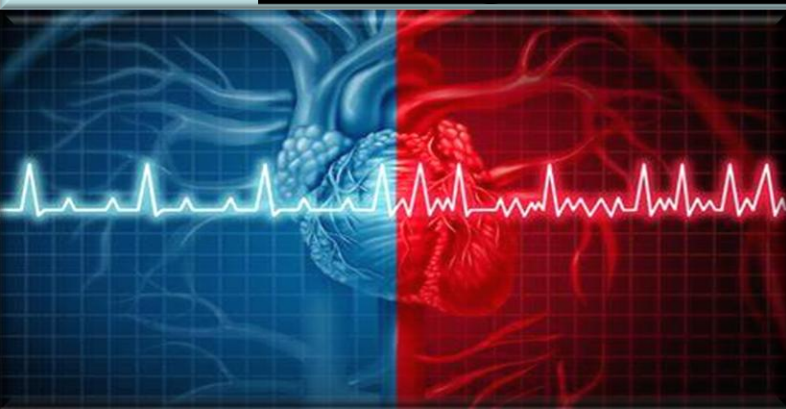


MASLD / MASH: Core Concepts & Cutting Edge

An 'Unrecognized' Public Health Crisis

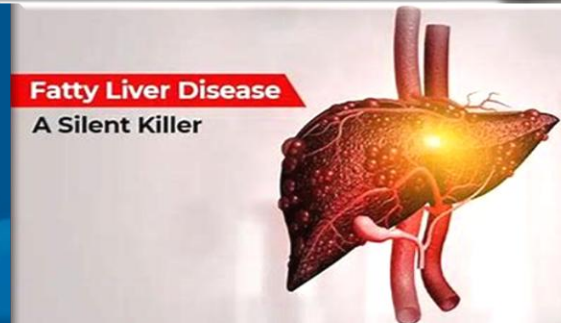
'Navigating the Maze': Growing Public Health Care Challenge Affecting Millions
Navigate Complexities MASLD/MASH Evolving Clinical Landscape
What Clinical Outcomes Most Concerned About For Patients With MASLD/MASH?
'Turning the Tides' For the Future Making What is Invisible... Visible



The Link Between
Obesity and
Cancer



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Medical Director, Beacon Diabetes & Endocrine Center
Kalamazoo, Michigan
MOA Annual Autumn Conference: October 25th, 2025; 9AM



Disclosures

- ❖ I Have the Following Financial Relationships to Disclose:
- ❖ Pharmaceutical Based Research On Safety, Efficacy, Outcome Trials And
- ❖ Speaker's Bureau for: BI / Lilly, Abbott, DexCom, Novo-Nordisk, Corsept Therapeutics, Abbvie, Amgen
- ❖ All Planners, Reviewers, And Course Directors Have No Relevant Financial Relationships With ACCME-Defined Commercial Interests.
- ❖ My Presentation Today Will Be Fair, Balanced, Free of Commercial Bias & Fully Supported By Scientific Evidence



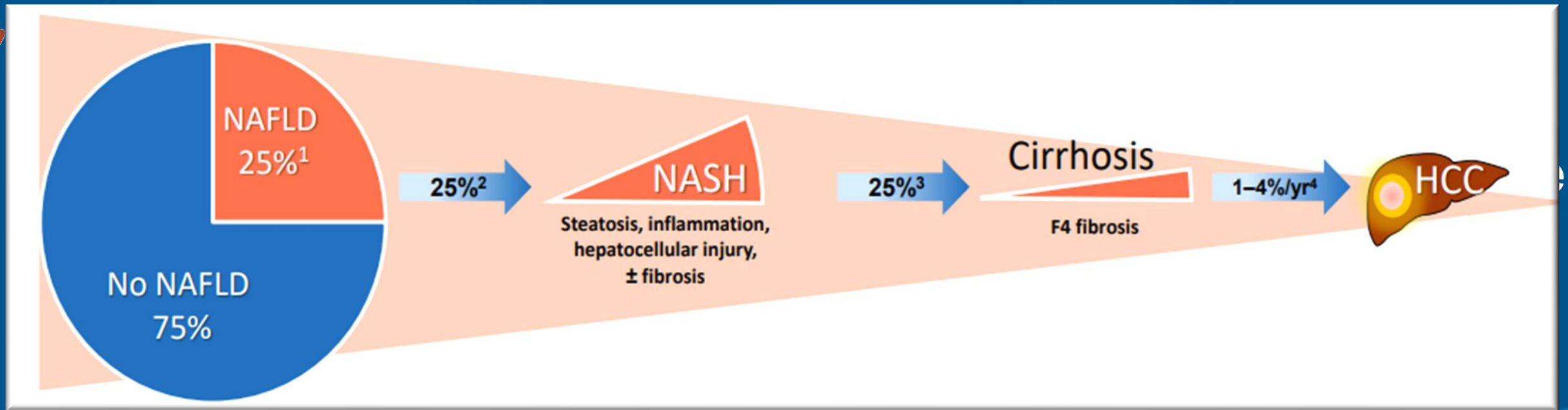
Objectives

- ❖ 1. Define NAFLD (Now MASLD) & Its Different Stages, Including Non-Alcoholic Steatohepatitis (Now MASH) & Fibrosis
- ❖ 2. Explain the Pathophysiology of MASLD Including the Role of Insulin Resistance & Fat Accumulation in the Liver (More Than Just 'No Alcohol')
- ❖ 3. Recognize Clinical Manifestations, Burden & Associated Complications of MASLD / MASH
- ❖ 4. Identify Patients at High Risk for MASH for Screening & If Needed Diagnostic Work-Up
- ❖ 5. Incorporate Guidelines, Best Practices & Timely Multidisciplinary Care into the Management of MASH with its Metabolic Comorbidities
- ❖ 6. Discuss New & Emerging Therapies for MASH with Respect to Mechanisms, Clinical Trial Data & Recommendations or Potential Place in Therapy



History of NAFLD & NASH

- ❖ A Casual Relationship Btw Hepatic Fat Accumulation & The Development of Fibrosis Had Been Observed in 1839 Followed By The Microscopic Finding That 'Fatty Degeneration' Develops Close To Inflammatory Deposits & Scarring

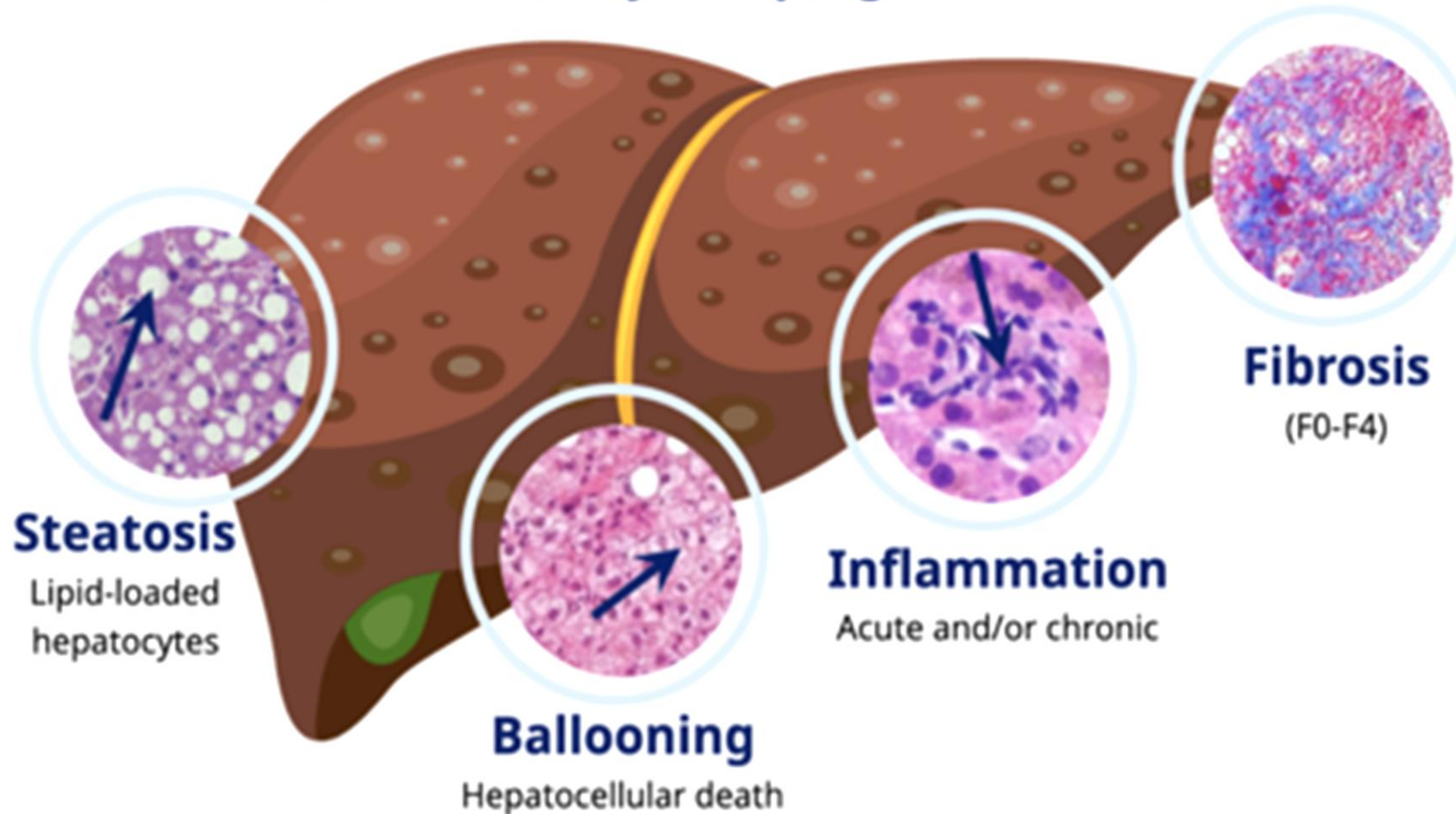


- ❖ Why Should We Care?

If You Treat Diabetes & / Or Obesity, It Is Important To Understand Fatty Liver Disease:

It Is Common & It Can Be Deadly

Disease activity and progression^{3,4}



≡ The New York Times

10/1/24

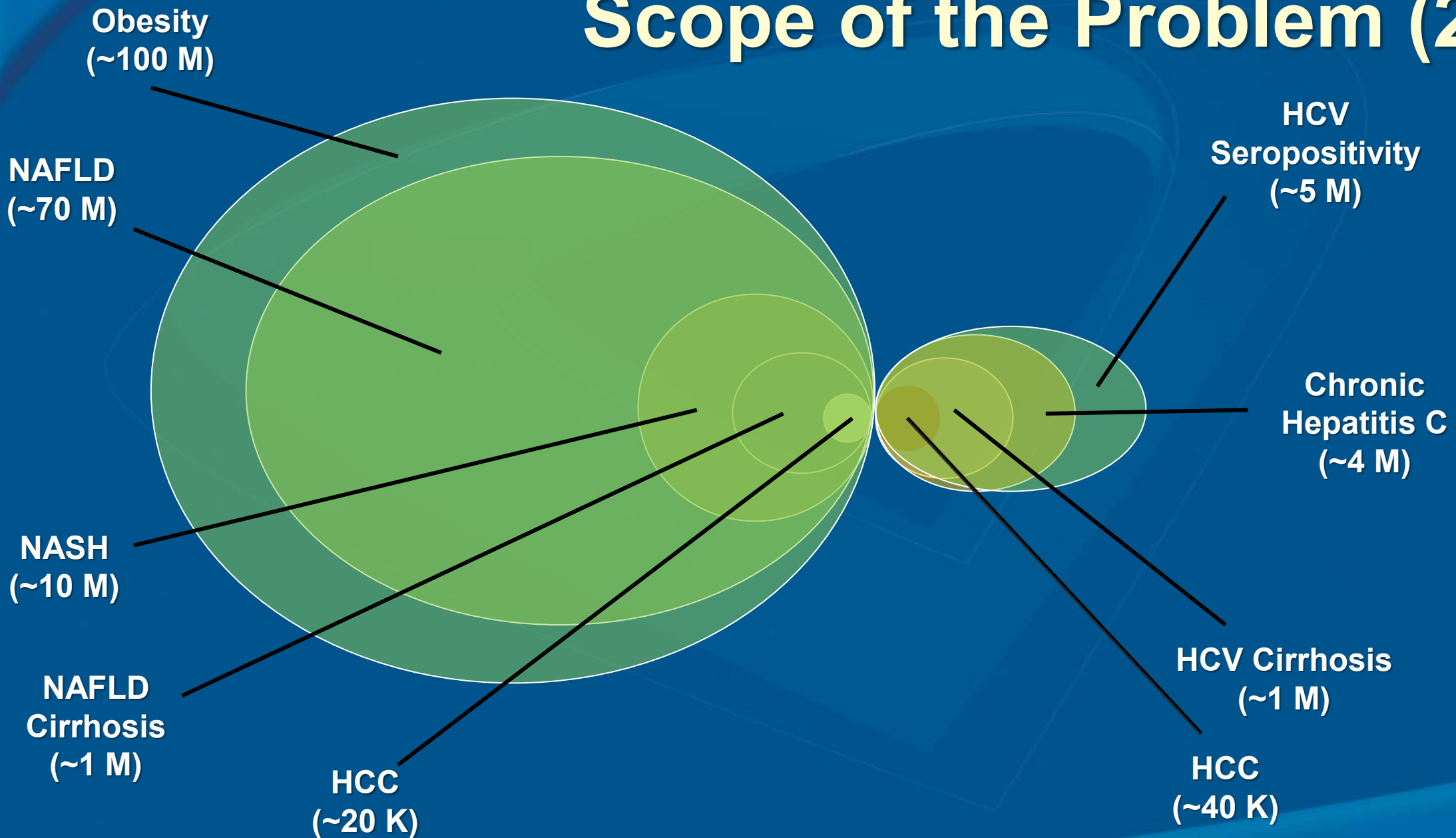
GIVE THE TIMES

This Disease Can Damage the Liver for Be

Ballooning Of Hepatocytes Best Prediction of Fibrosis

Four in 10 people are thought to have a potentially serious liver condition known as MASLD. Reversing it is possible if you catch it early.

Scope of the Problem (2014)



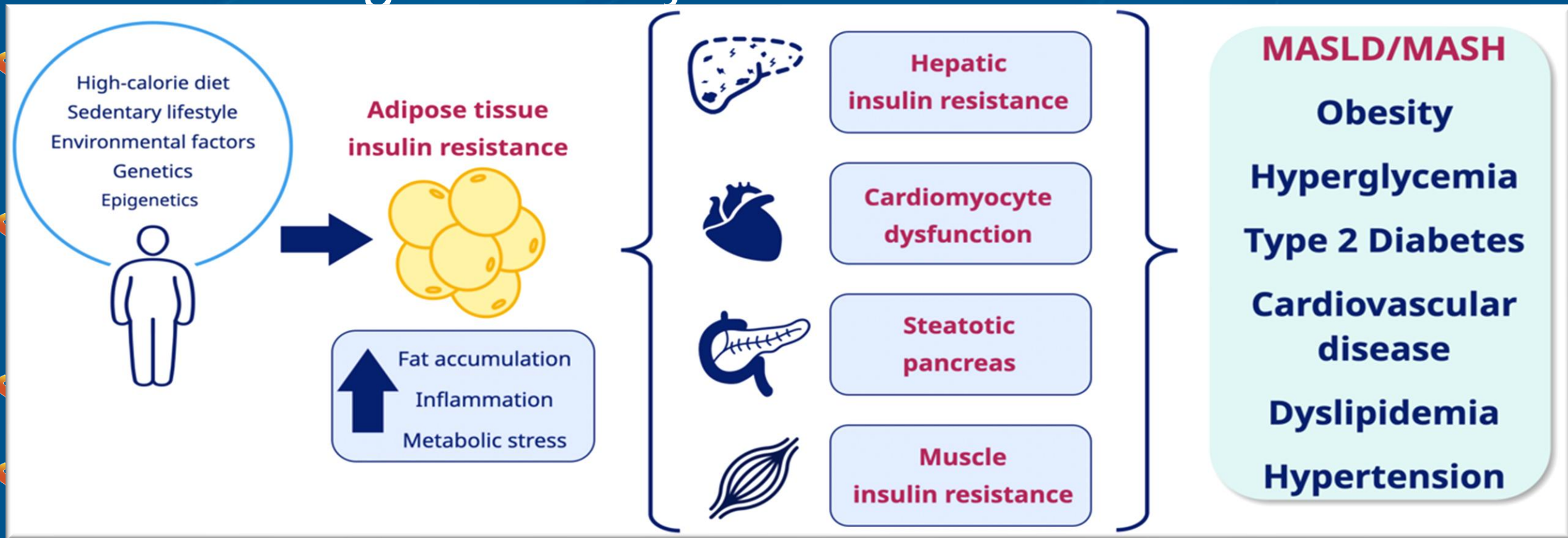
Future Projections

- ▶ Trends In Liver Transplantation: 2014 Hepatitis C Was the Leading Cause. Now Curable
- ▶ Today There is a Competition Btw ETOH Liver Disease / NASH Cirrhosis For The Leading Cause of Transplantation
- ▶ Global Epidemic of Obesity Fuels Metabolic Conditions – Increasing the Clinical / Economic Burden of NAFLD.
- ▶ Models Predict Growth ~ 30% in Total NAFLD Cases by 2030
- ▶ NASH Prevalence Predicted To Increase ~ 50% While Advanced Liver Dz Will More Than Double As A Result of Ageing Western Populations



More Than A Liver Dysfunction

- ▶ Reclaim This Condition & Route It Where It Belongs
- ▶ Name Change Is Timely



1. Godoy-Matos et al. *Diabetol Metab Syndr*. 2020;12:60
2. Chakravarthy MV. *Endocrinol Diabetes*. 2020;3(4):e001122



MALSD / MASH Is A Problem

- ❖ Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) (Non-Alcoholic Fatty Liver Disease [NAFLD])
 - Most Common Cause Chronic Liver Disease.
 - Prevalence of MASLD in People with Obesity and/or T2DM is 70-80%.
- ❖ MASLD Can Lead to Metabolic Dysfunction-Associated Steatohepatitis (MASH) (Non-Alcoholic Steatohepatitis [NASH])
 - Which Can Lead to Cirrhosis and Hepatocellular Carcinoma (HCC).
- ❖ Early Screening for MASLD, & Treatment of Obesity and T2DM, Can Help in Preventing Progression to Cirrhosis and HCC.
 - ~ 5% of Persons with MASLD are Aware of Such. (~ 1 in 80 Dx ICD-10)

MALSD / MASH Is A Problem

- ▶ Most Common Causes of Death in Patients with MASLD Overall are CVD Followed by Non-Hepatic Malignancy, Lastly Liver Dz.
 - Amount of Liver Fibrosis Identified Histologically in MASLD Strongly Linked to the Development of Liver-Related Outcomes and Death.
- ▶ MASLD is Under-Diagnosed and Under-Treated ...Why??
 - Clinicians Have Inadequate Knowledge of MASLD
 - Until Recently, Guidelines Varied Considerably / Inconsistent Guidance & Risk Stratification / Inconsistent Application In Clinical Practice as There was an Absence of a Unifying Strategy Encompassing All Disciplines in the Management of the MASLD Spectrum
 - Shift in the Understanding / Recent Progress in Understanding the Pathophysiology of MASLD / MASH

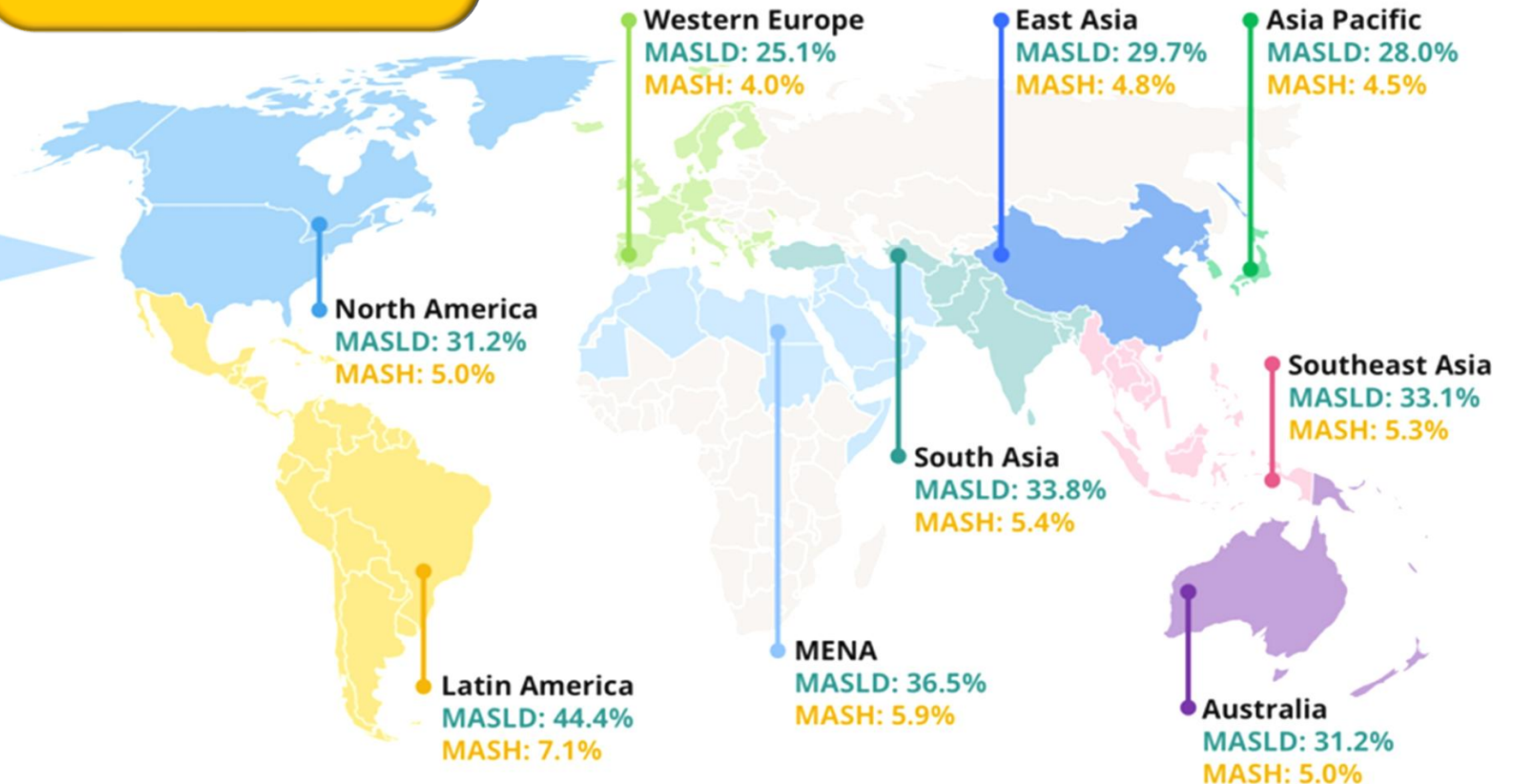
**80 – 100 Million
Americans**

**~ 2 in 3 adults in
U.S + Diabetes
Tripled Since
2004**

Tsunami Silent & Deadly

MASLD: 30% and MASH: 5.3%

~1 in 3
adults in the
United States
have MASLD



What We Don't See In Obesity?

