; T2D, type 2 diabetes mellitus.

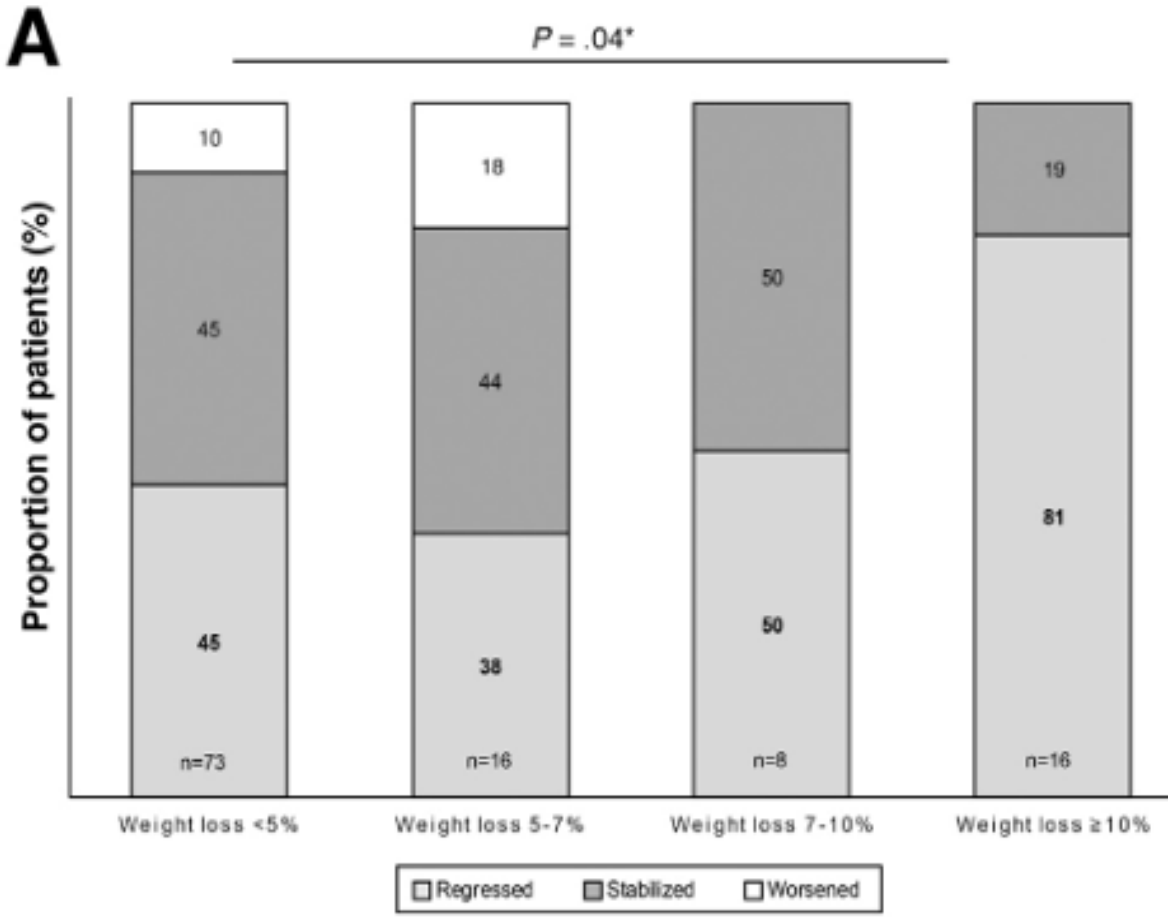


Life Style Modifications

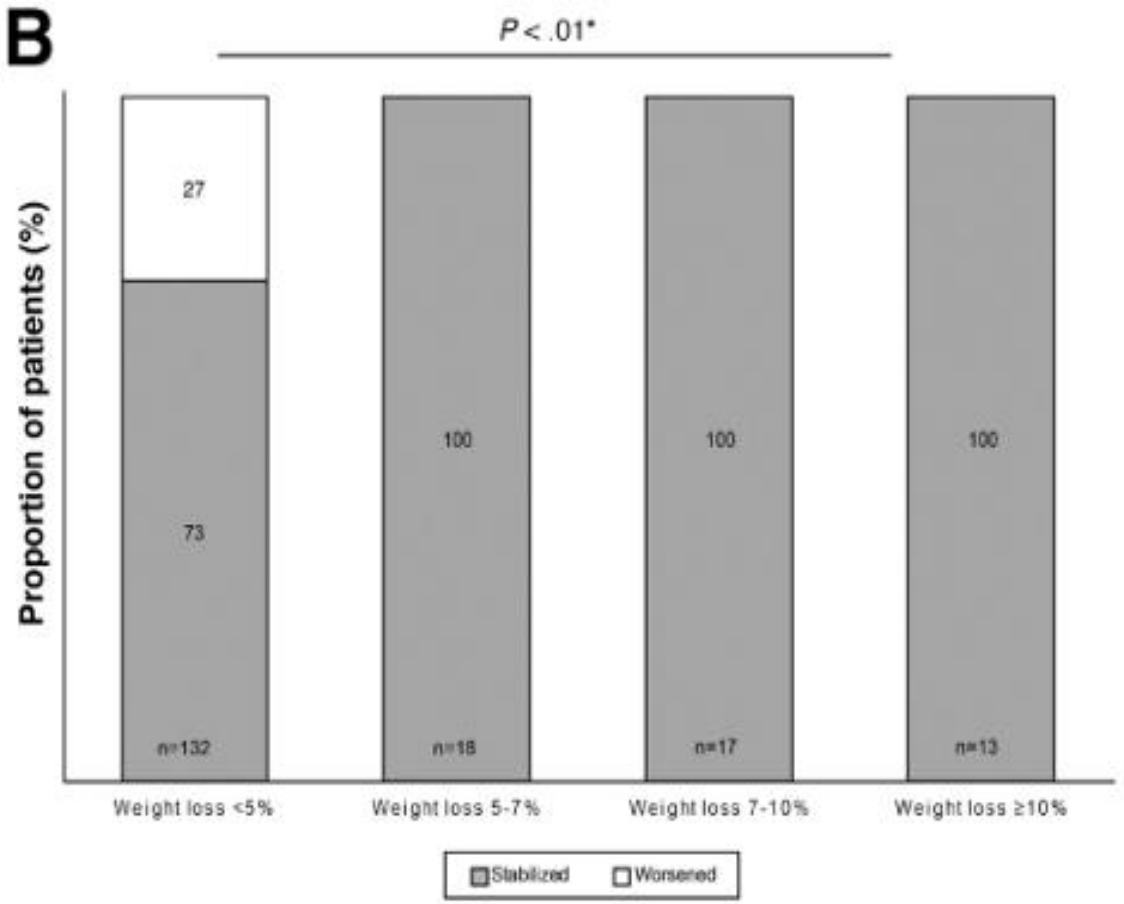
- **Exercise:** 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity aerobic exercise per week
- To achieve **weight loss** patient needs hypocaloric diet 1200-1500 kcal/d or a reduction of 500-1000 kcal/d from baseline
- Lean mass patient: Exercise. Diet to target a modest weight loss of 3-5%
- Intermittent fasting: The popular 5:2 fasting regimen, easy, no specific foods are prohibited. In mice it showed improvement in MASH and prevent liver cancer

Lifestyle Modification Significantly Reduces Features of MASH

Fibrosis at baseline



No fibrosis at baseline



Vilar-Gomez. Gastroenterology. 2015

Weight Loss Through Lifestyle Modification in MASLD

