Baffled By NAFLD?
And Why Is It Now MASLD?

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Disclosures of Conflict of Interest

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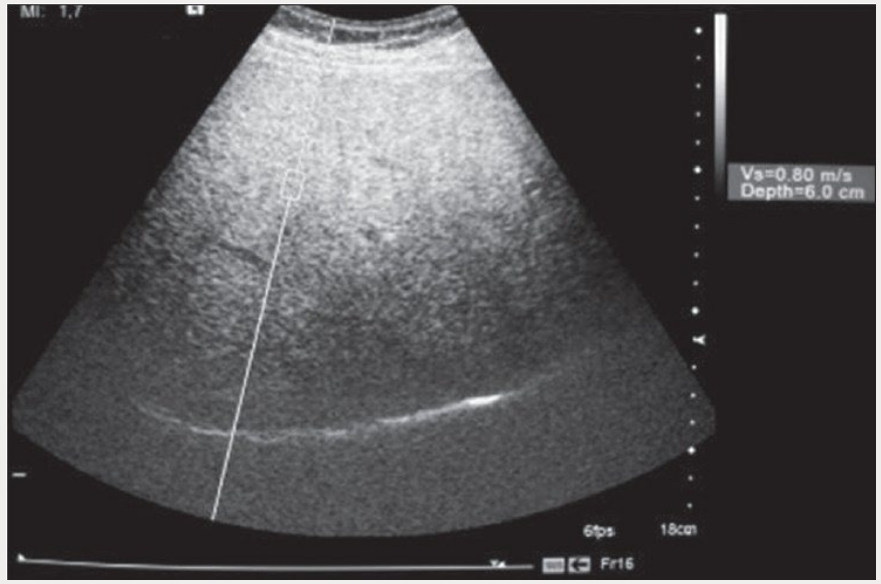
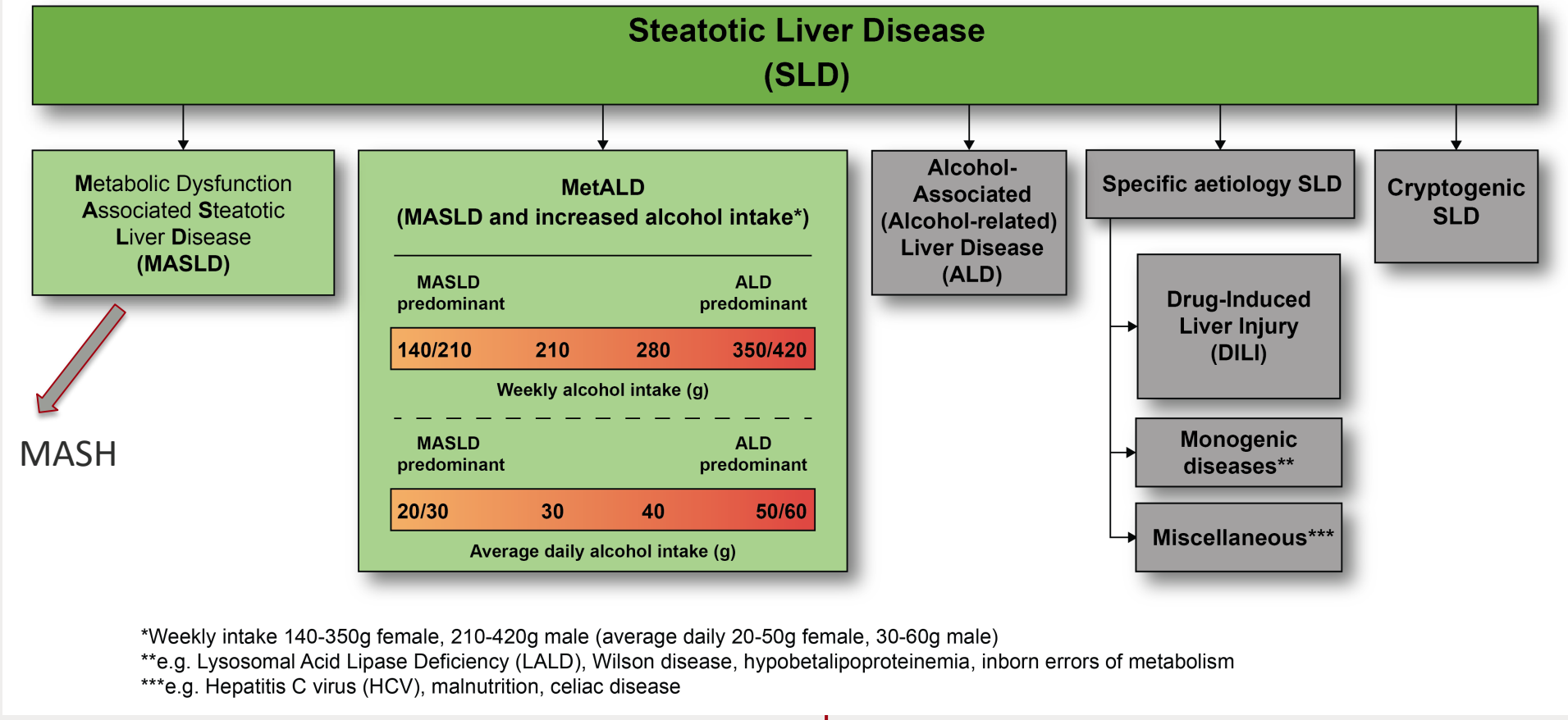
What to do with Liver Steatosis on Ultrasound?

- Patient with:
  - Right upper quadrant pain and fatigue
  - Hepatomegaly
  - Unexplained serum aminotransferase (ALT) abnormalities
- Or incidental finding of fat in liver on imaging done for another reason



Consensus nomenclature change for NAFLD

Fibrosis staging unchanged



*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

Rinella, Lazarus, Ratziu…Newsome on behalf of the NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature *Hepatology* 2023
Rinella et al. *Journal of Hepatology* 2023
Rinella et al. *Annals of Hepatology* 2023

Definition

Affirmative set of diagnostic criteria for MASLD.

Near universal agreement to err on side of being inclusive

Minimize patient heterogeneity and be adaptable to future insights

Simple, readily available and easily measurable parameters

The diagnostic criteria were also selected to align with cardiometabolic risk factors already well established and validated in other metabolic health disorders

The set of criteria for adults was then submitted to a subcommittee of five pediatric hepatologists who adapted them for the pediatric population

MASLD diagnostic criteria

Steatosis or undergoing evaluation for suspected steatosis

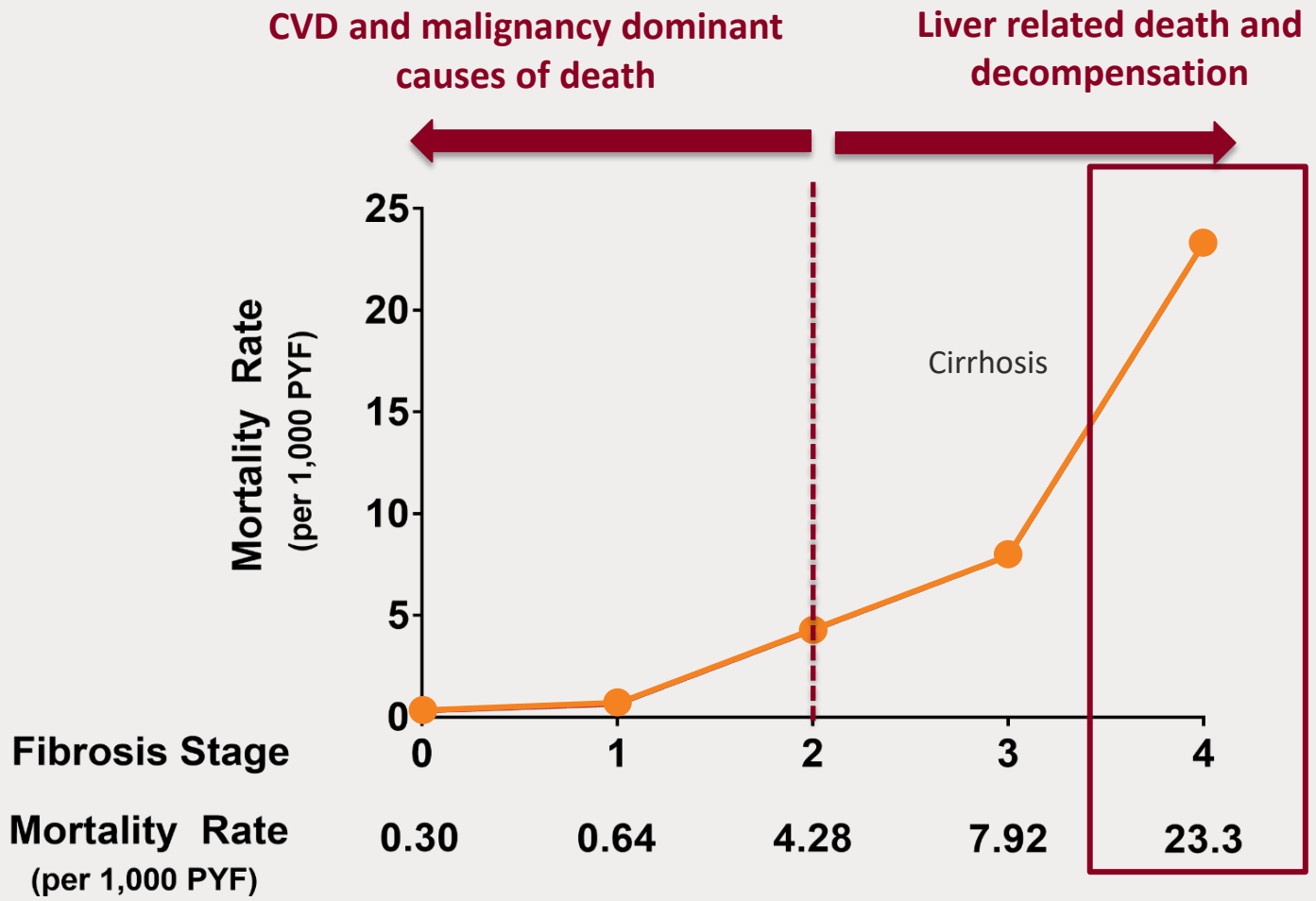
+

One or more of the following in the presence of confirmed or suspected hepatic steatosis

- **Diabetes/pre-diabetes:** Fasting serum glucose ≥ 100mg/dL or 2-hour post load glucose levels ≥ 140mg/dL or HbA1c ≥ 5.7% or type 2 diabetes or anti-diabetic treatment
- **Central obesity:** BMI > 25 kg/m2 (23 Asia) or waist circumference >94 cm (M), 80cm (F) or ethnically adjusted for Asian populations
- **Hypertension:** Blood pressure > 130/85 mmHg or use of antihypertensive therapy
- **Metabolic dyslipidemia**
  - Plasma triglycerides ≥ 150 mg/dL or use of lipid lowering therapy
  - Plasma HDL-cholesterol ≤40 mg/dL (M), or ≤50 mg/dL (F) or use of lipid lowering therapy

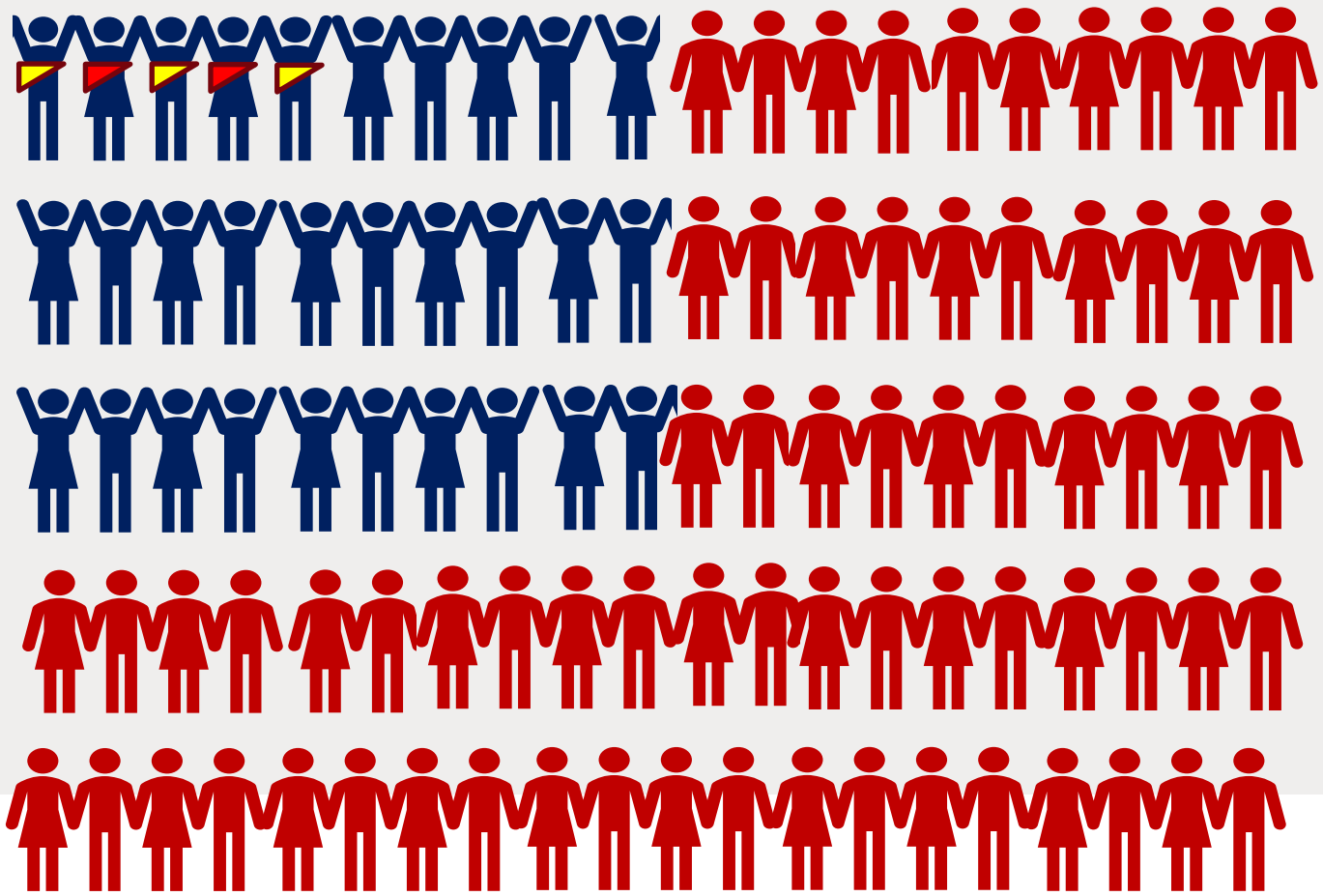
Rinella, Lazarus, Ratziu…Newsome on behalf of the NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature *Hepatology* 2023
Rinella et al. *Journal of Hepatology* 2023
Rinella et al. *Annals of Hepatology* 2023

Liver-related mortality is linked to fibrosis stage



Dulai, et al. *Hepatology.* 2017.

