Brigham and Women's Hospital
Founding Member, Mass General Brigham

Update in MASLD

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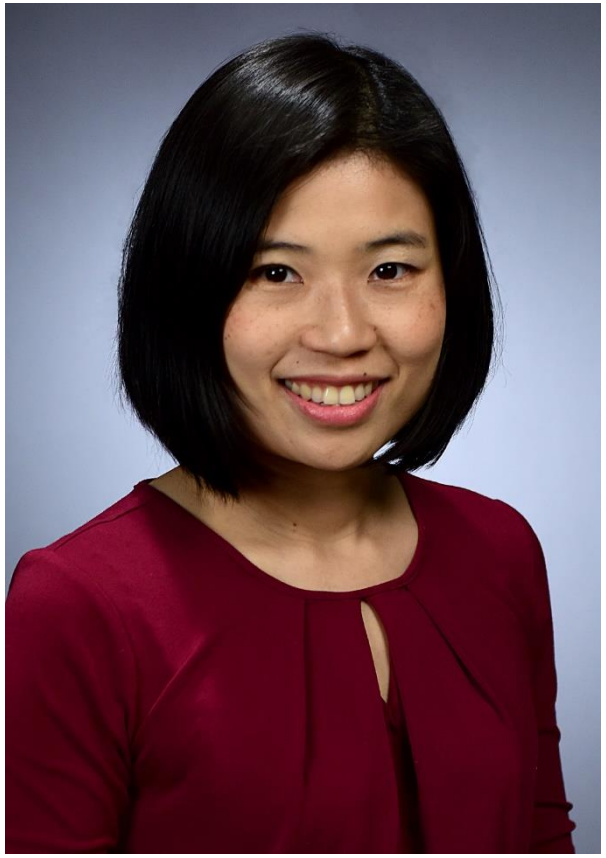
M. Valerie Lin, MD



- Medicine Residency @ Pennsylvania Hospital, Penn Medicine
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- Assistant Professor of Medicine @ UMass School of Medicine
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- Associate Program Director for Advanced Hepatology Fellowship @ Lahey Hospital & Medical Center
- Clinical focus: Transplant oncology; metabolic steatohepatitis; chronic liver disease and cirrhosis
- Research focus: Transplant oncology & liver tumors; frailty and prehabilitation in cirrhosis; acute on chronic liver failure

DISCLOSURES

- I have no financial disclosures

OBJECTIVES

- Review “new” MASLD nomenclature and diagnostic criteria
- Outline the risk stratification algorithm for patients with MASLD
- Discuss non-invasive tests (NITs) for liver fibrosis
- Review the current treatment options for patients with MASLD

CASE STUDY

- 45 yo F of Hispanic origin presented to establish care
- PMHx: hypertension and obesity (BMI 43)
- FHx: Mother is “overweight and has fatty liver”
- Ongoing alcohol use, 1-2 beers/day during the weekends only
- Routine blood work:
  - LFT: AST 55, ALT 50, ALP 175 and TB 0.8
  - Hgb 15g/dL, MCV 96, platelet 145k
  - Ferritin 400ng/dL; iron saturation 25%
  - HBA1c 6.1%
  - Negative viral and autoimmune serologies
- Ultrasound showed hepatic steatosis

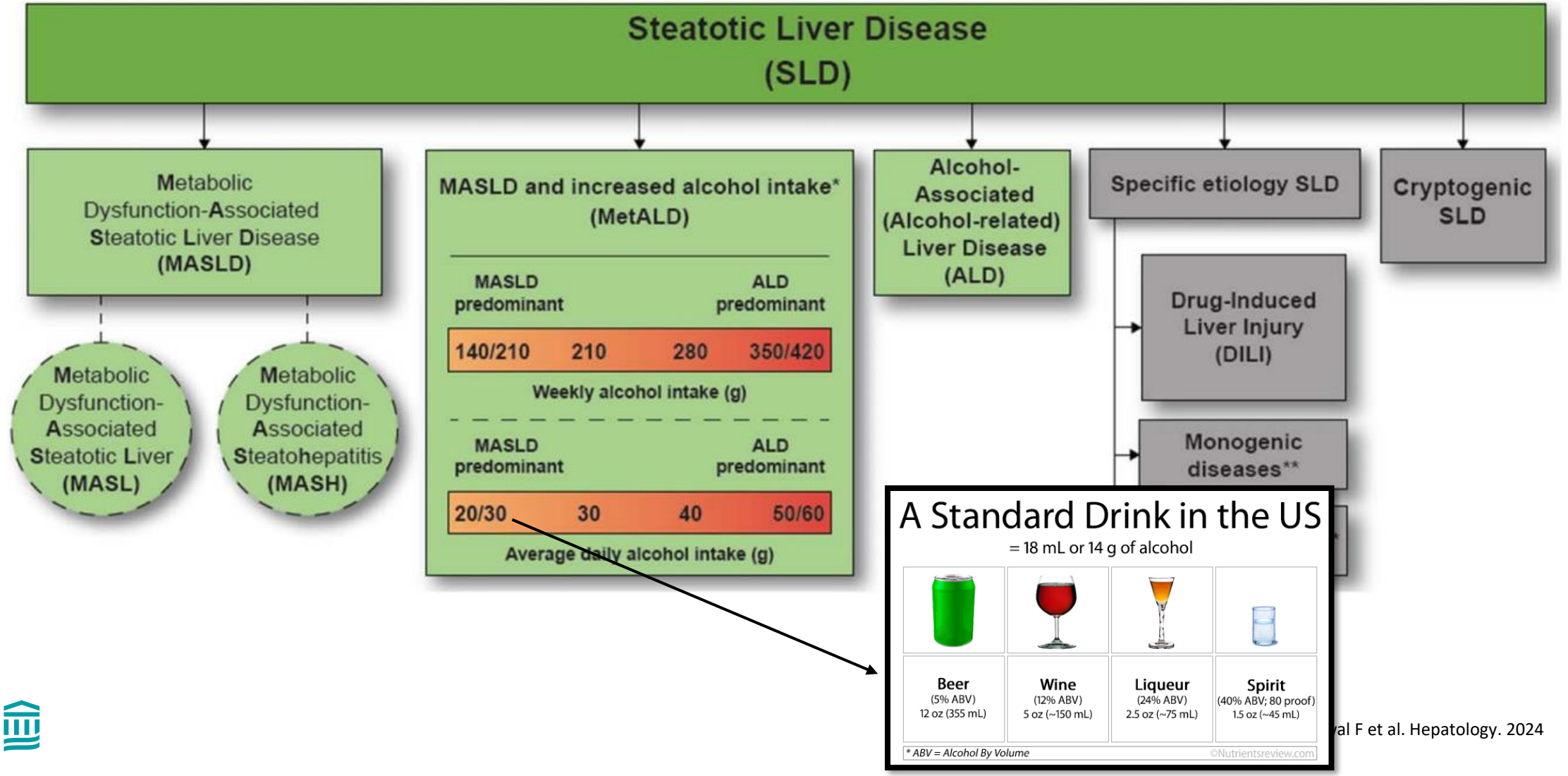
NOMENCLATURE CHANGES

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

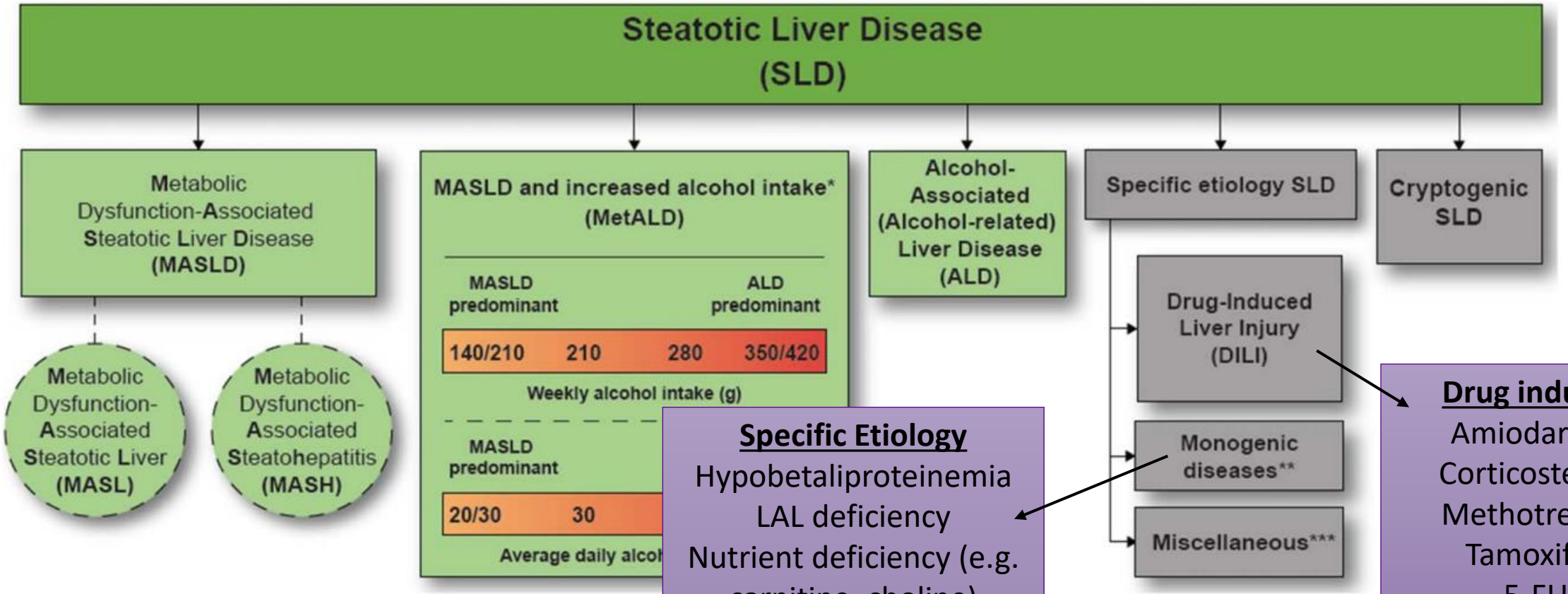
Old Name	New Name	Definition
NAFLD Nonalcoholic Fatty Liver Disease	**MASLD** Metabolic Dysfunction-Associated Steatotic Liver Disease	Hepatic steatosis (>5% on bx) + 1 metabolic feature
NASH Nonalcoholic Steatohepatitis	**MASH** Metabolic Dysfunction-Associated Steatohepatitis	HS + inflammation: Mallory bodies, ballooning hepatocytes +/- fibrosis
NASH + ASH Nonalcoholic Steatohepatitis **+** Alcoholic Steatohepatitis	**MetALD** Metabolic Dysfunction-associated and Alcohol-associated Liver Disease	MASLD + 20g/30g to 50g/60g of alcohol daily

Terrault NA et al. AASLD 2023

STEATOTIC LIVER DISEASE (SLD)



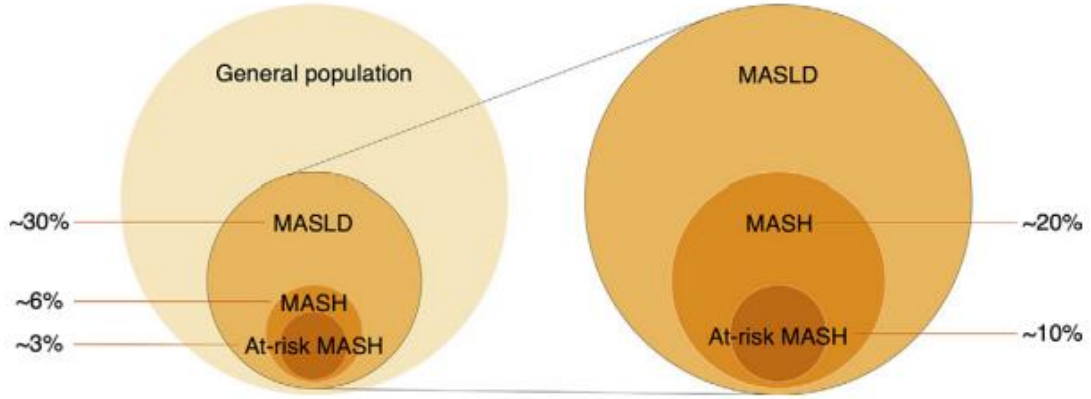
STEATOTIC LIVER DISEASE (SLD)



Kanwal F et al. Hepatology. 2024

THE AT-RISK POPULATION FOR MASLD

- Overall prevalence of MASLD is 25 to 30%
  - 55% has BMI >30
  - 66% has T2DM
  - 74% has metabolic syndrome
  - 90% has class ≥2 obesity
- Male has 2x prevalence than female
- Hispanic > White> African American
- Genetic polymorphisms associated with increase risk of MASH
  - PNPLA3/148M
  - TM6SF2
  - MBOAT7



MASLD DIAGNOSTIC CRITERIA

Presence of hepatic steatosis + ≥1 cardiometabolic risk factors

Hepatic Steatosis

- Imaging modalities (ultrasound, CT, MRI)
- Histology ≥ 5% macrovesicular steatosis
- MRI-PDFF >5.5%
- Controlled attenuation parameters (CAP ≥ 288 dB/min)
- Attenuation Imaging (ATI 0.66dBcm/MHz)

Cardiometabolic risk factors

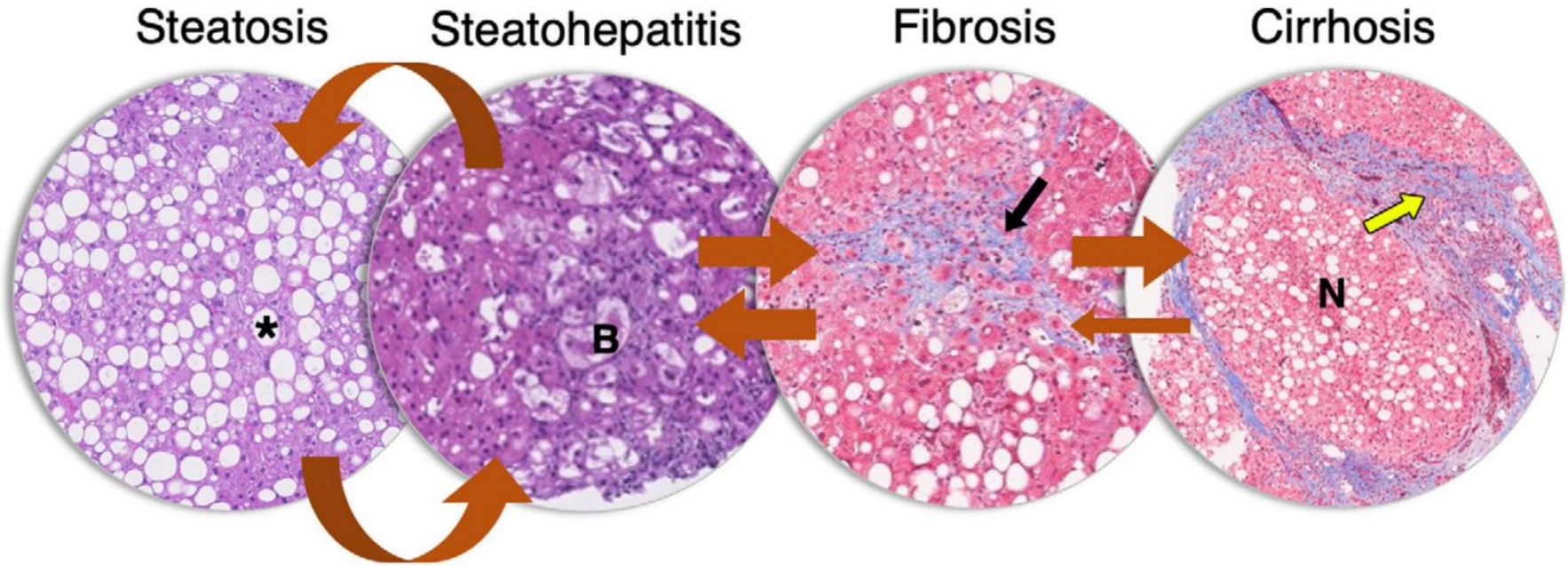
Adult Criteria

At least 1 out of 5:

- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

Kanwal F et al. Hepatology. 2024

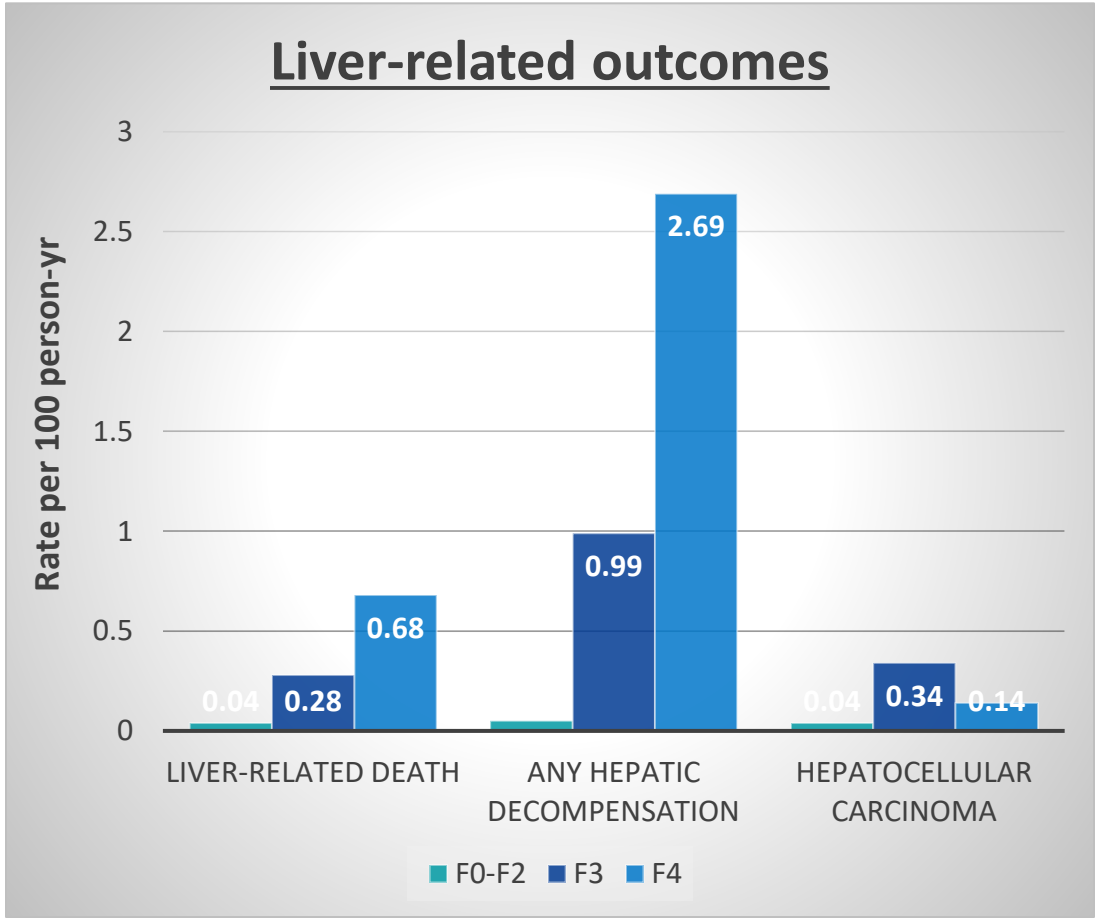
COURSE OF HEPATIC FIBROSIS PROGRESSION

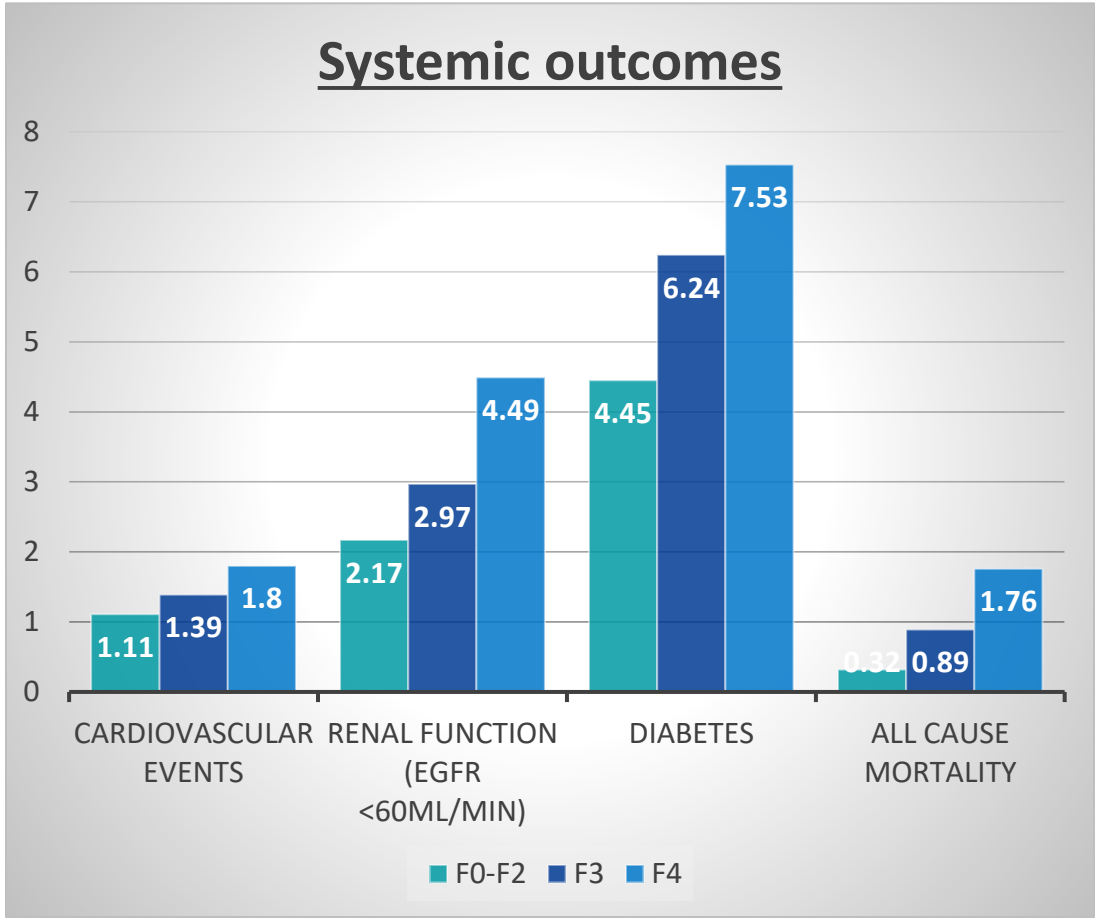


Screening recommended	Prevalence of advanced fibrosis, %
T2DM	6-19
Medically complicated obesity	4-33
MASLD in context of moderate alcohol use	17
First-degree relative with MASLD or MASH cirrhosis	18

Shabanan SH et al. Radiographics 2024; Younossi et al. Hepatology 2018;64:73-84; Rinella et al. Hepatology 2023

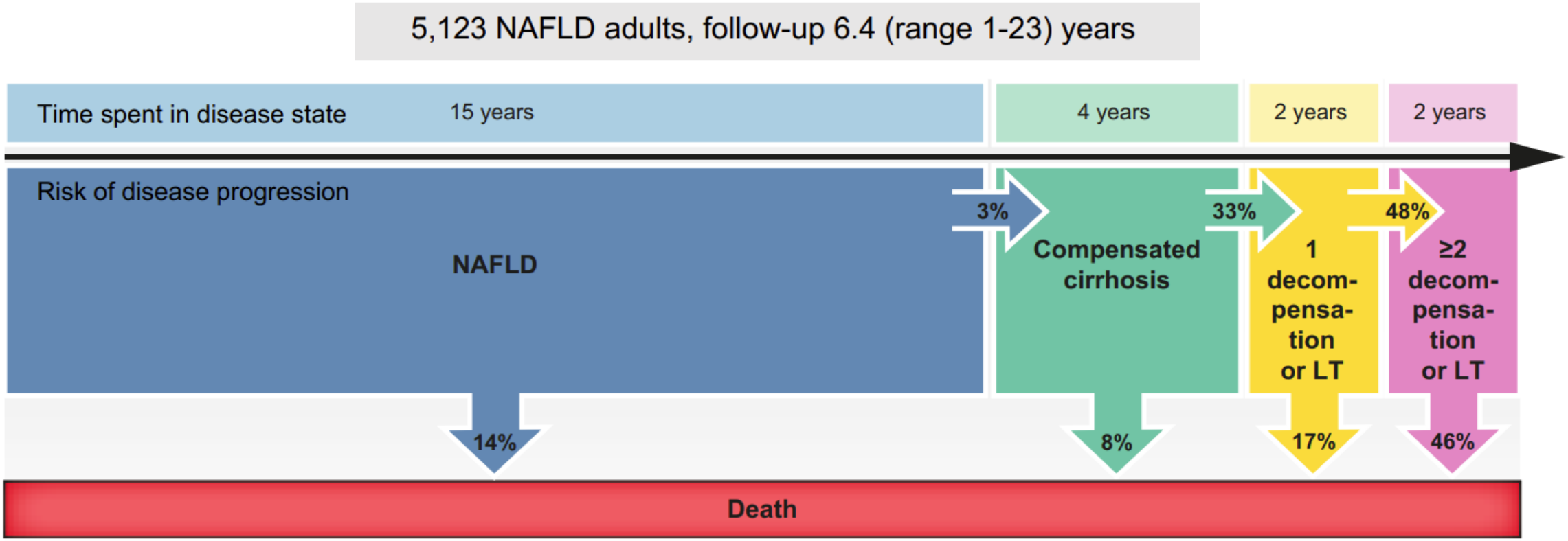
FIBROSIS STAGES IS ASSOCIATED WITH INCREASED RISKS OF LIVER RELATED COMPLICATIONS & DEATH



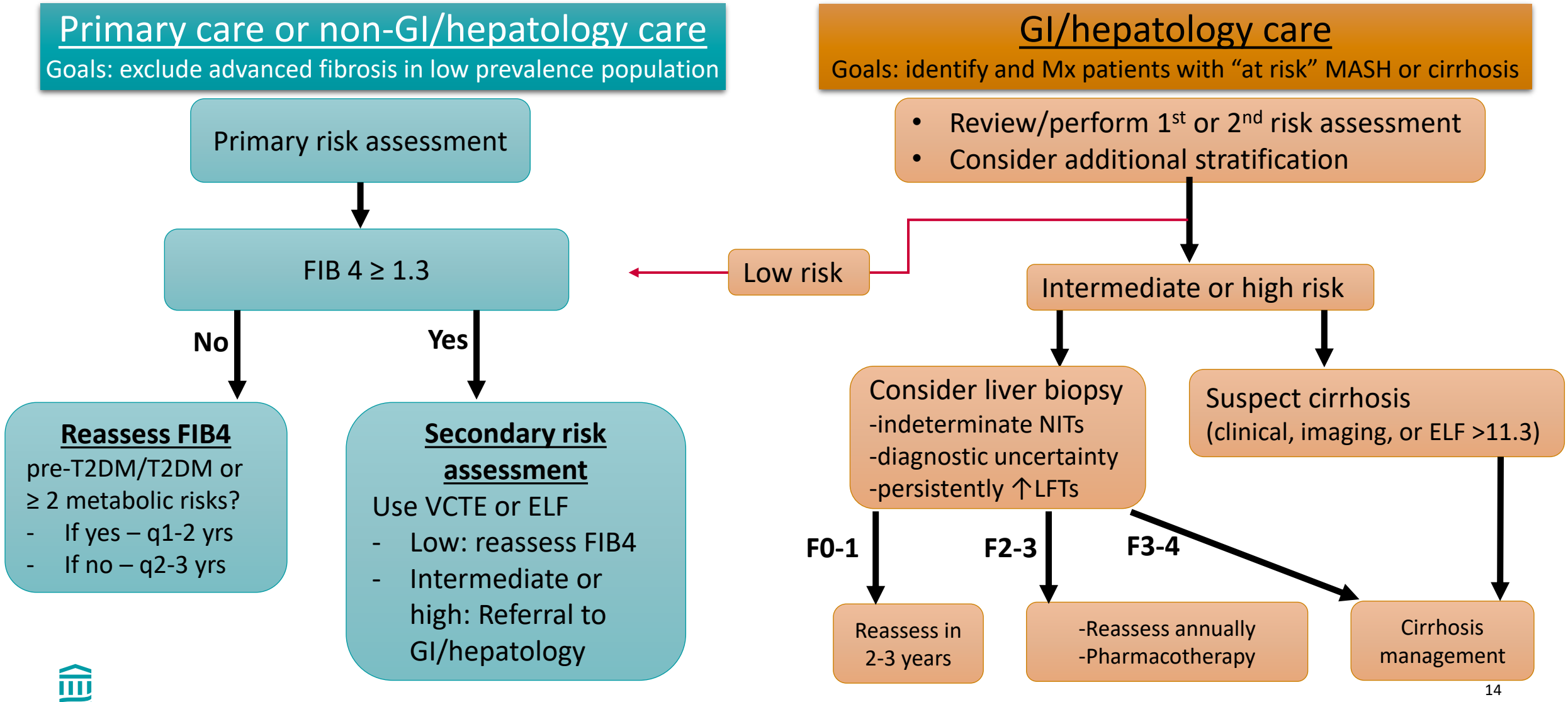


Sanyal A.J. et al. NEJM 2021

CLINICAL COURSE OF MASH



GUIDELINE FOR RISK STRATIFICATION



Rinella et al. Hepatology 2023

NON-INVASIVE TESTS (NITS) OF LIVER FIBROSIS

Blood-based Tests

Simple

-FIB-4

-NAFLD Fibrosis Score (NFS)

-AST/Platelet ratio (APRI)

Complex/Patent

- Enhanced liver fibrosis (ELF)
- Fibrospect II
- FibroMeter
- FibroSure
- HepaScore