THIS IS ONLY THE BEGINNING

5.1% (1.8-8.4) Realize They Have
A 'Liver Disease'

- Ticking Time Bomb
- Unrecognized Major Public Health Crisis
- Hiding In Plain Sight

Fatty Liver

**MASH: Leading Cause of
Liver Transplantation
Females / Age > 54 years /
Medicare Patients**

Endocrine

- Thyroid dysfunction

Vascular

- Atherogenic dyslipidemia
- Coronary artery disease

Extrahepatic malignancies^{1,3}

- Colorectal
- Stomach
- Pancreas

Hepatic

- Gallstones disease
- Progressive liver fibrosis
 - Liver cirrhosis
- Hepatocellular carcinoma

Reproductive

- Polycystic ovarian syndrome
- Breast cancer

Neurological complications

- Cerebrovascular disease
- Neurocognitive dysfunction and depression

Respiratory

- Obstructive sleep apnea

Cardiovascular

- Valvular heart disease
- Left ventricular dysfunction
- Cardiac arrhythmias
- Myocardial infarctions

Renal

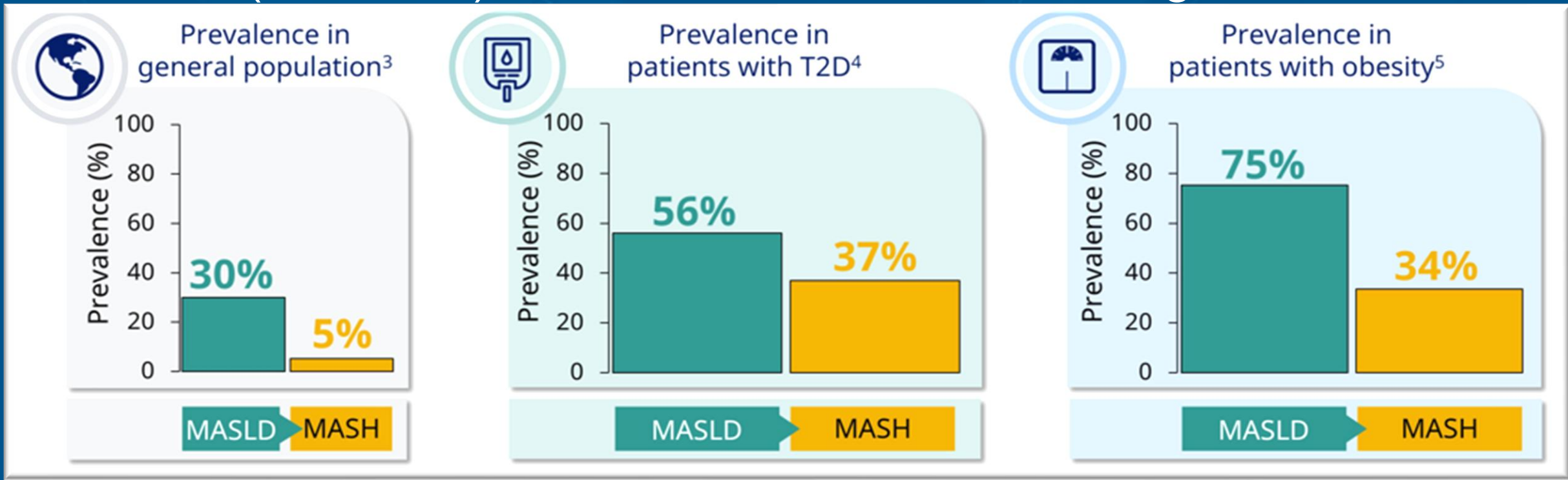
- Chronic kidney disease

Pancreatic

- Type 2 diabetes

Co-Morbid Conditions

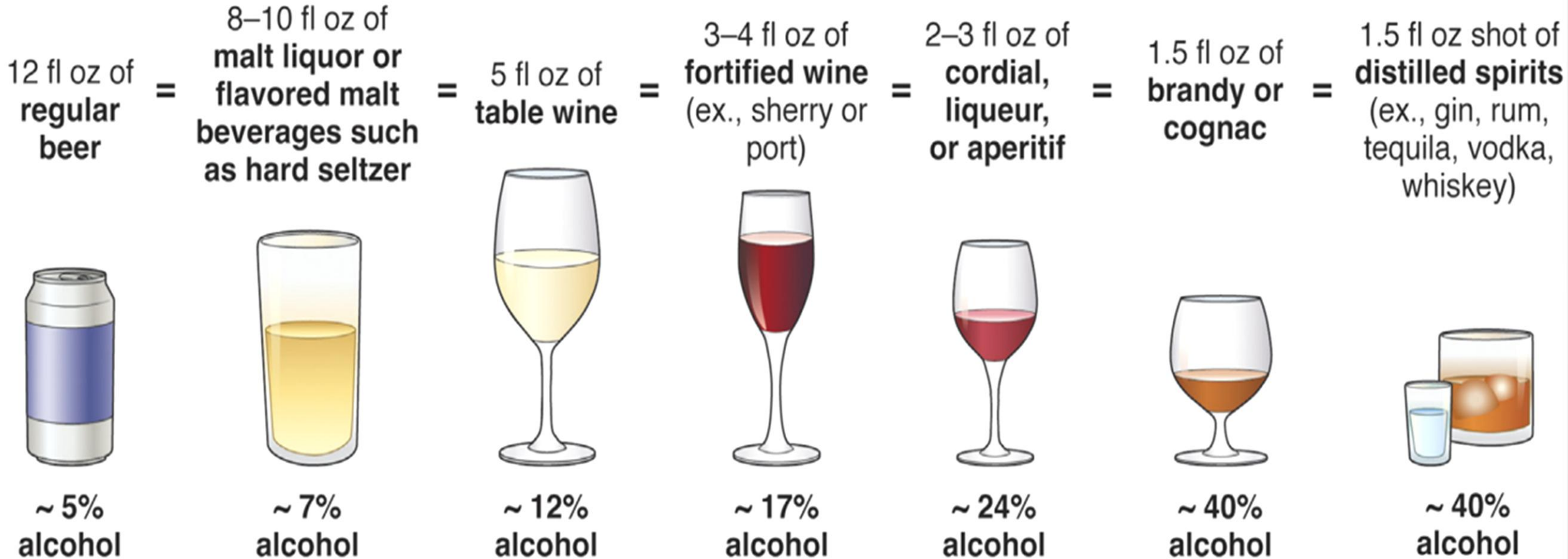
- ▶ **Obesity:** Android Fat Distribution – IR, CVD, Hepatic Fibrosis
Regardless of BMI; Release of FA & Lipid Accumulation.
- ▶ **T2DM:** *Most Impactful* For Fibrosis & HCC; Poor Glycemic Control
Ass'd w Cellular Injury & Fibrosis; All w MASLD Need to be
Screened (2 hr-GTT). Fat Accumulation In The Organs



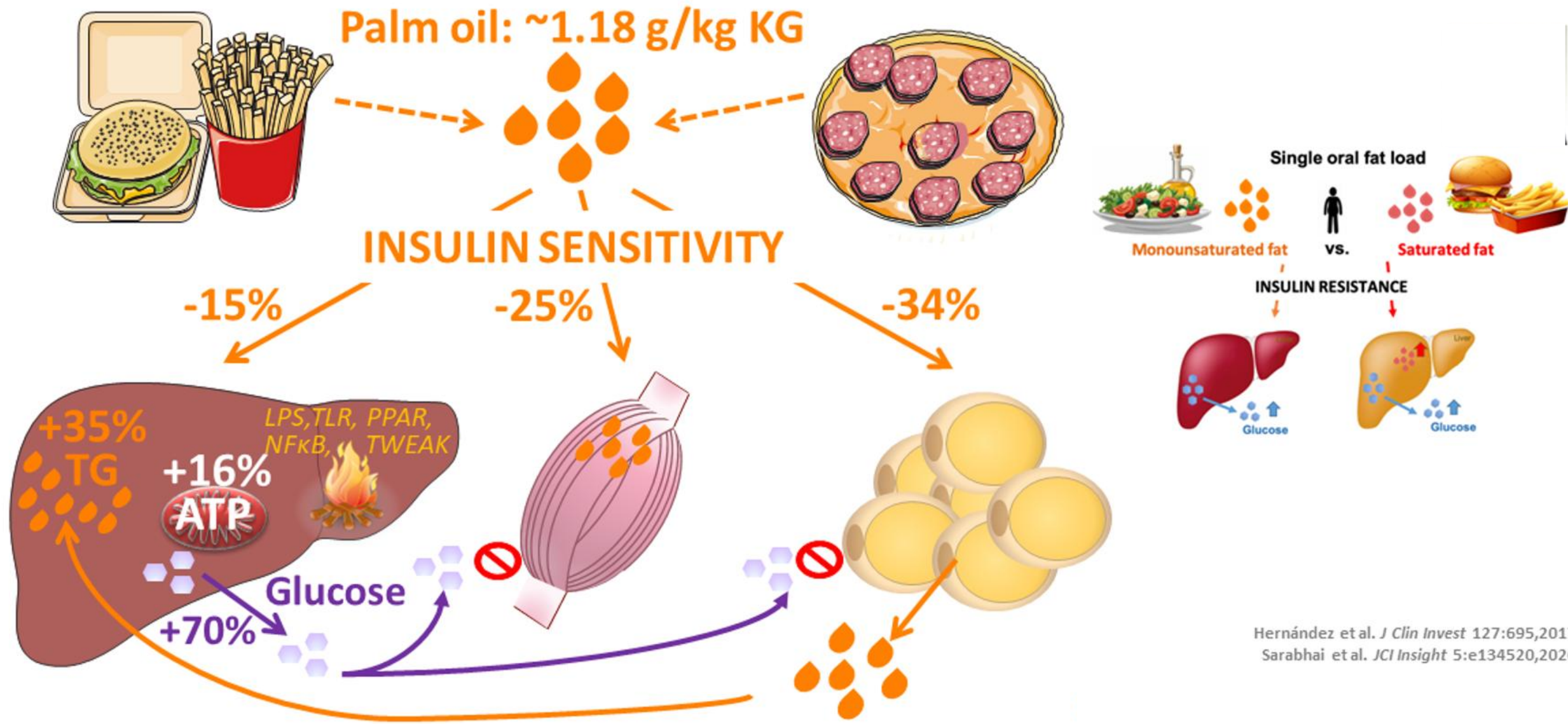
Definition

➤ > 5% Steatosis (Macrovesicular) & the Absence of Other Causes
With Little or No ETOH (< 20 g/d W; < 30 g/d M)

Standard drink (SD) in the US

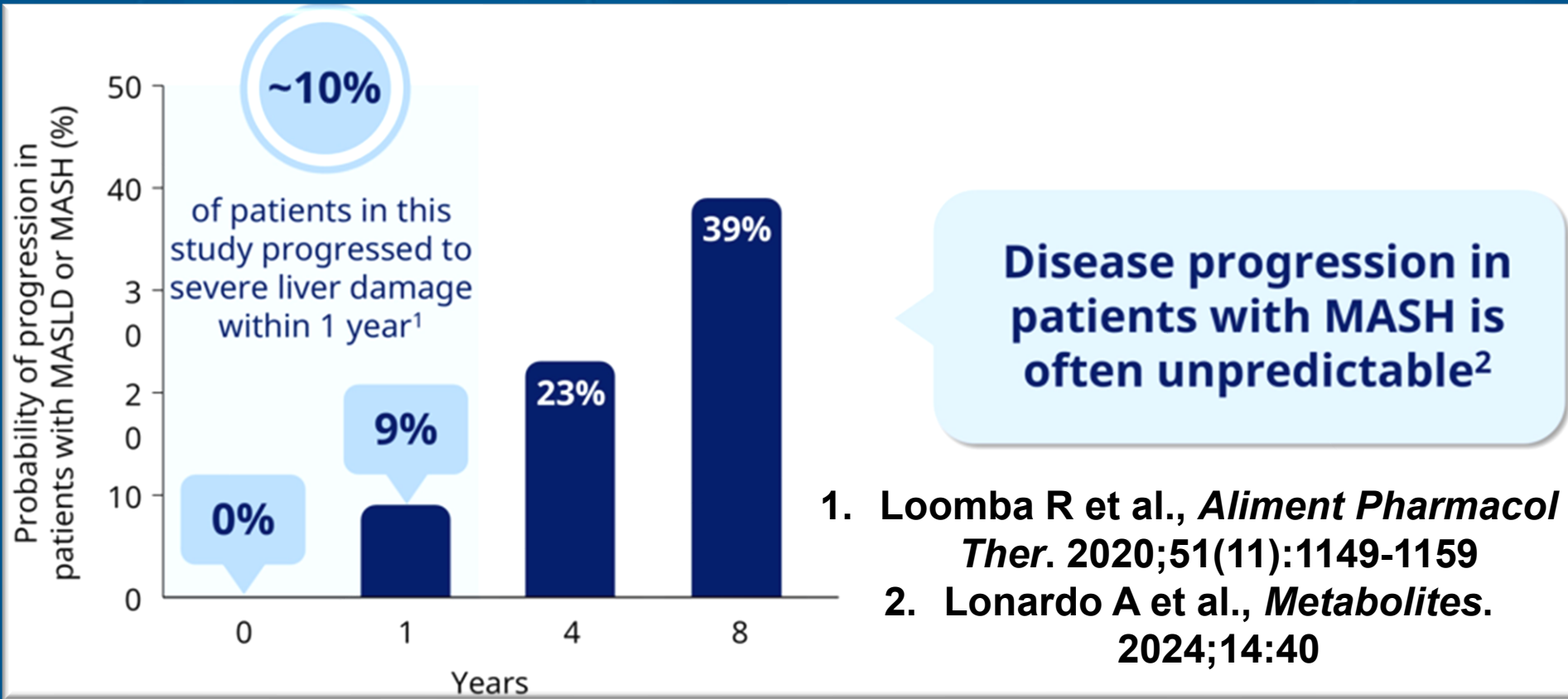


Chronic Liver Injury: Disease Progression & Fibrosis In MASLD / MASH

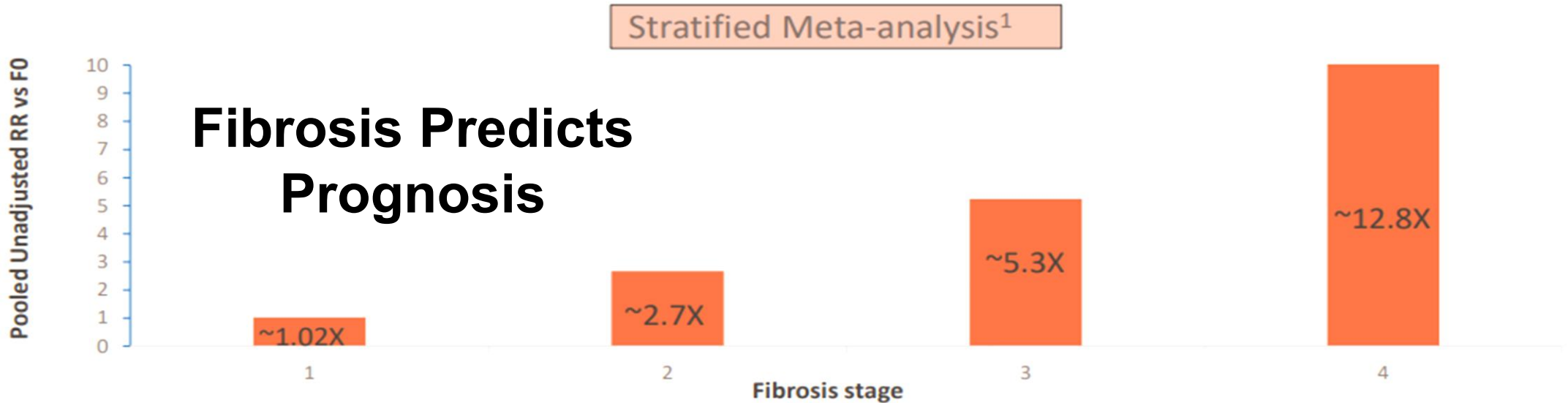


Fibrosis Predicts Prognosis

- Increased **Fibrosis**: Increased Liver Related Morbidity & Mortality; Increased All-Cause Mortality; Increased Non-Hepatic Malignancies



Fibrosis Severity & Liver Morbidity: Retrospective Meta-Analysis Derived From Multiple Studies



Fibrosis Stage	1	2	3	4
Pooled unadjusted RR Vs. F0 (95% CI)	1.02 (0.58-1.89)	2.67 (1.58-4.51)	5.24 (3.97-9.98)	12.78 (6.85-23.85)

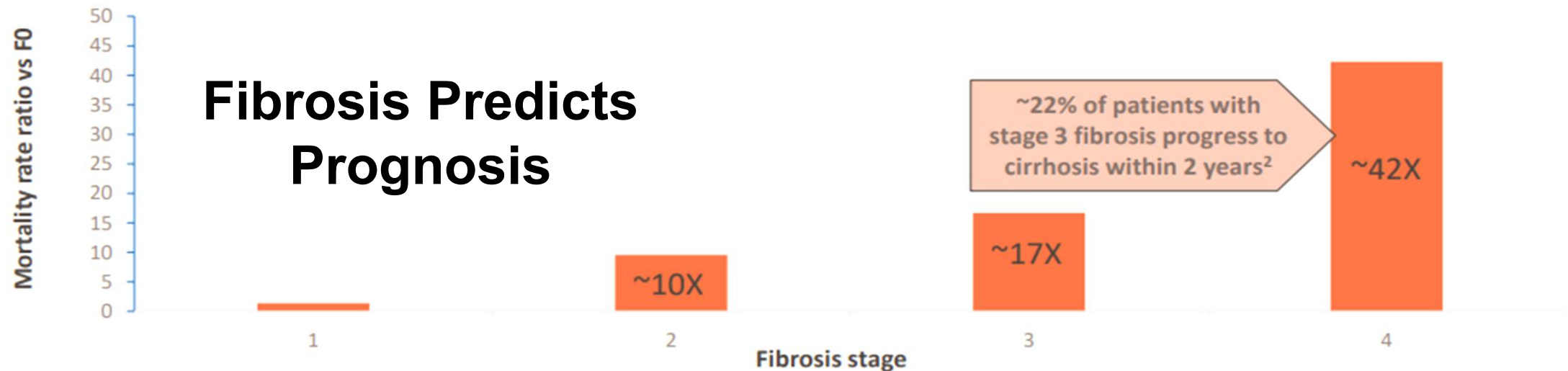
*Liver morbidity defined differently across multiple studies in Metanalysis - Search terms included: ascites, esophageal varices, cirrhosis, cancer, decompensation, encephalopathy

1. Taylor RS et al. *Gastroenterology* 2020. May;158(6):1611-1625.e12.



Fibrosis Severity & Liver Mortality From A Retrospective Analysis Derived From Multiple Studies

Risk Of Liver Related Death Statistically Higher After Progression To F2



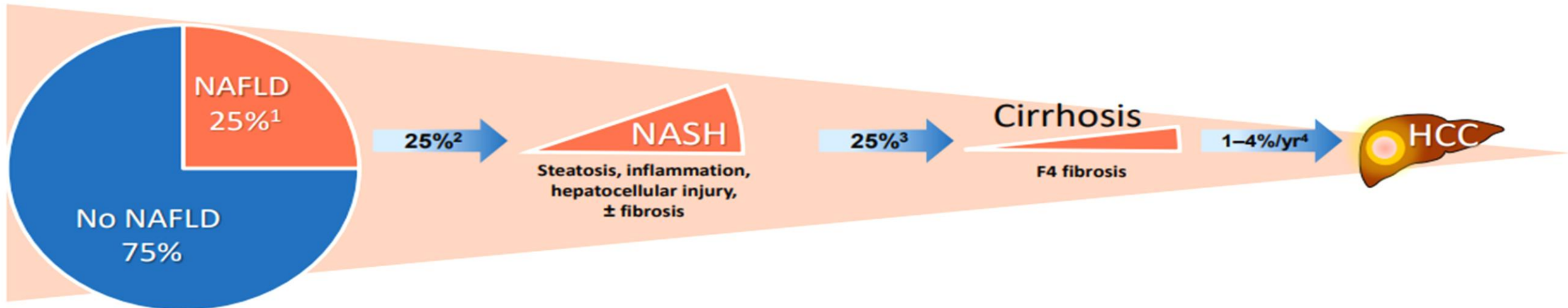
Fibrosis Stage	1	2	3	4
Mortality Rate Ratio (95% CI)	1.41 (0.17–11.95)	9.57 (1.67–54.93)	16.69 (2.92–95.36)	42.30 (3.51–510.34)

1. Dulai PS et al., *Hepatology*. 2017;65:1557-1565. 2. Loomba R. *Hepatology* 2019;70(6):1885-1888



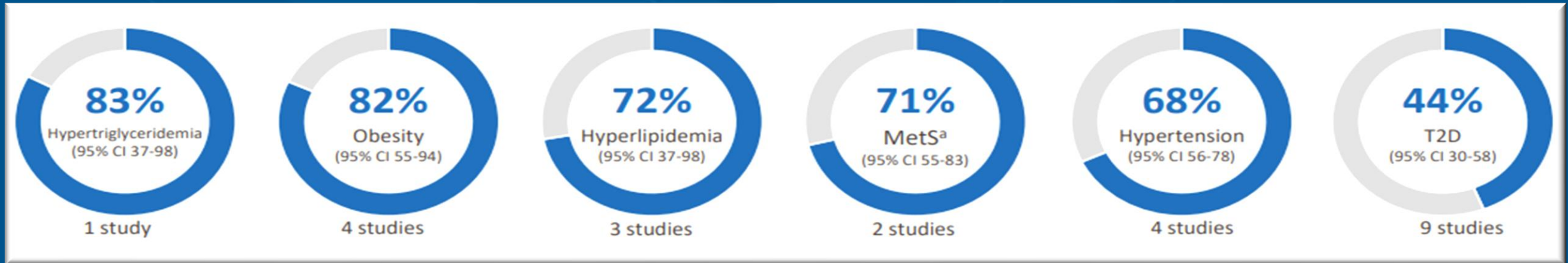
Progression of MASLD / MASH: Cirrhosis & Hepatocellular Carcinoma

- ▶ MASH Can Progress to Cirrhosis, End-Stage Liver Disease & Need for Liver Transplant
 - 10 Year Cumulative Incidence HCC 1.7 per 1000 Pts w MASLD
 - ~ 20% MASH - Related HCC Identified in Pts Without Cirrhosis
 - Risk of Progression From Compensated Cirrhosis to Decompensation & Death is ~ 10% / Year