State of the Union - MASH in the United States in 2023



331 million people
208 million adults
120.4 million lean adults
87.6 million with obesity
27 million with T2DM (**17.4m** on metformin)
2-11 million with NASH with NAS ≥4, FS≥2
0.6 - 5 million with F3-4
50-100k with decompensated cirrhosis
2-3k undergoing liver transplant / year

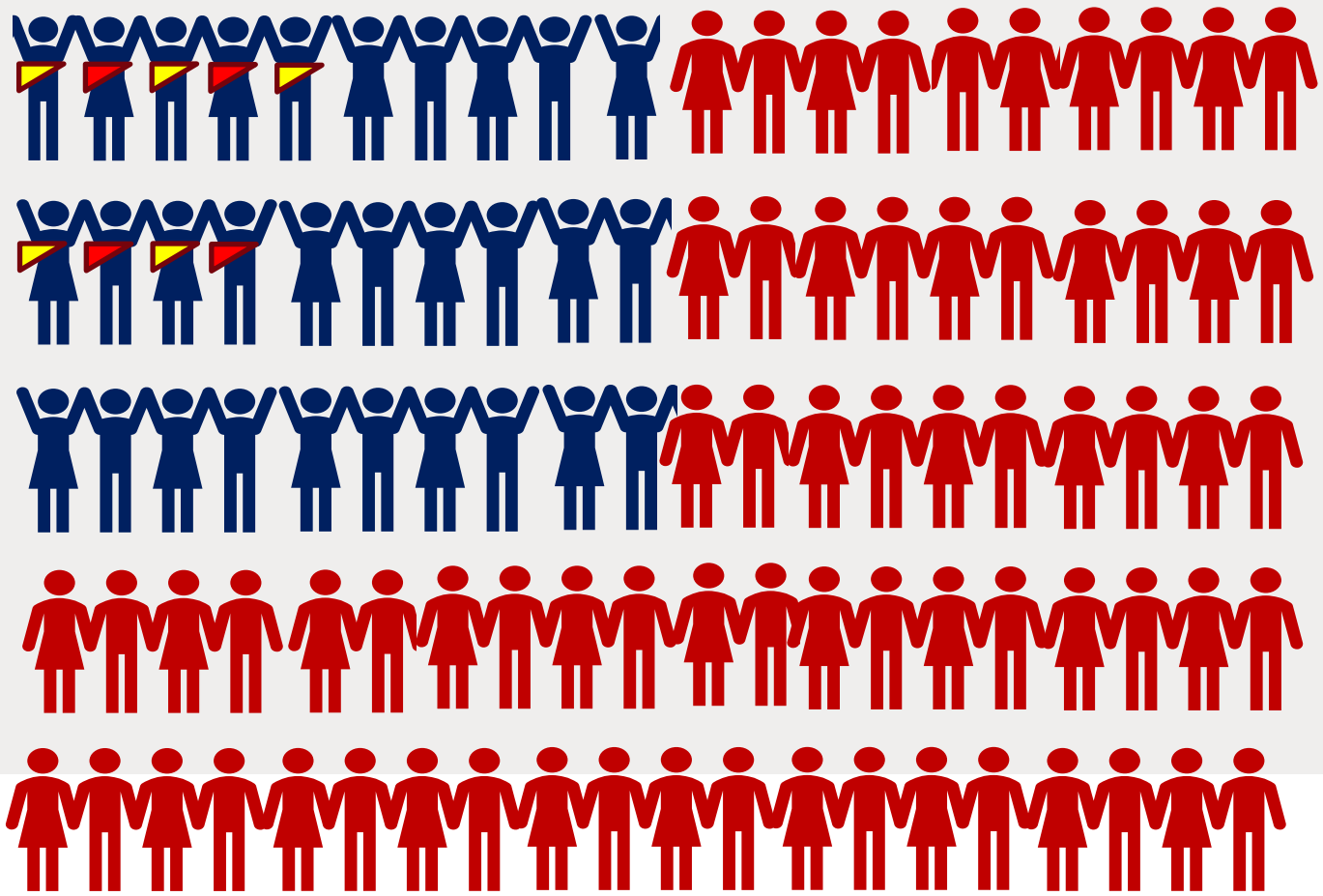
MASH FS≥2

MASH FS 3-4

no-MASH

Vilar-Gomez E, et al., *Clin Gastroenterol Hepatol*. 2021, U.S. Agency for Healthcare Research and Quality Global NASH Epidemiology Study 2016 Total diagnosed NASH population (US claims and electronic medical records analyses (Humedica, Pharmetrics and SHA) Jamil et al. Transplantation. 2022 Oct 1;106(10):2006-2018.

State of the Union - MASH in the United States in 2023



↑ **168%** decompensation
↑ **178%** liver related death
↑ **137%** increase in HCC

MASH FS≥2

MASH FS 3-4

no-MASH

Vilar-Gomez E, et al., *Clin Gastroenterol Hepatol*. 2021, U.S. Agency for Healthcare Research and Quality Global NASH Epidemiology Study 2016 Total diagnosed NASH population (US claims and electronic medical records analyses (Humedica, Pharmetrics and SHA) Jamil et al. Transplantation. 2022 Oct 1;106(10):2006-2018.

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Modifiers of MASLD

Comorbidities	Genetic	Microbiome products	Nutrition/Behavior
***Obesity**	***PNPLA3**	ETOH	***Alcohol**
***Metabolic Syndrome**	***TM6SF2**	Lipopolysaccharide	**Cholesterol**
***Insulin Resistance**	***A1AT Pi*Z**	Reactive oxygen species	**Fructose**
***Type 2 DM**	HSD17B13	Cholesterol oxidation products	**Exercise**
Dyslipidemia	LYPLAL1	Butyrate	**Coffee**
***Hypertension**	GCKR	Acetate	
OSA	MBOAT	Phenylacetate	
PCOS	DNA methylation	Secondary bile acids	
***Hypopituitarism**	Chromatin remodelling	Choline deficiency	
Low GH	Non-coding RNAs		
Low testosterone			
Thyroid disease			
LAL-D			
Iron overload			

Black = Association with evolving evidence

Red = Established association

Green = protective

***Bold = Drives NASH progression**

Summary of (selected) key concepts to guide clinical practice:

Pearls for the assessment of MASLD

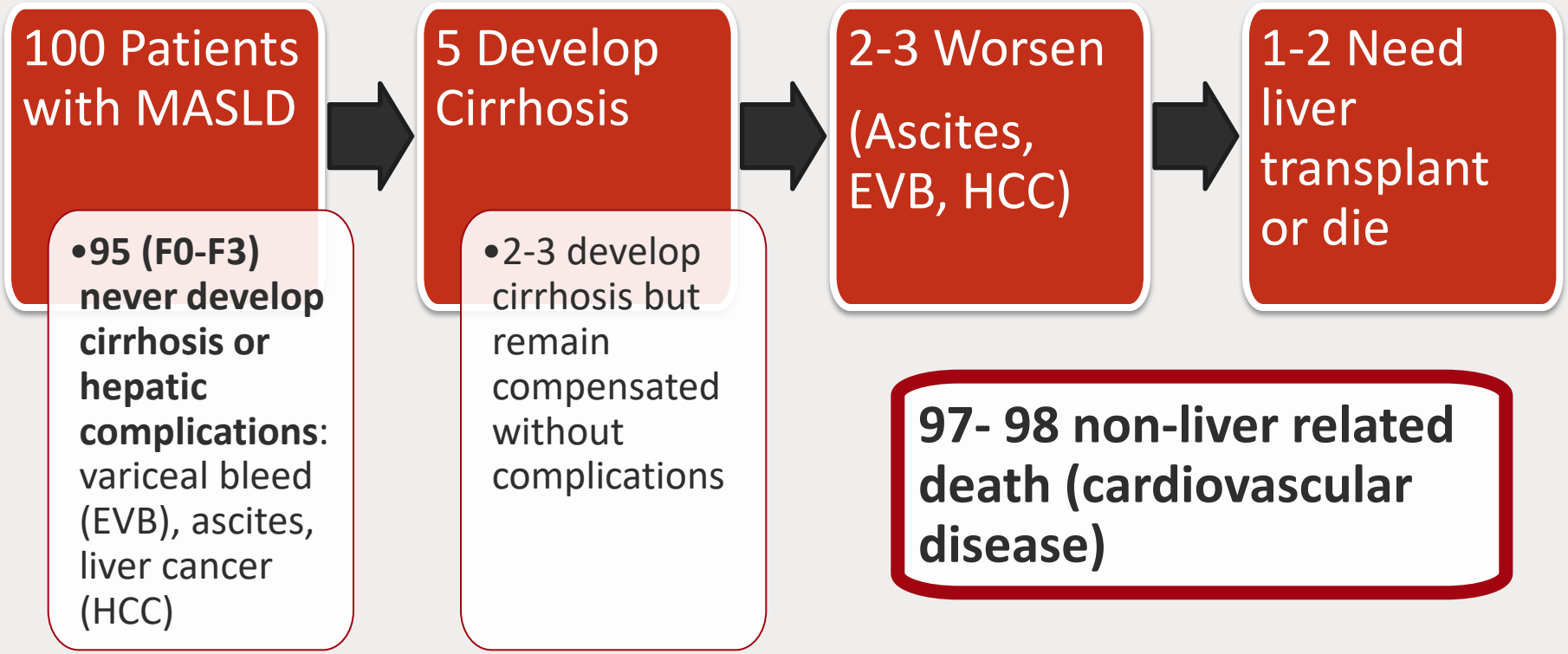
- *Aminotransferase levels are frequently normal in patients with advanced liver disease due to MASH and should not be used in isolation to exclude the presence of MASH with clinically significant fibrosis.*

- *Normative values for ALT reported by most laboratories exceed what is considered a true normal. As a general rule, ALT>30U/L should be considered abnormal.*

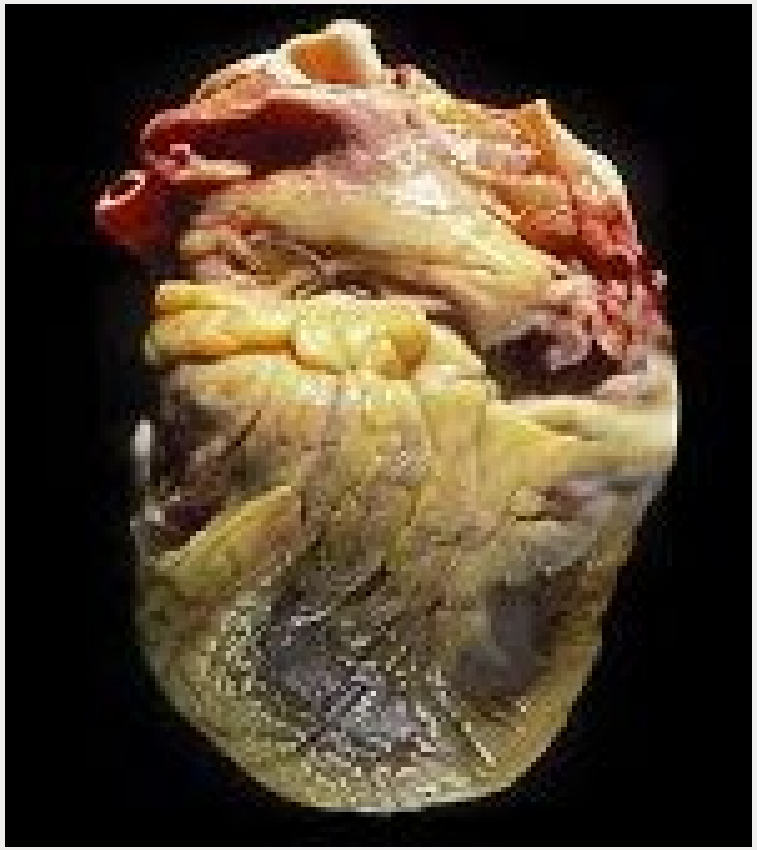
- *While standard ultrasound can detect hepatic steatosis, it is not recommended as a tool to identify hepatic steatosis due to low sensitivity across the MASLD spectrum.*