Weight Loss	Outcome Among Patients Achieving Weight Loss	Patients Sustaining Weight Loss at 1 Yr[1]
≥ 10%	Fibrosis regression (45% of patients)[1]	< 10%
≥ 7%	MASH resolution (64% to 90% of patients)*	18%
≥ 5%	Ballooning/inflammation improvement (41% to 100% of patients)*	30%
≥ 3%	Steatosis improvement (35% to 100% of patients)*	Not reported

*Depending on degree of weight loss.

Vilar-Gomez. Gastroenterology. 2015

The Chemo-protecting Effect of Coffee

- The global population consumes 2.2 billion cups daily
- Coffee has been associated with improvement

Of multiple liver diseases including improvement

In the liver fat

- Has been associated with lower rate of HCC 38%

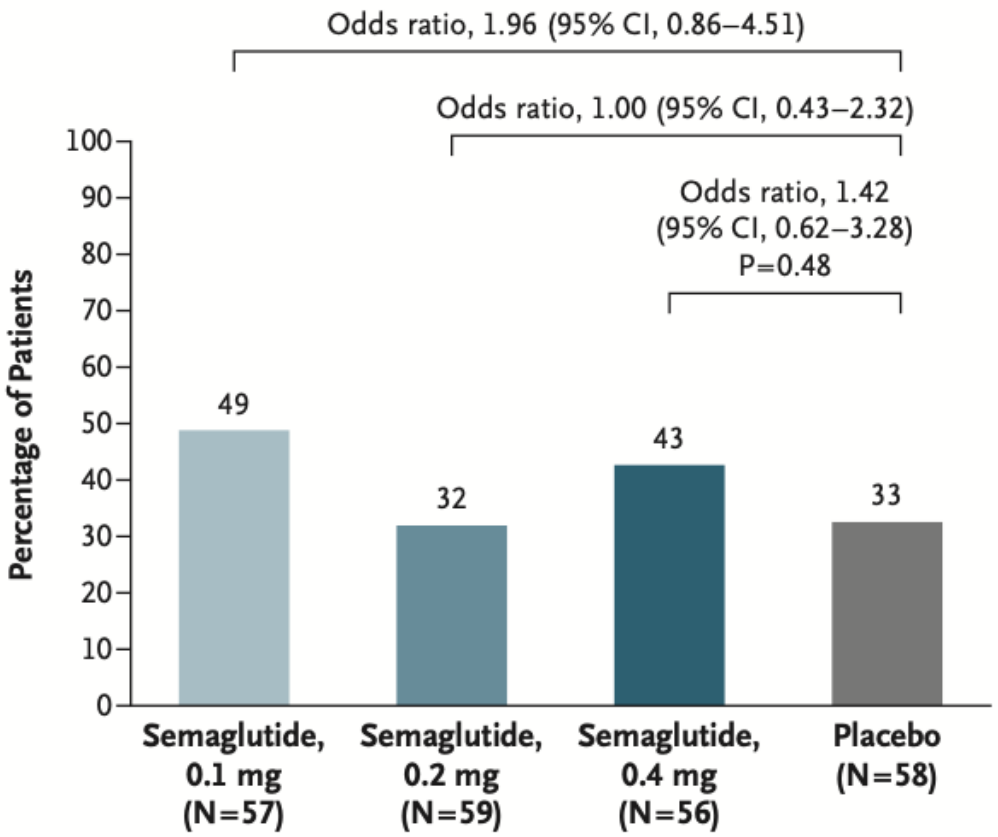
Among those who drink any amount compared