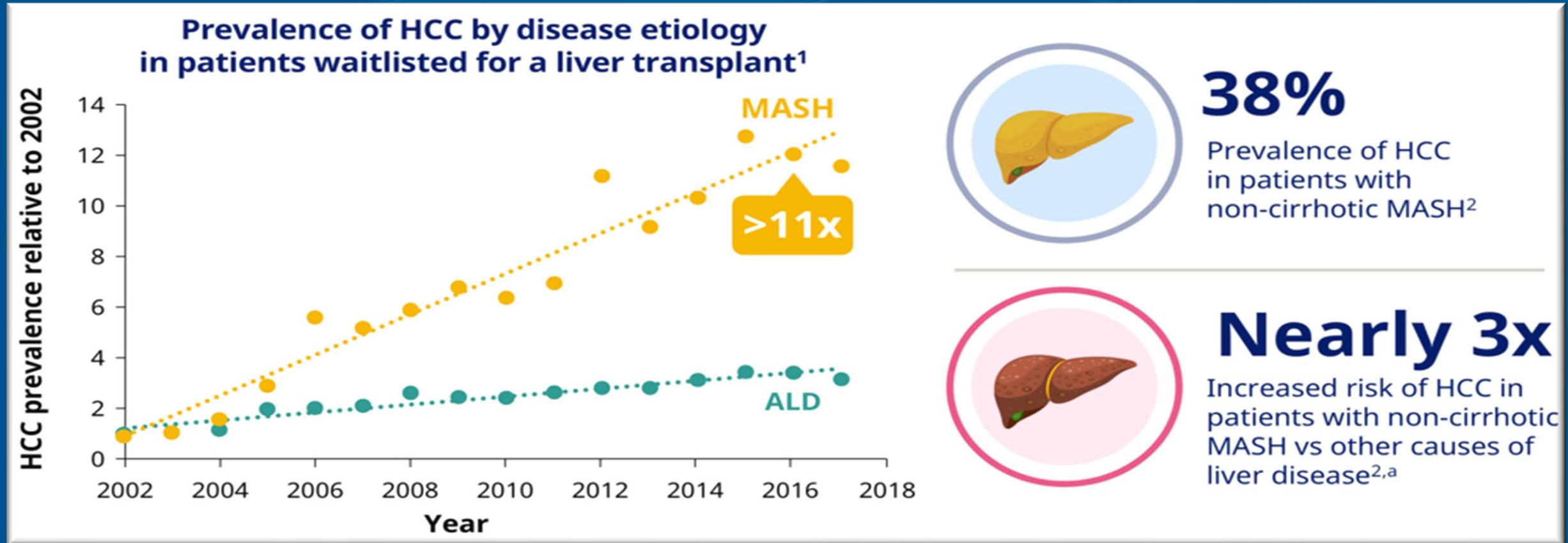
Comorbidities Among Pts With MASH – Retrospective Meta-Analysis

- Simultaneously, Patients With These Conditions May Experience MASH as a Comorbidity, Highlighting Reciprocal Relationship
 - MASH Can Occur Without Met S, Obesity, or DM but Comorbidities Are Common



1. Younossi ZM et al., *Hepatology*. 2016;64(1):73-84.
2. Chalasani N et al., *Hepatology* 2018;67(1):328-357.
3. Rinella ME et al., *Gastroenterol Hepatol*. 2014;10.
4. Allen AM. *J Hepatol*. 2022 Nov;77(5):1237-1245.

MASH Comorbidities / Morbidity & Mortality From Retrospective Meta-Analysis

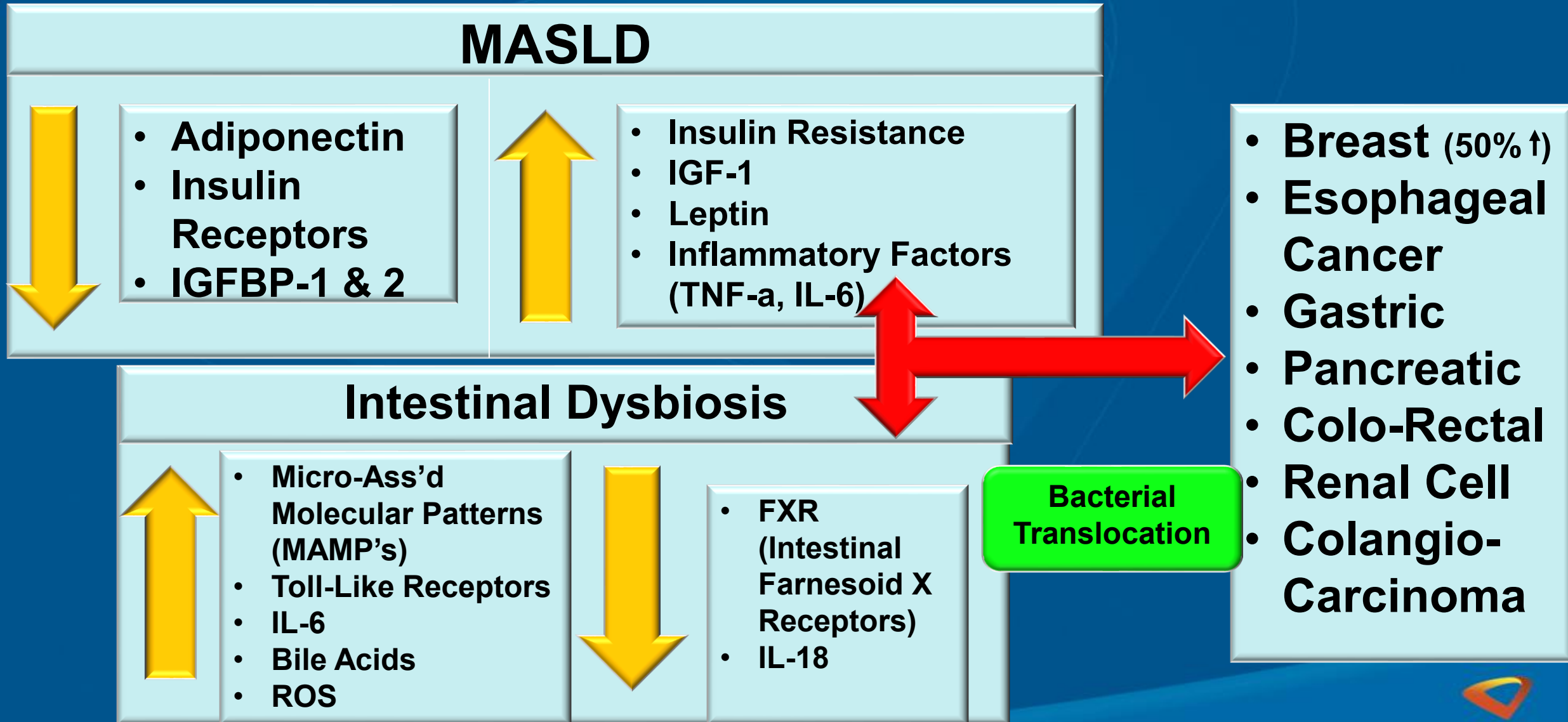


a. Composite ALD, Chronic Hep B/C, Autoimmune Liver Dz, Cholestatic Liver Dz, Wilson's Dz, Hereditary Hemochromatosis

1. Younossi Y et al. *Hepatology*. 2016;64(1):77-84. / Younossi Z et al. *Gastroenterol Hepatol*. 2019;17(4):748-755. 2. Angulo et al. *Gastroenterology*. 2015;149:389-397



MASLD & Extra-Hepatic Cancers



MASLD & CVD

Zheng et al. *Cardiovascular Diabetology* (2024) 23:346
<https://doi.org/10.1186/s12933-024-02434-5>

Cardiovascular Diabetology

REVIEW

Open Access

Metabolic dysfunction-associated steatotic liver disease and cardiovascular risk: a comprehensive review



MASLD & Cardiac Function

ANNALS OF MEDICINE

2024, VOL. 56, NO. 1, 2306192

<https://doi.org/10.1080/07853890.2024.2306192>

RESEARCH ARTICLE

 OPEN ACCESS

 Check for updates

The association of metabolic dysfunction-associated steatotic liver disease (MASLD) with the risk of myocardial infarction: a systematic review and meta-analysis



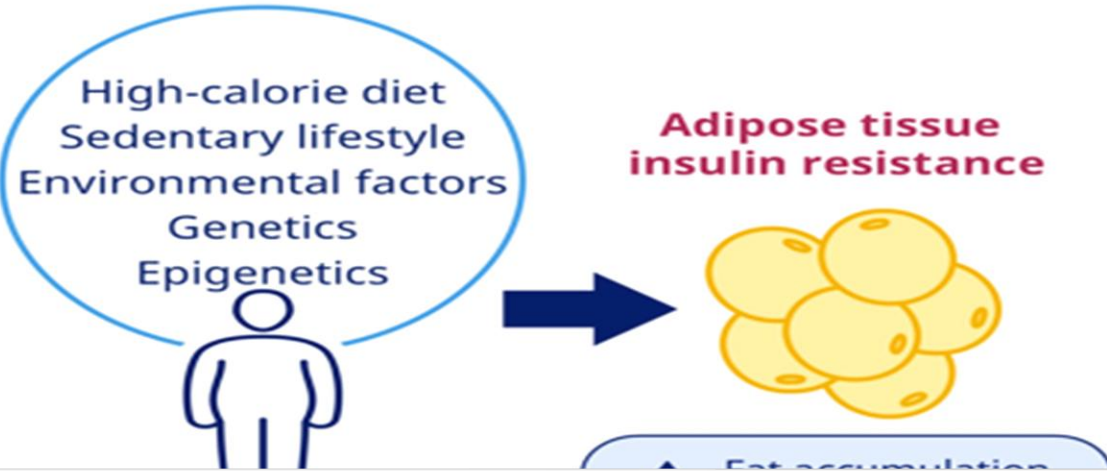
MASLD & Cardiac Function

Gut Microbiota Alteration

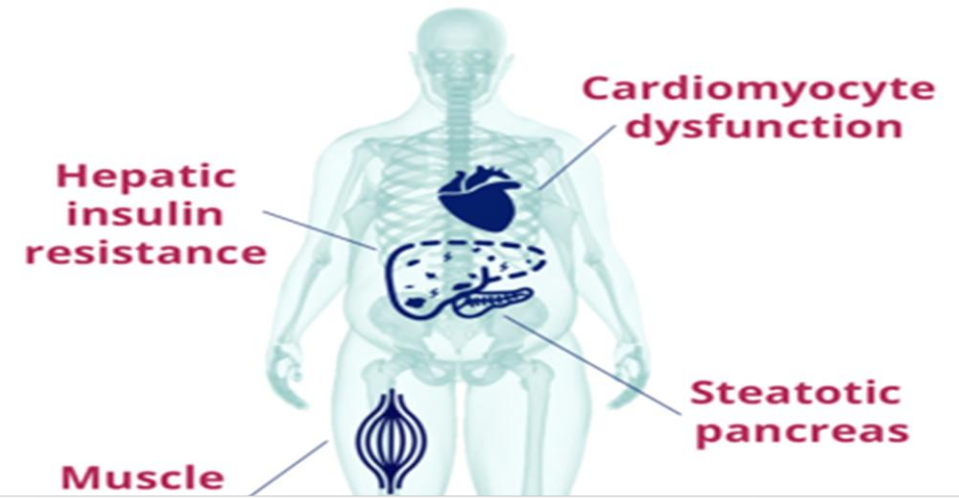
- ▶ High Saturated Fats
- ▶ Sucrose Sweetened Drinks
- ▶ Caloric Dense / Energy Poor Processed Foods
 - Shape the Microbiota To A Less Favorable Profile
- ▶ **Specific Microbiota Signature Unique to MASLD / MASH**
 - Increased CAD
 - Increased Ischemic Stroke
 - Vascular Calcification
 - Prothrombotic Effect

Microbiome is the Seed of the Problem. Alterations In Gut Bacteria Fueling Inflammation. Gram (–) Rods Producing Cytokines / Toxic Products. Bacterial Translocations. Integrity of Gut Disrupted – Toxins Flow into Portal / System Circulation Causing Havoc

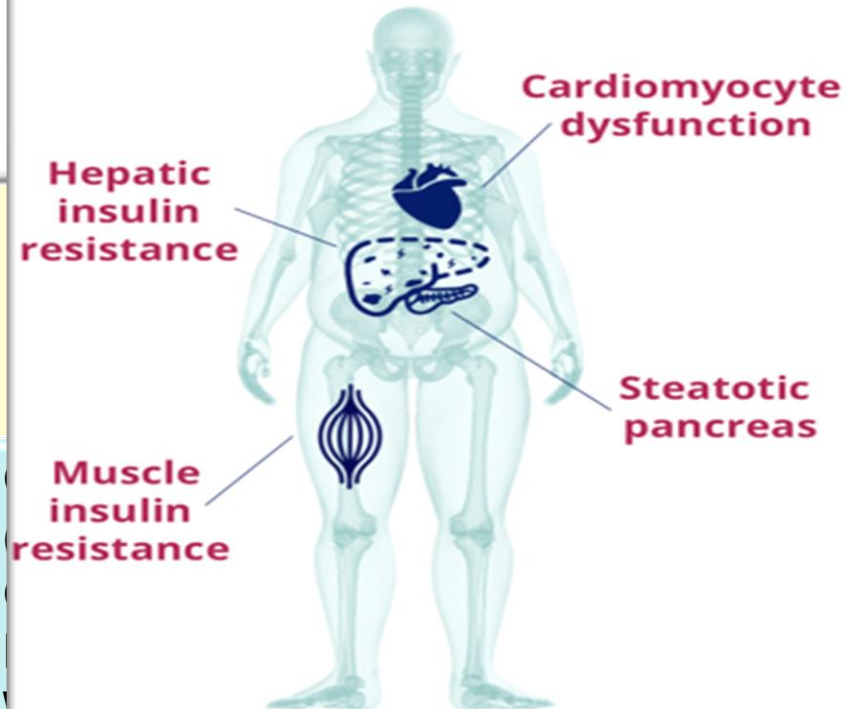
Underlying Metabolic Impairment



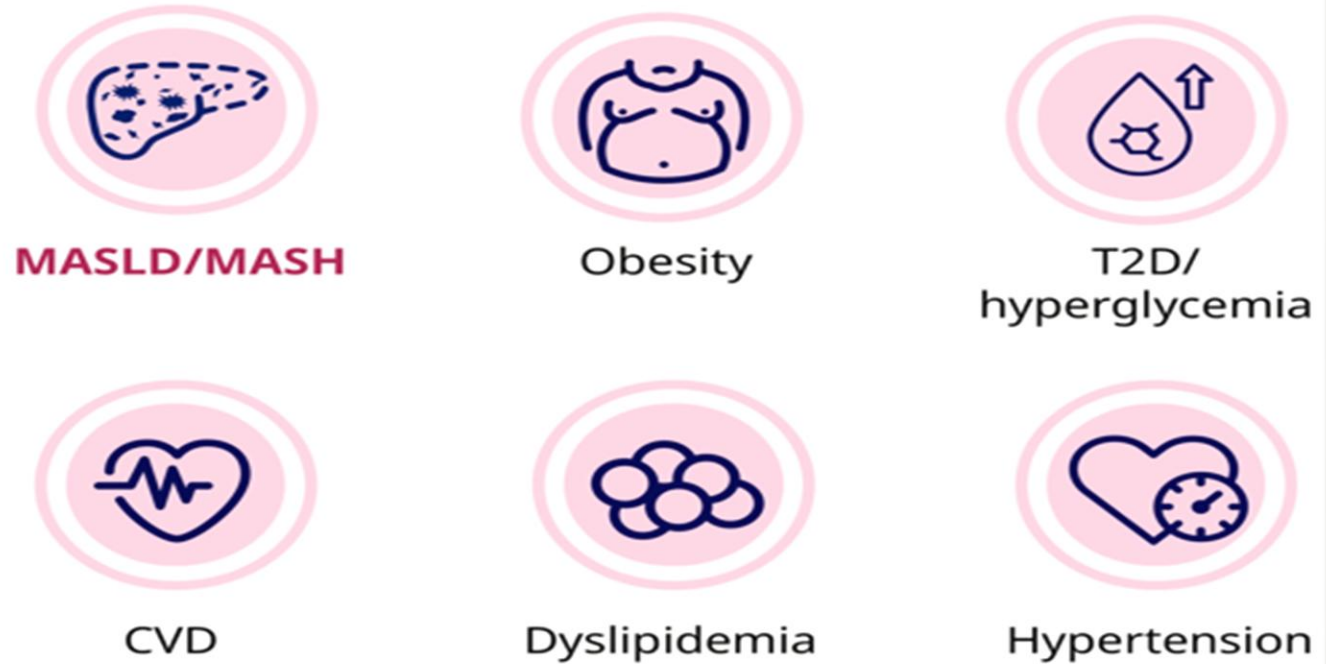
Multiorgan Dysfunction



Multiorgan Dysfunction



Potential Metabolic Conditions



Accelerated Renal Disease

- ▶ Meta-Analysis – 13 Studies; 1.3 Million Patients, 28.1% with NAFLD 33,840 with Incident CKD Stage ≥ 3
- ▶ Median F/U 9.7 Years
- ▶ NAFLD Higher Risk CKD (HR 1.43)
- ▶ Risk Independent Age, Sex Obesity, HTN, DM, & Other CKD Risk Factors
- ▶ The Kidney Is Also A Target Organ

Alessandro Montovani MD et Al.,

https://eprints.soton.ac.uk/445427/1/NAFLD_CKD_Risk_metaanalysis_accepted.pdf



Obesity Is Common, Serious, And Costly

Obesity Impacts Our Nation's Health, Economy, Military Readiness



**1 in 5 Children &
1 in 3 Adults** Struggle
With Obesity



The US Spends
\$147 B
Annually
Obesity Related
Health Costs



Only **2 in 5 Young
Adults** Are Weight Eligible
& Physically Prepared For
Basic Training

Americans Don't Eat Healthy Or Get Enough Physical Activity

Fewer Than 1 in 10 Eat
Recommended Daily Amount
of Vegetables

**Fewer Than 1 in 4
Youth** Get Enough
Aerobic Physical Activity

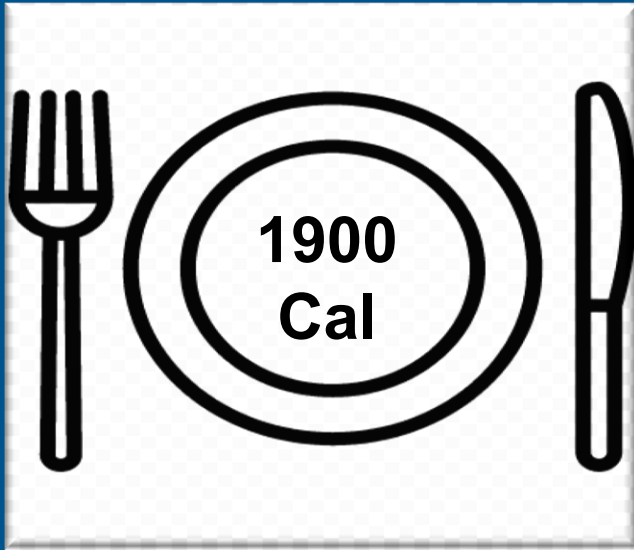
Just 1 in 4 Adults Meet
the Physical Activity
Guidelines

Many Americans Lack Healthy, Affordable Foods / Places To Be Active

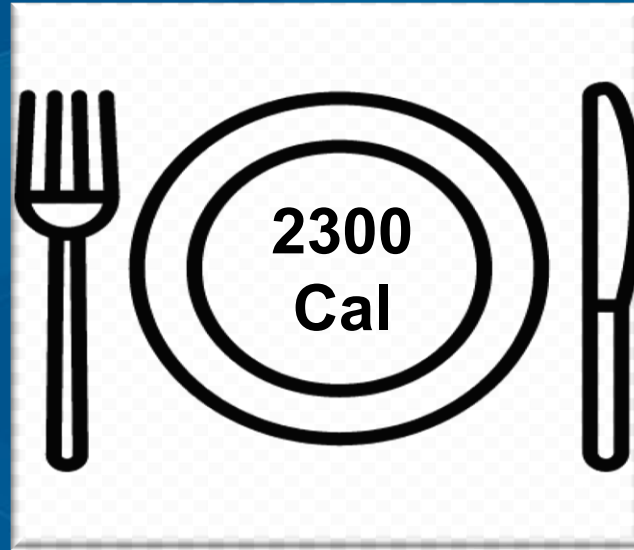
More Than Half of Americans Don't
Live Within Half A Mile of a Park

40% of All US Households Do Not Live
Within One Mile of Healthier Food Retailers

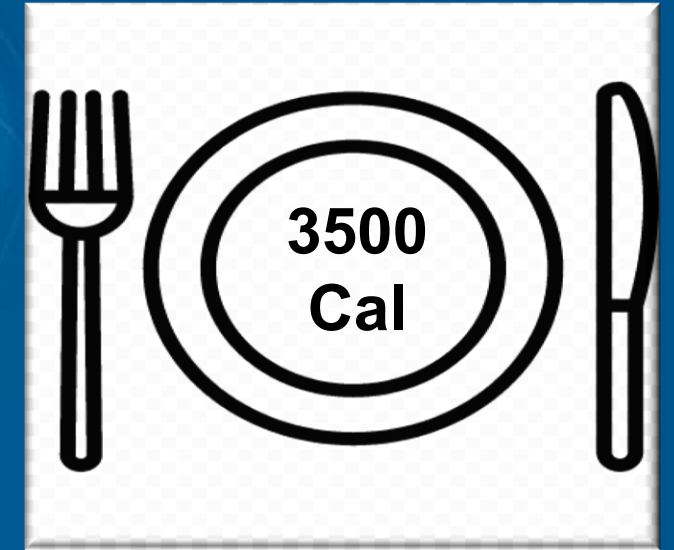




1970



2000



2020

**Calories Up / Exercise Down
Eating Out Up / Cooking At Home Down**



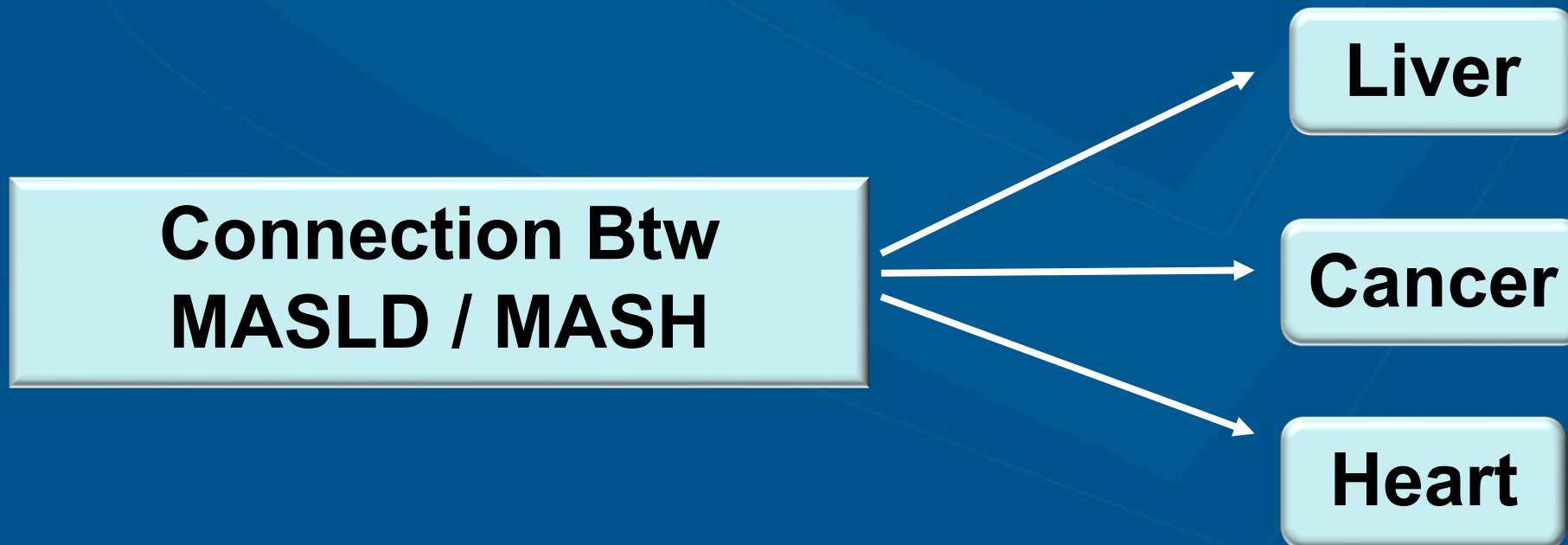
WHAT

NOW?