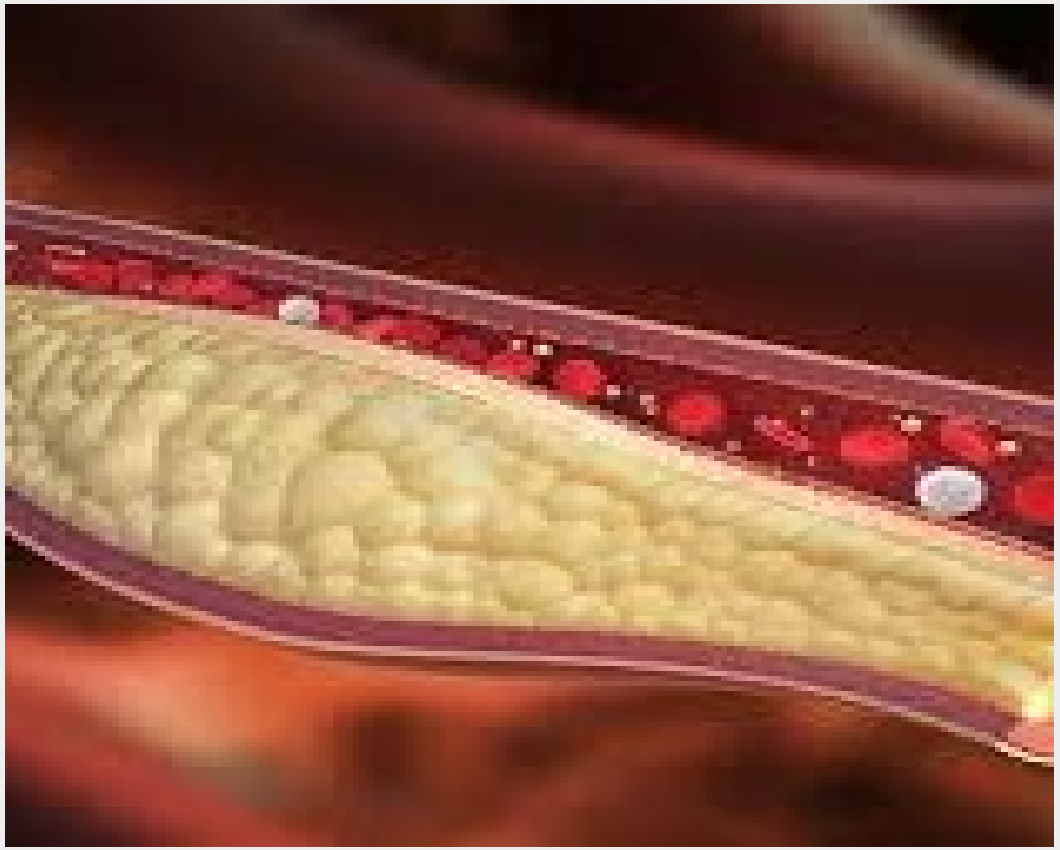
- *CAP or MRI-PDFF may be used to detect steatosis, though MRI-PDFF can accurately quantify hepatic steatosis.*

MASLD
Natural History



Patients with MASLD Are Twice as Likely To Die of Heart Attack and Stroke





Statins should be started when indicated

Noninvasive assessment of MASLD

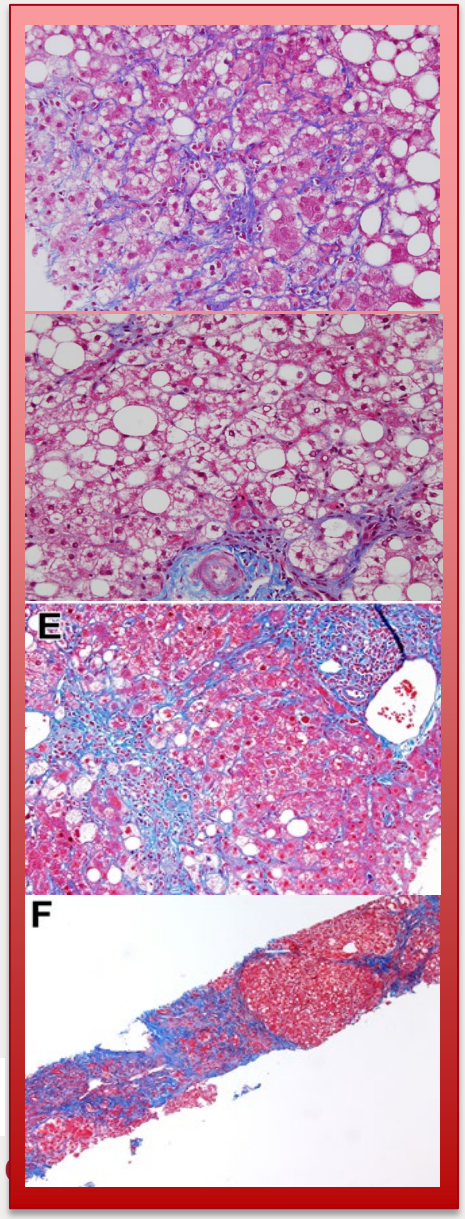
Stage 1

Stage 2

Stage 3

Stage 4

Cirrhosis



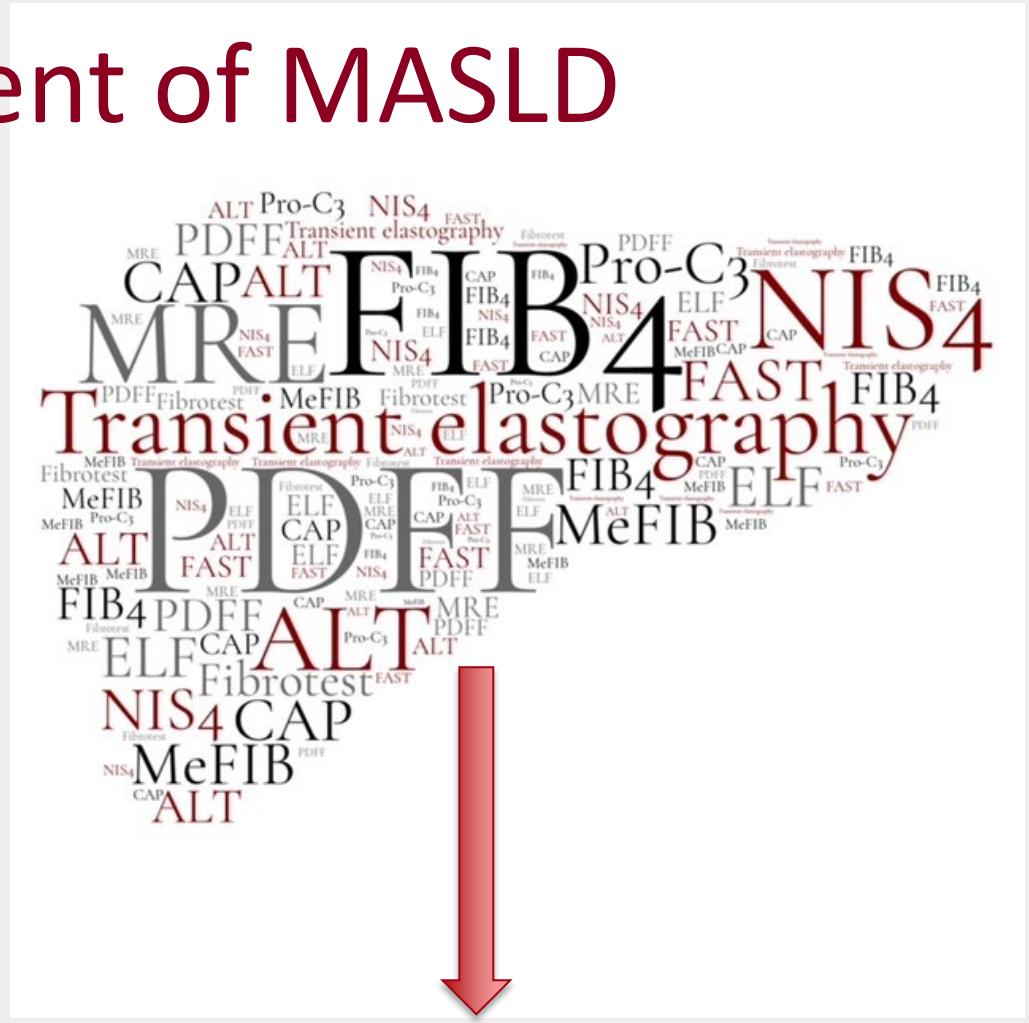
Low risk

Clinically significant fibrosis

Moderate risk

Advanced fibrosis

High risk



Outcomes

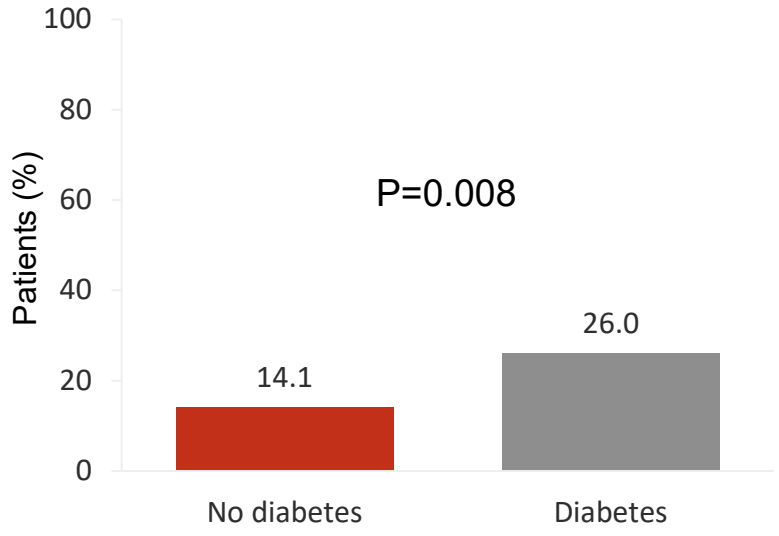
FIB-4 performance may be suboptimal in some patient populations

- Diabetes
- Race/ethnicity
- Age>65

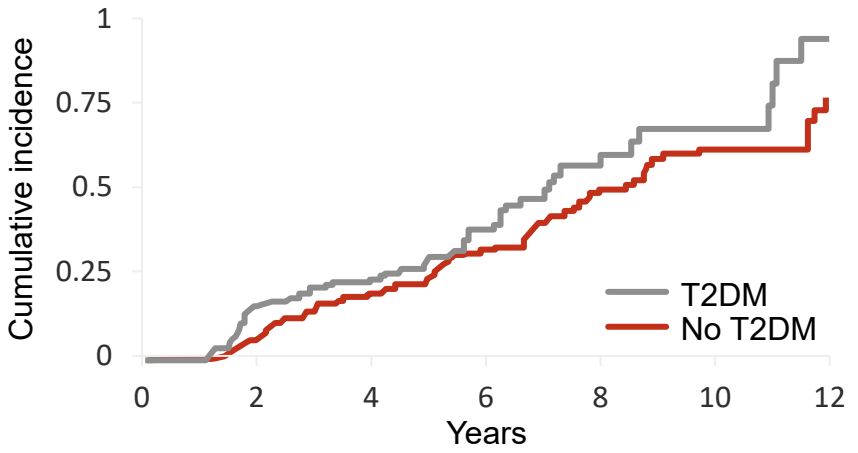
Kim et al, *Diabetes Care,* 2022.
Graupera et al, *Clin Gastro Hep*, 2022.
Van Dijk et al, *Hep Comm*, 2022.
McPherson et al, *Am J Gastro*, 2017

Fibrosis progression in diabetic versus non-diabetic patients with biopsy-proven MASLD: Multi-center prospective study

Progression to advanced fibrosis



Fibrosis progression by ≥1 stage



Number at risk

196	124	85	38	11	6	1
231	172	115	74	38	23	7

Cumulative incidence (95% CI)

	T2DM	No T2DM
4 years	0.24 (0.18, 0.31)	0.20 (0.14 0.26)
8 years	0.60 (0.47, 0.73)	0.50 (0.41, 0.59)
12 years	0.93 (0.76, 0.99)	0.76 (0.64, 0.87)
Adjusted HR	1.69 (1.17, 2.43); P=0.005	

Presence of T2DM is associated with more rapid progression of MASLD

Huang D, et al. AASLD 2022. Oral #10

Screening for advanced fibrosis in high-risk populations

Prevalence of advanced fibrosis in background MASLD population (0.9-2%) [20-23]

Screening recommended	Prevalence of advanced fibrosis
Type 2 diabetes mellitus (T2DM)	6-19% [1-8]
Medically complicated obesity	4-33% [9-17]
MASLD in context of moderate alcohol use	17% [18]
First degree relative of a patient with cirrhosis due to NAFLD	18% [19]

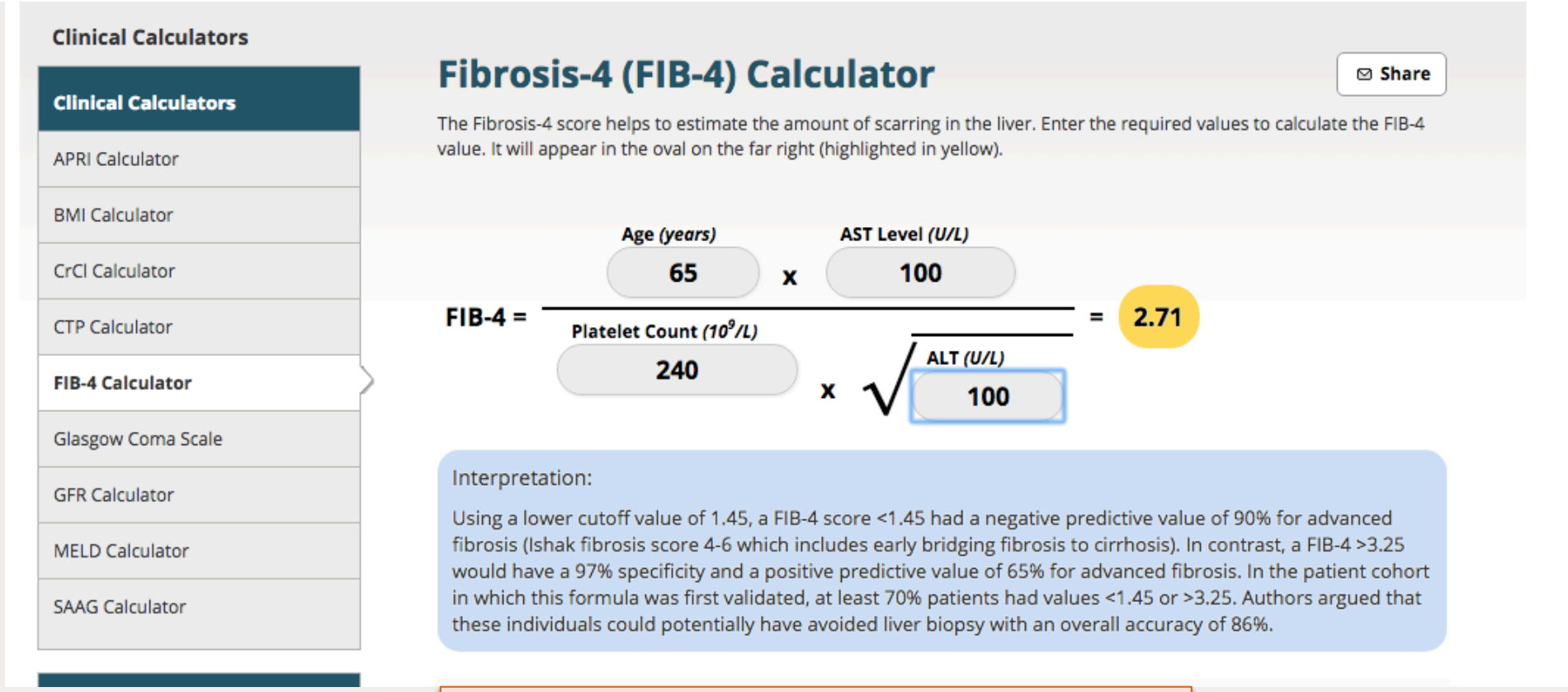
Rationale

- Populations enriched with advanced fibrosis
- Delayed diagnosis increases morbidity, mortality and cost
- Off-label use of available medications with mortality benefit (non hepatic) and probable benefit on NAFLD based on Ph2 trials