Imaging-based Tests

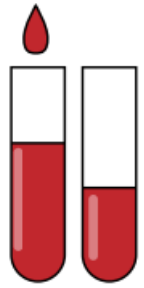
Elastography

-VCTE/Fibroscan (1D)

-Ultrasound shear waves (2D)

-MRI (3D)

LABORATORY ASSESSMENT OF FIBROSIS



Simple Blood Test

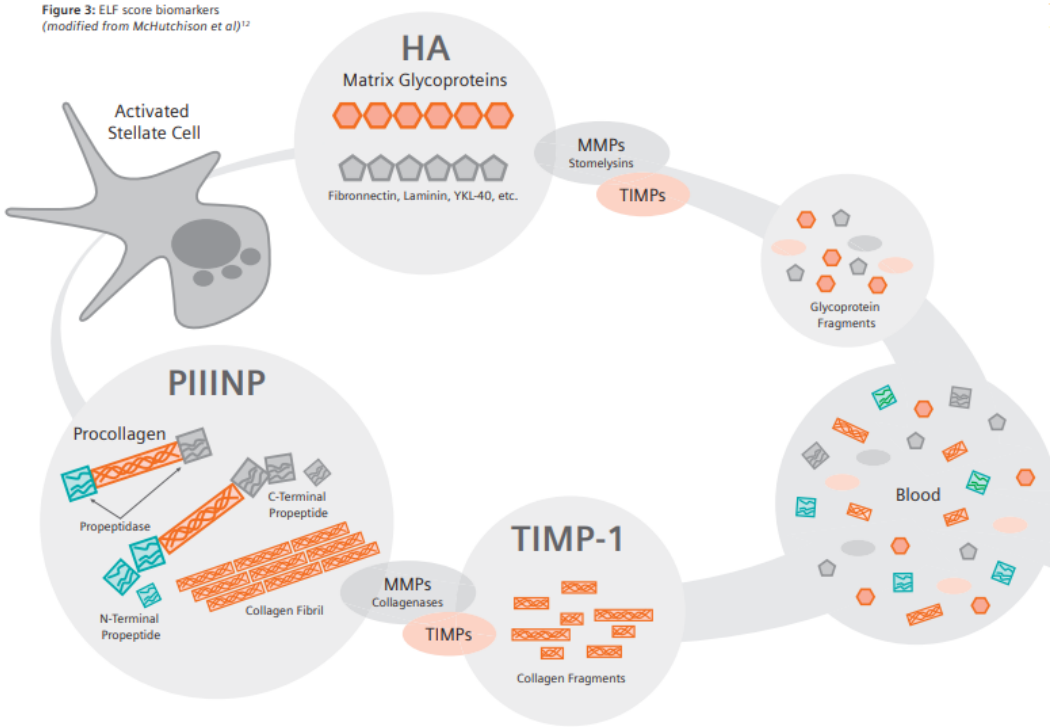
NAFLD Fibrosis Score (NFS)

FIB-4 Score

Parameters
Age, years
AST
ALT
Platelet counts, cells x 10^9
BMI
Albumin, g/L
Impaired fasting glucose/diabetes?

Low Probability of Stage 3 or 4	Indeterminate	High Probability of Stage 3 or 4
FIB4: <1.3 NFS: - 1.455	FIB4: 1.3-2.67 NFS:- 1.455 – 0.67	FIB4: >2.67 NFS: >0.67

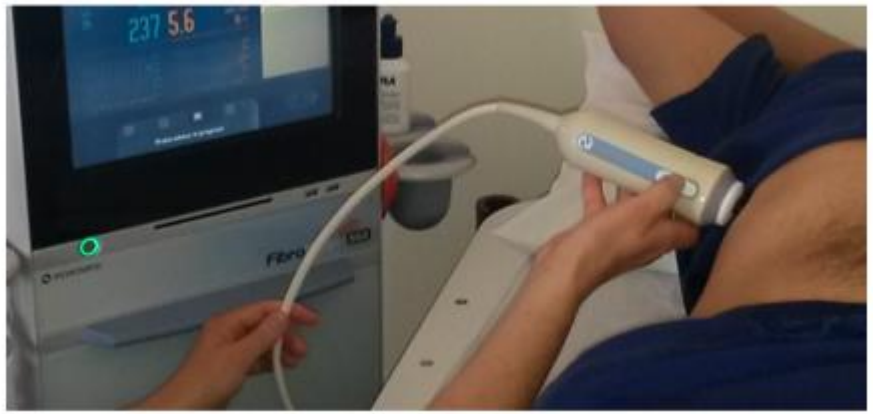
Complex Blood Test

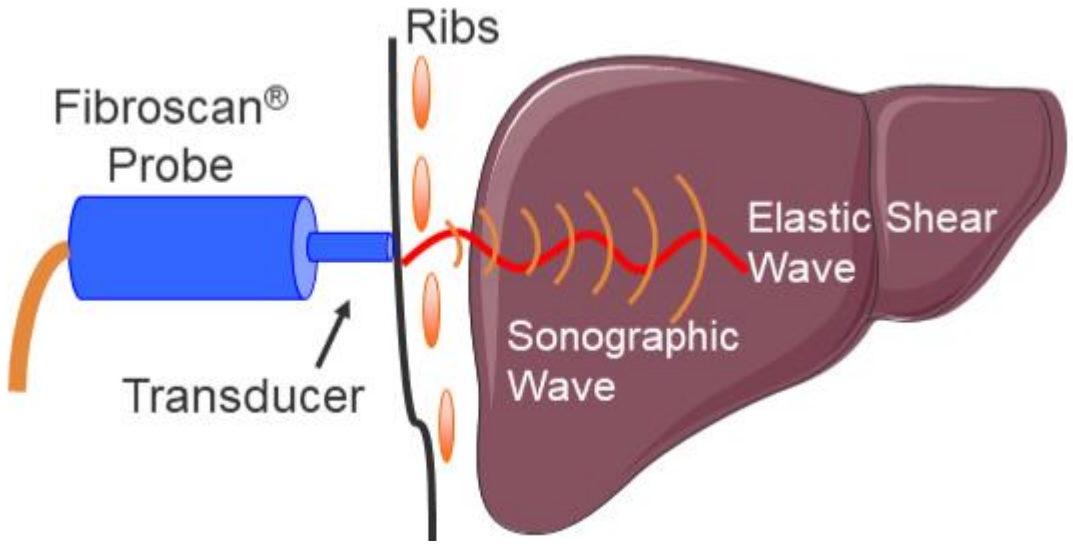


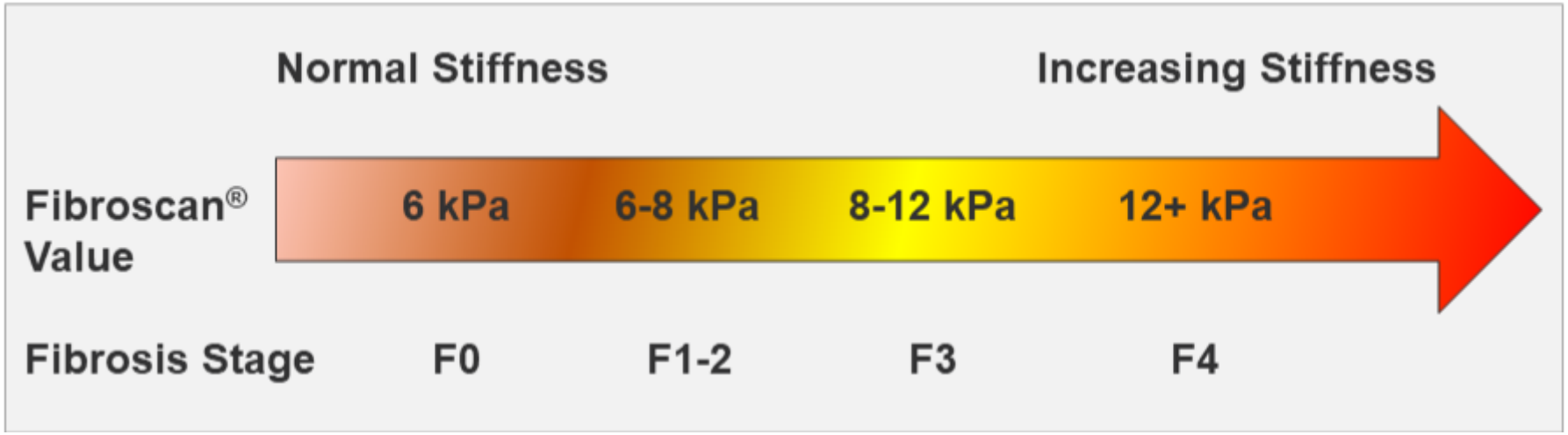
Elf score	Interpretation†
<9.8	Low risk
9.8 to <11.3	Moderate risk
>=11.3	High risk

Vali Y et al. J of Hepatology 2020; Rosenberg et al. Gastroenterology 2004

VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY (VCTE/FIBROSCAN)

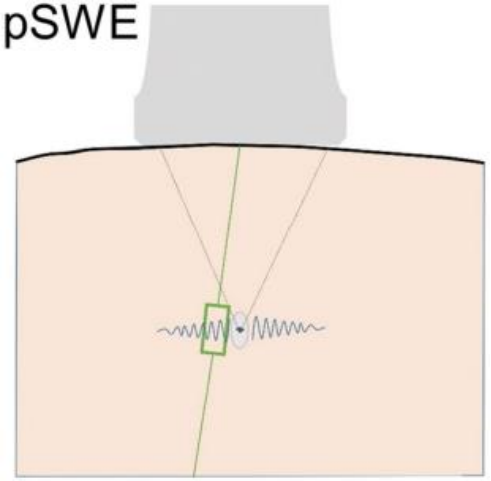


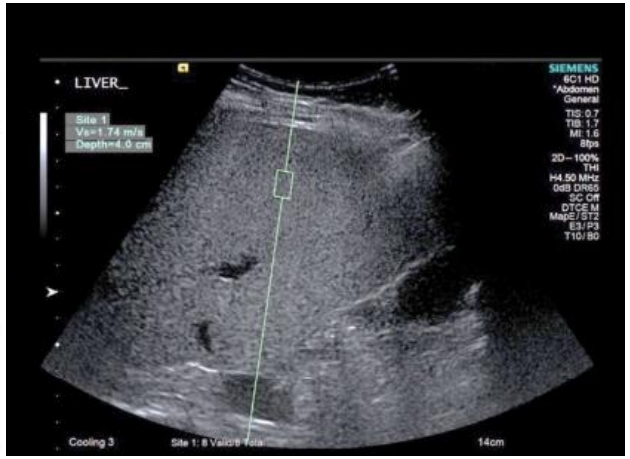




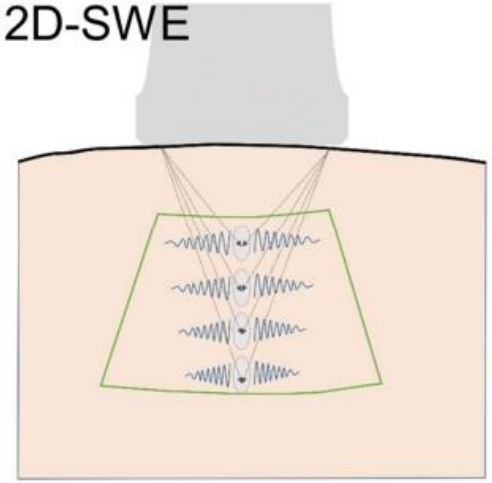
ULTRASOUND SHEAR WAVES ELASTOGRAPHY (SWE)