Education

- ▶ **MASLD / MASH** is A Cardiac, Hepatologic & Oncologic Disorder With Significant Morbidity & Mortality
- ▶ Drive Awareness, Drive Urgency, & Call To Action



Screen, ID, Risk Stratify

- ▶ Patients Must Be Identified & Appropriately Risk – Stratified
- ▶ Delay In Dx: Silent Dz – No Sx Until Progressed
- ▶ Similar To Screening For CKDz, Annual Dilated Eye Exam, Comprehensive Foot Exam

**Make Visible What Is
Invisible**

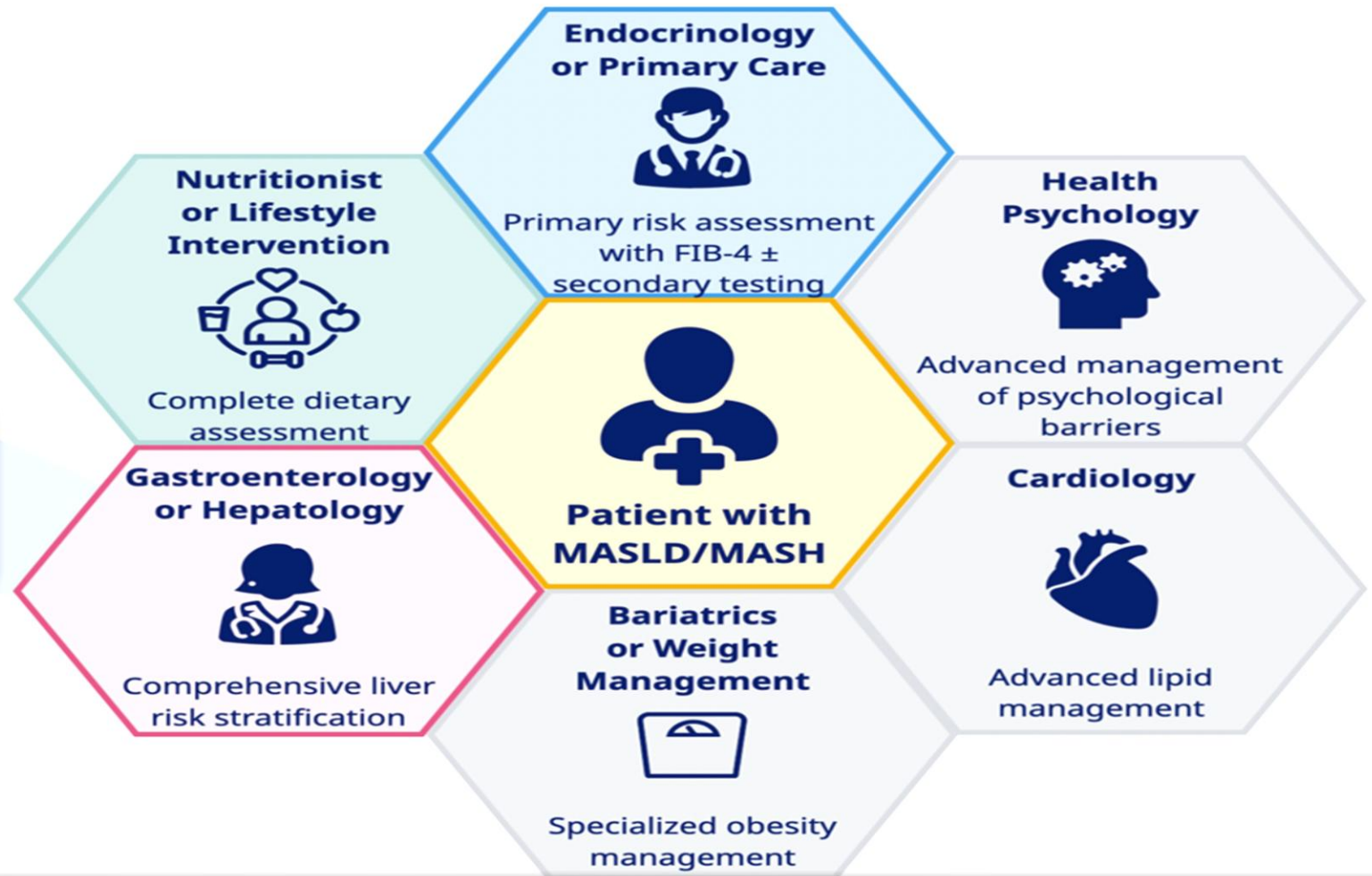


This is The **New** Paradigm



Disease Centered Vs. Patient Centered Care

A collaborative approach to managing cardiometabolic risk is important in the care of patients with MASH



MASLD & T2DM

JIM

Journal of
Internal Medicine

Founded in 1863

Original Article

 Open Access

Evaluating the prevalence dysfunction-associated steatosis type 2 diabetes mellitus in

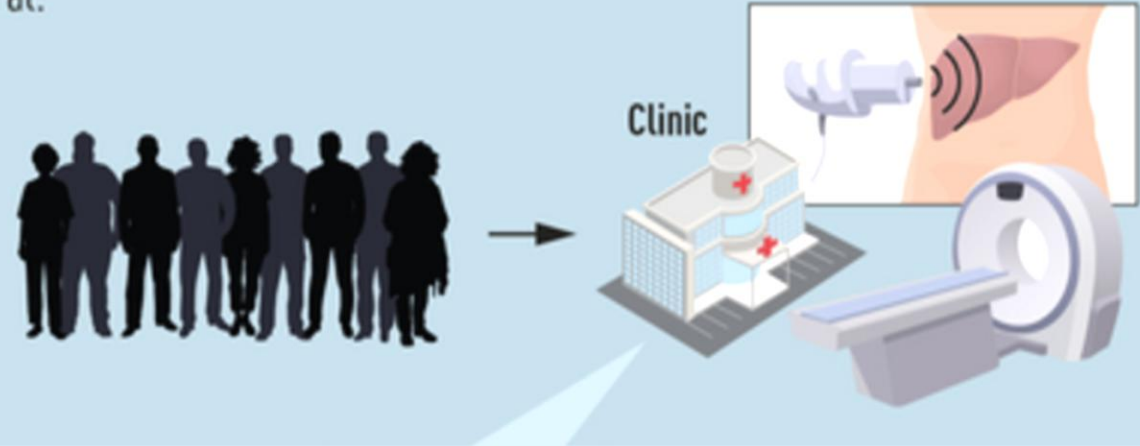
- ✓ 59% MASLD
- ✓ 7% Signs of Advanced Fibrosis
- ✓ Obesity Increased Risk Fibrotic MASLD 8x
- ✓ MASLD Linked to CV Changes / Ectopic Fat
- ✓ Screening Needed DM Primary Care

First published: 16 June 2025 | <https://doi.org/10.1111/jim.15700>

Evaluating the prevalence and severity of MASLD in patients with type 2 diabetes mellitus in primary care

Balkhed et al.

Primary care
Individuals
with T2D
n = 308



T2D

59%



MASLD

7%



≥10 kPa

1.9%



≥ 15 kPa/
clinical cirrhosis

T2D and MASLD

11%



≥10 kPa

2.8%



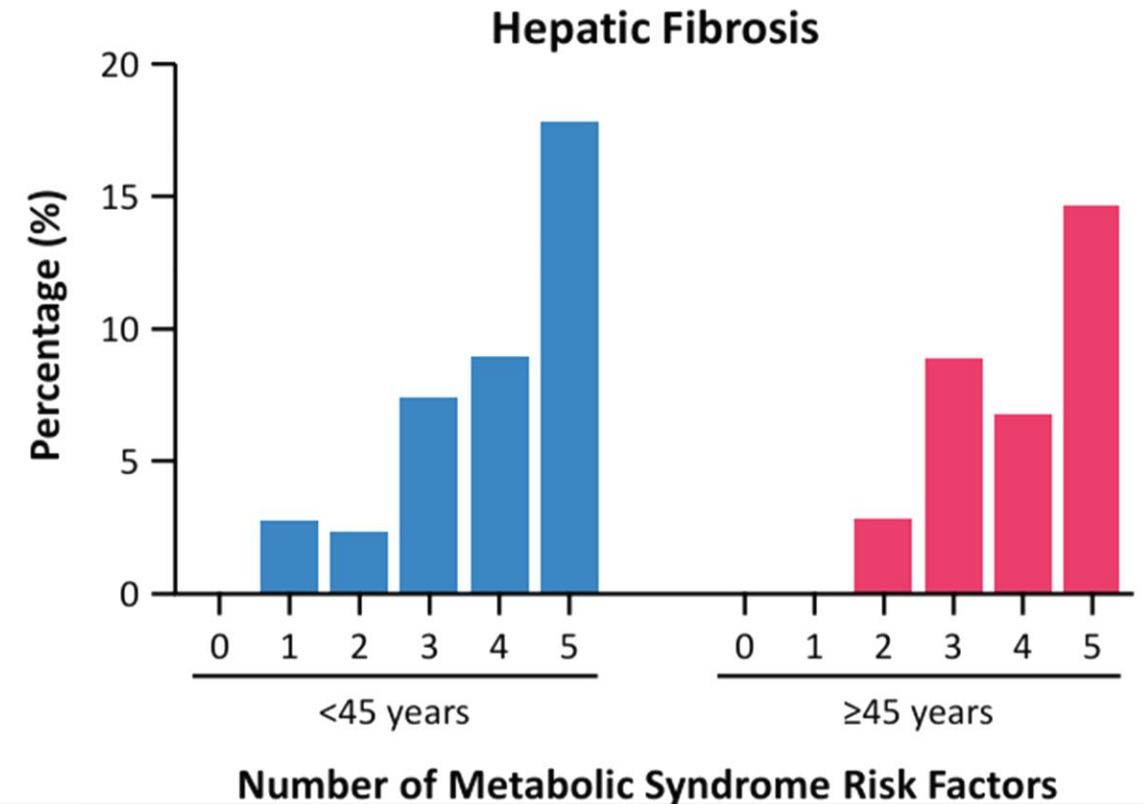
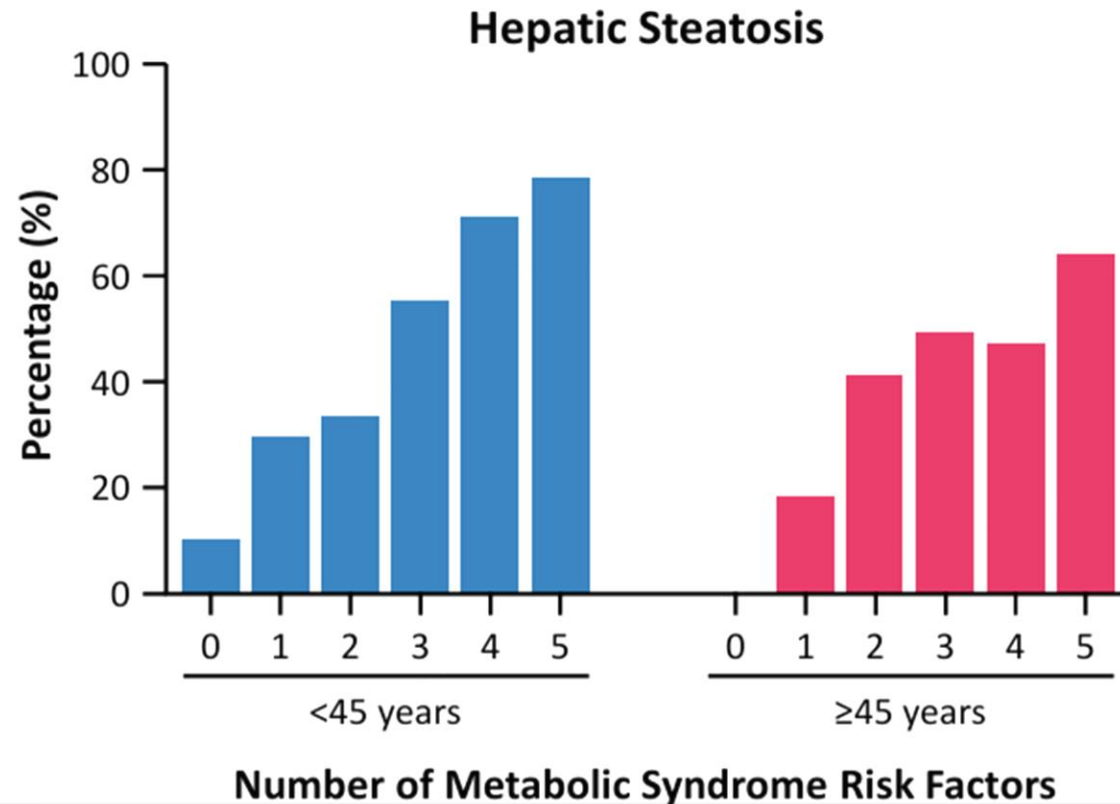
≥ 15 kPa/
clinical cirrhosis

Desc

The Need To Screen: Obesity Increases Hepatic Fibrosis In Young Adults With T2DM

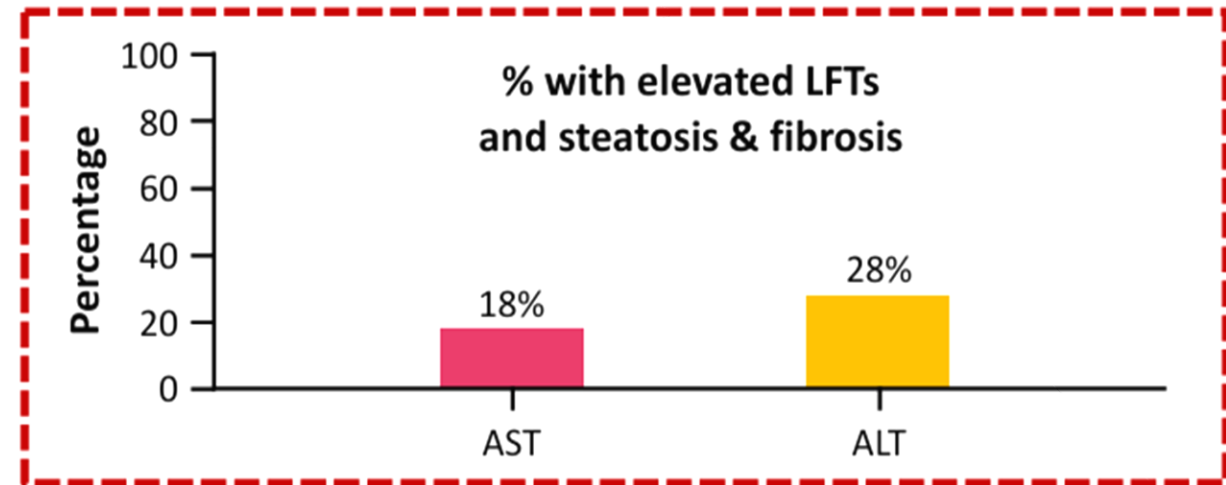
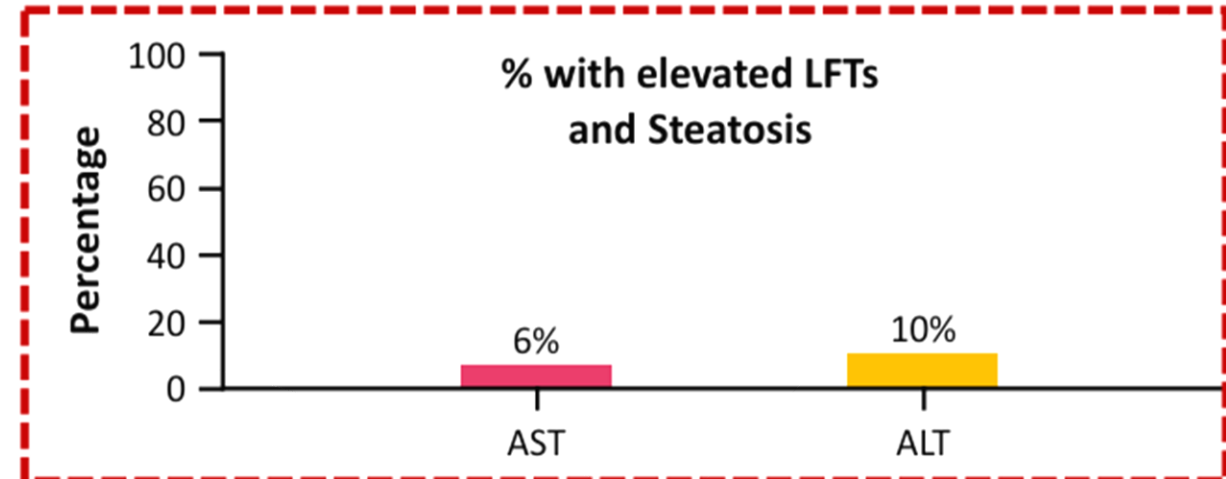
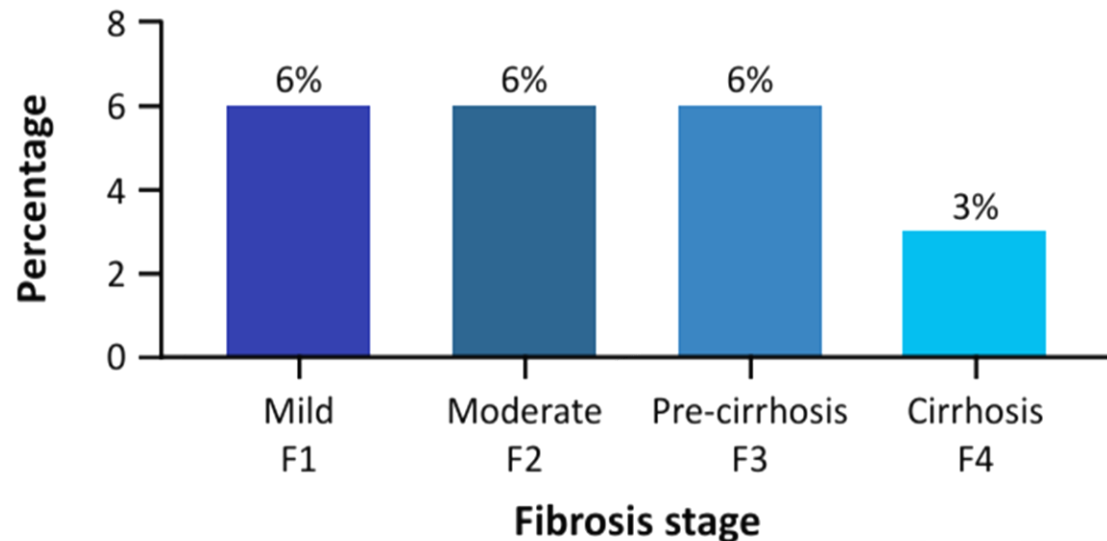
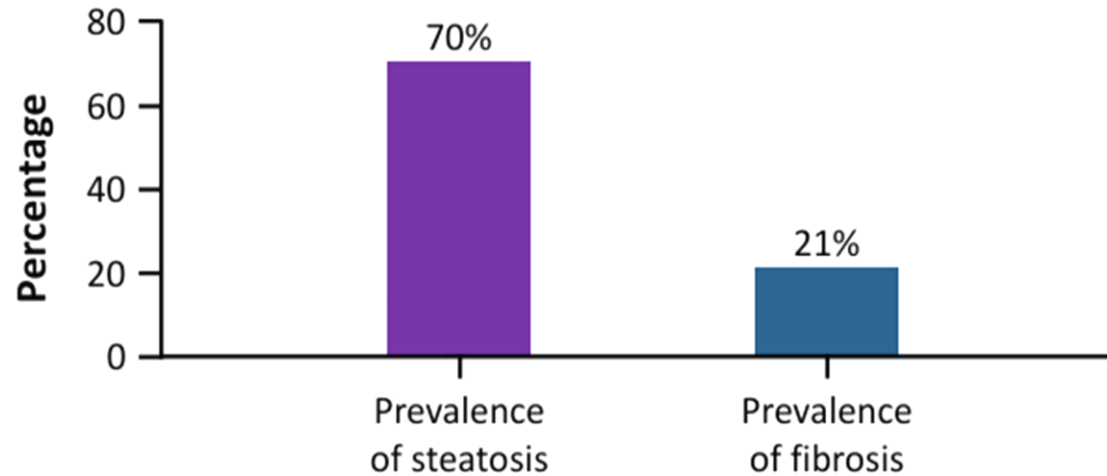
Population: 1420 individuals with (63%) or without type 2 diabetes mellitus who attended internal medicine or endocrinology clinics and did not have a known history of MASLD. **A total of 243 participants were ages <45 years.**

Screening: transient elastography for steatosis and LSM; if $\text{LSM} \geq 6.5$ kPa MRE, cT1 and liver biopsy if $\geq \text{F2}$ suspected.