Rinella et al. Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2022 (accepted)

[1]Stefan N Lancet Diabetes Endocrinol 2022; [2]Younossi J Hepatol 2019; [3]Ciardullo Diabetes Care 2021; [4]Doycheva APT 2016; [5]Noureddin Gastro 2020; [6]Chen PloS One 2020; [7]Lomonaco R Diabetes Care 2021; [8]Mantovani Diabetes Metab 2020; [9]Soresi M, BioMed Res Int 2020; [10]Udelsman BV, Surg Obes Relat Dis 2021; [11]Udelsman BV, Surg Obes Relat Dis 2019; [12]Ciardullo S, Obes Surg 2022; [13]Luger M, Obes Surg 2016; [14]Alqahtani SA, Obes Surg 2021; [15]Mofrad P, Hepatology 2003; [16]McPherson S, Gut 2010; [17]Rinella ME, Therap Adv Gastroenterol 2016; [18]Blomdahl J, Metabolism 2021; [19]Caussy C, J Clin Invest 2017; [20]Harrison SA, J Hepatol 2021; [21]Wong VW-Gut 2012; [22]Harris R,Lancet Gastroenterol Hepatol 2017; [23]Kang KA, Aliment Pharmacol Ther 2020

Fibrosis-4 Score Can Guide Need For Biopsy and Provide Assurance



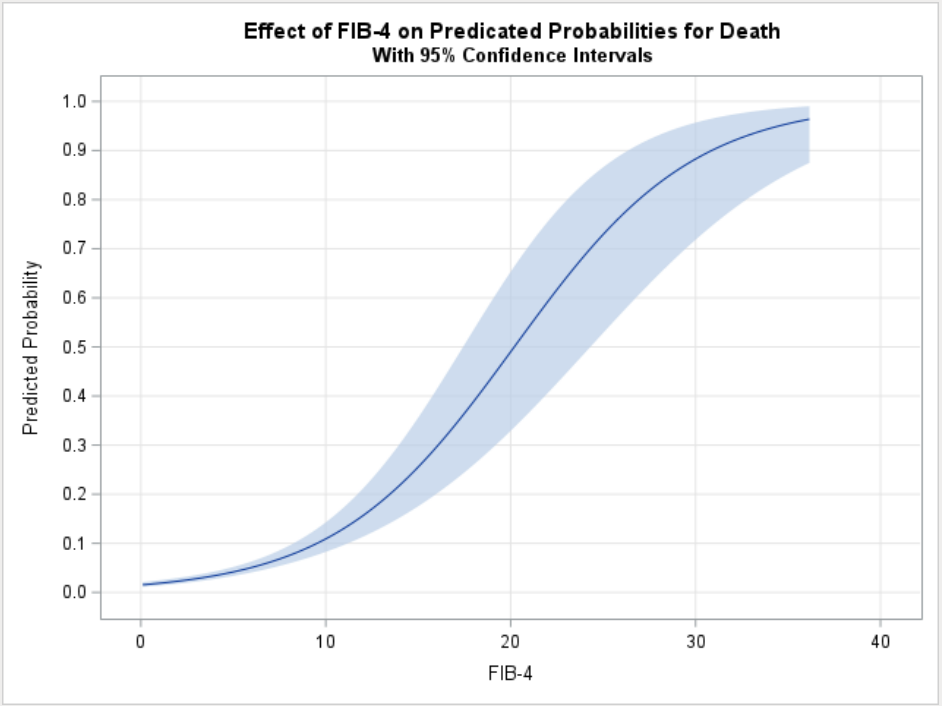
<1.45 90% NPV advanced fibrosis

A prospective validation of FIB4 to predict death in MASLD

Incidence rate (per 100 person years) by risk classification at baseline

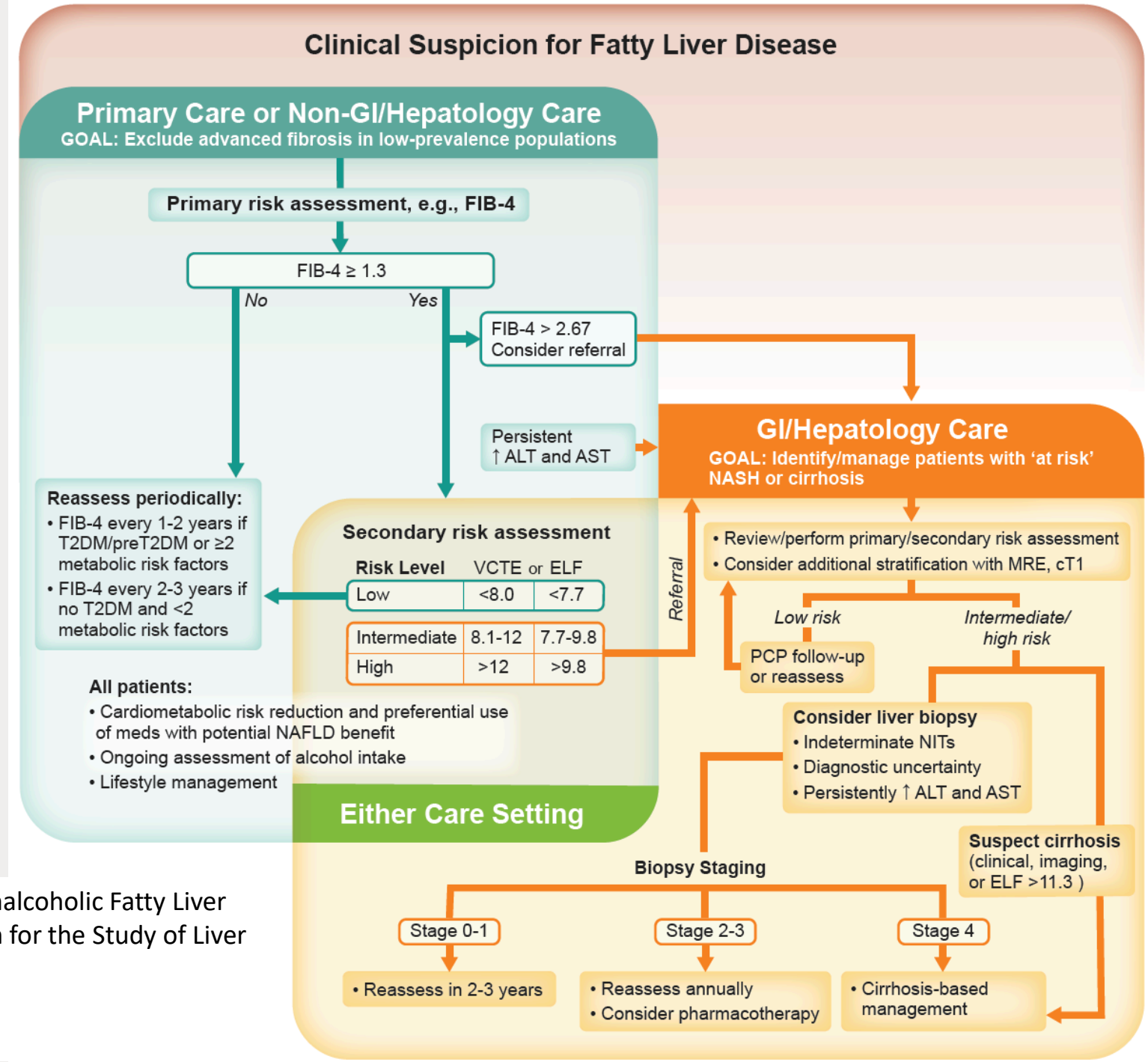
	Included Using FIB4 and/or LSM Criteria		
Rate per 100 person yrs	Class A (n=554)	Class B (n=536)	Class C (n=846)
Deaths *	0.07	0.42	3.08
Liver events *	0.21	1.32	9.33
MACE *	0.83	1.60	2.54
HCC *	0	0.07	1.08

N= 2523 (median follow up 3 years)



Class A: FIB4 < 1.3, LSM < 8kPa
Class B: FIB4 1.3-2.6, LSM 8-12.5 kPa or class A FIB4/LSM but with AST:ALT > 1, platelet < 150k
Class C: FIB 4 > 2.6, LSM > 12.5 kPa

Sanyal et al, AASLD 2020

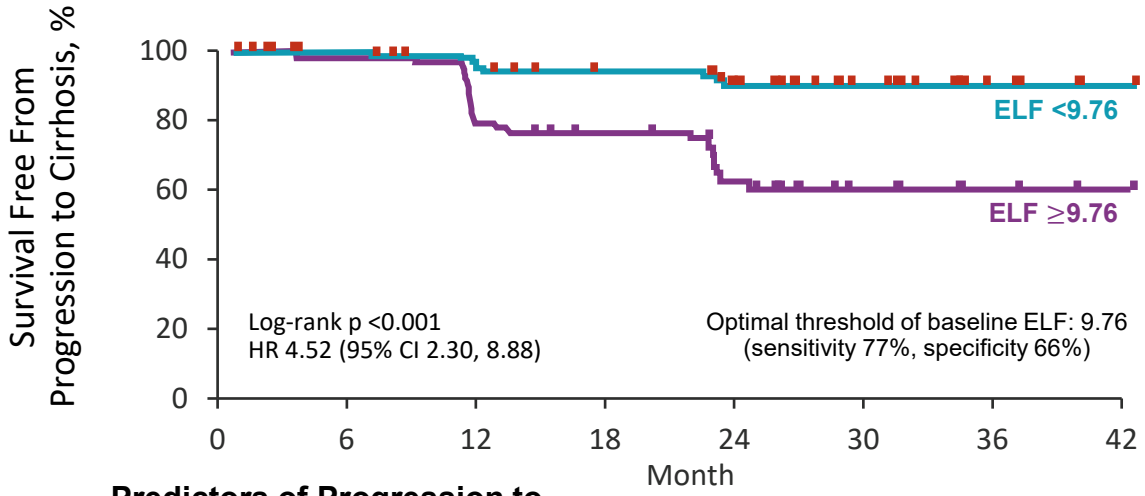


Rinella et al. Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2023

ELF for prognostication in MASH

NASH and bridging fibrosis (n=219)

Progression to Cirrhosis According to Baseline ELF

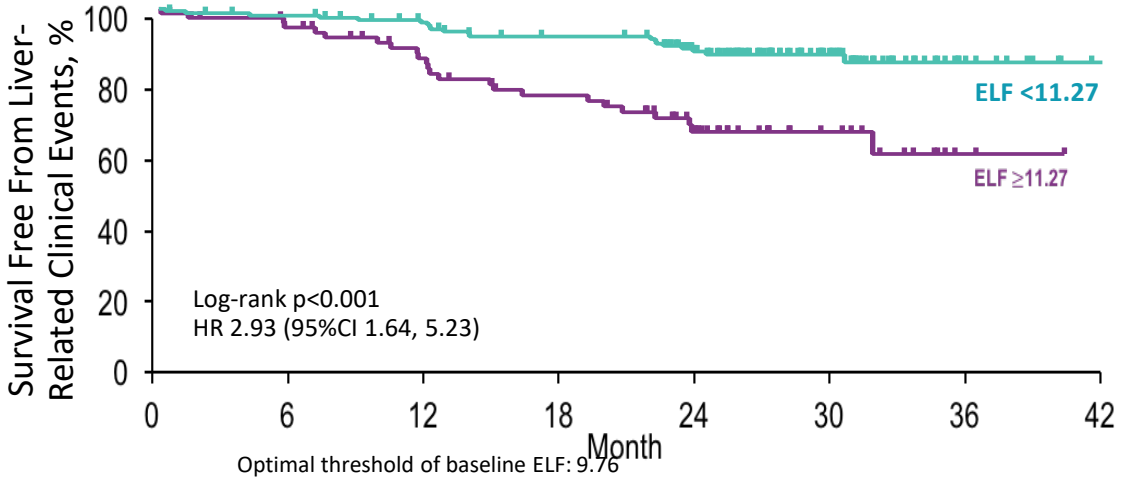


Predictors of Progression to Cirrhosis

Parameter	Adjusted HR (95% CI)	*P*-value
Baseline ELF	3.20 (2.33, 4.39)	**<0.001**
Change in ELF	1.60 (1.19, 2.16)	**<0.01**
Ishak stage 4 vs 3	0.87 (0.47, 1.59)	**0.64**

Compensated cirrhosis (n=258)

Liver-Related Clinical Events According to Baseline ELF



Optimal threshold of baseline ELF: 9.76
(sensitivity 77%, specificity 66%)

Parameter	Adjusted HR (95% CI)	*P*-value
Baseline ELF	2.40 (1.70, 3.38)	**<0.001**
Change in ELF	1.53 (1.09, 2.14)	**0.01**
Ishak stage 6 vs 5	0.89 (0.47, 1.68)	**0.71**

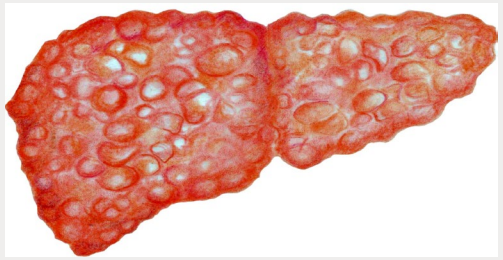
A unit change in ELF is associated with a doubling of risk of liver-related outcome.