To none

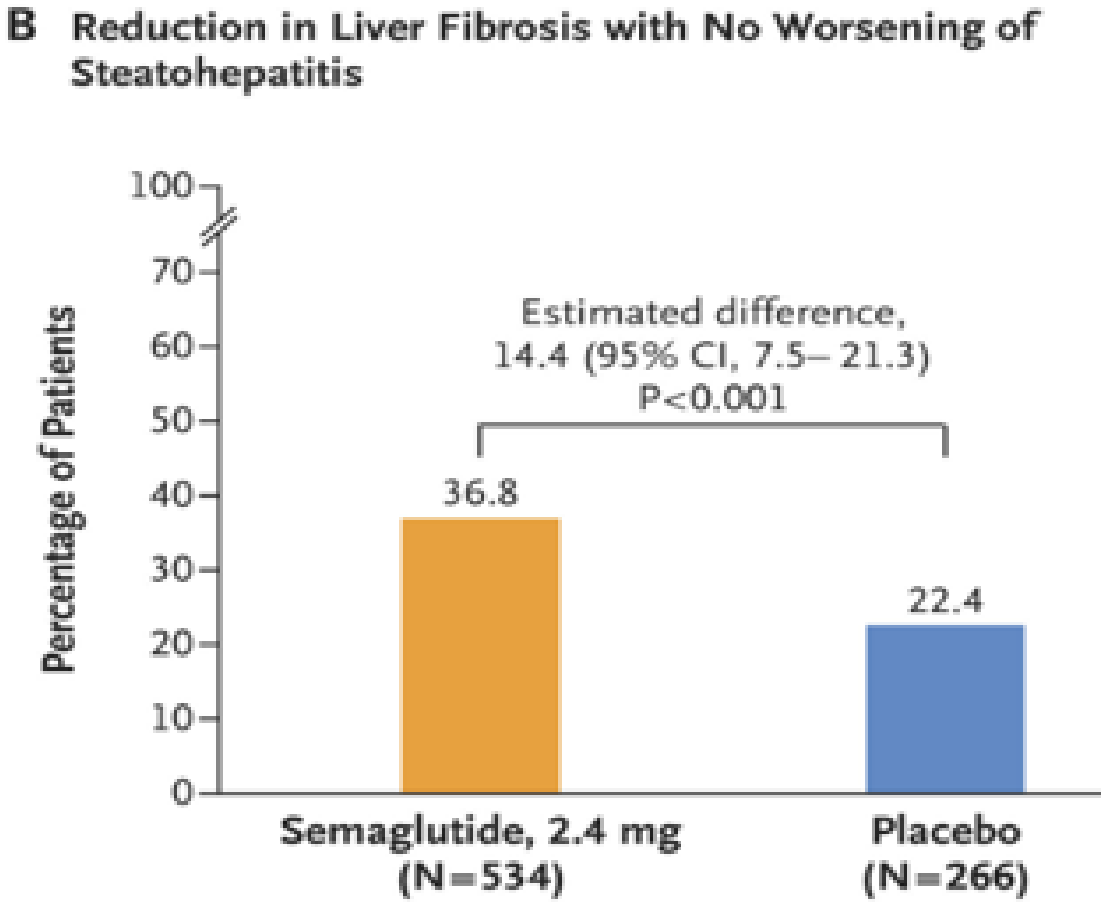
Those who drink coffee have ½ rate of having chronic liver disease compared to those who do not