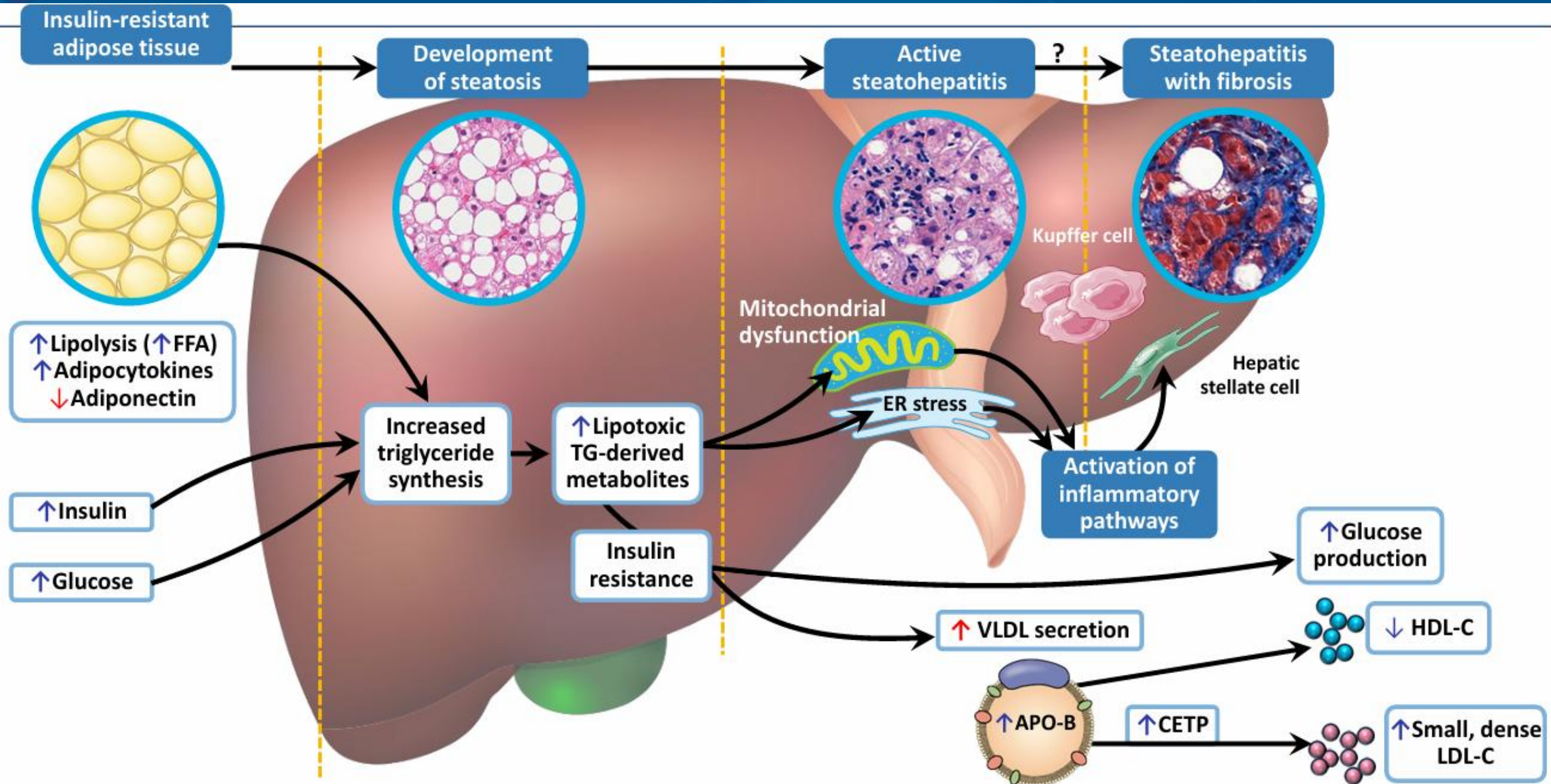
LFT Abnormalities In Steatosis / Fibrosis: T2DM Not Previously Dx MASLD / MASH

N = 561 patients with type 2 diabetes from outpatient PCP and endocrine clinics

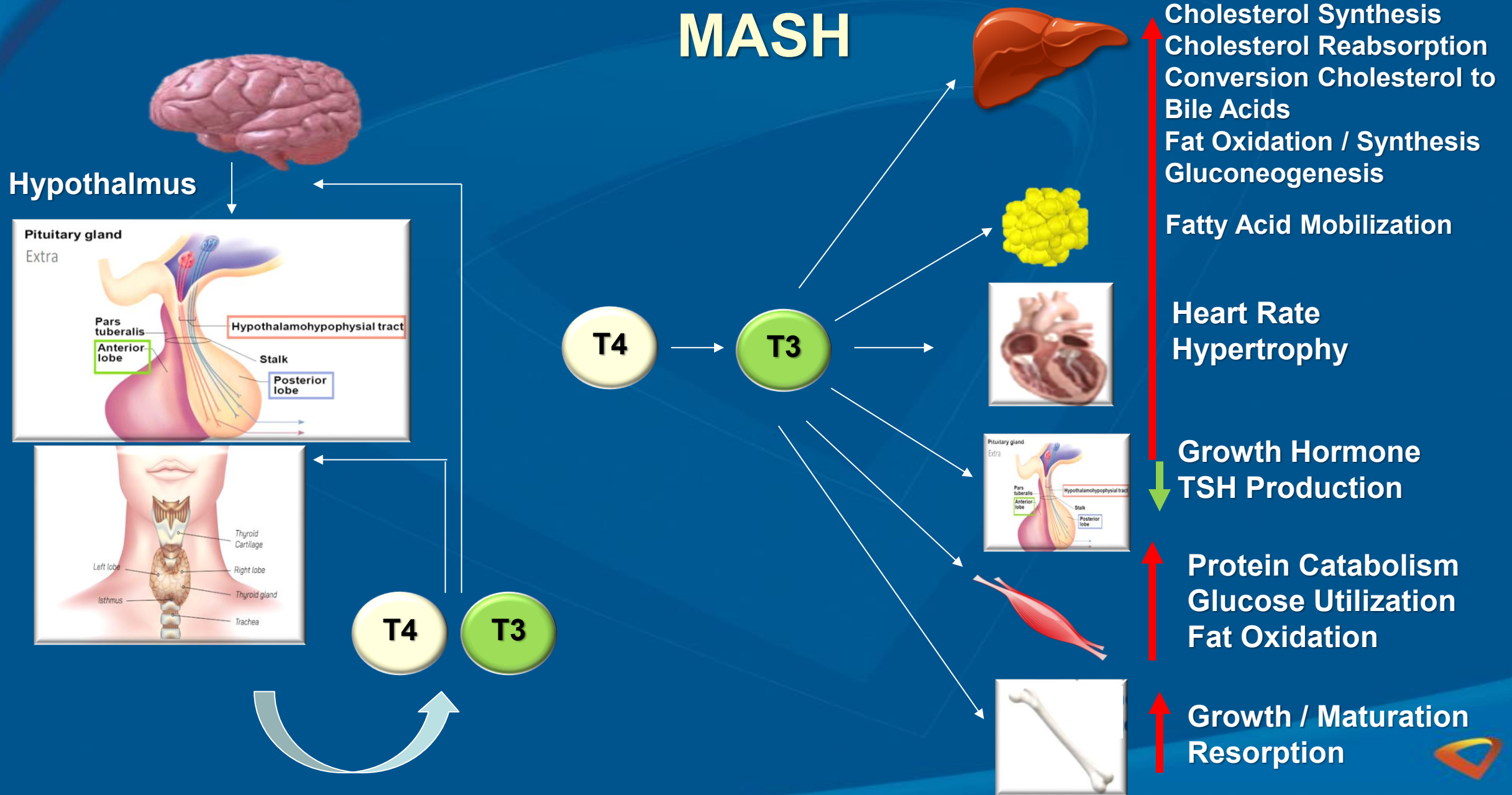


Patients with Elevated LFTs

MASH Pathophysiologic Pathways



Role Of Thyroid Hormone Dysregulation In MASLD / MASH



Thyroid Hormone Receptor Alpha / Beta

- ▶ THR-Alpha – Predominantly In Heart, Brain & Bone
 - Responsible For Effects In Heart & Bone, Thyrotoxicosis Side Effects of TH Excess
- ▶ THR-Beta - Predominantly In Liver, Kidney & Pituitary Gland
 - Responsible For Effects On Metabolism
 - Crucial Role In The Liver, Including Activation of Liver Fat Oxidation
- ▶ The Liver is the Only Organ Where THR-B is Expressed Higher Than THR-A

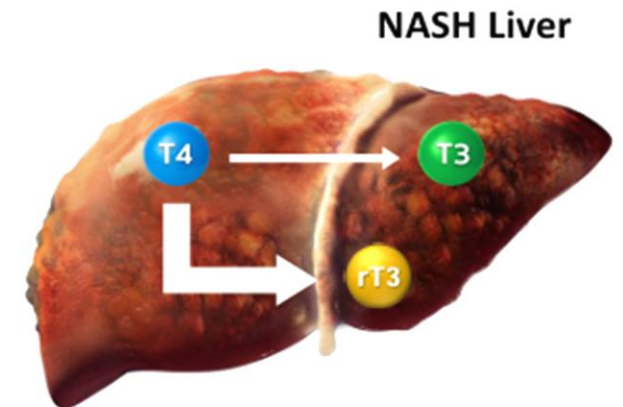
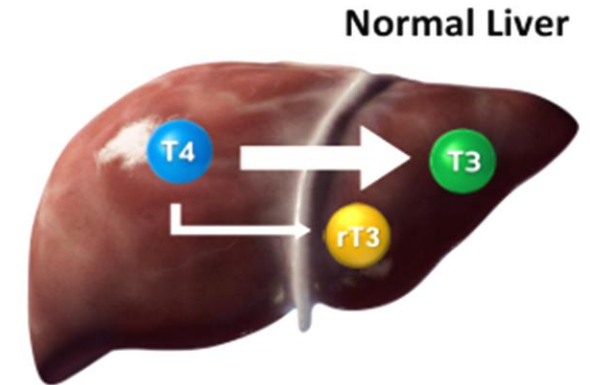
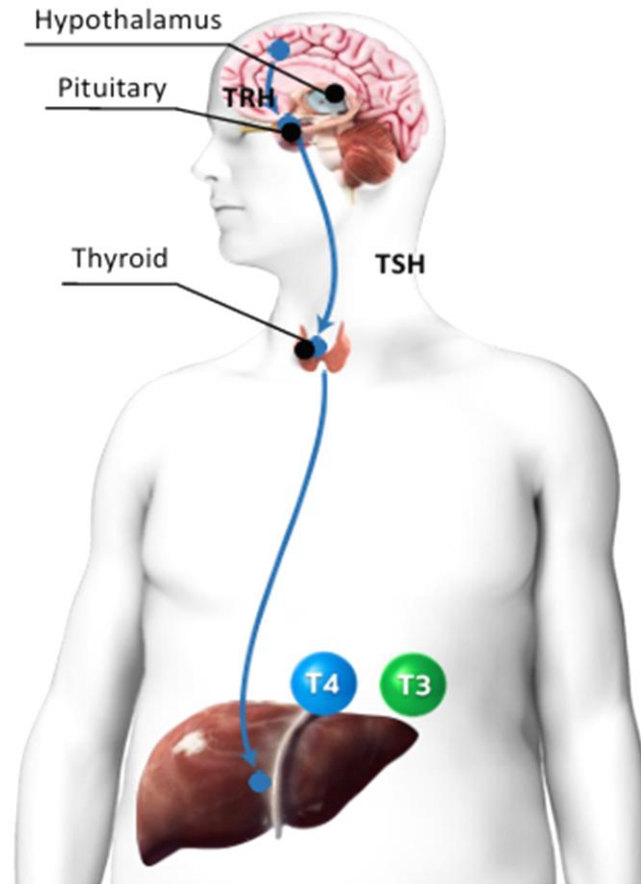


Role Of Thyroid Hormone Dysregulation In MASLD / MASH

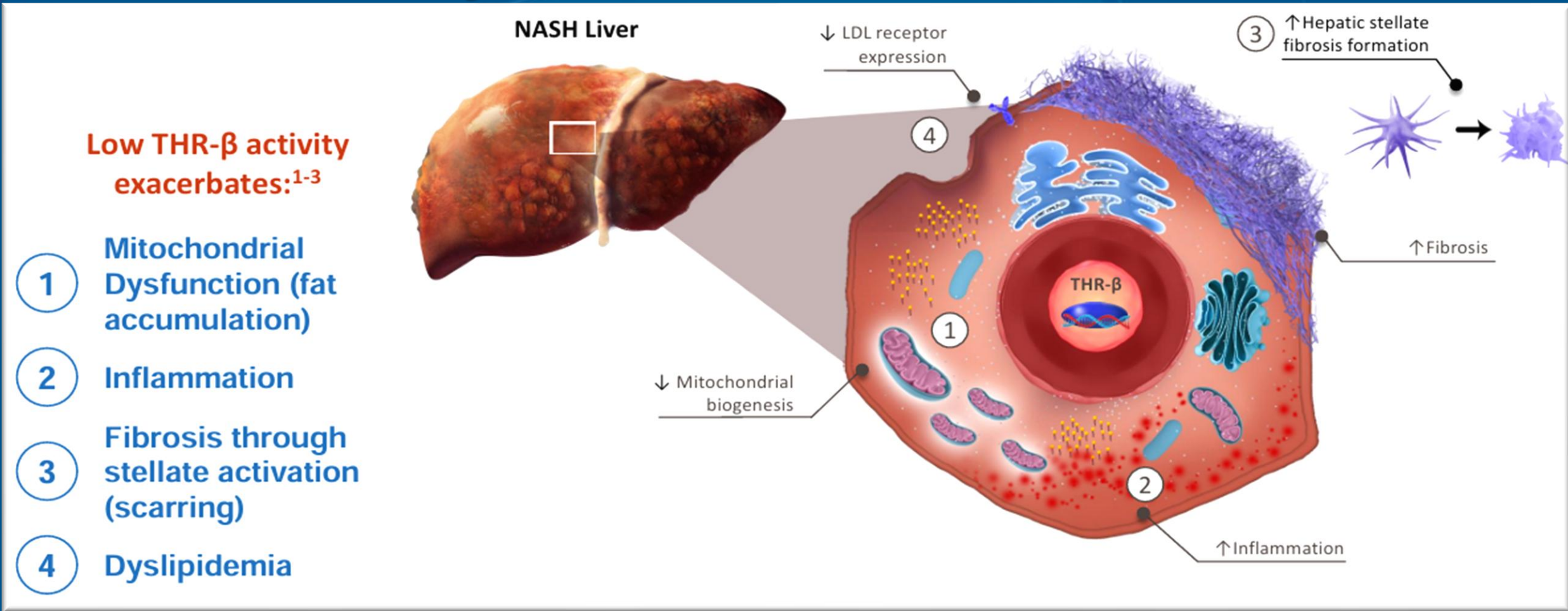
- Altered patterns of gene expression in fatty liver
 - T3 conversion genes downregulated
- Inflammation is a hallmark of NASH
 - Disruption of thyroid hormone conversion (T4 to T3) pathway occurs
 - rT3 is inactive
- **Hypothyroidism In The Liver**

Hypothyroidism Ass'd ↑ Risk MASLD / MASH
Free T4 Levels Lower MASLD

Low Free T3 = Risk Factor Advanced Fibrosis



Thyroid Hormone Dysfunction Influences Key Pathways Involved In MASLD / MASH



1. Sinha RA, et al. *Nat Rev Endocrinol*. 2018;14:259-269. 2. Karim G, Bansal MB. *touchRev Endocrinol*. 2023;19:60-70. 3. *Proc Natl Acad Sci USA*. 2016;113(24):E3451-E3460



MASLD Guidelines For PCP's / Endocrinologists

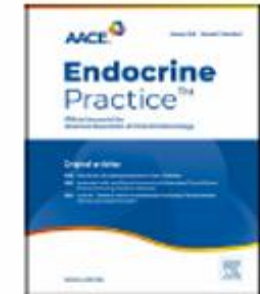
Endocrine Practice 28 (2022) 528–562



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journal homepage: www.endocrinepractice.org



Clinical Practice Guidelines

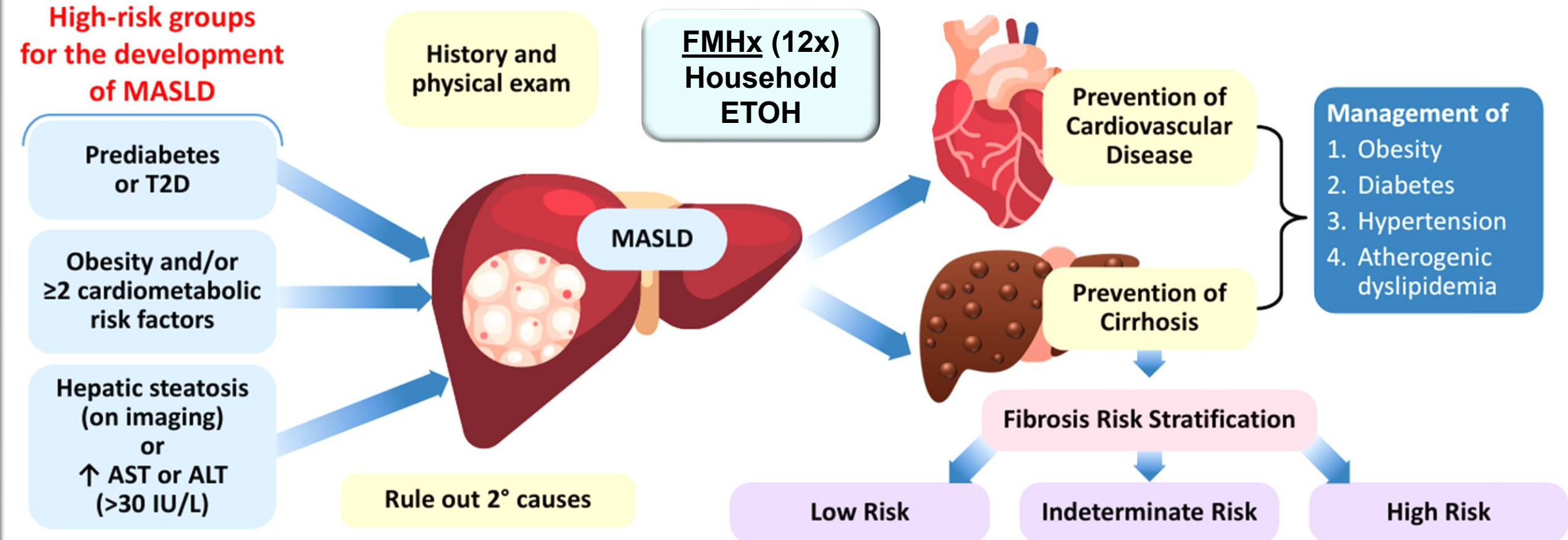
American Association of Clinical Endocrinology Clinical Practice
Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver
Disease in Primary Care and Endocrinology Clinical Settings
Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)



Kenneth Cusi, MD, FACE, FACP, Co-Chair ^{1,*}, Scott Isaacs, MD, FACE, FACP, Co-Chair ²,
Diana Barb, MD, ECNU ³, Rita Basu, MD ⁴, Sonia Caprio, MD ⁵,
W. Timothy Garvey, MD, MACE ⁶, Sangeeta Kashyap, MD ⁷,
Jeffrey I. Mechanick, MD, ECNU, MACE, FACP, FACN ⁸, Marialena Mouzaki, MD, MSc
Karl Nadolsky, DO, FACE, DABOM ¹⁰, Mary E. Rinella, MD, AASLD Representative ¹¹,
Miriam B. Vos, MD, MSPH ¹², Zobair Younossi, MD, AASLD Representative ¹³

**PCP's Gate-Keepers
Crucial For Timely
Identification
Standardized
Screening Guidelines**

MASLD / MASH Algorithm



AST > 40 w / DM = Concern
ALT $>$ AST = MASLD
AST $>$ ALT $\uparrow$ Prob Adv Fib

Cusi K et al. *Endocrine Practice* 2022;28:528-562



Meet Patient Ms Smith

- ❖ 60 y/o F Returns to Clinic for Incidental Abnormal LFT's, Long-Standing Hx Obesity Refractory to Lifestyle Changes.
- ❖ PMHx: T2DM (A1c 7.1%), Obesity, Metabolic Syndrome.
- ❖ Meds: Metformin
- ❖ Labs: AST 49 IU/L, ALT 61 IU/L Hepatitis C Serology Negative

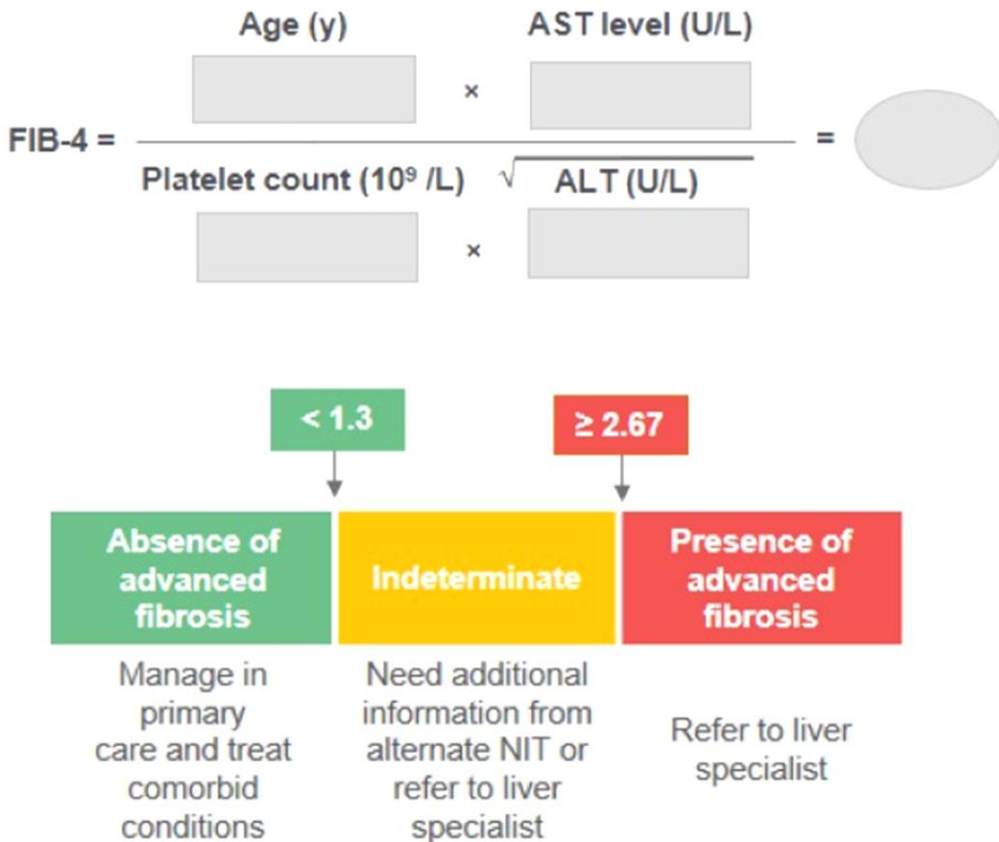
Which of the Following Is Required to Estimate Ms. Smith's Risk for Hepatic Fibrosis?