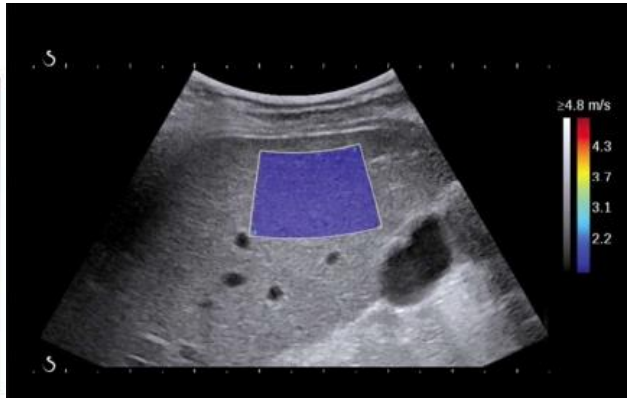
pSWE





2D-SWE

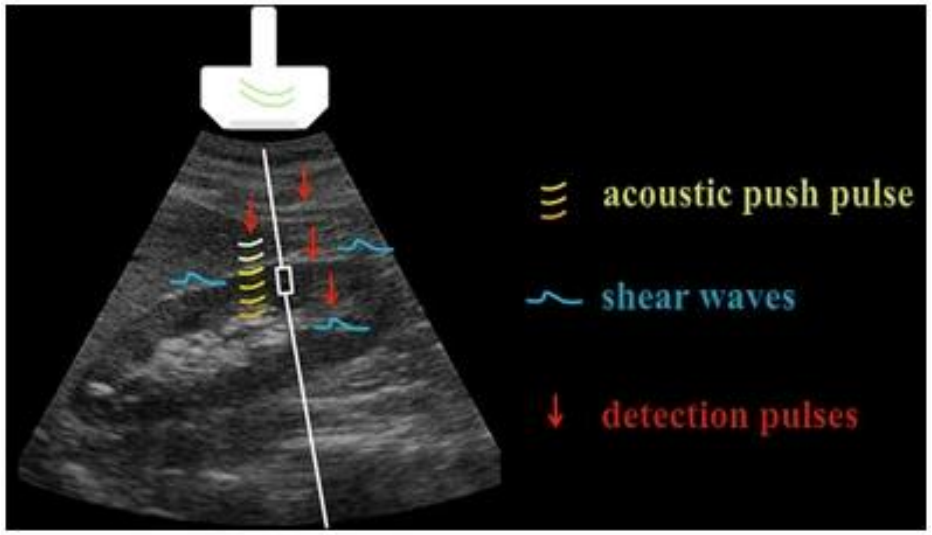




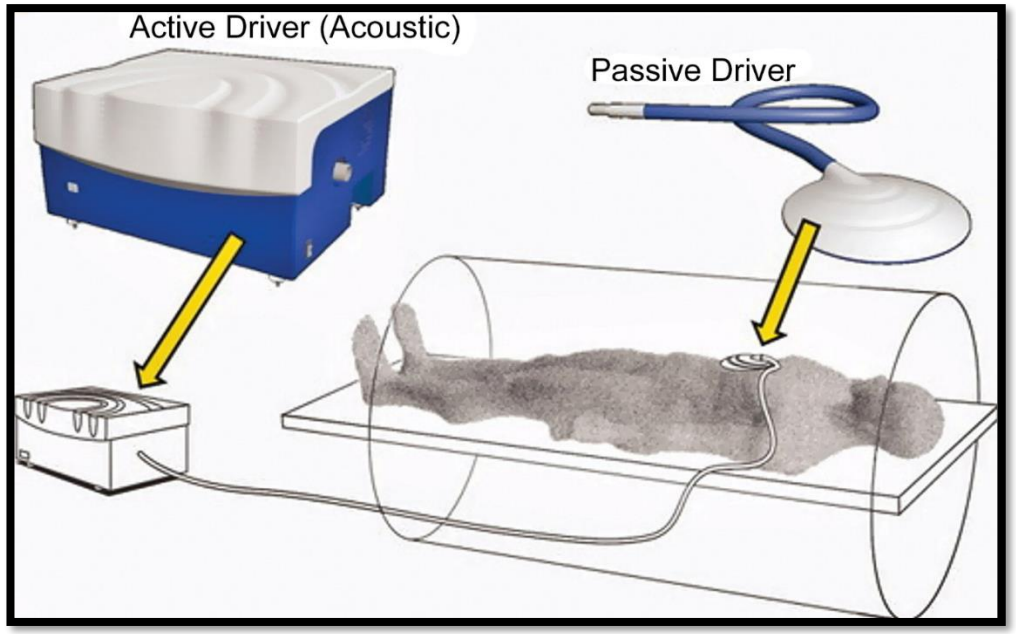
High intensity focus ultrasound pulses

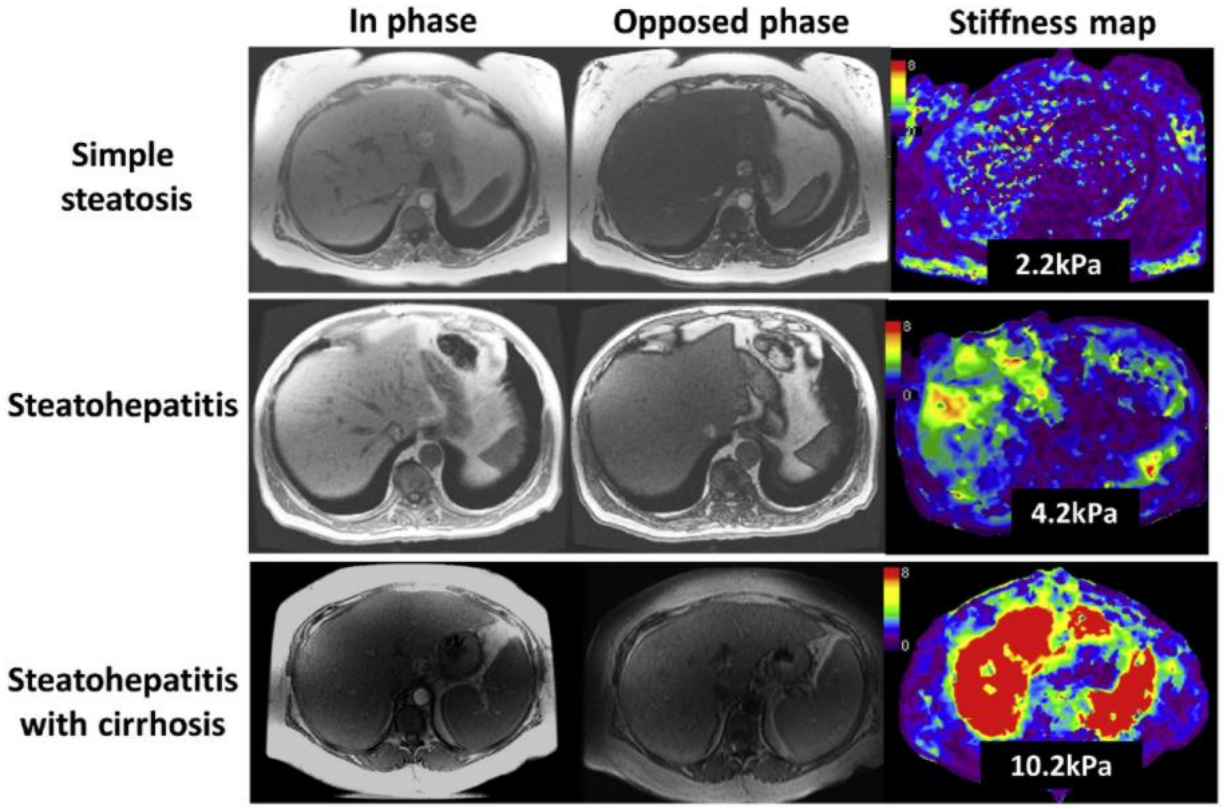
Short-duration acoustic pulses

Acoustic Radiation Force Impulse (ARFI)



MAGNETIC RESONANCE ELASTOGRAPHY (MRE)

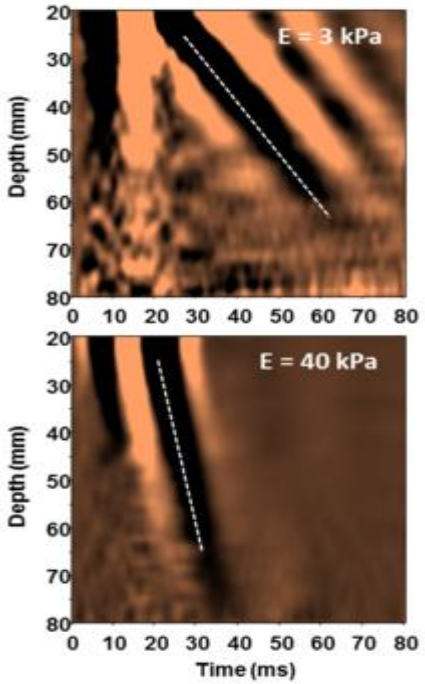


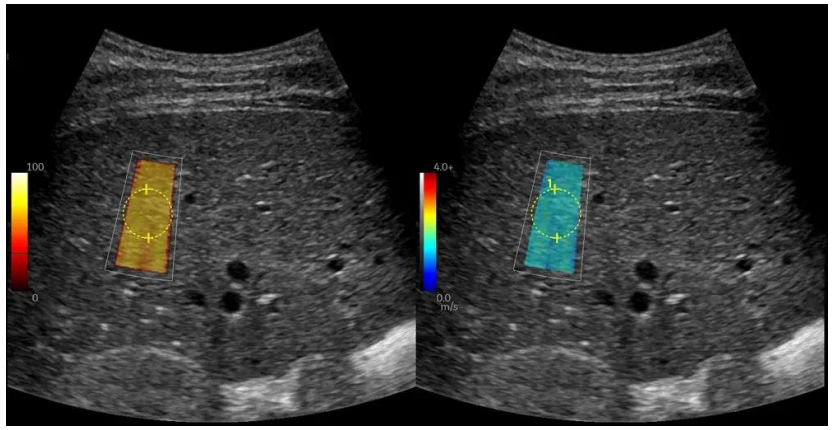


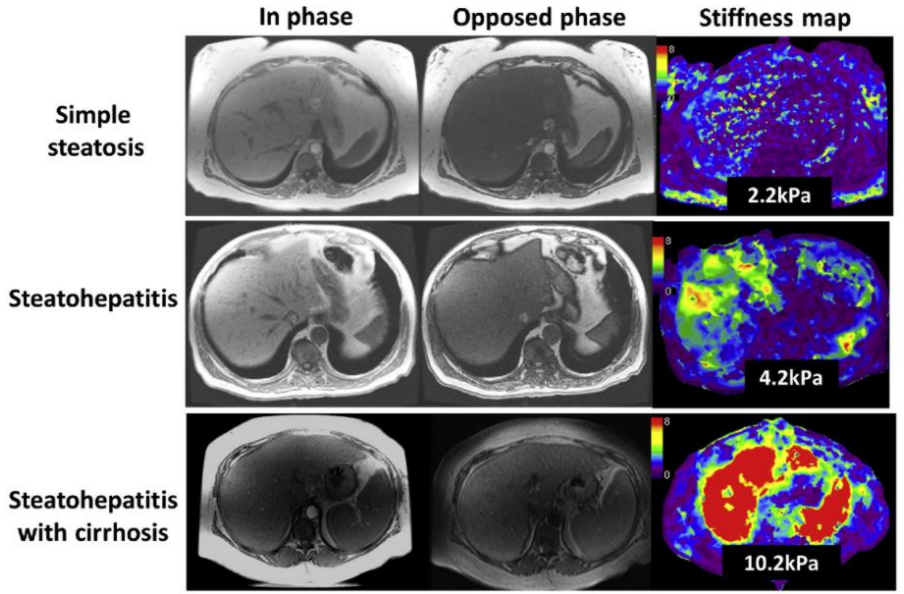
Guglielmo F et al. Radiographics 2019

SOURCES OF VARIABILITY IN IMAGE-BASED ELASTOGRAPHY

- Etiology
- Obesity
- Non-fasting
- Alcohol use
- Inflammation
- Congestion
- Ascites
- Operator experience





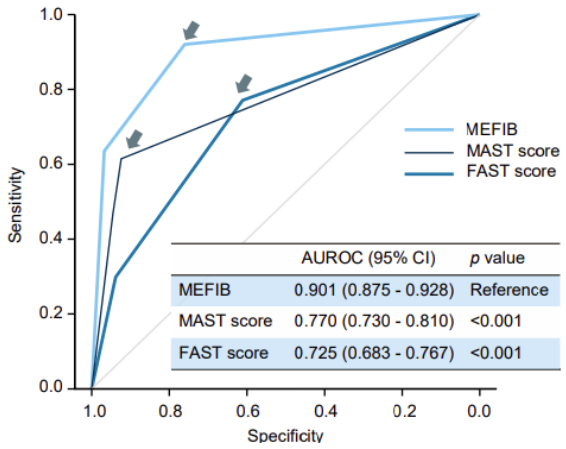


Barr RG et al. Radiology 2015;276:845-861

COMBINING NON-INVASIVE TESTS FOR MASLD

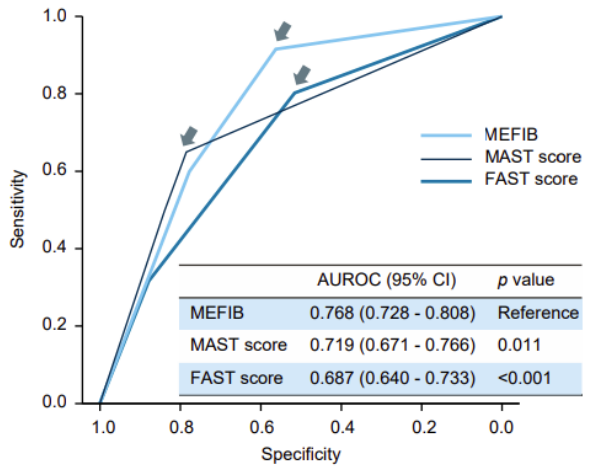
Head-to-head comparison between NITs for detecting ≥ stage 2 fibrosis in NAFLD

MEFIB is superior to **MAST** or **FAST** or the detection of ***significant fibrosis***



	AUROC (95% CI)	*p* value
MEFIB	0.901 (0.875 - 0.928)	Reference
MAST score	0.770 (0.730 - 0.810)	<0.001
FAST score	0.725 (0.683 - 0.767)	<0.001

MEFIB is superior to **MAST** or **FAST** for the detection of ***"at risk" NASH***

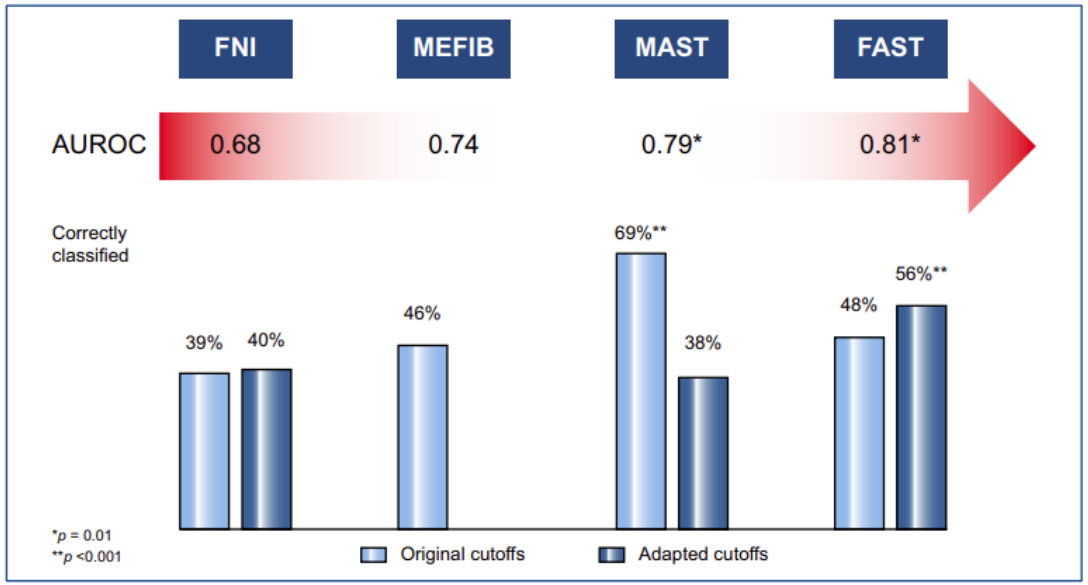


	AUROC (95% CI)	*p* value
MEFIB	0.768 (0.728 - 0.808)	Reference
MAST score	0.719 (0.671 - 0.766)	0.011
FAST score	0.687 (0.640 - 0.733)	<0.001

Conclusion: MEFIB was better than MAST and FAST for detecting significant fibrosis and "at risk" NASH