Semaglutide Effect on Liver Fibrosis

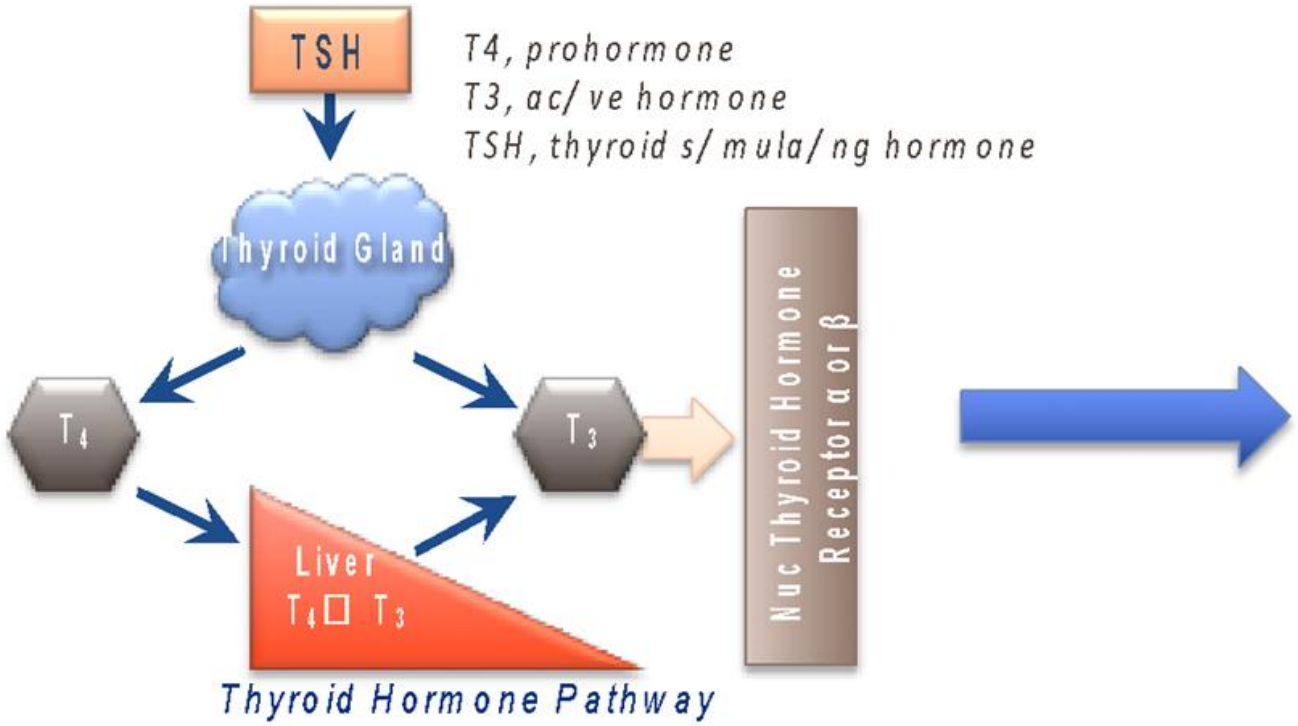
Phase 2



Phase 3



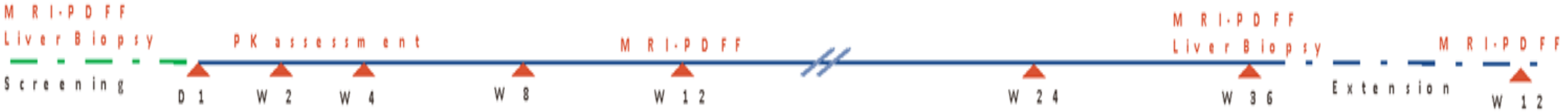
Resmetirom: Selective Thyroid Hormone Receptor-Beta Agonist



In humans THR-β agonism:

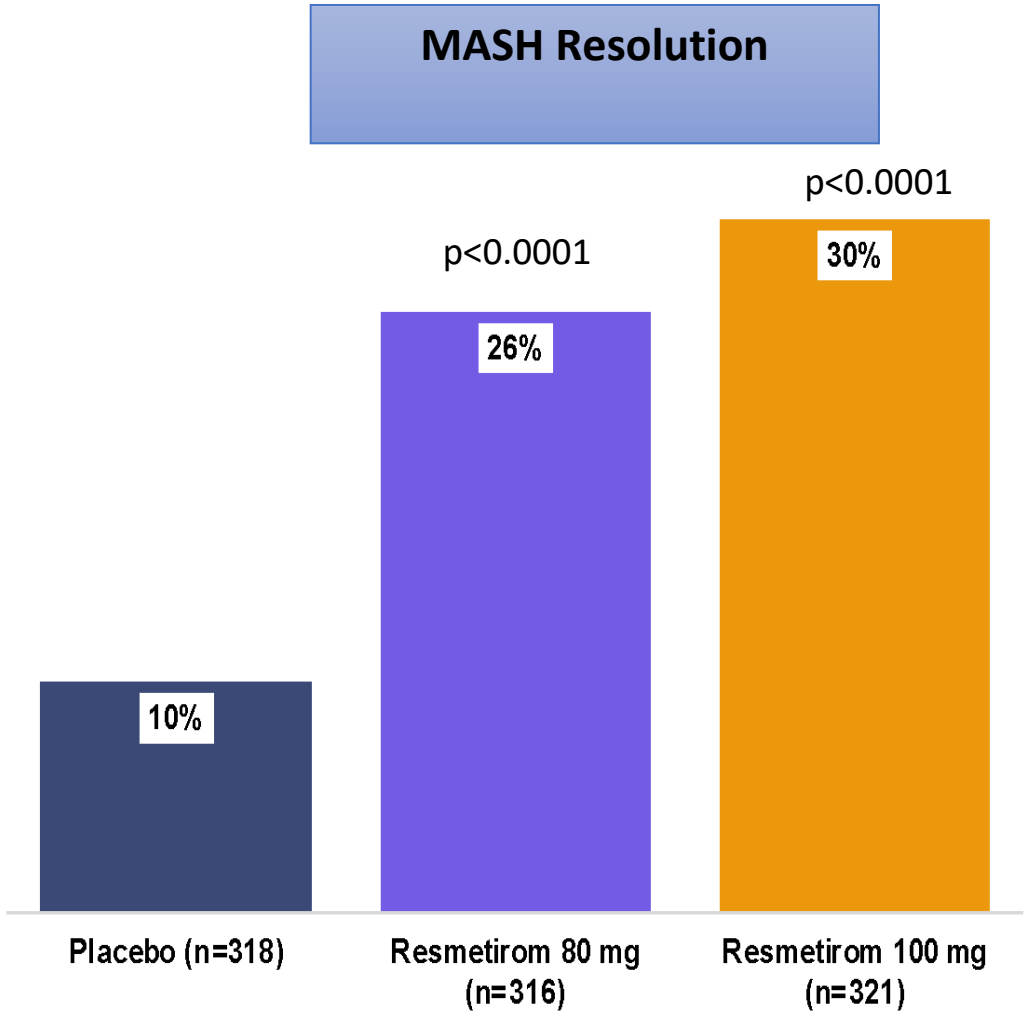
- Lowers LDL-cholesterol
- Lowers triglycerides
- Lowers liver fat, potentially reducing lipotoxicity, NASH