- A. Abnormal LFT's**
- B. Bilirubin**
- C. BMI**
- D. Creatinine Clearance**
- E. Platelet Count**



Risk Stratification Tools

FIB-4 Score^[1-3]



Enhanced Liver Fibrosis Test^[2,3]

Combines 3 biomarkers of fibrosis: Hyaluronic acid, TIMP-1, and P3NP



Fibroscan[®]^[2]

Uses elastography to assess liver stiffness, which increases with fibrosis severity



American Diabetes Association (ADA) 2025 Guidelines: Focus on Fibrosis Risk Statification To Prevent Cirrhosis

MASLD with clinically significant fibrosis: Stages 2, 3 and 4 = or “at risk” MASH (i.e., at risk for cirrhosis)

Histological stages of fibrosis:

Stage 0: no fibrosis

Stage 1: mild

Stage 2: moderate

Stage 3: advanced (“precirrhosis”)

Stage 4: cirrhosis

**Associated with increased risk of liver cirrhosis,
hepatocellular carcinoma and CVD**



ADA 2025 MASLD Consensus Report

Key Tests Primary Care / Endocrinology



Blood-based biomarkers^{1,2,a}

 FIB-4	Age, platelets, AST, and ALT
 ELF™	TIMP-1, hyaluronic acid, PIIINP
NFS	Age, platelets, AST:ALT ratio, albumin, BMI, impaired fasting glucose, and/or diabetes



Imaging biomarkers^{1,2,a}

 VCTE (eg, FibroScan®)	Measure liver stiffness through elastography to detect and diagnose fibrosis or cirrhosis
MRE	
SWE	
cT1	Iron-corrected T1 from MRI



Combination biomarkers^{1,a}

FAST	FibroScan® and AST
MAST	MRI-PDFF, MRE, and AST
MEFIB	MRE and FIB-4



FIB - 4 Score Reflects Long –Term Health Outcomes

Risk of major adverse liver outcomes^b

>4x
greater

High FIB-4
vs
Low FIB-4
(*>2.67 vs <1.3 at baseline*)



Decrease in FIB-4 score from
high to low/indeterminate



decrease in
MALO^b and
expanded MACE^c

Risk of heart failure hospitalization

>2x
greater

High FIB-4
vs
Low FIB-4
(*>2.67 vs <1.3 at baseline*)



Increase in FIB-4 score from
low to indeterminate/high



increase in MALO^b,
expanded MACE^c,
and HFH

The risk of certain adverse events increases and decreases in proportion with changes to the FIB-4 score

^aBased on a retrospective analysis of a cohort of patients (Objective 1: 19,395, 18,828, 19,435, and 17,511 patients for the 2- and 3-point MACE, expanded MACE, HFH, and MALO outcomes, respectively; Objective 2: 11,934, 11,570, 11,991, and 10,655 for 2- and 3-point MACE, expanded MACE, HFH, and MALO outcomes, respectively) diagnosed with MASH between Oct 1, 2015, and June 30, 2022, utilizing the Optum Clinformatics database. Adult patients with MASH were indexed on their first NIT 180 days prior to and up to 180 days following the diagnosis of MASH. MASH was defined as the presence of ≥ 1 ICD-10-CM diagnostic code for the disease (K75.81) in the absence of other competing diagnoses that could induce liver damage. It consisted of 2 objectives: 1. Investigate the association between baseline NIT scores and major clinical outcomes (mortality, MALO, MACE, and other cardiac endpoints); 2. Investigate the association between changes in NIT scores and major clinical outcomes (MALO, MACE), and other cardiac endpoints. ^bDefined as occurrence of any of the following: cirrhosis (or complications attributable to cirrhosis), hepatocellular carcinoma, liver transplant recipient, or all-cause mortality. ^cIncluded AMI, coronary revascularization, stroke, HFH, and all-cause mortality. AMI, acute myocardial infarction; FIB-4, Fibrosis-4 index; HFH, heart failure hospitalization; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; MACE, major adverse cardiovascular events; MALO, major adverse liver outcomes; MASH, metabolic dysfunction-associated steatohepatitis; NIT, noninvasive test.
Data on File; 2024-Liv-RWE-00004



FIB - 4 Risk of Advanced Fibrosis

FIB-4

Risk of advanced fibrosis (stages 3-4)

Low:
<1.3
(F0-F1)

Indeterminate:
1.3 – 2.67
(F1-F2)

High:
>2.67
(F3-F4)

PARAMETERS

Age

AST

ALT

Platelets

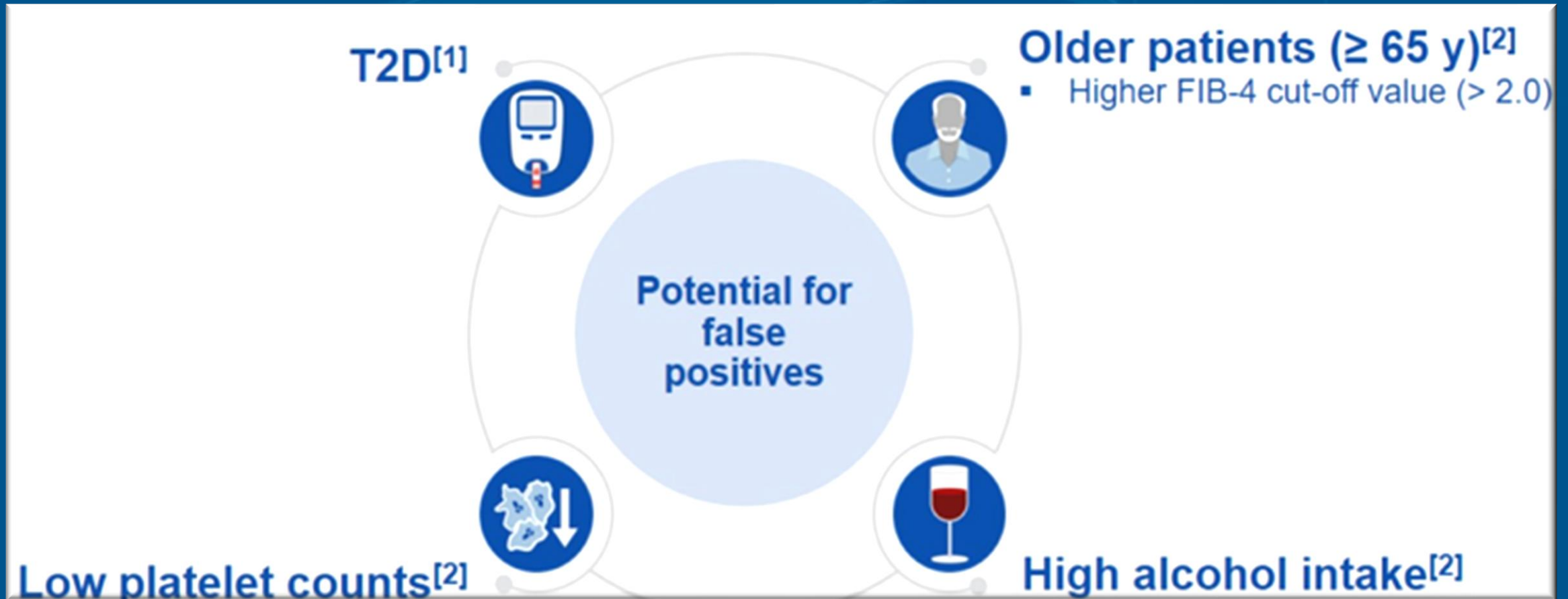
$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}} = 2.69$$

Age (years): 60
AST Level (U/L): 49
Platelet Count (10⁹/L): 140
ALT (U/L): 61

Plat < 150 Concern For Portal HTN. Liver Makes Platelet Growth Factor. Decreased With Scarring + Blood Backs Up Spleen = Hypersplenism



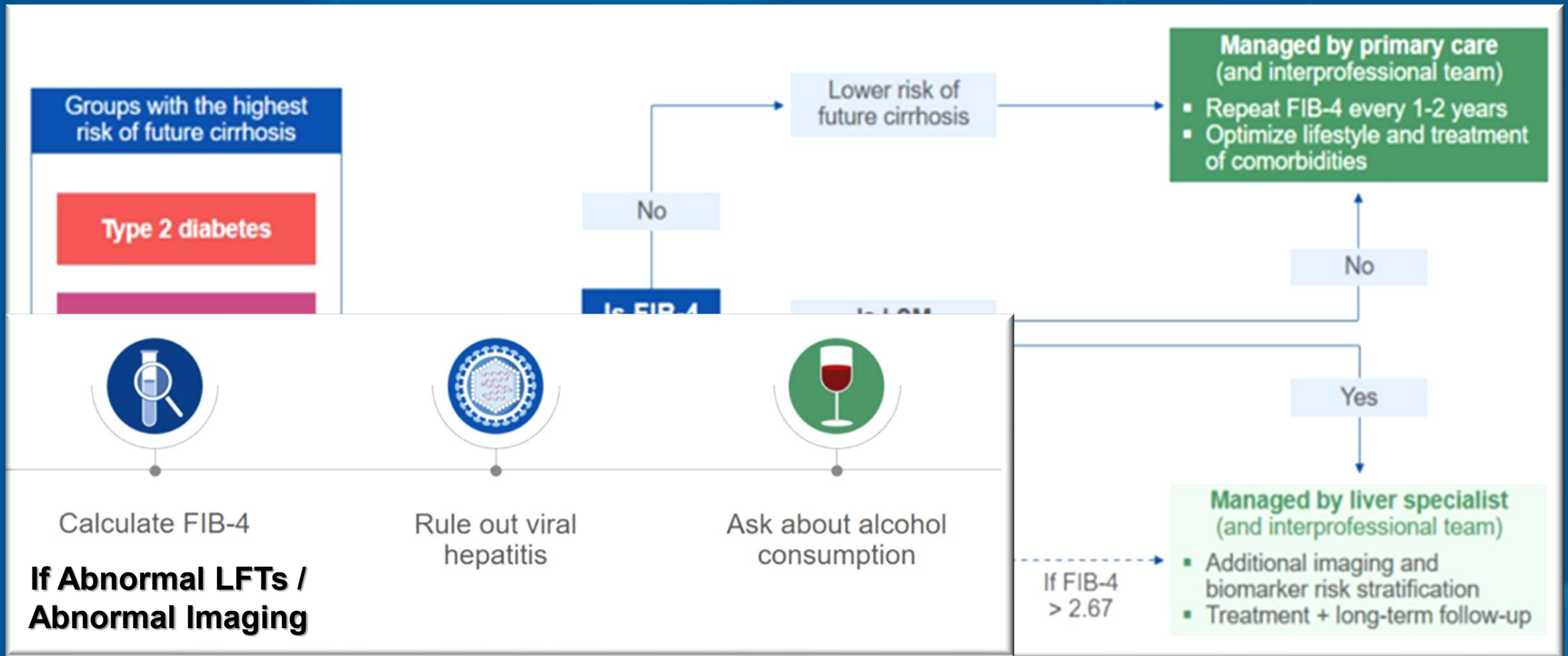
Limitations of FIB-4 In Certain Populations



King RG et al., *Diabetes Care* 2022;45:2449-2451. 2. AASLD 2024



ADA 2025 Guidance: MASH Dx Algorithm



Patient Ms Smith

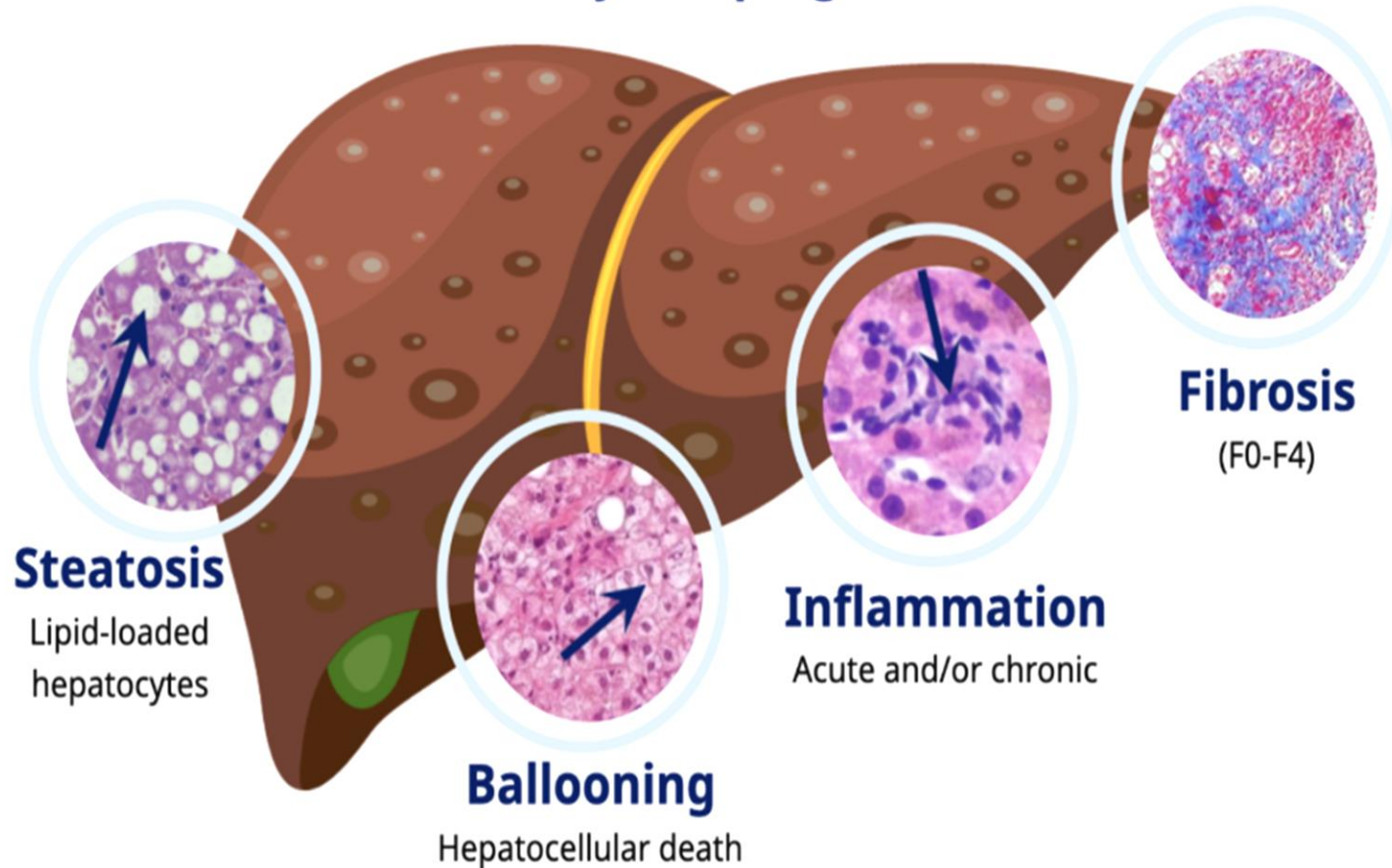
- ▶ 60 y/o F With Abnormal LFT's, Hx Obesity Refractory to Lifestyle Changes.
- ▶ PMHx: T2DM (A1c 7.1%), Obesity, Metabolic Syndrome.
- ▶ Social: CAGE ? Negative
- ▶ Meds: Metformin
- ▶ Labs: AST 49 IU/L, ALT 61 IU/L Hepatitis C Serology Negative, Platelets 140 (150-400)
- ▶ FIB - 4 Index 2.69

Which of the Following Would Be Your Next Step In Management?

- A. Watchful Waiting Given Low Risk For Hepatic Fibrosis**
- B. Liver Transient Elastography**
- C. Liver U/S**
- D. Liver Biopsy**

Elastography – Based Imaging For Fibrosis IN MASLD

Disease activity and progression^{3,4}

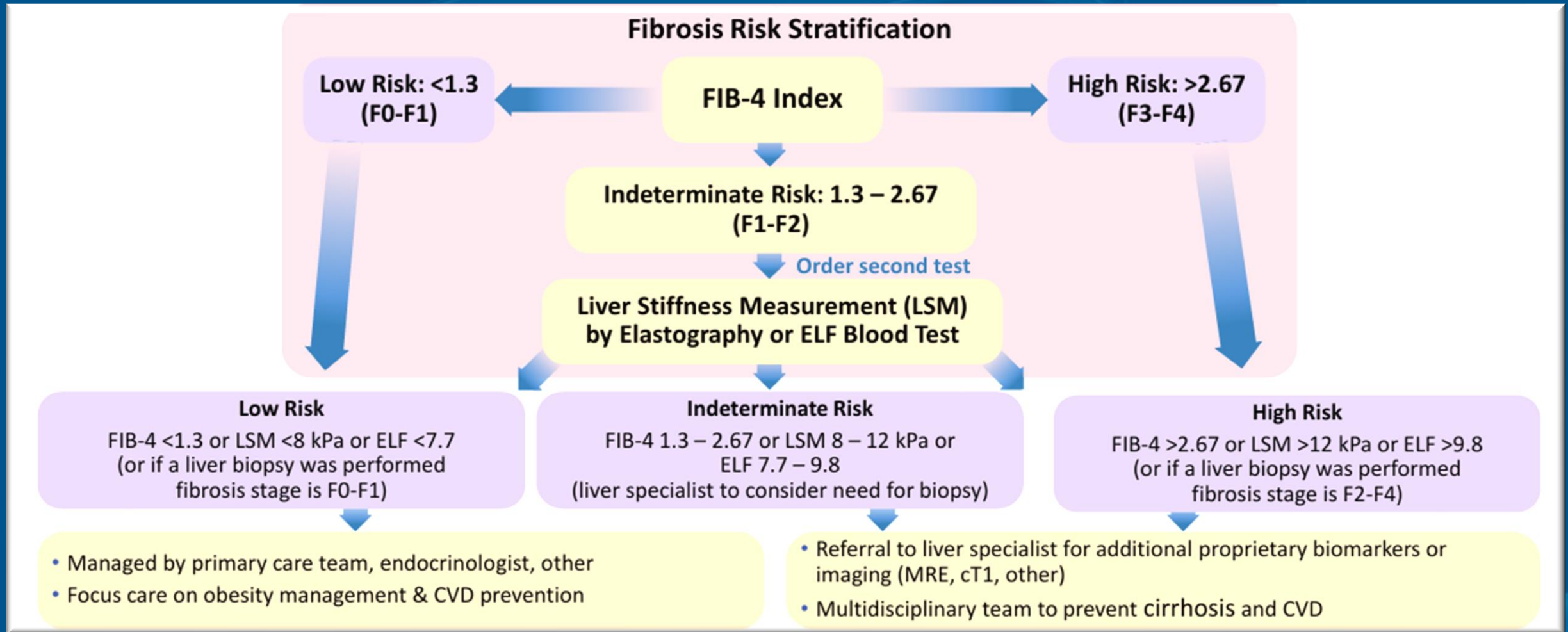


LFTs & U/S Not Considered Screening. Lack Sensitivity / Specificity For Screening
Liver biopsy is costly, invasive, and carries risk of potentially serious complications⁵

Small Pieces
1-1.5 cm Length, 1.2-2 mm Diameter
Mis-Staging in 40% Cases
~1/50,000 of the Liver / Sampling Variability
Bleeding (0.35%)

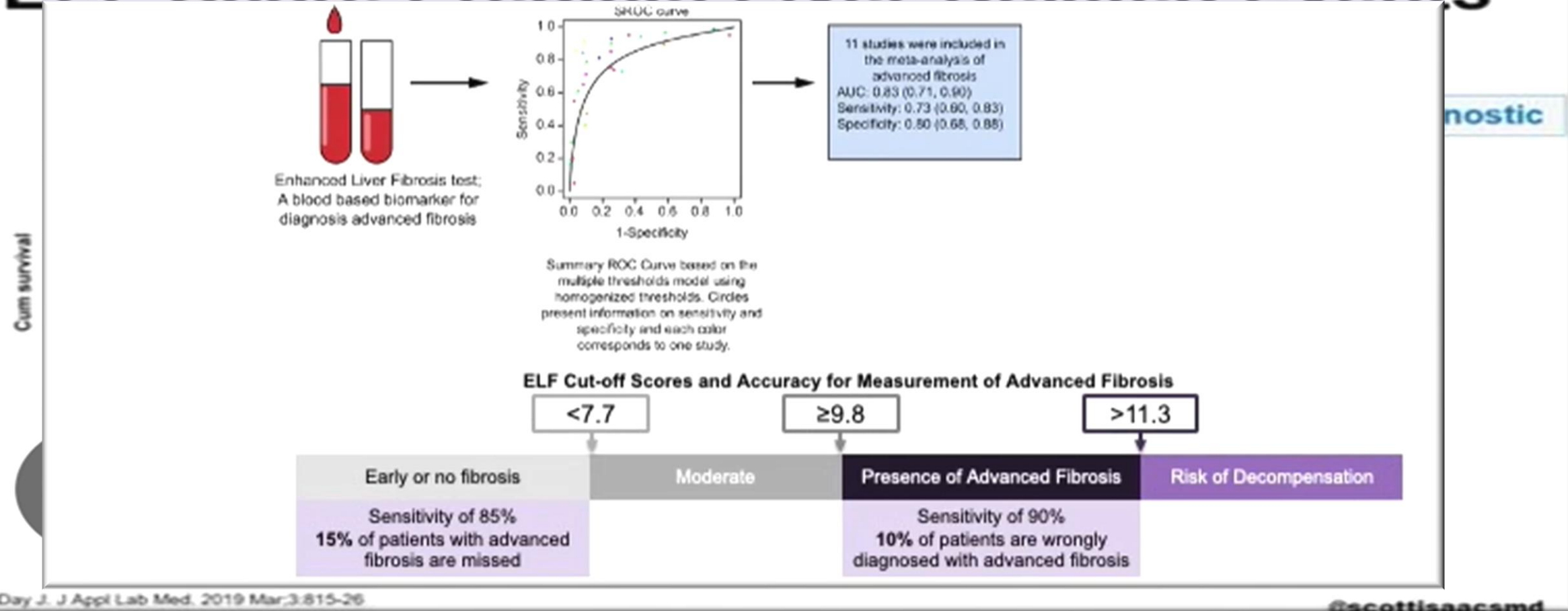


Cirrhosis Prevention in MASLD



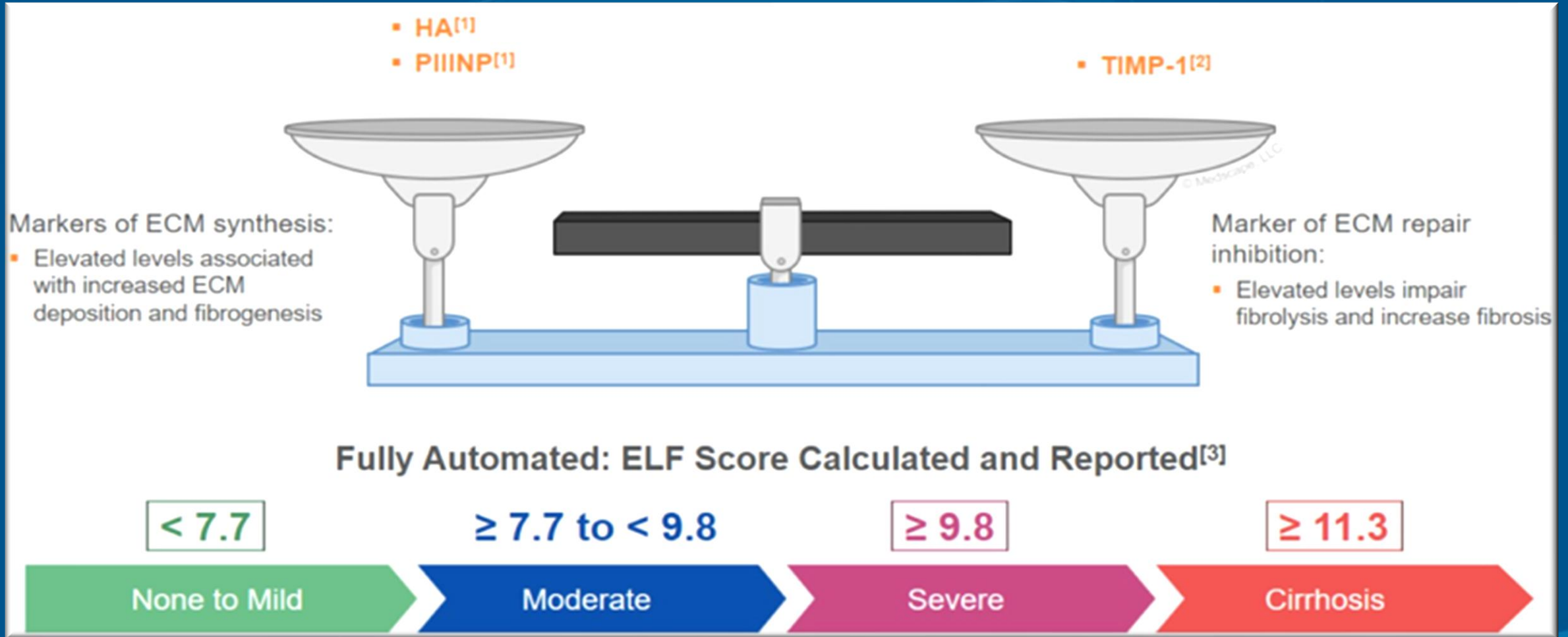
Enhanced Liver Fibrosis (ELF) Blood Test