Higher baseline ELF and greater change in ELF were associated with liver-related clinical events

Sanyal, et al. *Hepatology.* 2019

Imaging to Assess MASH Fibrosis: Elastography

Soft → Stiffness → Firm



Vibration controlled transient elastography (*FibroScan*)

- Accurate in detecting advanced fibrosis
- Predicts risk of decompensation and complications
- Correlates fairly well with portal pressure
- Most reliable in ruling out advanced disease
- Most widely used

Shear wave elastography (SWE)

- Uses acoustic radiation force impulse (ARFI) technology
- Point quantification SWE or 2-D supersonic shear imaging (SSI) SWE

MR elastography

- Most accurate of the imaging modalities
- Costly, no point-of-care access

Noninvasive parameters for ‘at risk’ MASH

Identification of ‘at risk’ NASH				
Combined	FAST	≥0.67	<0.35	• ≤0.35 (sensitivity 90%) • ≥ 0.67 (specificity 90%) • In validation cohorts, the PPV of FAST ranged between 0.33 and 0.81.(1-2)
Combined	MEFIB	FIB-4 ≥ 1.6 plus MRE ≥ 3.3 kPa	FIB-4 < 1.6 plus MRE < 3.3 kPa	• Sequential approach identifies patients with at least stage 2 fibrosis with > 90% PPV.(3)
	MAST	≥0.242	≤0.165	0.242 (specificity 90%), 0.165 (sensitivity 90%)(4)
	cT1	≥ 875 msec	< 825 msec	• Requires further validation as data is derived from one study(4)

Newsome et al. Lancet Gastro Hep 2020 [1]; Woreta et al PLoSONE 2022 [2]; Jung et al. Gut 2021 [3]; Noureddin M et al. J Hepatol 2022 [4] Andersson et al. CGH 2022 [5]

Noninvasive parameters for advanced fibrosis and cirrhosis

Detection of advanced fibrosis				
Serum	FIB-4	≥ 2.67	<1.3	• No added cost[1-3] • Not accurate in age < 35 years and lower rule-out threshold among high-risk individuals who have high pre-test probability
Serum	ELF	≥ 9.8	<7.7	• Blood test sent to a reference laboratory[4] • Cost
Imaging	VCTE	≥12 kPa	< 8 kPa	• Point of care[5]
Imaging	MRE	≥3.63 kPa	<2.55 kPa	• MRE LSM ≥3.63 kPa (associated with advanced fibrosis, AUROC of 0.93)[6]

Diagnosis of cirrhosis (rule-in or rule out)				
		Rule-in	Rule-out	
CPR	FIB-4	≥3.48	< 1.67	• 90% specificity cut-point for ruling-in and 90% sensitivity for ruling-out cirrhosis, respectively[6, 7]
Serum	ELF	≥11.3	<7.7	• ELF ≥ 11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis[4]
Imaging	VCTE	≥ 20 kPa	< 8 kPa	• LSM by VCTE ≥ 20 kPa is associated with cirrhosis but for ruling out cirrhosis optimal cut-point is < 8 kPa[5]
Imaging	MRE	≥ 5 kPa	< 3 kPa	• LSM by MRE ≥ 5 kPa has a very good (approaches 95%) specificity for diagnosis of cirrhosis and is also associated with increased risk of incident hepatic decompensation[8, 9]

Barb et al. Obesity 2021[1]; McPherson et al AJG 2017 [2]; Graupera et al. CGH 2022[3]; Day et al. J Applied Lab Med 2019 [4]; Mózes et al. Gut 2022 [5]; Loomba et al. Hepatology 2014 [6] ; Brandman et al. APT 2022 [7] ; Hsu et al. CGH 2019 [8]; Loomba et al. Hepatology 2014 [9];

Prime Culprit in MASLD is High Fructose Corn Syrup

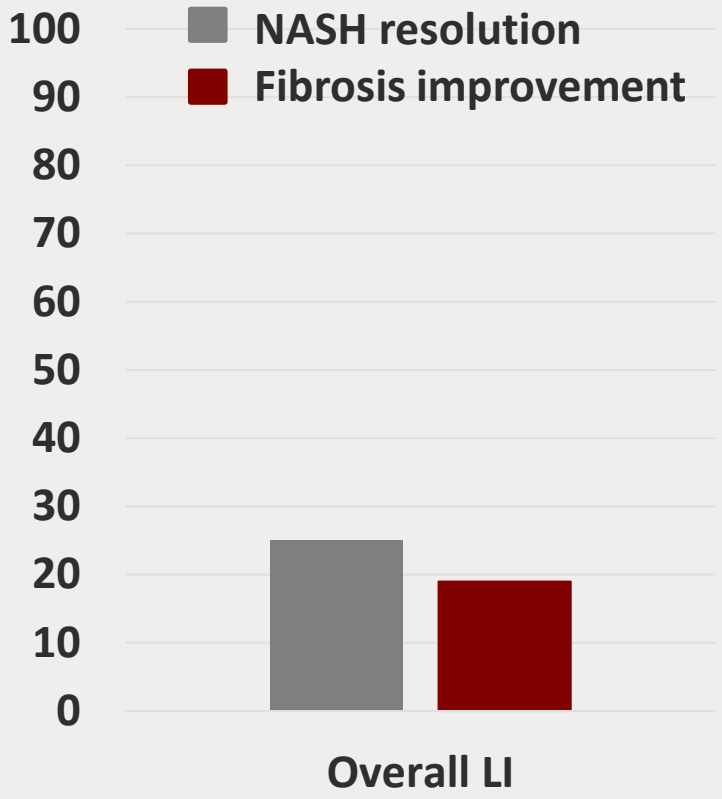
De novo Lipogenesis

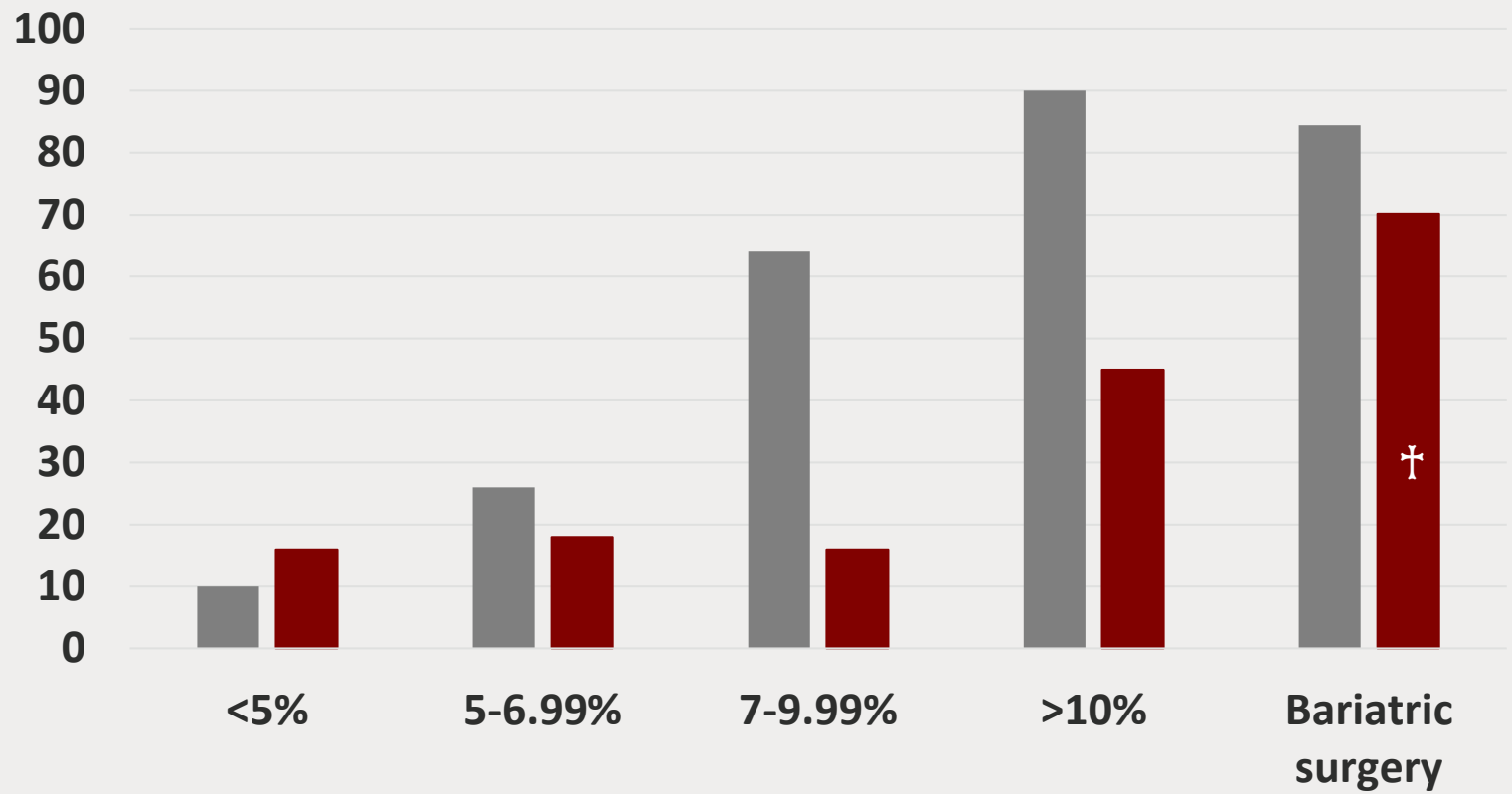
- No regulation of liver uptake
- No regulation of conversion to fat
- No increase in leptin

Weight Loss and Exercise Cornerstone of Treatment of MASLD

- **Up to 3-5% weight loss improves steatosis**
- **Up to 7-10% weight loss has been associated with significant improvement in MASLD Activity Score**

Impact of lifestyle intervention and weight loss





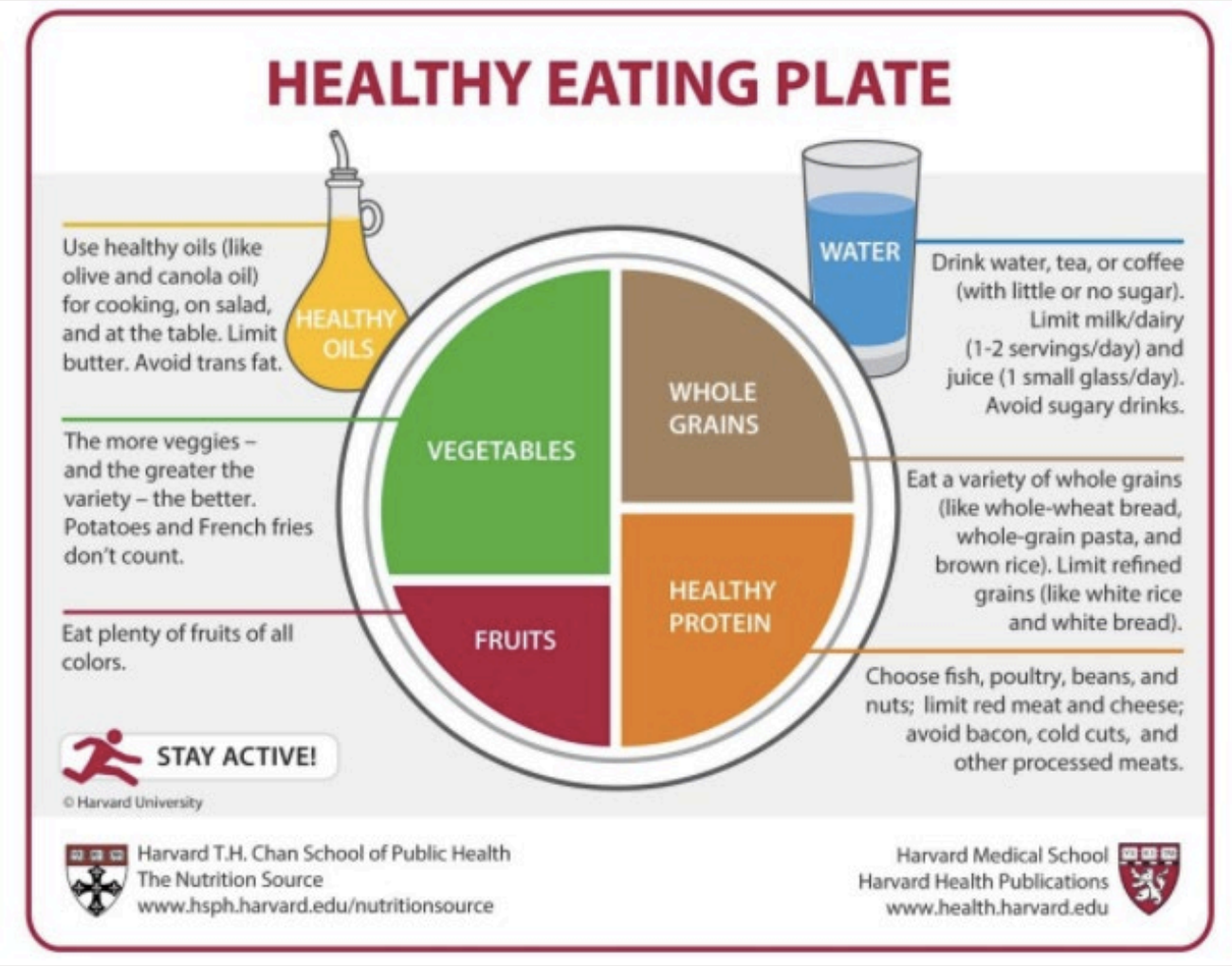
†: 5-yr data

Vilar Gomez et al, *Gastroenterology* 2015 Aug;149(2):367-78; Lassailly et al. Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis. *Gastroenterology* 2020