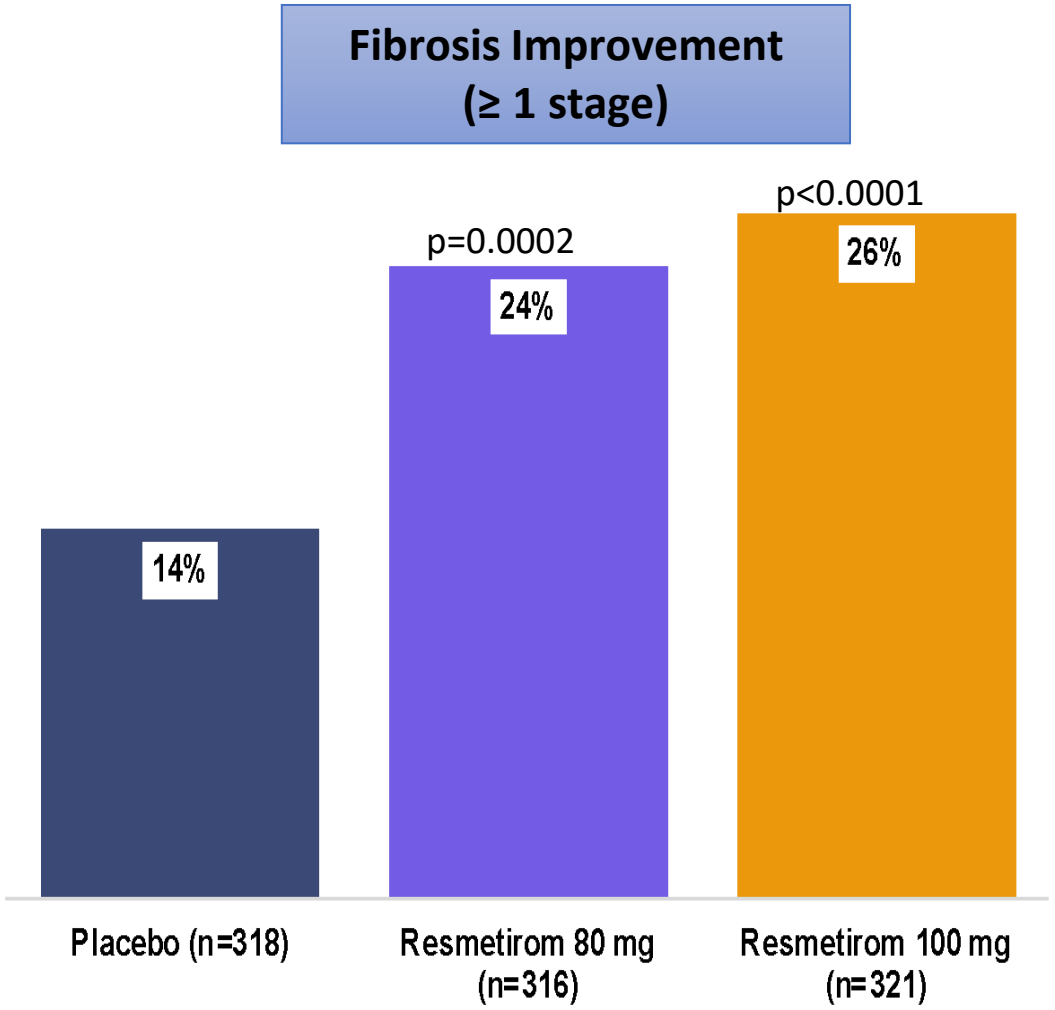
No thyrotoxicosis (THR-α effect)