ELF Score Predicts Liver-Related Events

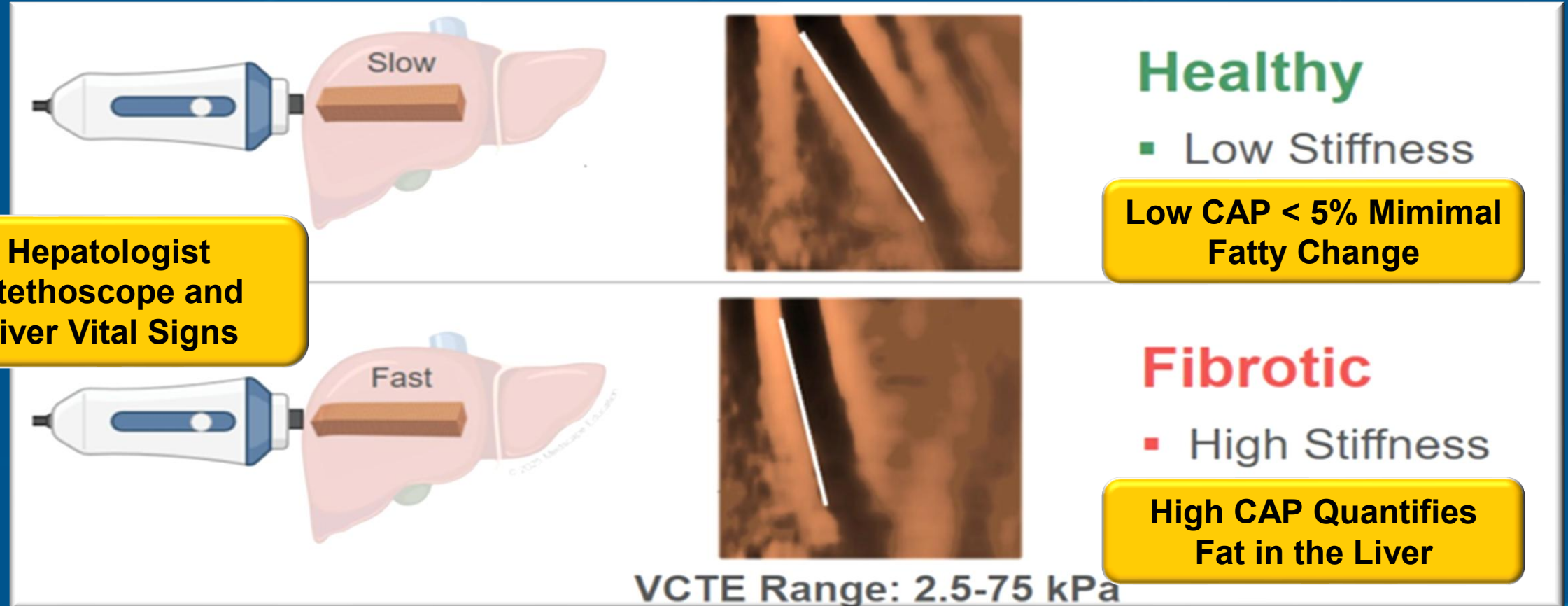


Liguori A, D'Ambrosio F, Viceconti N, et al. Prognostic Significance of ELF Test Compared to Liver Biopsy in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Abstract Presented at: AASLD 2024; November 15-19, 2024. San Diego, CA. Abstract 874.

ELF Test For Prognosis In Advanced MASH



Vibration Controlled Transient Elastography: Liver Stiffness Correlates To Fibrosis Level



Eddowes PJ et al., *Gastroenterology*. 2019;156:1717-1730



Revisit Patient Ms Smith

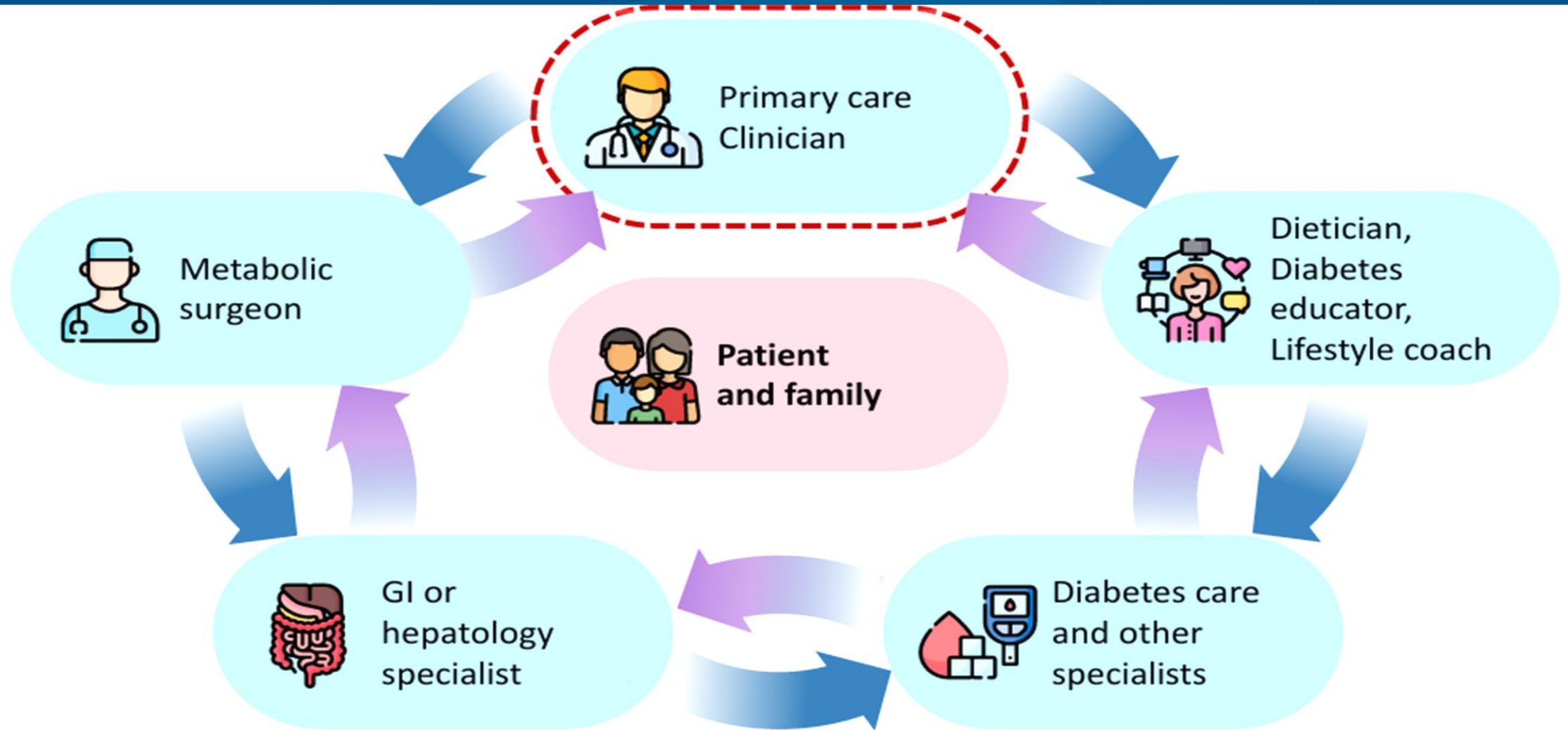
- ▶ 60 y/o F With Abnormal LFT's
- ▶ PMHx: T2DM (A1c 7.1%), Obesity (BMI 34.6 kg/m²), Metabolic Syndrome (Refractory to LSM).
- ▶ Social: CAGE ? Negative
- ▶ Meds: Metformin
- ▶ Labs: AST/ALT 49 / 61 Plat 140, Hepatitis C Serology Negative
- ▶ FIB-4 Index 2.69
- ▶ VCTE: LSM 10.9 kPa (MASH with Fibrosis F3)

What is the Most Appropriate Next Step in Management?

- A. Wait & Watch**
- B. Re-Emphasize LSM**
- C. Optimize Pharmacologic Rx For DM Benefits For MASH**
- D. Refer to Hepatology**



The Multi-Disciplinary Team For MASLD



Cusi K et al. Diabetes Spectr 2024;37(1):29-38.



Management Approach

❖ Avoidance of ETOH

❖ Weight Loss:

- 3-5% Improve Steatosis; > 10% MASH Fibrosis. Multi-Disciplinary Approach

Vilar-Gomez E et al. *Gastroenterology* 2015;149(2):367-378
Aminian A et al. *JAMA*. 2021;326(20):2031-2042
Rinella ME et al., *Hepatology* 2023;77(5):1797-1835

Mean weight loss

<5%

5%–6.99%

7%–9.99%

≥10%



Bariatric surgery in patients with MASH and obesity was associated with¹:



12.4%

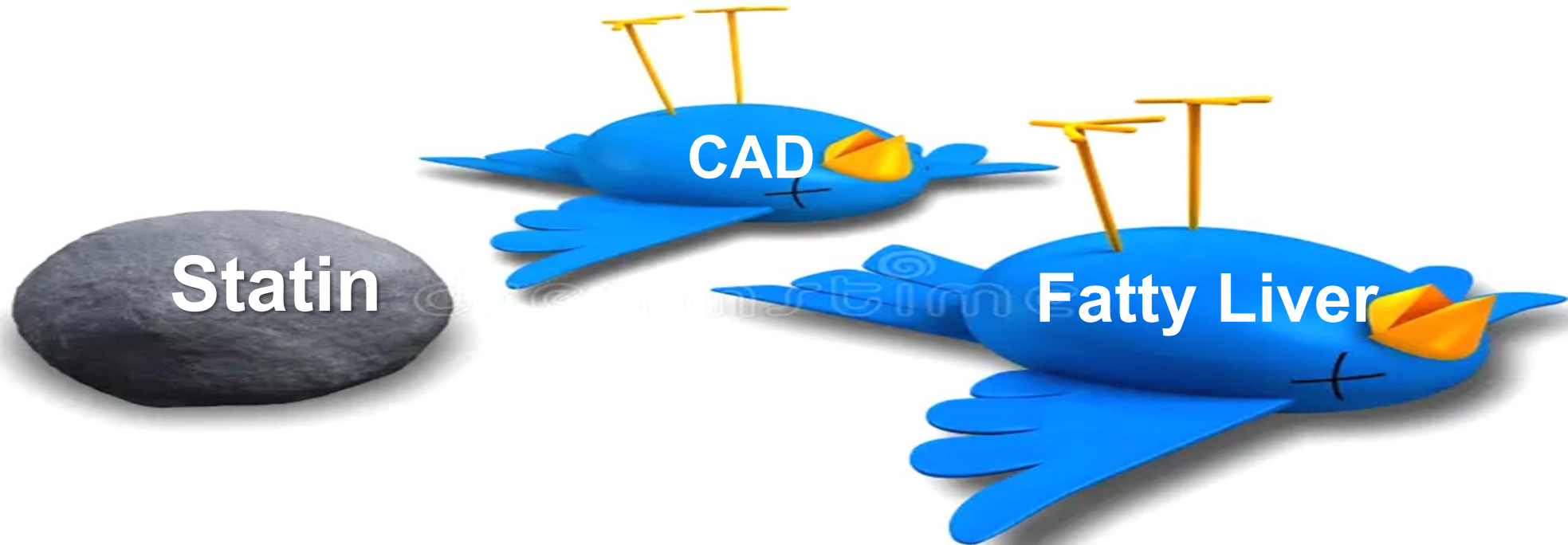
Adjusted 10-year absolute risk difference of major adverse liver outcomes^a



13.9%

Adjusted 10-year absolute risk difference of major adverse cardiovascular events^b

ADA 2025 Recommendations: Recommendations For CV Risk Reduction



Medications For T2DM

Effects In MASLD

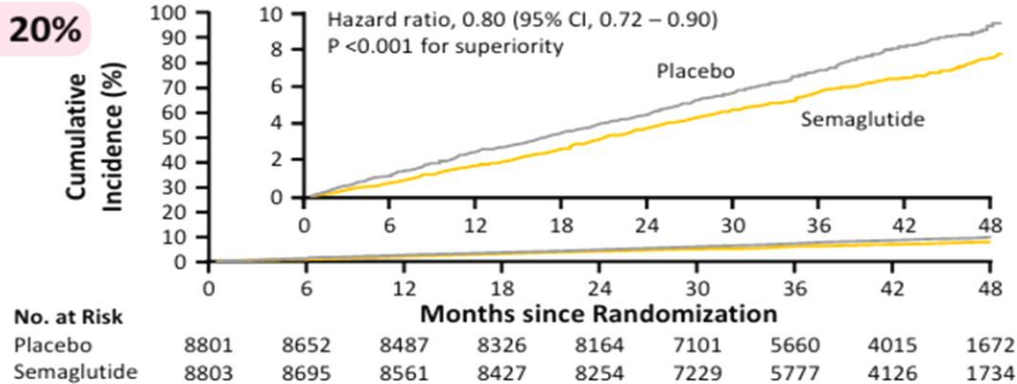
Drug/Drug Class	Steatosis	Steatohepatitis	Fibrosis	Cardiovascular Risk
Pioglitazone			Reduces progression	
GLP-1 receptor agonists			Reduces progression	
SGLT2 inhibitors		?	?	



SELECT Trial: Semaglutide, MACE, Mortality

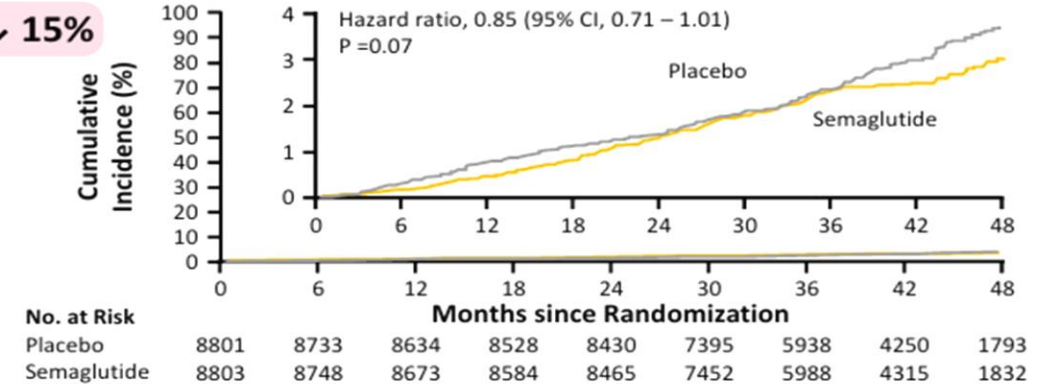
A. Primary Cardiovascular Composite End Point

↓ 20%



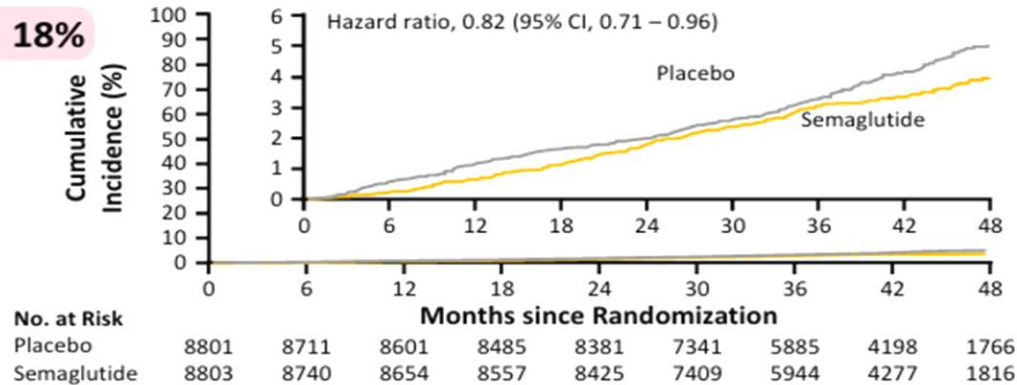
B. Death from Cardiovascular Causes

↓ 15%



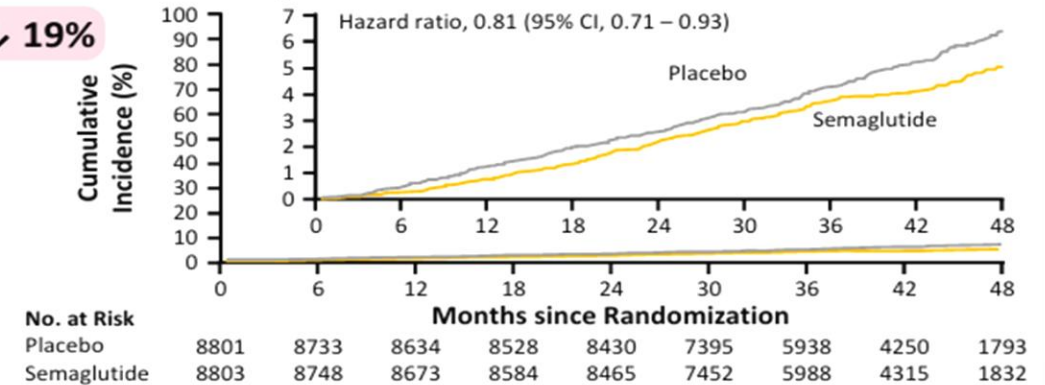
C. Heart Failure Composite End Point

↓ 18%



D. Death from Any Cause

↓ 19%



Lincoff AM et al. N Engl J Med 2023;389:2221-2232.



Studies Of GLP-1 RA MASLD

Primary outcome: relative reduction in liver fat on imaging

Author	GLP1-RA	Weight change	Reduction in liver fat content
Vanderheiden et al, 2016	Liraglutide	↓ 2.2%	↓ 31%
Feng et al, 2017	Liraglutide	↓ 6.4%	↓ 19%
Petit et al, 2017	Liraglutide	↓ 4.4%	↓ 19%
Frossing et al, 2018	Liraglutide	↓ 5.7%	↓ 32%
Kuchay et al, 2020	Dulaglutide	↓ 2.6%	↓ 20%

Primary outcome: percentage of patients with resolution of MASH (by liver histology)

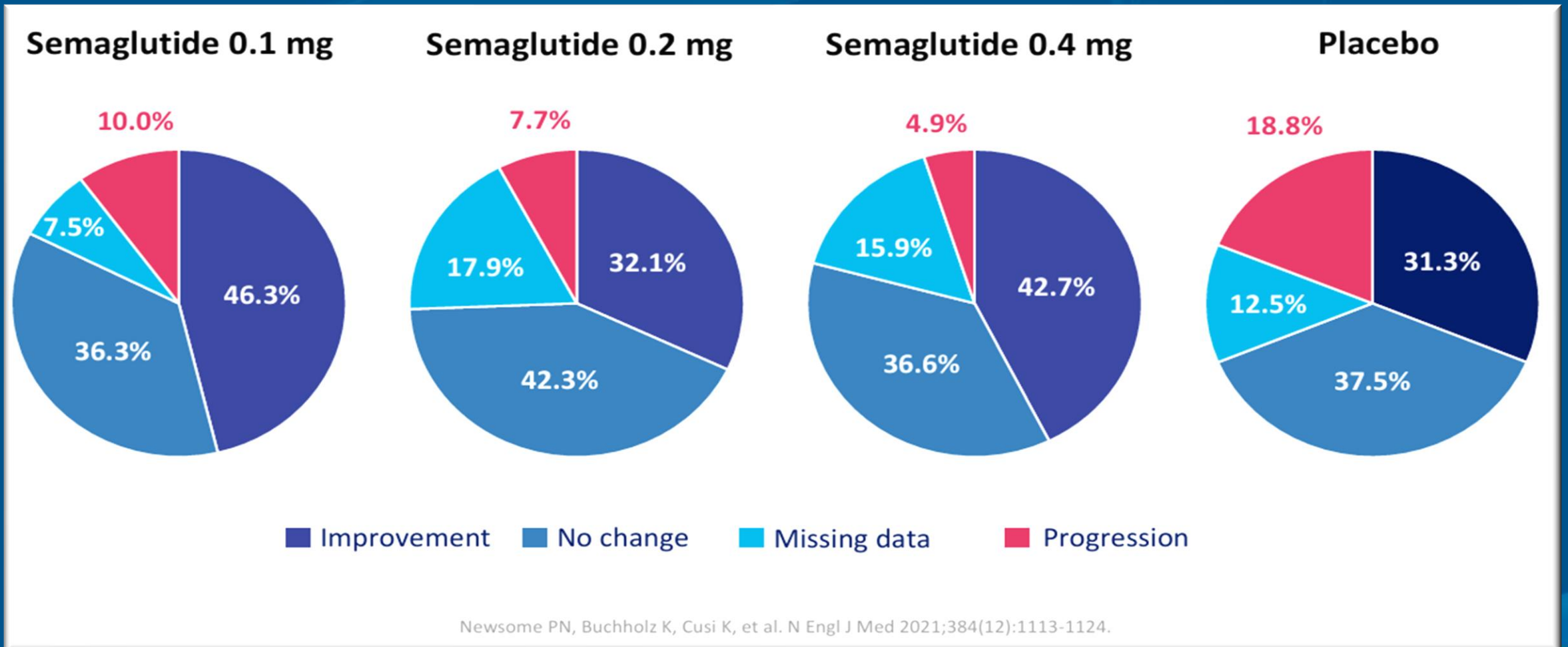
Author	GLP1-RA	Weight change	NASH resolution
Armstrong et al, 2016	Liraglutide	↓ 4.8%	30%
Newsome et al, 2020	Semaglutide	↓ 4%-12%	19%-42%

Studies with a minimal treatment period of ≥24 weeks and ≥50 patients. Arrows indicate statistically significant changes vs comparator.
Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; RCT, randomized controlled trial.