Kim BK et al. J of Hep 2022

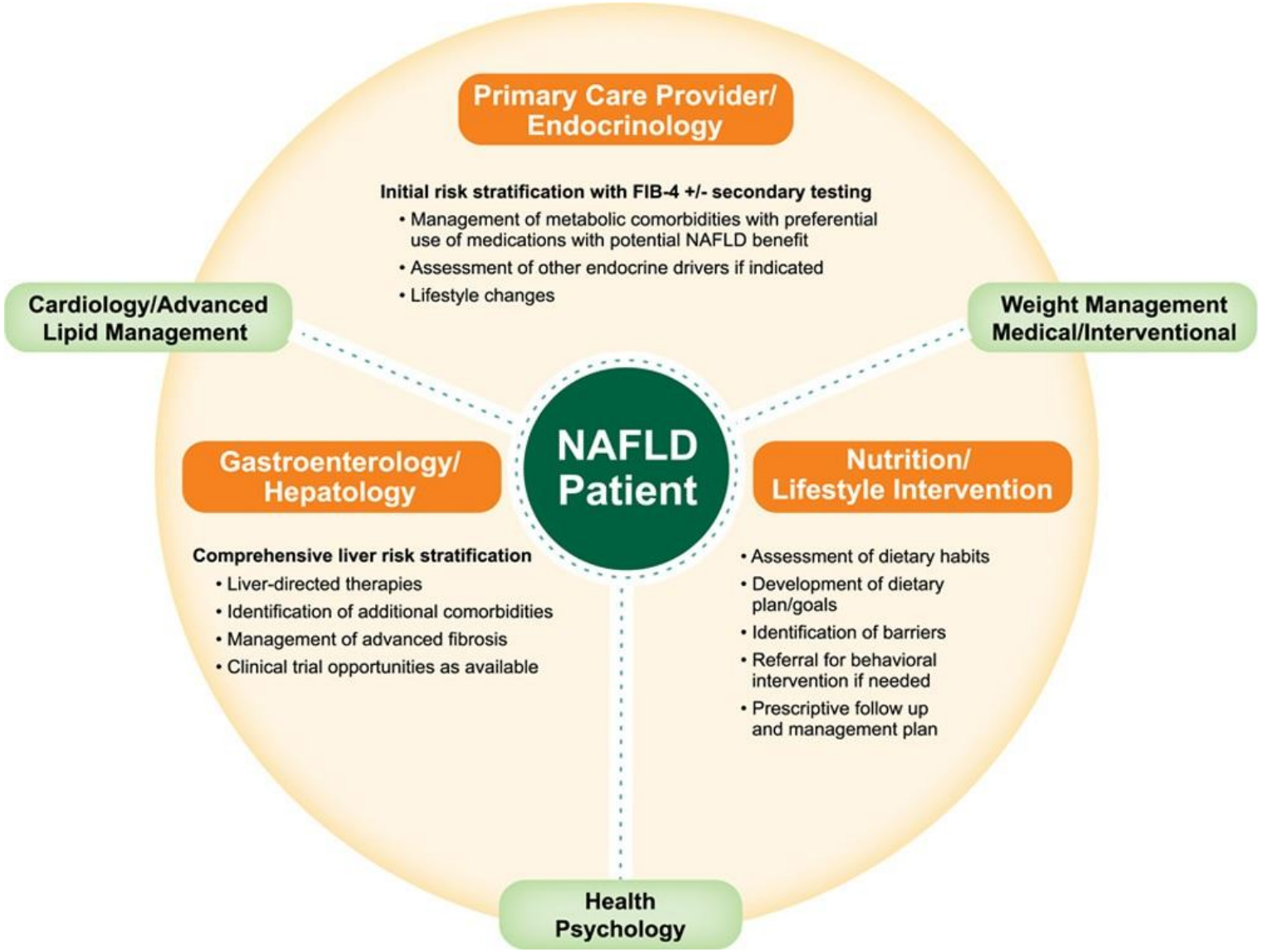
Prospective head-to-head comparison of NITs in T2DM patients for diagnosis of fibrotic MASH



Conclusion: FAST and MAST scores outperformed MEFIB and FNI in T2DM and MASLD

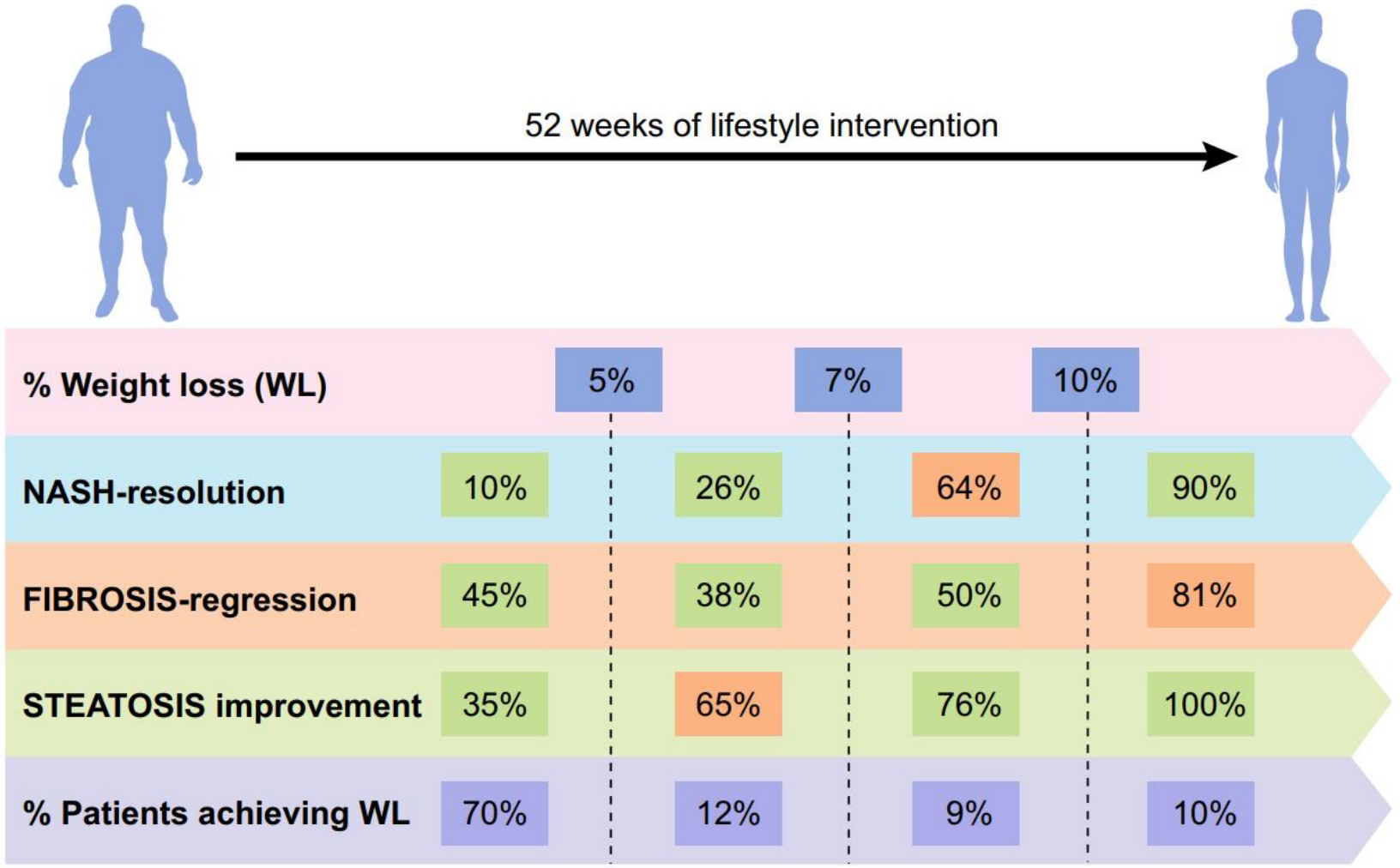
Castera L et al. J of Hep 2024

MULTIDISCPLINARY MANAGMEENT OF MASLD



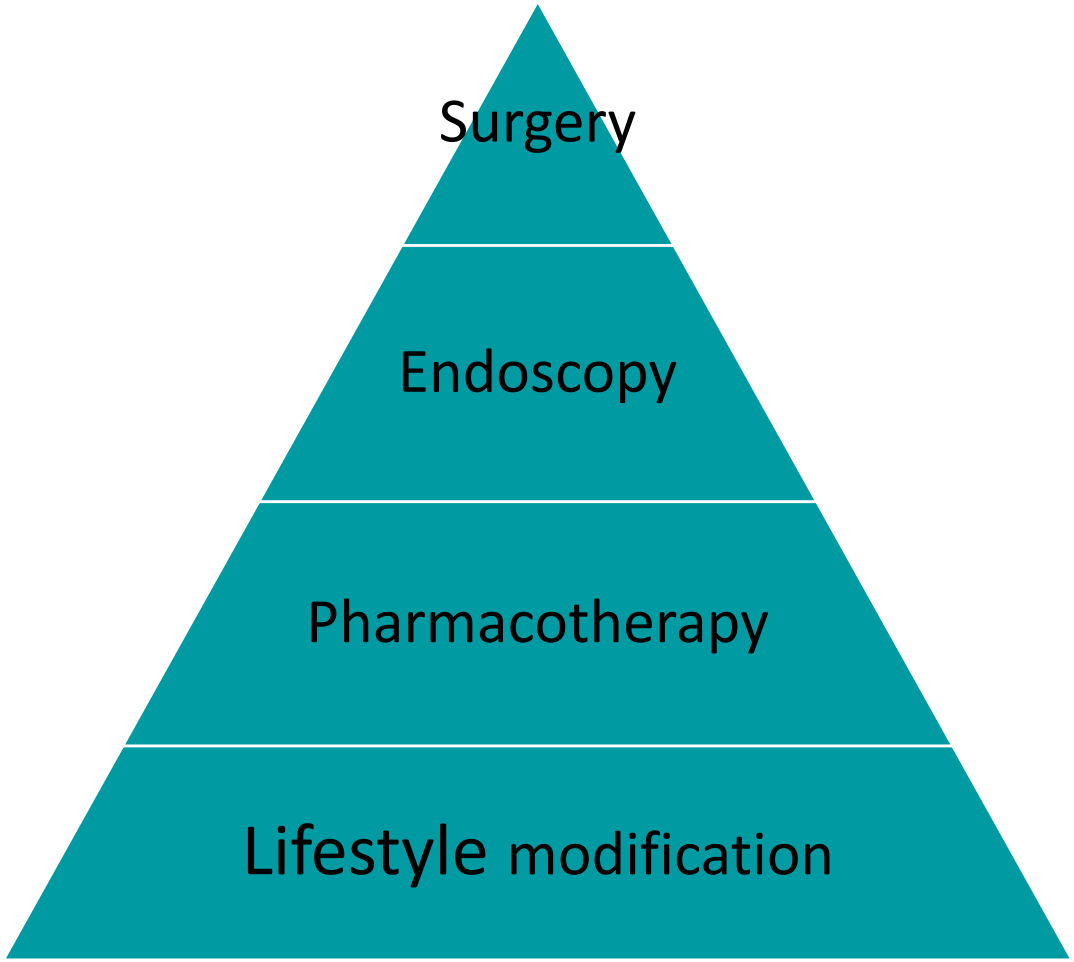
Rinella et al. Hepatology 2023.

WEIGHT LOSS IS THE KEY TO TREAT MASLD/MASH



Romero-Gomez M et al. J of Hep 2017

CURRENT AVAILABLE TREATMENTS FOR OBESITY



Indications	Efficacy
BMI ≥ 35 or ≥ 30 with a comorbidity	10-25% total weight loss
BMI ≥ 30 or ≥ 27 with a comorbidity	10-25% total weight loss
BMI ≥ 30 or ≥ 27 with a comorbidity	5-20% total weight loss
Any BMI	3-5% total weight loss

LIFESTYLE INTERVENTION

Weight reduction

Overweight/obesity NAFLD

- 5-10% weight reduction achieved by any healthy diet that the patient can adhere to in the long-term

Non-obesity NAFLD

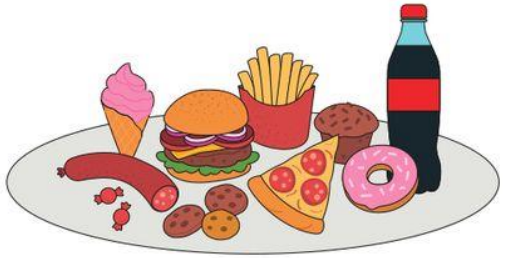
- 3-5% reduction of weight even within the normal BMI range (especially if recent weight gain ocurred or if abdominal obesity is present)

Lifestyle advice for ALL patients with NAFLD

Recommended foods

- n-3 fatty acids found in fish, and walnuts
- Olive oil
- Fruits, vegetables, polyphenols
- Home-cooked meals
- Mediterranean dietary pattern

Non-recommended foods/ minimize consumption



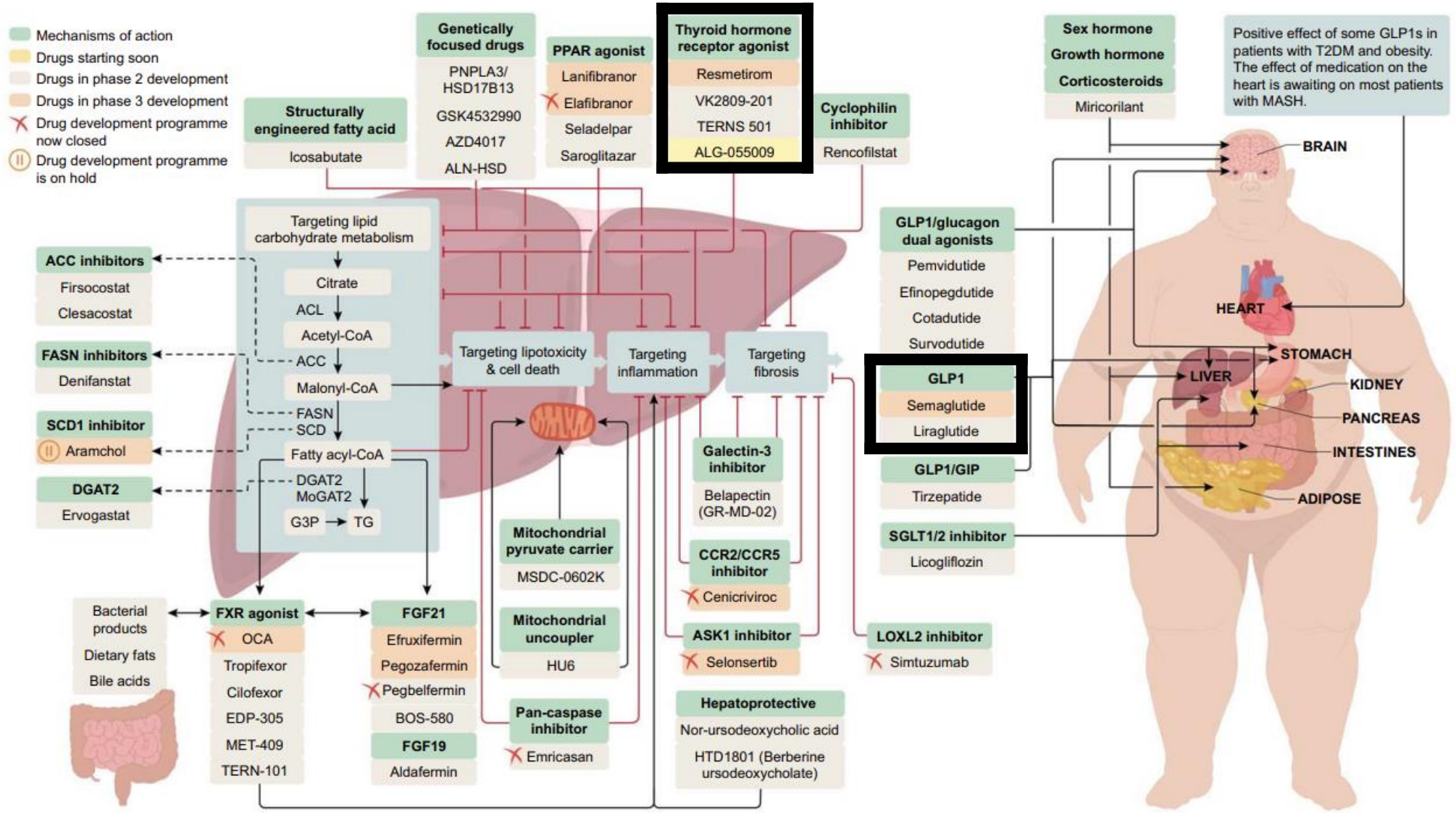
- Added sugar (eg. by reducing sweets, processed foods, sugared dairy products and beverages)
- Saturated fat and cholesterol (eg. by eating low fat meat and low fat dairy products)
- Ultra-processed foods and drinks, red and processed meat