Healthy Eating Should Be Cornerstone of Treatment

- Keep the focus positive
  - Goal is lifelong consistency
  - Not “Dieting”
- Limit simple sugars
- Use healthy oils and limited amounts
- Include protein in meals
- Mediterranean diet most studied but any reduced calorie diet may be similar
- Avoid large portions
  - Split restaurant meals

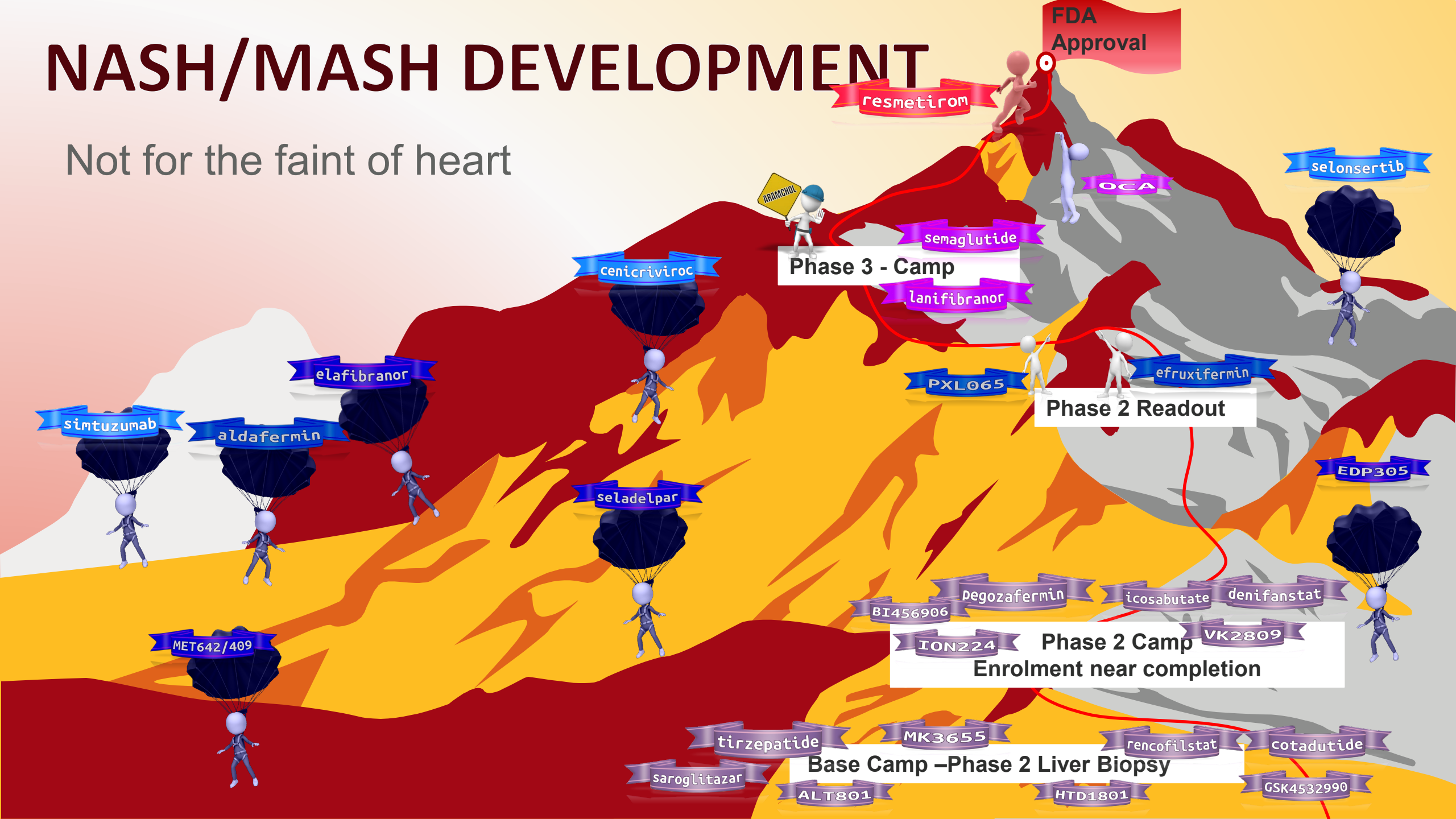
Harvard Healthy Eating Plate Can Be Used to Guide Patients



Available in 20 languages

NASH/MASH DEVELOPMENT

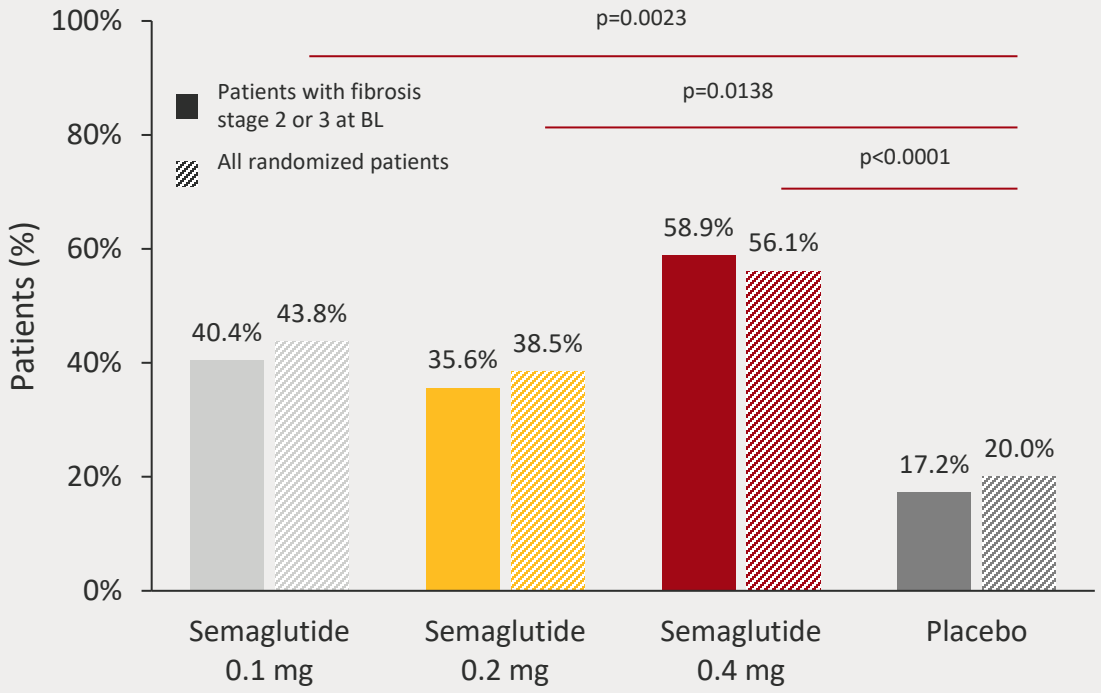
Not for the faint of heart



Efficacy and Safety of Semaglutide SC QD vs PBO in patients with MASH

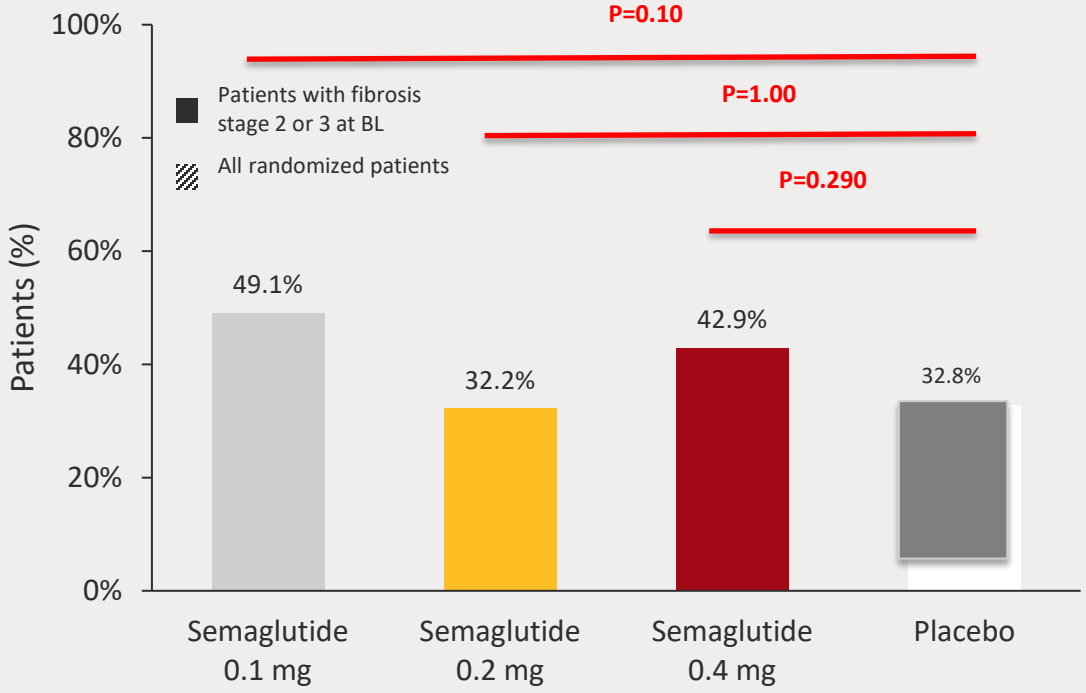
Resolution of **steatohepatitis** and no worsening in liver fibrosis

Patients with fibrosis Stage 2 or 3 at BL and all randomized patients



Improvement in liver **fibrosis** and no worsening in steatohepatitis

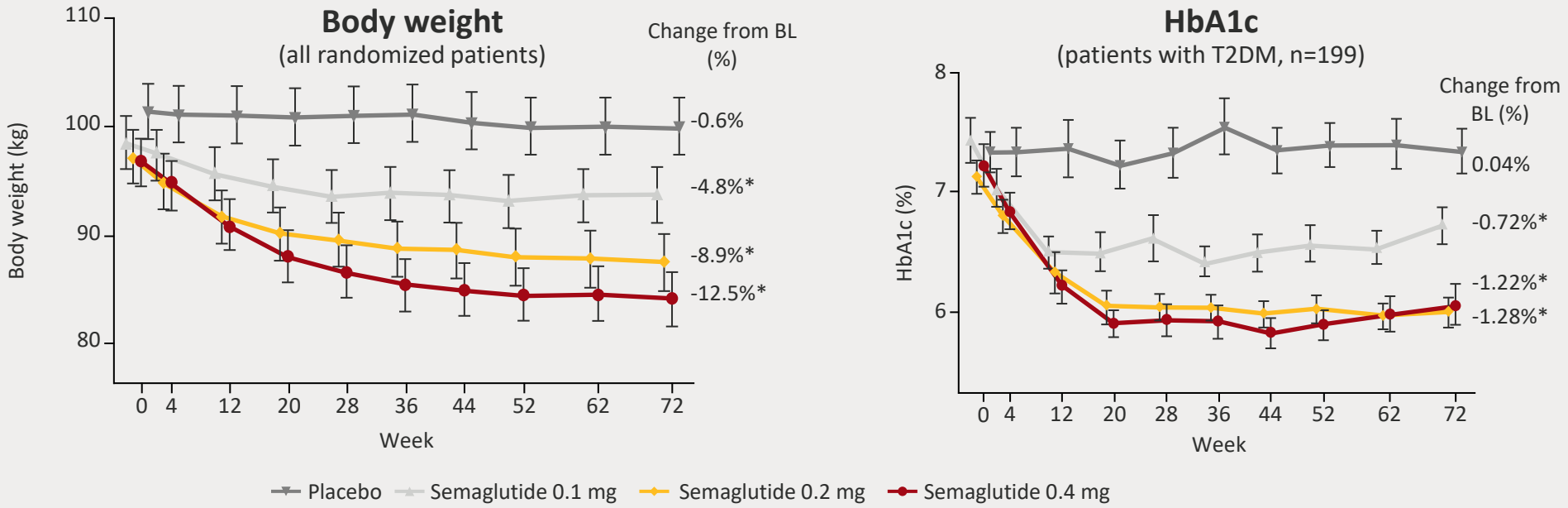
Patients with fibrosis Stage 2 or 3 at BL and all randomized patients



N=320

Newsome PN, et al. *NEJM* 2021 ;384(12):1113-1124.

Impact of semaglutide versus placebo on body weight and HbA1c



- SEMA 0.4 mg resulted in increased HDL-C and decreased free fatty acids, triglycerides, and VLDL-C versus placebo

Data are observed means with standard error of the mean.
*p<0.05 for estimated treatment difference versus placebo.