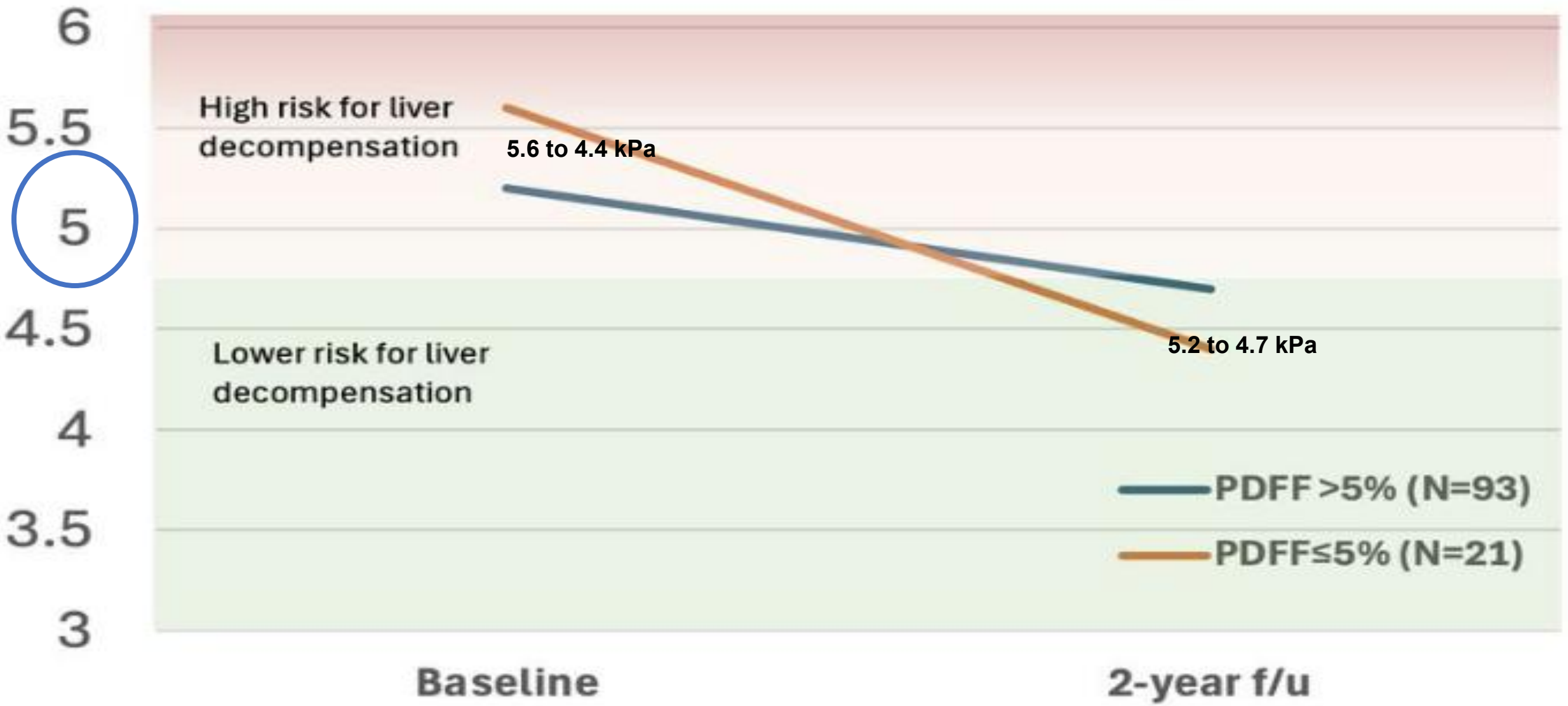
MAESTRO-MASH

Liver Biopsy (ITT) at Week 52





Resmetirom Effect on cCirrhosis



Resmetirom Reduces Liver Stiffness in MASH-Compensated Cirrhosis. AJMC. 2025

Resmetirom is an oral, once-daily tablet that can be taken with or without food

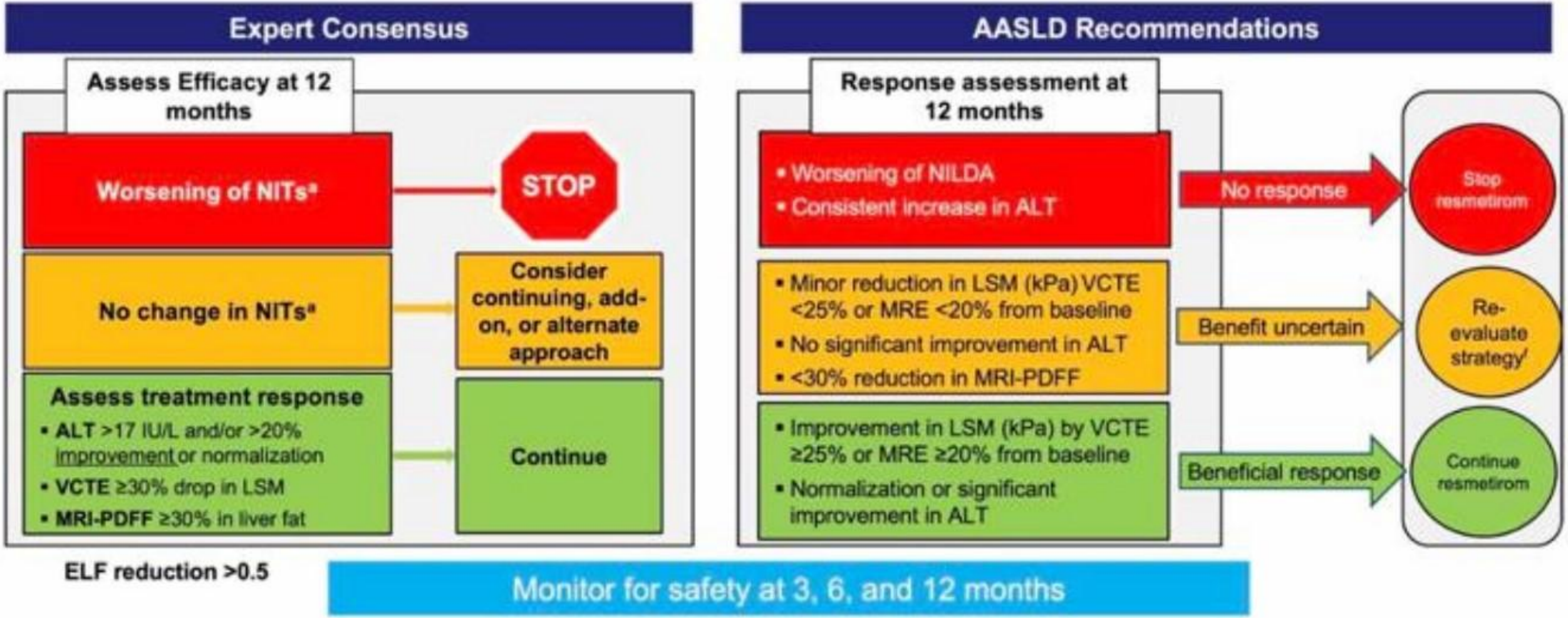
Recommended dosage and administration

	80 mg	100 mg
Dosage	**One tablet QD**	**One tablet QD**
Weight	<100 kg (220 lbs)	≥100 kg (220 lbs)

Drug Interactions

- Concomitant use of Resmetirom with strong CYP2C8 inhibitors (eg, gemfibrozil) or with OATP1B1 or OATP1B3 inhibitors (eg, cyclosporine) is not recommended
- For concomitant use of Resmetirom with moderate CYP2C8 inhibitors (eg, clopidogrel), reduce the dose of Resmetirom:
  – 60 mg if <100 kg (220 lbs) and 80 mg if ≥100 kg (220 lbs)
- Resmetirom increased plasma concentration of some statins.
  - Limit the daily dosage of rosuvastatin and simvastatin to 20 mg; pravastatin and atorvastatin to 40 mg