Recommended activity

- Aerobic exercise ≥ 3 days/week (≥ 150min/week moderate intensity)
- Resistance exercise ≥ 2 days/week
- Reduce sedentary behaviour

Patel NS, et al. Clin Gastroenterol Hepatol. 2017; Rinella M et al. Hepatology 2023

CURRENT PIPELINE OF MASH DRUGS



Noureddin M. Hepatology 2024

PHASE 3 STUDIES FOR MASH DRUGS

Compound	Mechanism	Status: Phase 3 trials	Routine of admin
Resmetirom	THR-β agonist	MAESTRO-NASH – ongoing Sub-part H Approval Granted 3/2024	Oral
Lanifibranor	Pan-PPAR agonist	NATIV3 – ongoing	Oral
Semaglutide	GLP-1R agonist	ESSENCE – ongoing	Injectable
Survodutide	GCGR/GLP-1R dual agonist	LIVERAGE – ongoing	Injectable
Efruxifermin	FGF21 analogue	SYNCHRONY – ongoing	Injectable
Pegozafermin	FGF21 analogue	ENLIGHTEN-Fibrosis - ongoing	Injectable

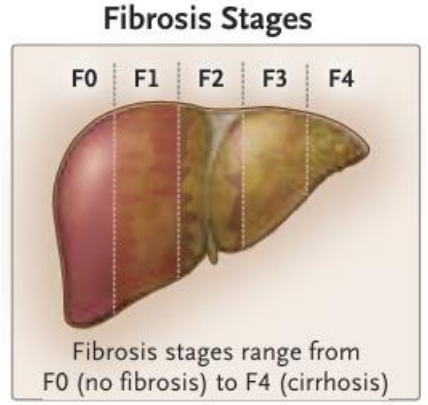
RESMETIROM –FIRST FDA APPROVED MASH DRUG

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2024 VOL. 390 NO. 6

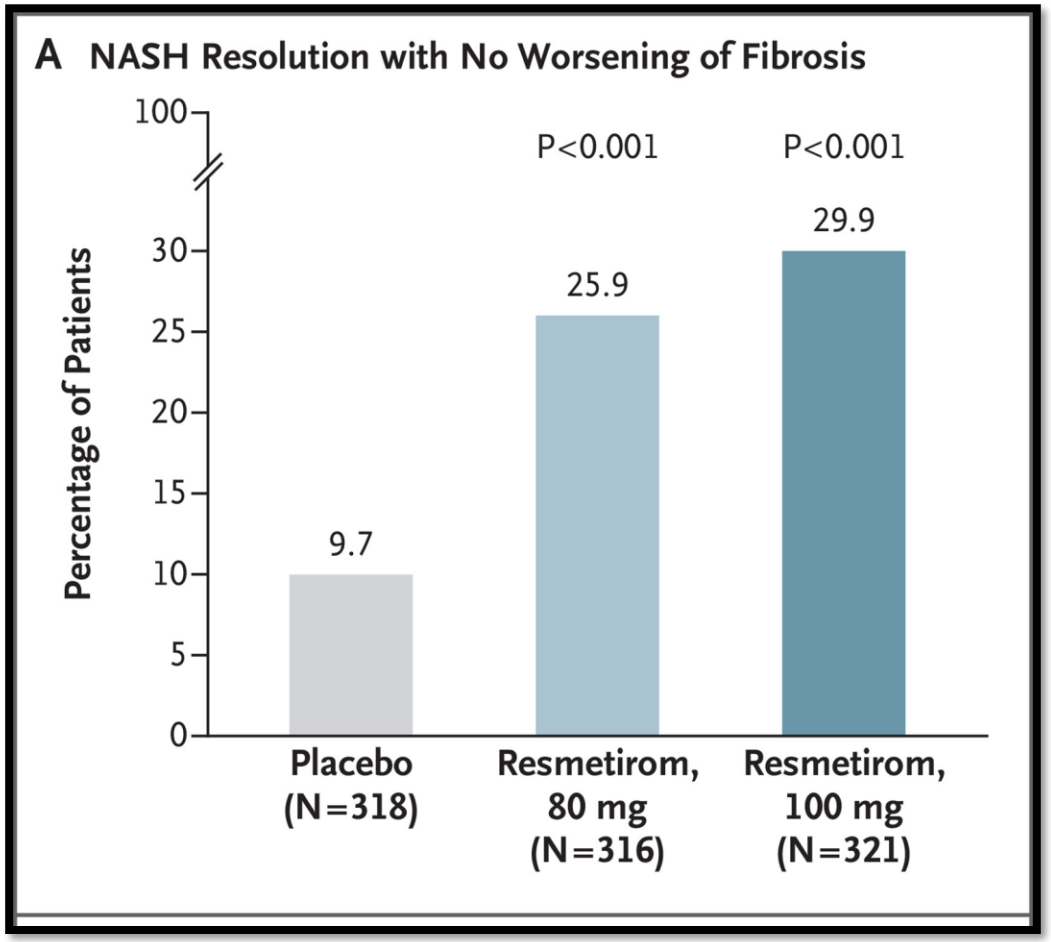
A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

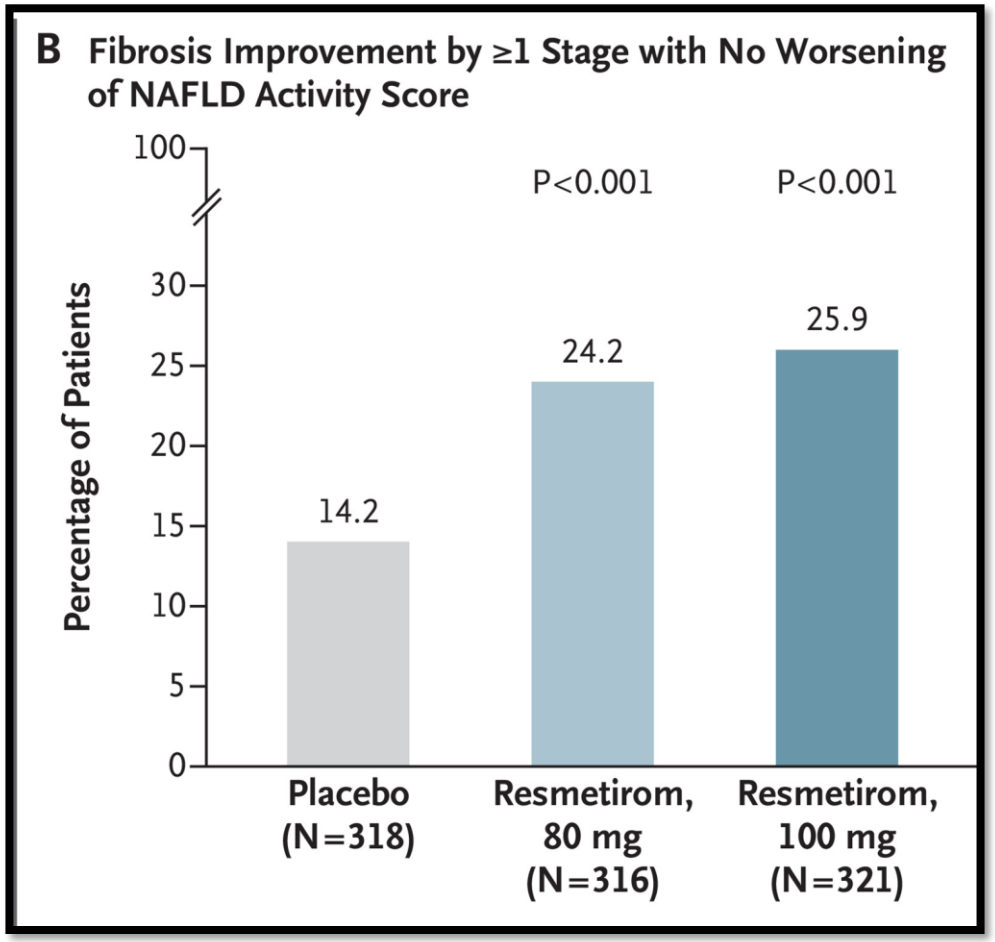
- Oral, liver-directed, thyroid hormone receptor beta agonist
- 966 patients F1B, F2, F3 (>50% were F3)
- Resmetirom 80mg vs. 100mg vs. placebo
- Update at 52 weeks
- Liver biopsy at enrollment and week 52
- Ongoing trial planned for 54 months



Harrison, et al. NEJM 2024

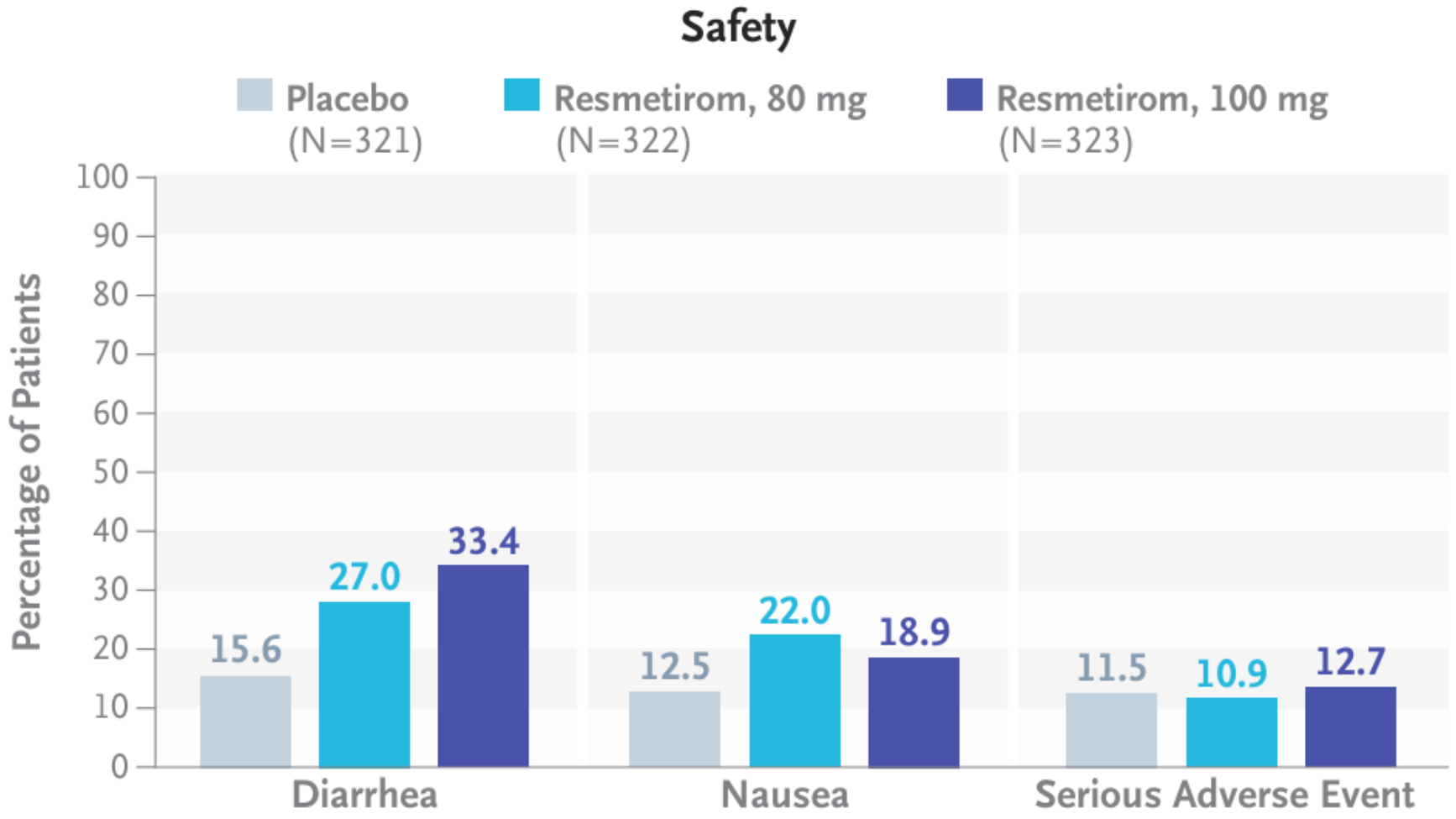
MAESTRO TRIAL - PRIMARY END POINTS





Harrison, et al. NEJM 2024

MAESTRO TRIAL - ADVERSE EFFECTS



PRACTICE RECOMMENDATIONS FOR RESMETIROM

Patient selection and dosage

- Adult with MASH and moderate to advance liver fibrosis (F2-F3)
- Weight based dosing
  - 100mg/day for >100kg
  - 80mg/day for <100kg
- Dose reduction by 20mg/day if used concurrently with cytochrome p450 inhibitors (e.g. clopidogrel)

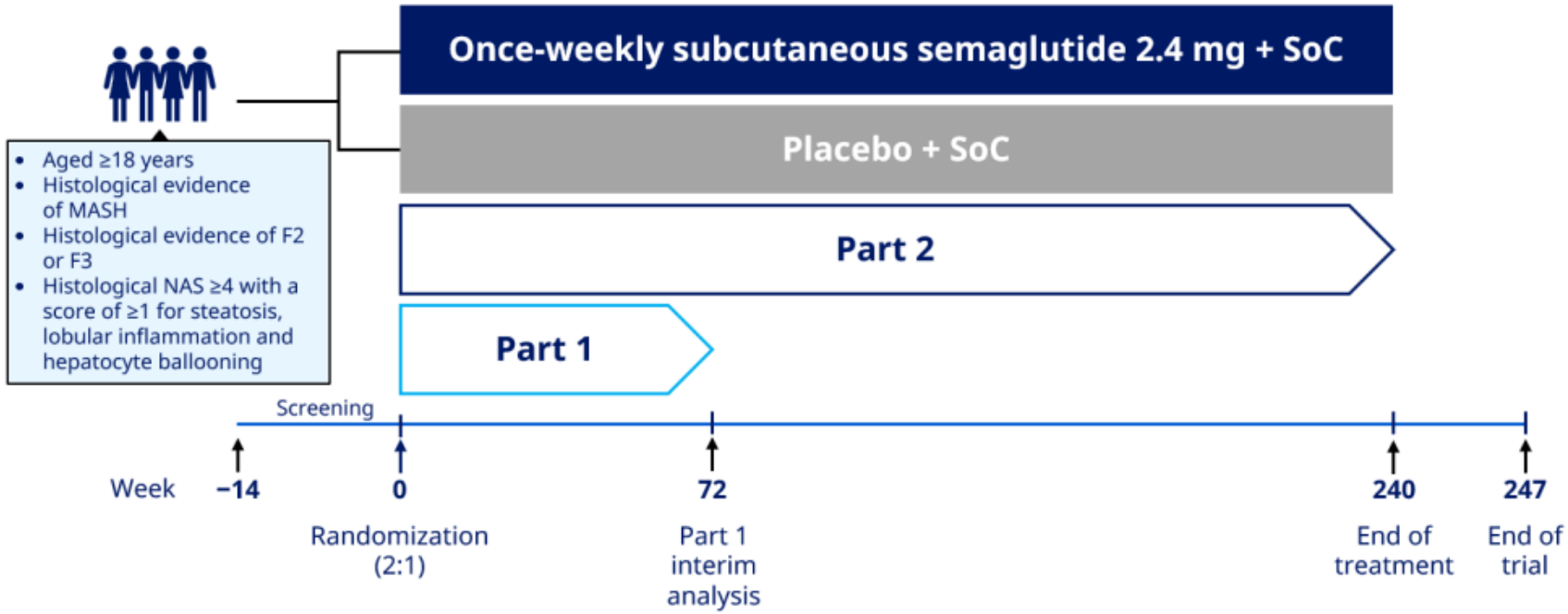
Pretreatment considerations

- Not recommended in cirrhosis, uncontrolled active liver diseases or ongoing alcohol use
- Not recommended in patients with symptomatic gallstone-related disorders
- Thyroid function assessment recommended prior to initiation