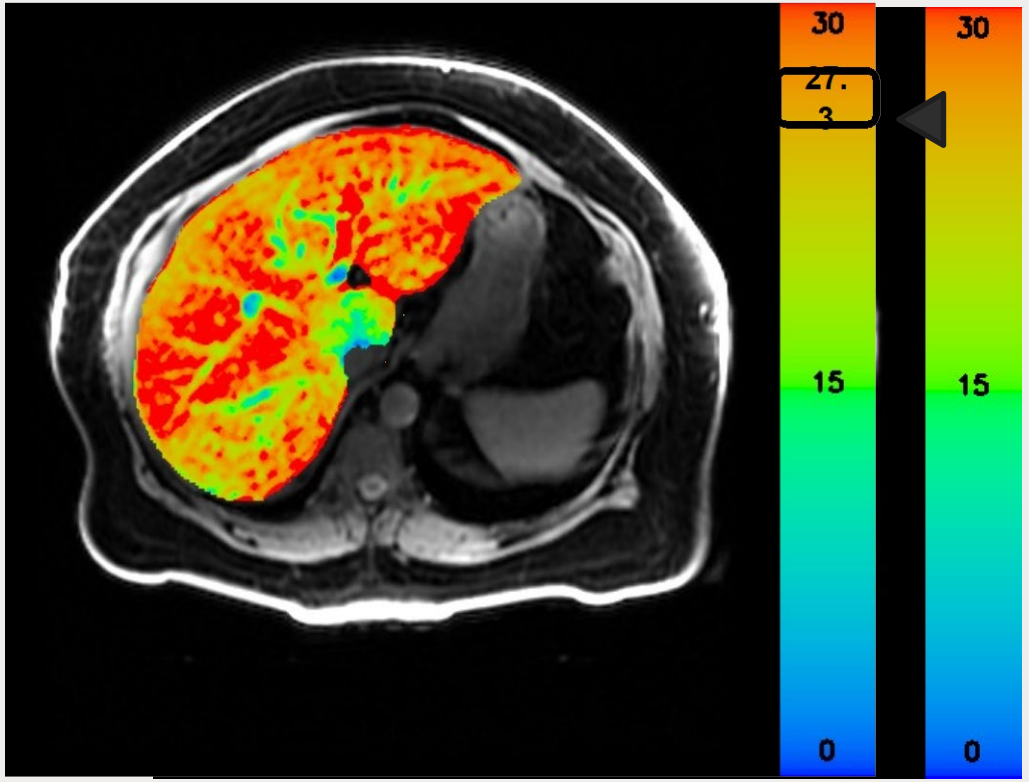
Safety profile: Major AEs were nausea, constipation, and vomiting, no drug discontinuation due to AEs

Newsome PN, et al. *NEJM* 2021 ;384(12):1113-1124.

SURPASS-3: Tirzepatide vs. Basal Insulin

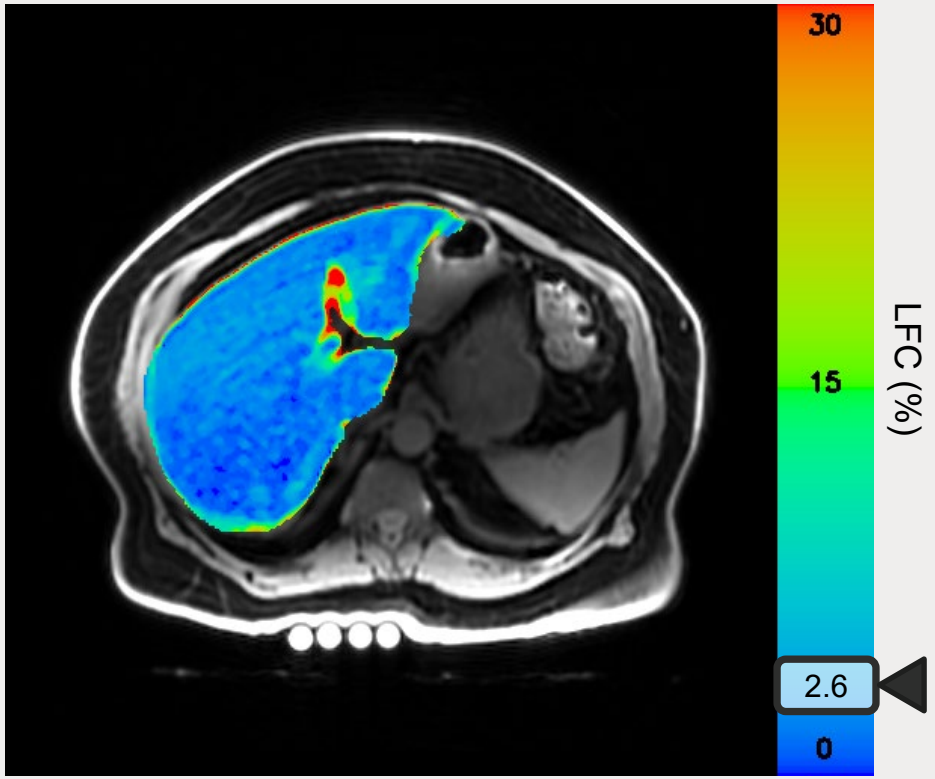
Liver Fat Content at Baseline and at 52 Weeks in a 59 year old male, on metformin + SGLT-2i randomised to tirzepatide 5 mg

MRI scan at baseline



BMI: 44.8 kg/m^2; body weight: 134.2 kg
HbA_{1c}: 78.1 mmol/mol (9.3%)
FSG: 10.3 mmol/L (186 mg/dL)

MRI scan at 52 weeks



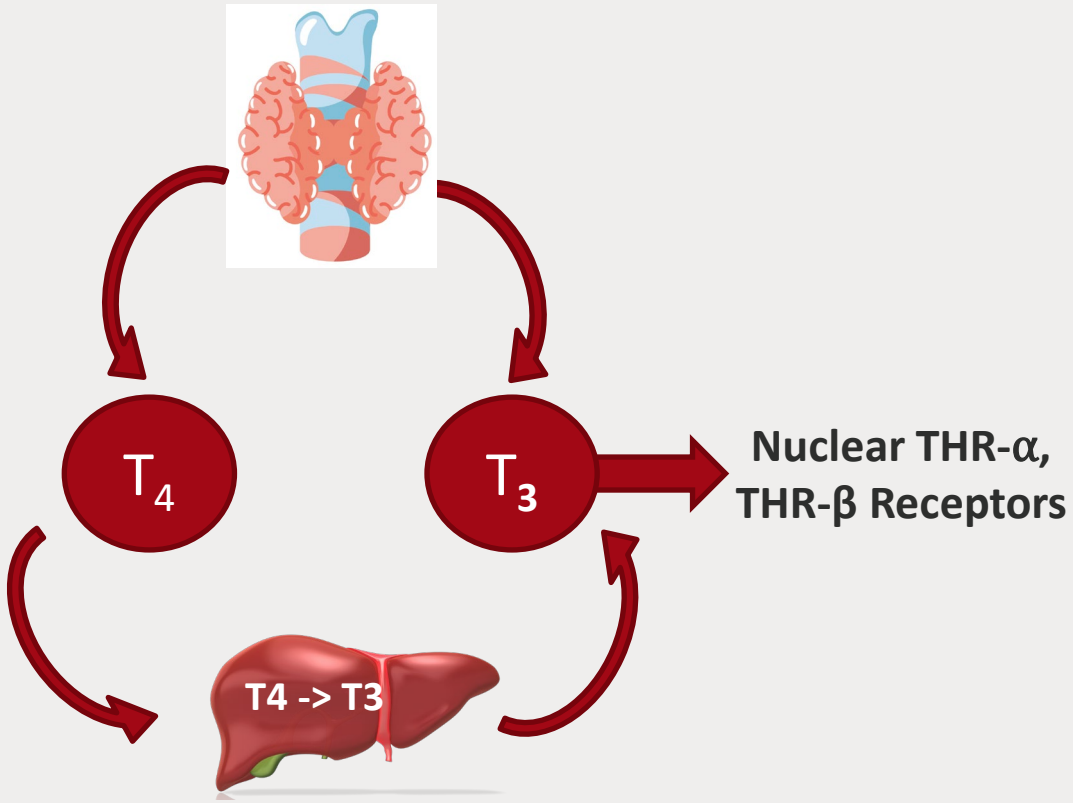
BMI: 36.2 kg/m^2; body weight: 108.4 kg
HbA_{1c}: 43.2 mmol/mol (6.1%)
FSG: 5.9 mmol/L (107 mg/dL)

Courtesy of Ken Cusi

SURPASS-3: Gastaldelli, Cusi, Landó et al. Lancet Diabetes Endocrinol. 2022 June;10:393-406.

Medication	FDA Indication	Population	Clinical Benefits	Potential Side Effects	Cardiac Benefit
Vitamin E (rrr-alpha) 800 IU daily[379, 488]	N/A	MASH without T2DM or cirrhosis	Improves steatosis NASH resolution? No proven benefit on fibrosis	Hemorrhagic stroke ? risk of prostate cancer	No
Pioglitazone 30-45mg po daily (387, 390, 489)	T2DM	MASH with and without T2DM	**Improves steatosis, activity and NASH resolution** **Fibrosis improvement?** **Improves insulin sensitivity** **Prevention of diabetes** **CV risk reduction and stroke prevention**	**Weight gain** **Risk of heart failure exacerbation** **Bone loss post-menopausal women**	**Yes**
Liraglutide* 1.8mg SC daily (T2DM) 0.6-3mg SQ daily (obesity) (404)	T2DM Obesity	MASH without cirrhosis	**Improves steatosis** **No proven impact on fibrosis** **Improvement in insulin sensitivity** **Weight loss** **CV risk reduction** **May slow progression of renal disease**	**Gastrointestinal** **Gallstones (related to weight loss)** **Pancreatitis**	**Yes**
Semaglutide ¥ 0.4mg SC daily 0.25-2.4mg SQ weekly (405)	T2DM Obesity	MASH without cirrhosis	**Improves steatosis, activity, and NASH resolution** **No proven benefit on fibrosis, but may slow fibrosis progression** **Improvement in insulin sensitivity** **Weight loss** **Improves CV and renal outcomes** **Stroke prevention**	**Gastrointestinal** **Gallstones (related to weight loss)** **Pancreatitis**	**Yes**
Tirzepatide (406, 407)	T2DM	T2DM or Obesity with MASLD	Reduces steatosis on imaging Improvement in insulin sensitivity Significant weight loss	Gastrointestinal Gallstones related to wt loss Pancreatitis	Unknown
SGLT2i (409, 413, 414)	T2DM	T2DM and MASLD	**Reduction in steatosis by imaging** **May improve insulin sensitivity** **Improves CV and renal outcomes** **Modest weight loss**	**Risk of genitourinary yeast infection, volume depletion** **Bone loss**	**Yes**

Resmetirom Mechanism of Action



Thyroid Hormone pathway

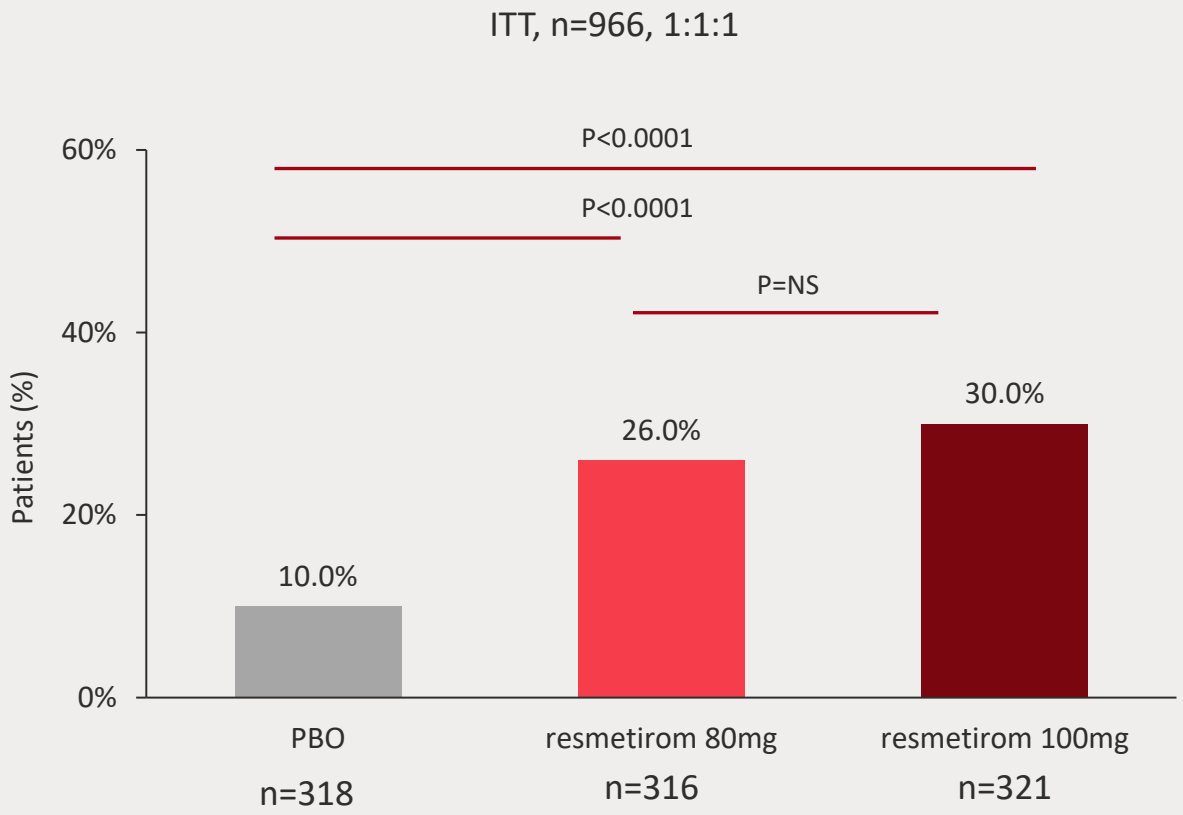
Resmetirom:

- **THR-β agonist** selective liver targeted molecule, administered once a day
- Decreases rT3 levels and increases the fT3/rT3 ratio

1. Sinha RA, et al. Autophagy. 2015;11(8):1341-57; 2. Sinha RA, Yen PM. Cell Biosci. 2016;6:46; 3. Taub R, et al. Poster presented at NASH-TAG, January 9-11 2020; 4. Loomba, et al. Oral presentation AS077. Presented at ILC 2020; 5. Taub R, et al. Poster #1969 presented at AASLD 2017; 6. Harrison SA, et al. Hepatol Commun. 2021;0:1-16. Figure adapted from Taub R, et al. Poster presented at NASH-TAG, January 9-11 2020.