Patient Follow-up Using NITs and Assessment of Treatment Response



Noureddin M, et al. Clin Gastroenterol Hepatol. 2024

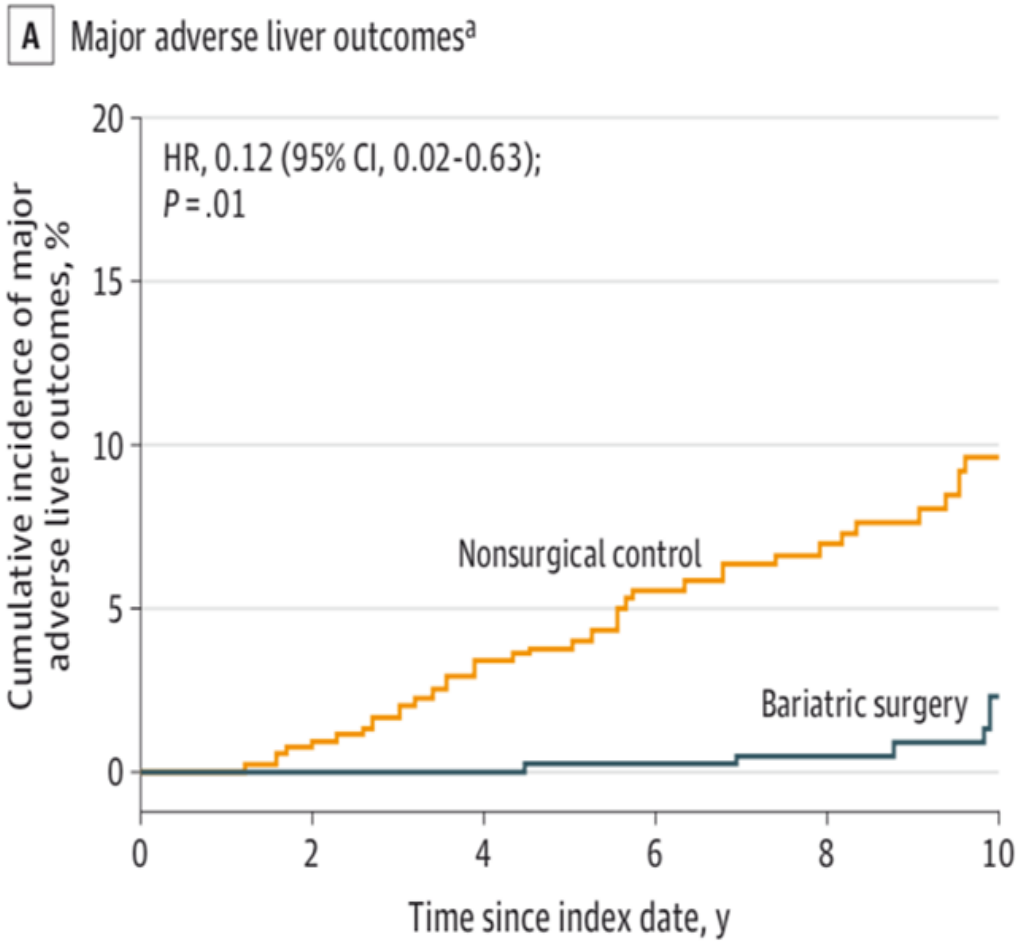
Chen VL, et al. Hepatology. 2025

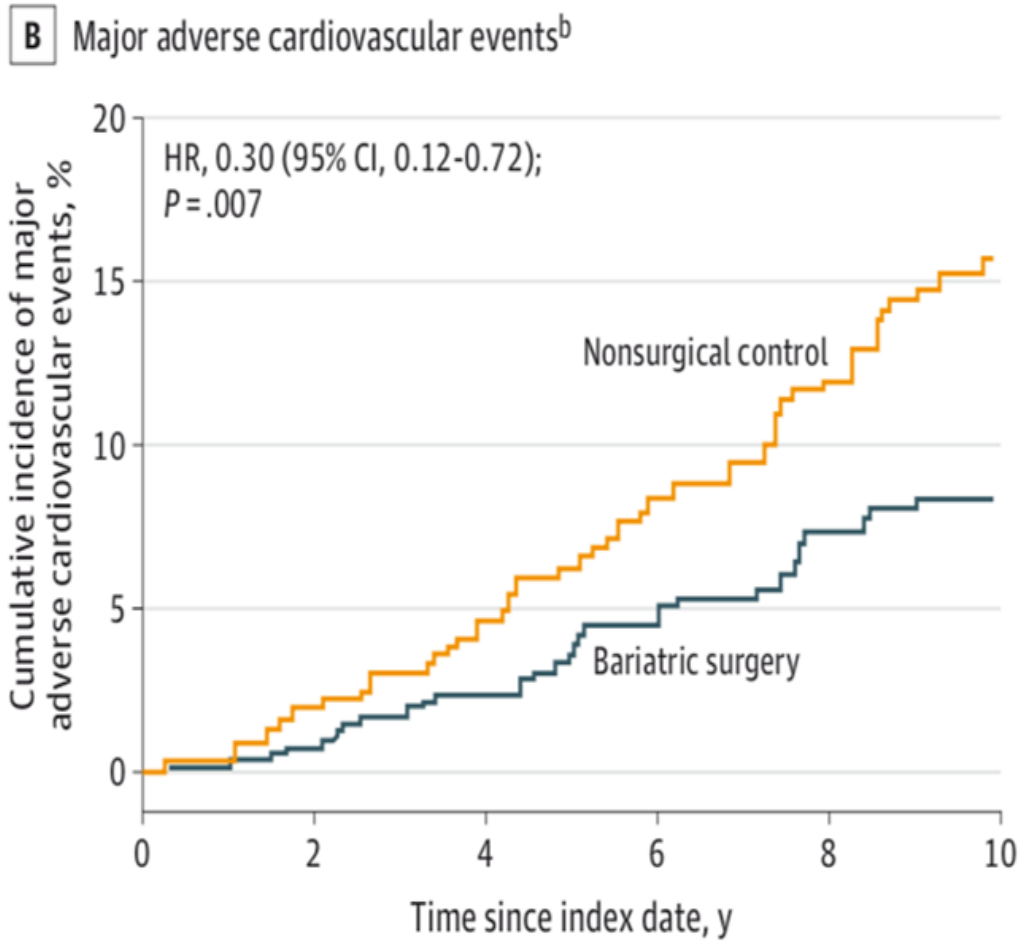
GLP1RA Vs Resmetirom

- MASLD is part of metabolic Syn
- ~70% of DM patients have MASLD
- Reduces the risk of cardiovascular M&M, dementia and Cancer
- High risk of S.E
- Long-term non-Compliance
- 45% longer treatment duration

- With 5% weight loss fibrosis improvement reaches up to 38%
- Direct effect on fibrosis
- Halts Fibrosis progression 91%
- Adds benefits to GLP1RA
- Improves cCirrhosis- In progress

Bariatric Surgery Vs Non-Surgical Management





No. at risk

Nonsurgical control	508	422	376	283	211	146
Bariatric surgery	650	525	463	381	252	153

508	417	370	270	202	136
650	523	455	365	234	141

Aminian A, et al. JAMA 2021

Take Home Message

3S : Screen**, S**tage and **S**tart treatment

- **Screening high-risk populations** (T2DM, MetS, family history of MASH cirrhosis) using FIB-4 and non-invasive imaging
- **Lifestyle interventions** remain foundational but pharmacotherapy is key for at-risk patients
- Engage in **shared decision-making** with patients, emphasizing both liver-specific and cardiovascular risk reduction
- **Combination therapy** may have a better role in achieving fibrosis and MASH improvement