PRACTICE RECOMMENDATIONS FOR RESMETIROM

	Safety/Efficacy assessments	Safety assessments		Efficacy assessments	
Timeframe	**Hepatic function panel[a]**	**Thyroid function[b]**	**Lipid profile[c]**	**Noninvasive measurement of liver stiffness[d]**	**MRI-PDFF[e]**
Before treatment initiation	✓	✓	✓	✓	Consider
3 months	✓				
6 months	✓	✓	✓		
12 months	✓	✓	✓	Repeat if imaging NILDA was used at baseline	Consider repeating if baseline data are available

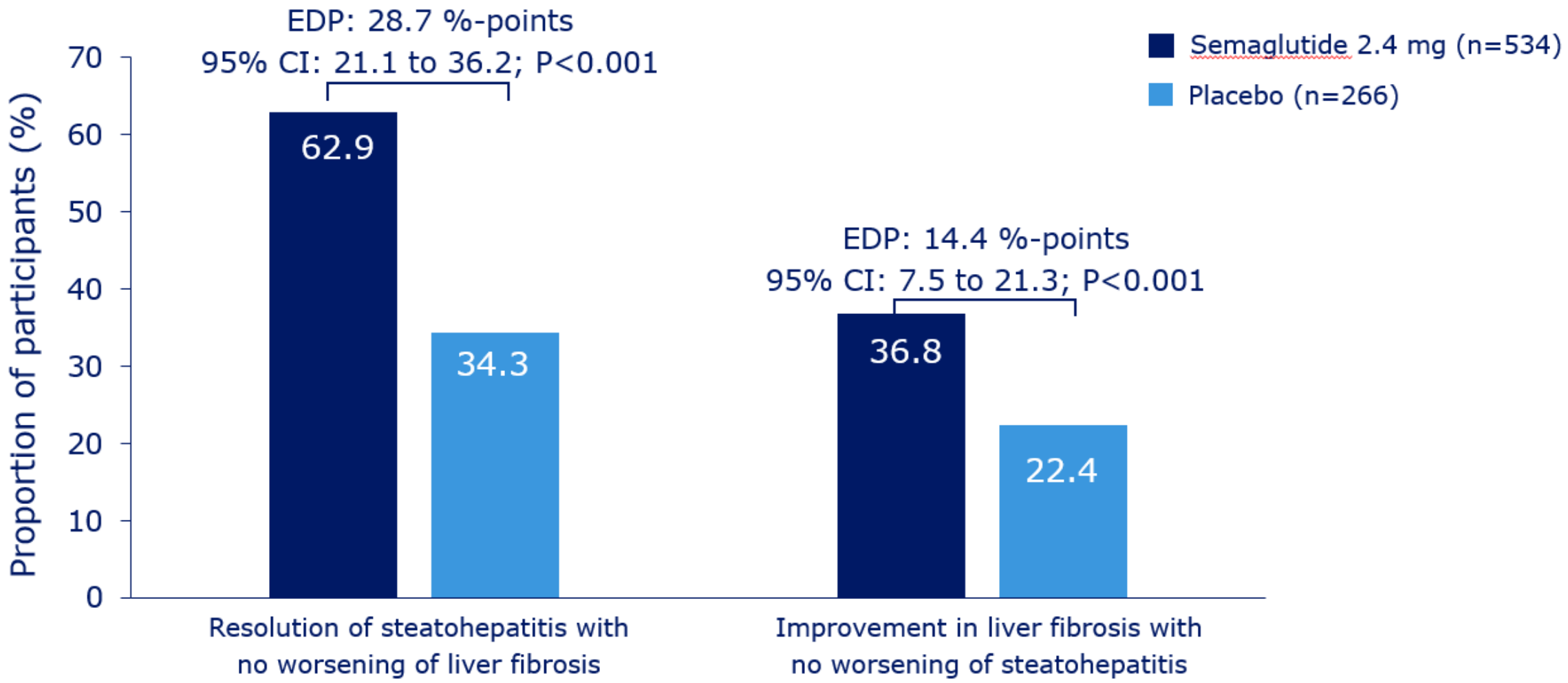
ESSENCE TRIAL – SEMAGLUTIDE IN MASH STUDY DESIGN



- Phase 3, randomized, double-blind, placebo-controlled trial, estimated 1200 pts/5yrs
- 2:1 randomization into semaglutide 2.4mg injection or placebo once weekly
- Two primary endpoints – liver histology (part 1) and risk of liver related clinical events (part 2)
- Secondary endpoints – change in body weight, resolution of steatohepatitis + liver fibrosis and
- changes in SF-36 bodily pain

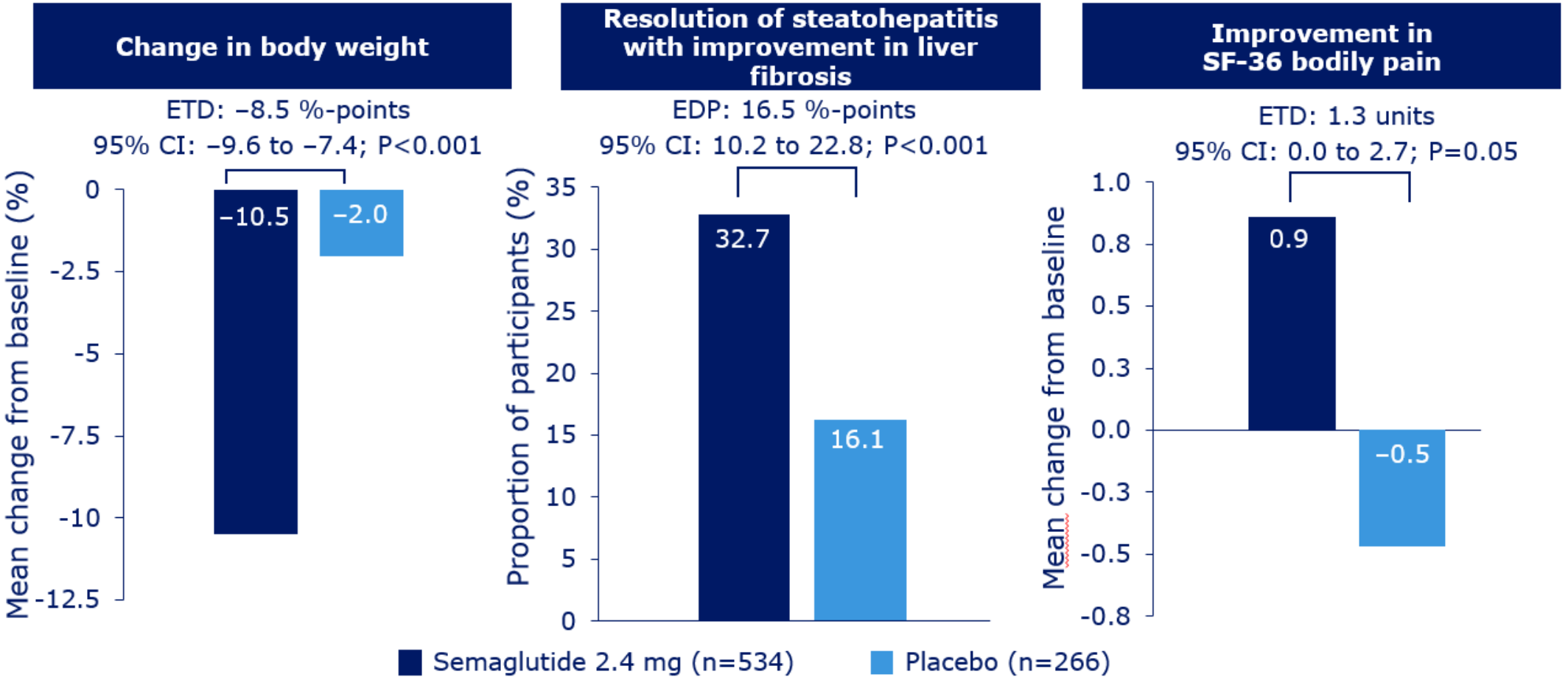
Newsome PN et al. Late breaker abstract AASLD Nov 2024; Ali phar & therapeutics Dec 2024

ESSENCE TRIAL – SEMAGLUTIDE IN MASH PRIMARY ENDPOINTS (ITT POPULATION)



Newsome PN et al. Late breaker abstract AASLD Nov 2024

ESSENCE TRIAL – SEMAGLUTIDE IN MASH SECONDARY ENDPOINTS (ITT POPULATION)

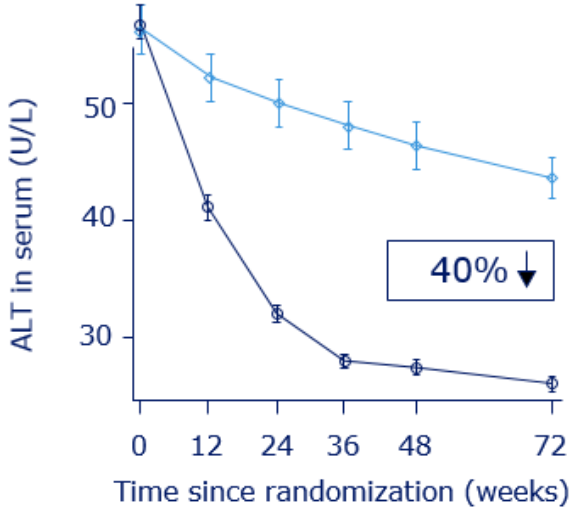


Newsome PN et al. Late breaker abstract AASLD Nov 2024

ESSENCE TRIAL – SEMAGLUTIDE IN MASH CHANGES IN LIVER ENZYMES

ALT

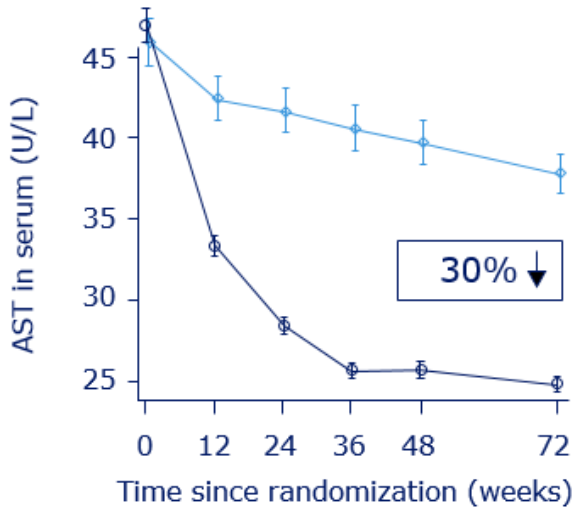
ETR: 0.6
95% CI: 0.6 to 0.7; P<0.0001



Number of participants						
Semaglutide 2.4 mg	534	518	511	509	502	493
Placebo	266	258	255	252	246	236

AST

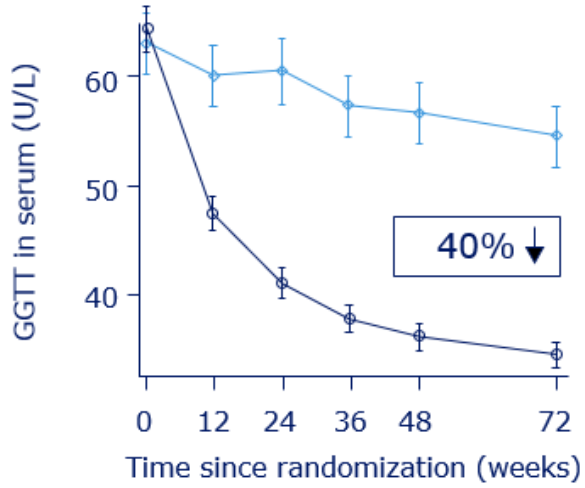
ETR: 0.7
95% CI: 0.6 to 0.7; P<0.0001



Number of participants						
Semaglutide 2.4 mg	534	516	508	504	500	490
Placebo	266	257	257	251	246	236

GGT

ETR: 0.6
95% CI: 0.6 to 0.7; P<0.0001



Number of participants						
Semaglutide 2.4 mg	534	520	512	510	503	494
Placebo	266	258	257	252	245	237

Semaglutide 2.4 mg Placebo

ESSENCE TRIAL – SEMAGLUTIDE IN MASH
CHANGES IN CARDIOMETABOLIC RISK PARAMETERS

Measure	Semaglutide 2.4 mg (N=534)	Placebo (N=266)	Difference between semaglutide and placebo at week 72 (95% CI)
Absolute change			
Systolic blood pressure, mmHg	-5.39	-1.39	-4.00 (-5.93 to -2.07)*
Diastolic blood pressure, mmHg	-1.90	0.24	-2.14 (-3.43 to -0.85)*
HbA_{1c}, % [without T2D]	-0.42	0.11	-0.53 (-0.61 to -0.44)*
HbA_{1c}, % [with T2D]	-1.08	-0.00	-1.08 (-1.27 to -0.89)*
hsCRP	-53.83	-19.83	-42.41 (-49.75 to -33.98)†
Total cholesterol, mg/dL	-6.03	-3.19	-2.93 (-5.60 to -0.19)†
Triglycerides, mg/dL	-16.77	-0.27	-16.54 (-21.02 to -11.81)†
LDL cholesterol, mg/dL	-6.07	-4.11	-2.04 (-6.35 to 2.46)†
HDL cholesterol, mg/dL	2.62	-1.95	4.66 (2.12 to 7.26)†

Newsome PN et al. Late breaker abstract AASLD Nov 2024

ESSENCE TRIAL – SEMAGLUTIDE IN MASH SAFETY PROFILE

	Semaglutide 2.4 mg (N=800)	Placebo (N=395)
	n (%)	n (%)
All AEs	690 (86.3)	315 (79.7)
Fatal AEs	3 (0.4)	6 (1.5)
Serious AEs	107 (13.4)	53 (13.4)
AEs leading to trial discontinuation	21 (2.6)	13 (3.3)
AEs affecting ≥10% of participants		
Nausea	290 (36.3)	52 (13.2)
Diarrhea	215 (26.9)	48 (12.2)
Constipation	178 (22.3)	33 (8.4)
Vomiting	149 (18.6)	22 (5.6)
COVID-19	134 (16.8)	74 (18.7)
Decreased appetite	112 (14.0)	11 (2.8)