MAESTRO-NASH Phase 3: Primary endpoint

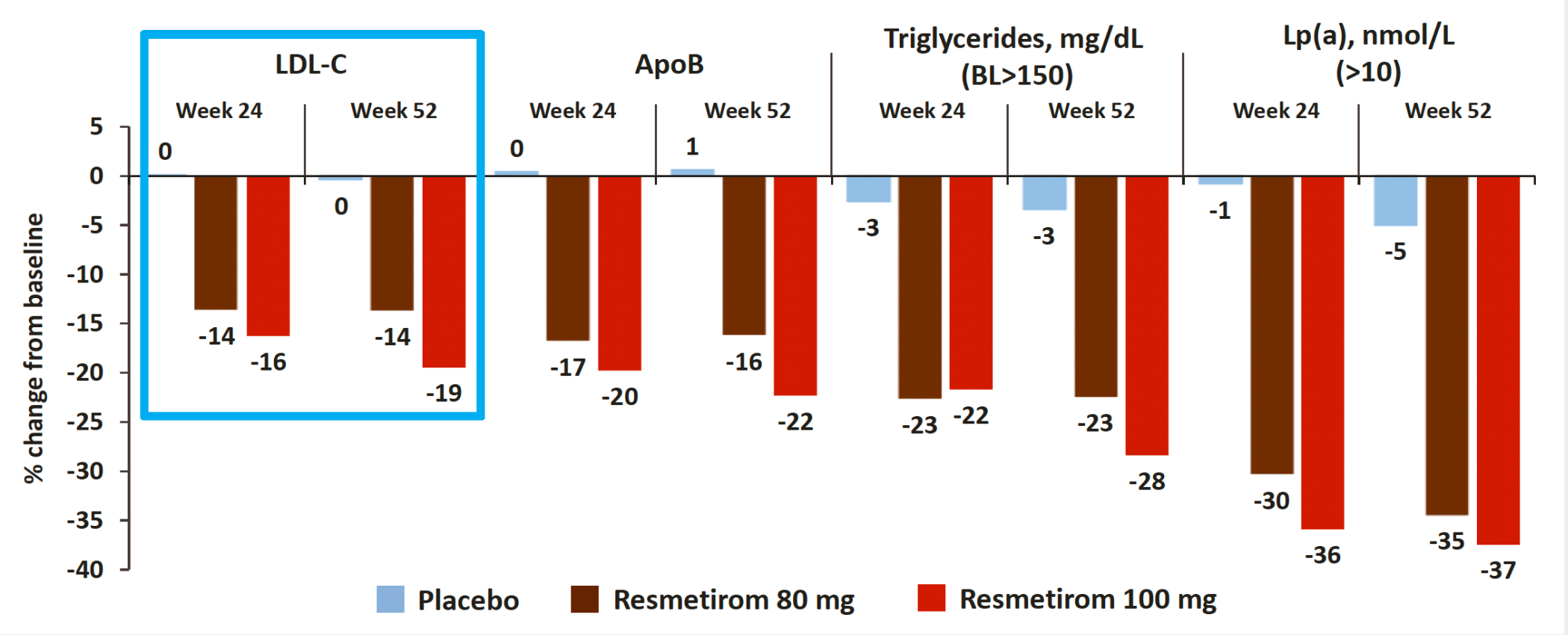
Resolution of NASH and no worsening in liver fibrosis



- 966 patients in primary analysis
- 52 weeks
- Primary endpoint:
  - NASH resolution without fibrosis worsening
    OR
  - Fibrosis improvement by ≥ 1 stage

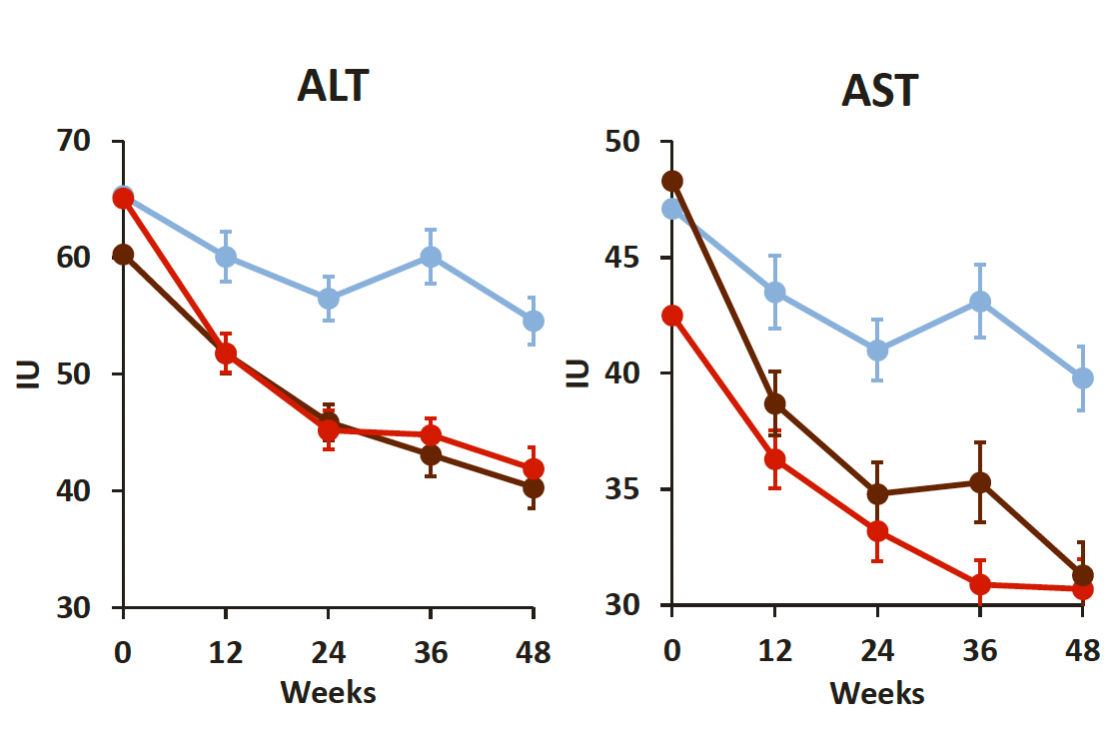
Harrison et al. 2024, in press

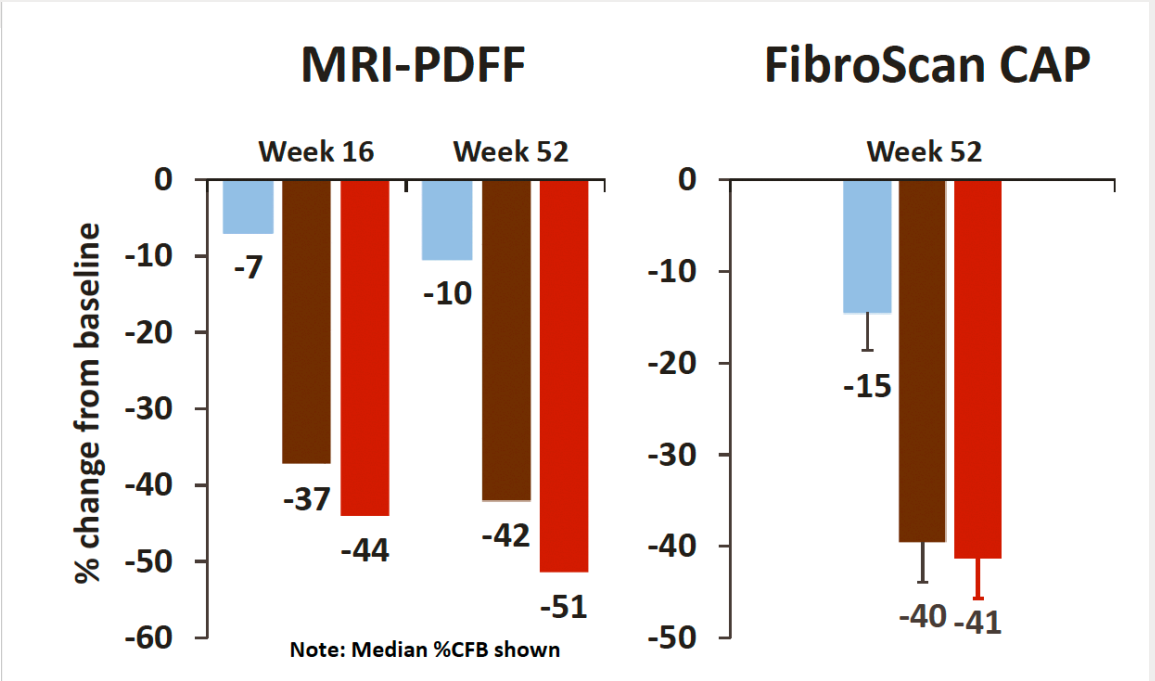
Potential impact on cardiovascular risk



Harrison et al. 2024, in press

Noninvasive markers of response

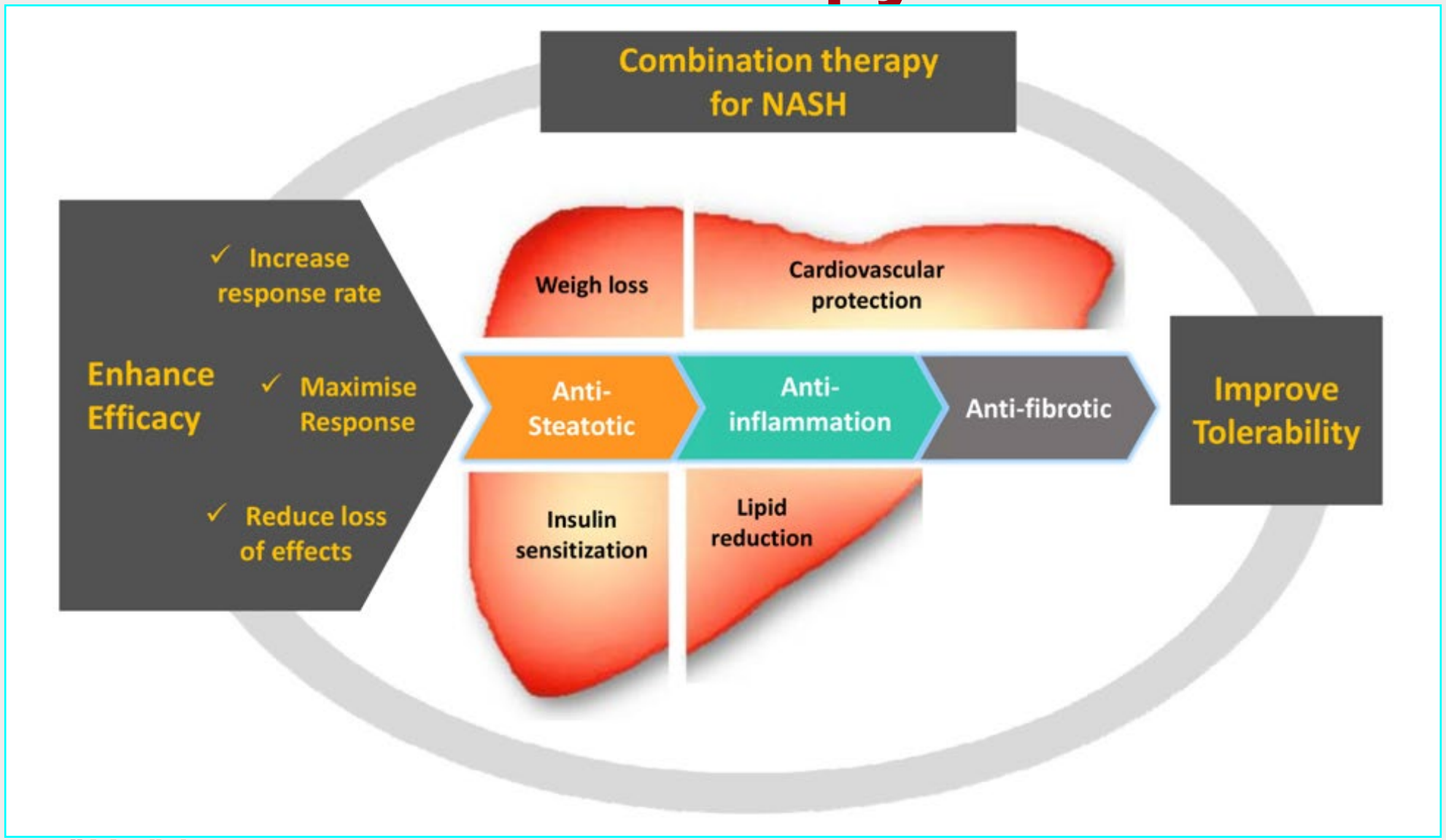




Placebo Resmetirom 80 mg Resmetirom 100 mg

Harrison et al. 2024, in press

Combination Therapy for MASH



Dufour, Caussy & Loomba; Gut 2020

Summary of (selected) key concepts to guide clinical practice:

Screening for advanced fibrosis and risk stratification

- *General population-based screening for MASLD is not advised*
- *Hepatic steatosis, or suspected MASLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4.*
- *Patients with pre-DM, T2DM or ≥2 met risk factors (or steatosis on imaging): Repeat FIB-4 every 1-2 years, and when available, consider secondary fibrosis assessment*
- *If FIB-4 ≥ 1.3, VCTE, MRE or ELF, may be used to exclude advanced fibrosis.*

Summary of (selected) key concepts to guide clinical practice:

Disease modifying interventions in patients with NAFLD

- *Patients with NAFLD who are overweight or obese should be prescribed a diet that leads to a caloric deficit. When possible, diets with limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats (e.g. Mediterranean diet) should be encouraged due to their additional cardiovascular benefits.*

- *Patients with NAFLD should be strongly encouraged to increase their activity level to the extent possible. Individualized prescriptive exercise recommendations may increase sustainability and have benefits independent of weight loss.*

- *Bariatric surgery should be considered as a therapeutic option in patients who meet criteria for metabolic weight-loss surgery as it effectively resolves NAFLD or NASH in the majority of patients without cirrhosis and reduces mortality from CVD and malignancy*

Summary of (selected) key concepts to guide clinical practice:

Alcohol and other considerations

- *In patients with MASLD, alcohol can be a co-factor for liver disease progression and intake should be assessed on a regular basis.*
- *Patients with clinically significant hepatic fibrosis (≥F2)should abstain from alcohol use completely.*
- *Improvement in ALT or reduction in liver fat content by imaging in response to an intervention may indicate histological improvement in disease activity.*
- *First-degree relatives of patients with MASH cirrhosis should be counseled regarding their increased individual risk and offered screening for advanced hepatic fibrosis.*

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