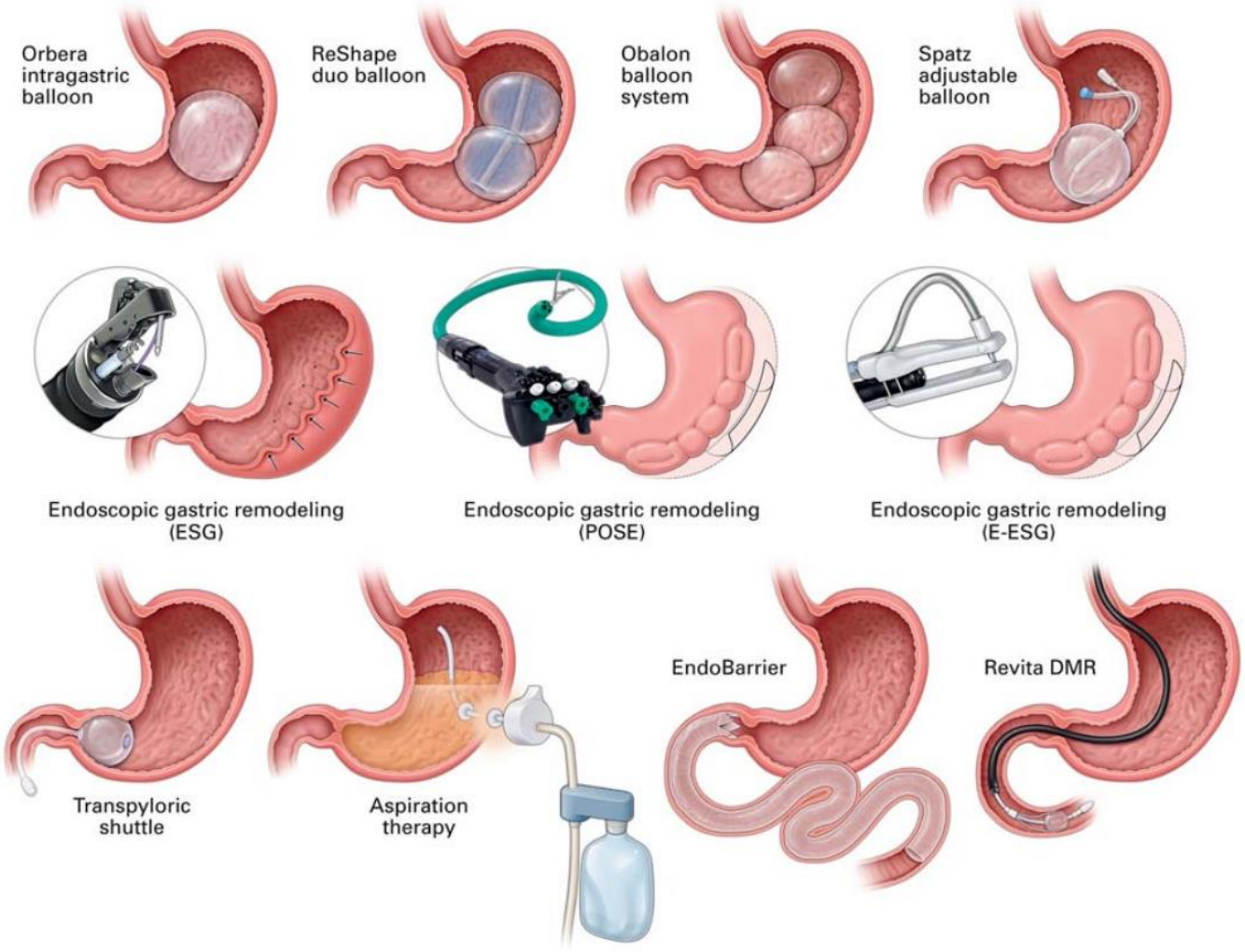
Newsome PN et al. Late breaker abstract AASLD Nov 2024

ESSENCE TRIAL – SEMAGLUTIDE IN MASH SAFETY PROFILE

	Semaglutide 2.4 mg (N=800)	Placebo (N=395)
	n (%)	n (%)
Gallbladder related disorders	20 (2.5)	6 (1.5)
Acute pancreatitis	3 (0.4)	2 (0.5)
Malignant neoplasms	13 (1.6)	9 (2.3)
Hypoglycemia		
Participants with T2D (n=446/n=222)†	33 (7.4)	12 (5.4)
Participants without T2D (n=354/n=173)	1 (0.3)	1 (0.6)
Neoplasms	66 (8.3)	37 (9.4)
Malignant neoplasms	13 (1.6)	9 (2.3)

Newsome PN et al. Late breaker abstract AASLD Nov 2024

ENDOSCOPIC BARIATRIC METABOLIC THERAPIES (EBMTS)



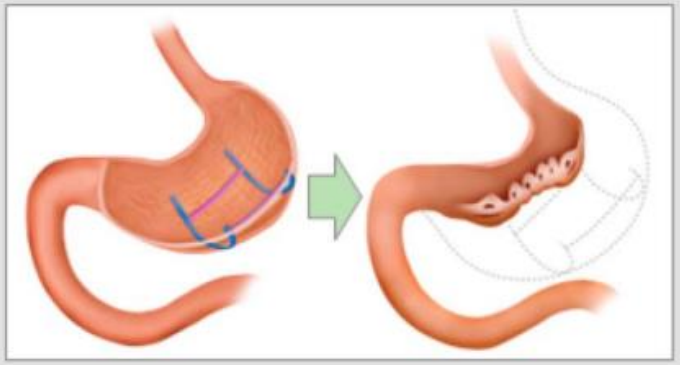
Three EBMTs are endorsed by American Society of Gastrointestinal Endoscopy

- Intragastric blaoon: 11.3% TWL in 12 months
- Endoscopic sleeve gastroplasty: 18.2% TWL in 12 months
- Primary Obesity Surgery Endoscopic (POSE): 16.5% TWL in 1 2months

ENDOSCOPIC BARIATRIC METABOLIC THERAPIES (EBMTS) IN MASLD

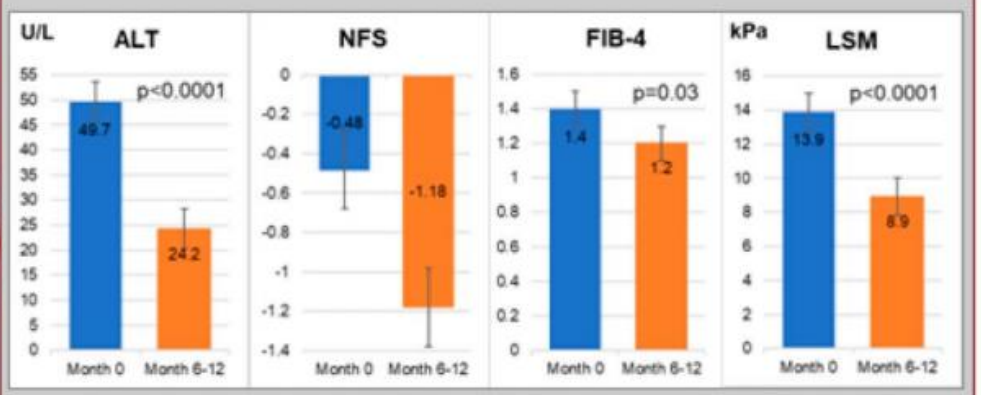
Effect of Endoscopic Gastric Plication on Hepatic Fibrosis in Patients with Nonalcoholic Fatty Liver Disease

Endoscopic Gastric Plication



- 45 patients with obesity and NAFLD and F2-F4 fibrosis
- All underwent endoscopic gastric plication to reduce gastric volume

Significant improvements in non-invasive tests for hepatic fibrosis

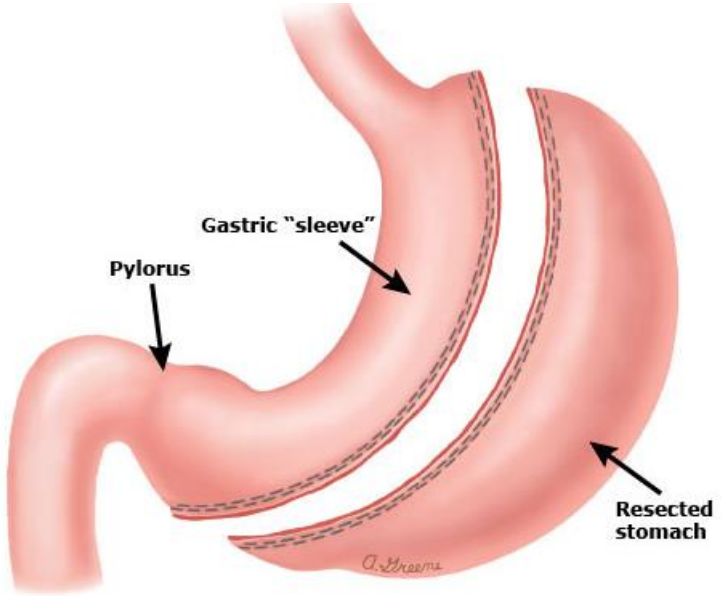


ALT: alanine aminotransferase, NFS: NAFLD fibrosis score, FIB-4: fibrosis-4 index, LSM: liver stiffness measurement on vibration-controlled transient elastography

- At 12 months, patients experienced 15.5% total weight loss and improvements in insulin resistance and hemoglobin A1c

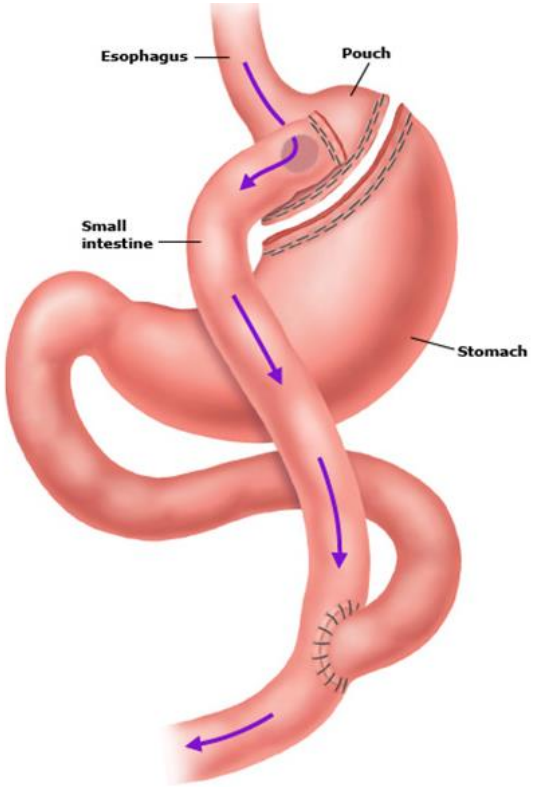
Jirapinyo P et al. Am J Gastro 2022

METABOLIC AND BARIATRIC SURGERIES



Sleeve Gastrectomy (SG)

23% TWL (12 months)



Roux-en-Y Gastric Bypass (RYGB)

32% TWL (12 months)

Buchwald H et al. Am J Med 2009

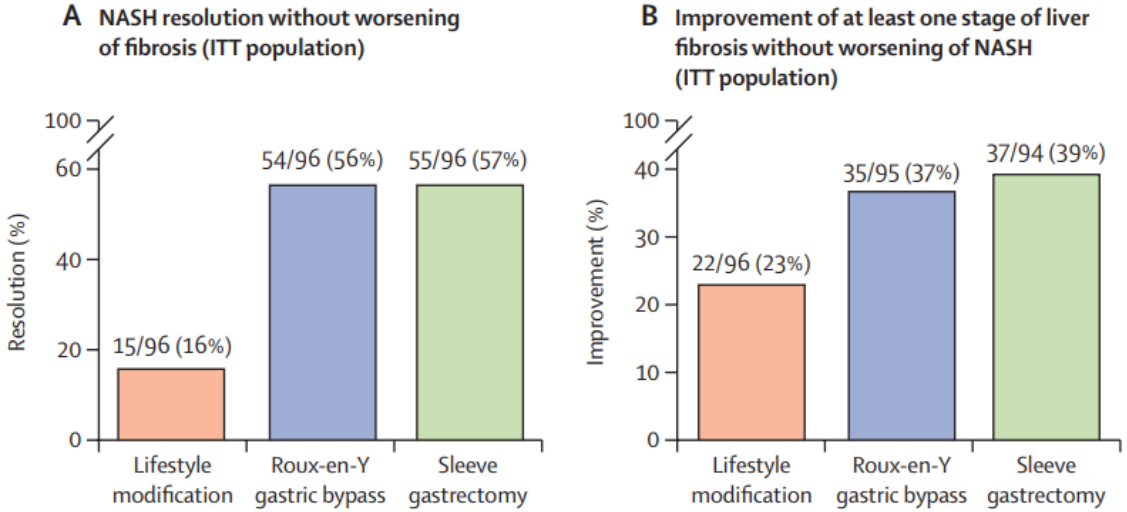
METABOLIC AND BARIATRIC SURGERIES IN MASH

Bariatric–metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial

Ornella Verrastro, Simona Panunzi*, Lidia Castagneto-Gissey, Andrea De Gaetano, Erminia Lembo, Esmeralda Capristo, Caterina Guidone, Giulia Angelini, Francesco Pennestrì, Luca Sessa, Fabio Maria Vecchio, Laura Riccardi, Maria Assunta Zocco, Ivo Boskoski, James R Casella-Mariolo, Pierluigi Marini, Maurizio Pompili, Giovanni Casella, Enrico Fiori, Francesco Rubino, Stefan R Bornstein, Marco Raffaelli, Geltrude Mingrone*

THE LANCET

- Multicenter, open-label, randomized trials
- Patient with obesity (BMI 30-55kg/m2) and histologic MASH (n=288)
- 1:1:1 to lifestyle modification vs. RYGB vs. SG
- All patients had liver biopsy at month 0 and 12
- Primary endpoint:
  - MASH resolution without worsening of fibrosis
- Secondary endpoint
  - Fibrosis improvement by ≥ 1 stage



Verrastro O et al. Lancet 2023

BACK TO THE CASE STUDY

- FIB4 – Intermediate
- Fibroscan – Intermediate
- Referral to GI/hepatology

- MRE – advanced fibrosis (stage 3)
- Advised weight loss with diet + exercise
- At 6 months, lost 10lbs (~4% TWL) and plateau

- Explore medicines vs. bariatric procedures as the next step

KEY TAKE HOME POINTS

- MASLD is the hepatic manifestation of metabolic syndrome
- It’s critical to risk stratify MASLD patients to identify advanced fibrosis
- Advanced fibrosis is associated with increased risk of liver related complications and death, and all cause mortality
- Low risk patients need to focus on CV risk reduction
- Weight loss is the cornerstone for treatment of MASLD/MASH
- Resmetirom is currently the only FDA approved treatment for stage 2-3 fibrosis (leads to MASH resolution and fibrosis improvement)
- There are currently multiple drugs in the pipeline for MASLD

QUESTIONS?

- Contact email: valerie.lin@lahey.org