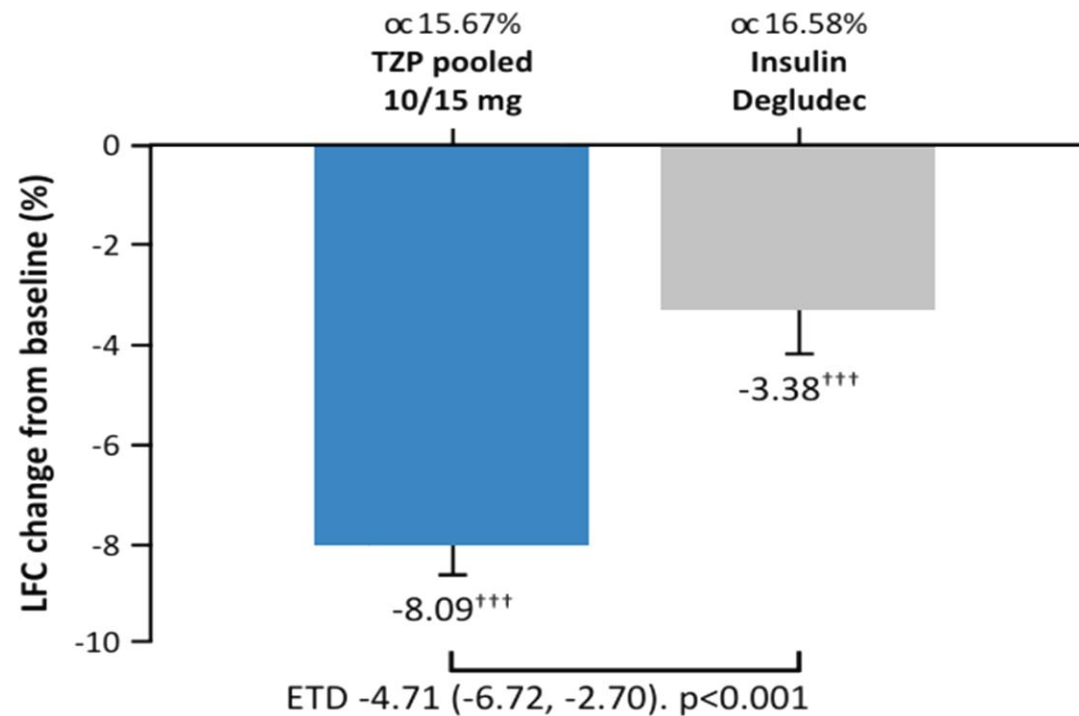
Chavez C, Cusi K, and Kadiyala S. JCEM 2022;107:29-38.



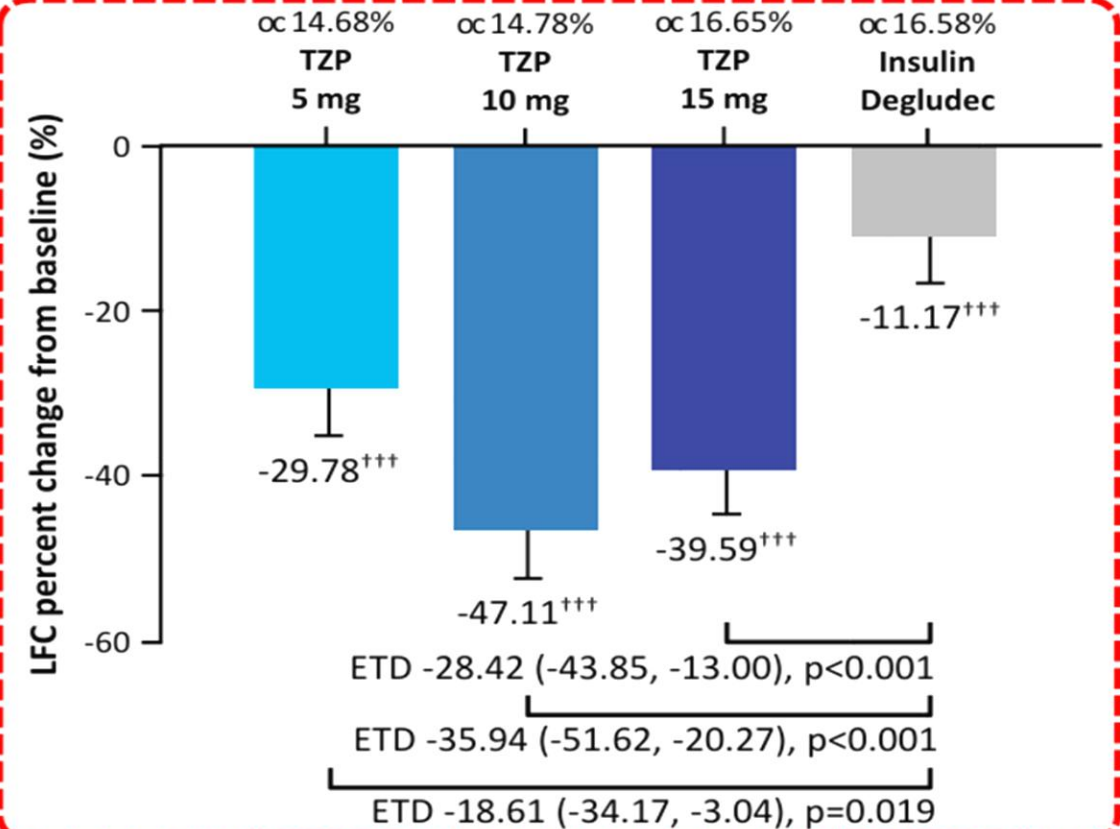
MASH In Patients On Semaglutide



SURPASS-3 Trial: Tirzepatide, Insulin, & Liver Fat Content



Data are LSM (SE) at 52 weeks. Estimated treatment differences (ETD) at 52 weeks are LSM (95% CI); mITT (MRI analysis set). ANCOVA analysis. † p<0.05; ††† p<0.001 vs. baseline within treatment group. α represents the mean value at baseline for the respective group.



Gastaldelli A, Cusi K, Landó L, et al. Lancet Diabetes Endocrinol. 2022;10:393-406.



SYNERGY-NASH: MASH In Patients On Tirzepatide

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

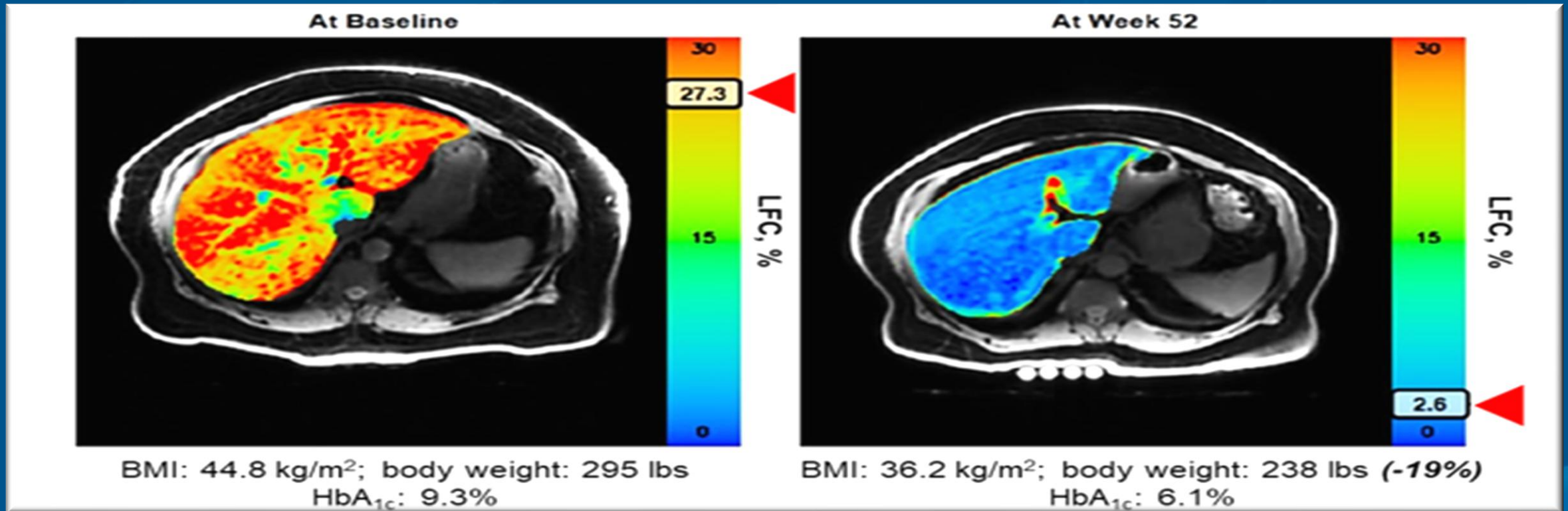
R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

Loomba R et al. N Engl J Med 2024;391:299-310.



SURPASS-3 MRI Sub-Study: MASLD Before & After 52 Weeks Tirzepatide

59 y/o Male: Metformin / SGLT-2i: Randomized to 5 mg Tirzepatide QWeek



Gastaldelli A et al., Lancet Diabetes Endocrinol. 2022;10:393-406



ESSENCE – New Top - Line Data

Semaglutide & MASH

Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis

Authors: Arun J. Sanyal, M.D., Philip N. Newsome, M.B., Ch.B., Ph.D., Iris Kliers, M.D., Laura Harms Østergaard, M.Sc., Michelle T. Long, M.D., Mette Skalshøi Kjær, M.D., Ph.D. , Anna M.G. Cali, M.D., Elisabetta Bugianesi, M.D., Ph.D., Mary E. Rinella, M.D., Michael Roden, M.D., and Vlad Ratziu, M.D., Ph.D., for the ESSENCE Study Group* [Author Info & Affiliations](#)

Published April 30, 2025 | N Engl J Med 2025;392:2089-2099 | DOI: 10.1056/NEJMoa2413258

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63.3%

of participants
had FIB-4 ≥ 1.3

64.0%

of participants
had liver stiffness
VCTE > 8 kPa

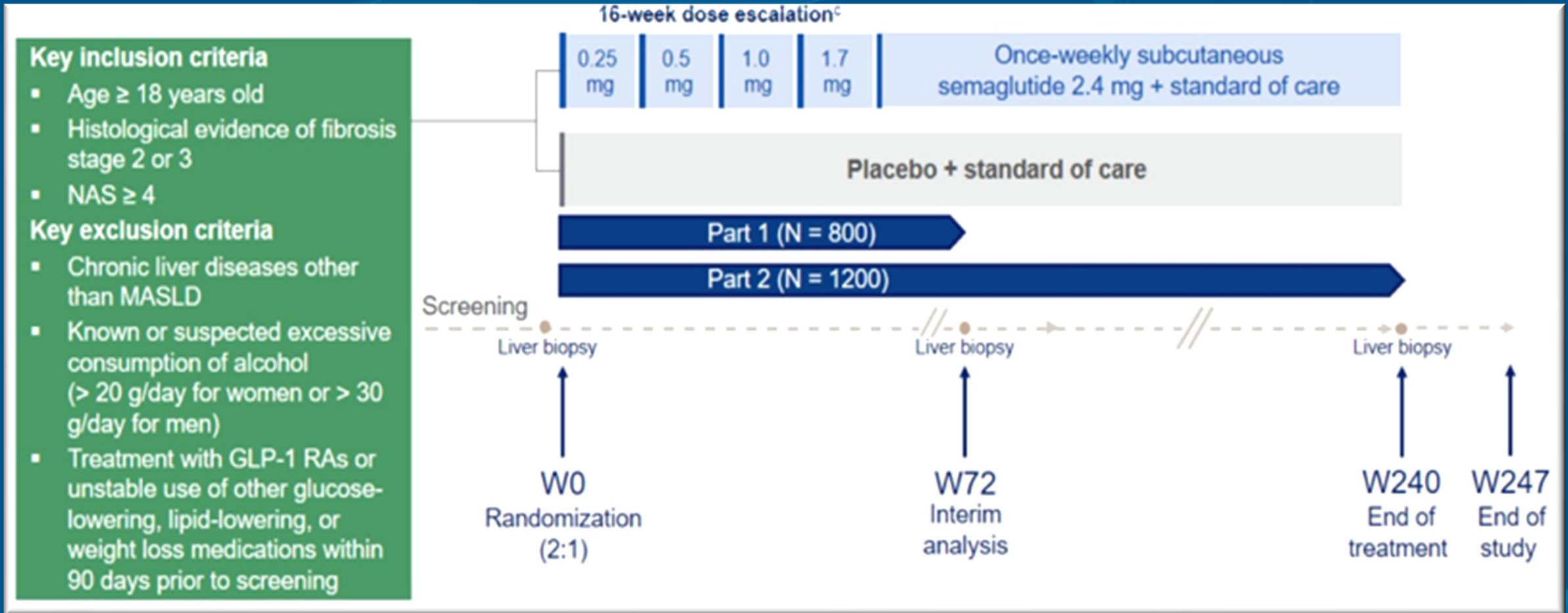
55.5%

of participants
had ELF ≥ 9.8

with Semaglutide

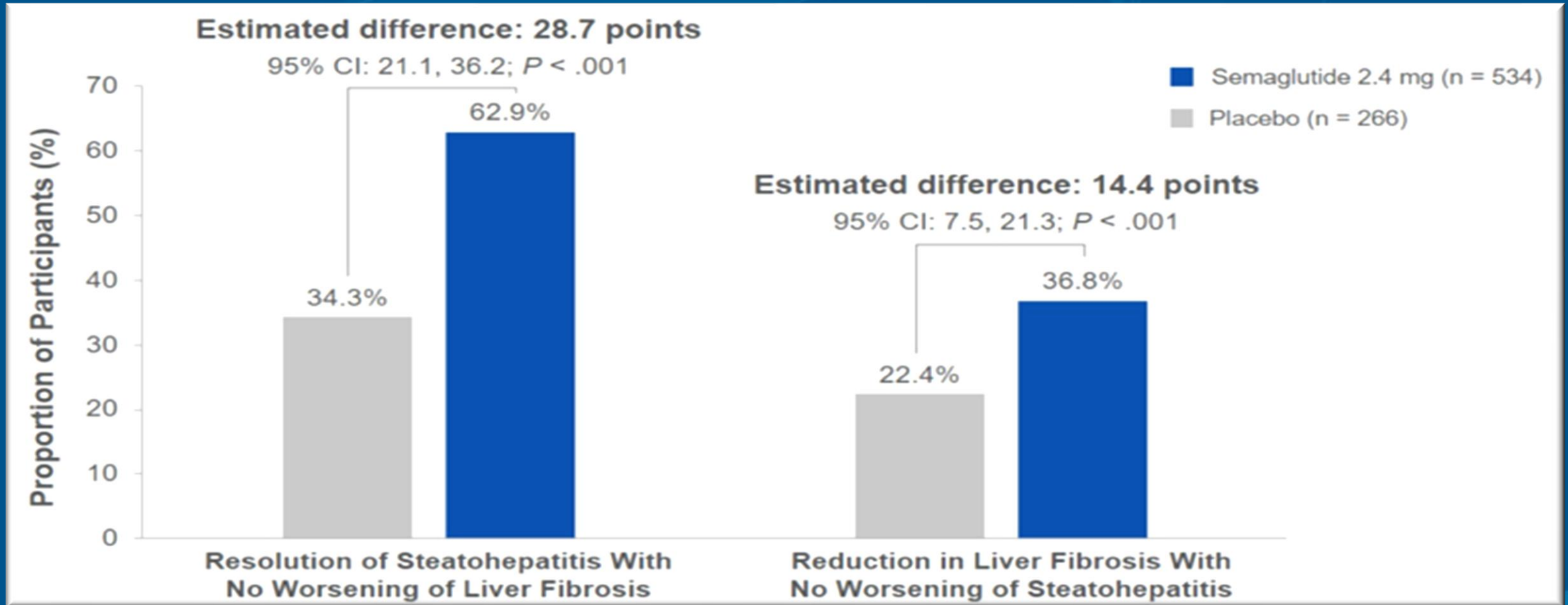
(Mod – Advanced Fibrosis)

Semaglutide In MASH: Phase 3 ESSENCE Trial Design

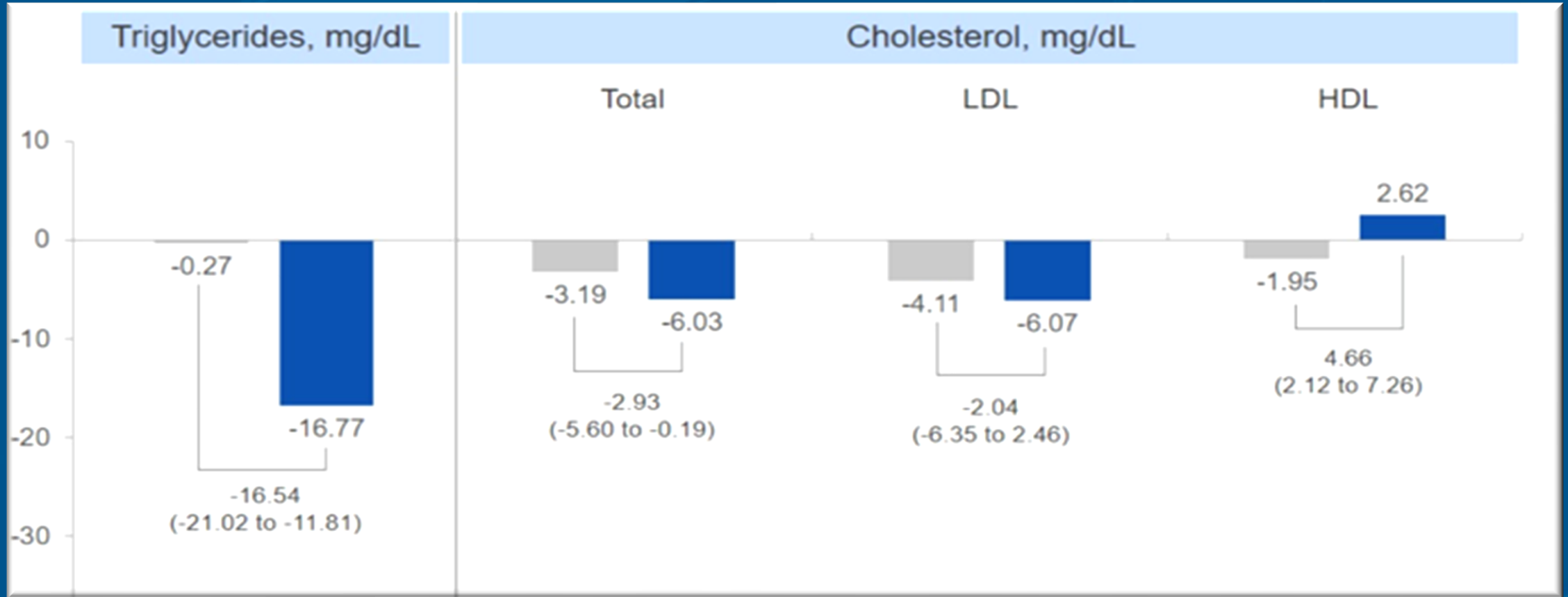


Semaglutide In MASH: ESSENCE Trial

Primary Endpoints



Semaglutide In MASH: Effects On Lipids



Semaglutide In MASH: ESSENCE Trial

Safety Summary

	Placebo (N = 395)	Semaglutide 2.4 mg (N = 800)
	n (%)	n (%)
All AEs	315 (79.7)	690 (86.2)
Fatal AEs	6 (1.5)	3 (0.4)
Serious AEs	53 (13.4)	107 (13.4)
AEs leading to trial discontinuation	13 (3.3)	21 (2.6)
AEs affecting $\geq 10\%$ of participants		
Nausea	52 (13.2)	290 (36.2)
Diarrhea	48 (12.2)	215 (26.9)
Constipation	33 (8.4)	178 (22.2)
Vomiting	22 (5.6)	149 (18.6)
COVID-19	74 (18.7)	134 (16.8)
Decreased appetite	11 (2.8)	112 (14.0)



Benefits GLP1-RA's In Patients With MASLD

GLP-1 RAs have benefits in patients with T2D, overweight or obesity, and MASLD at every fibrosis stage **except** decompensated cirrhosis

Indications for GLP-1 RA Use in MASLD

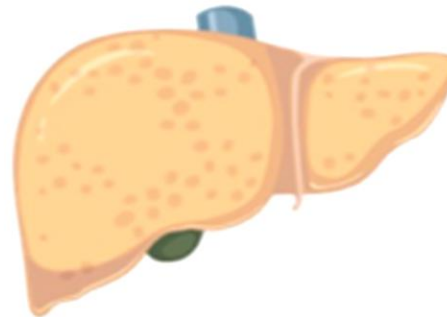
Overweight:
BMI > 27 with
2 obesity-related conditions

Obesity (BMI > 30)

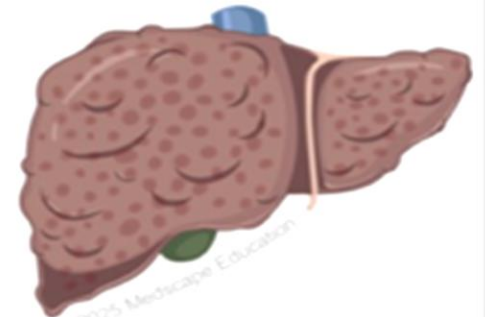
T2D



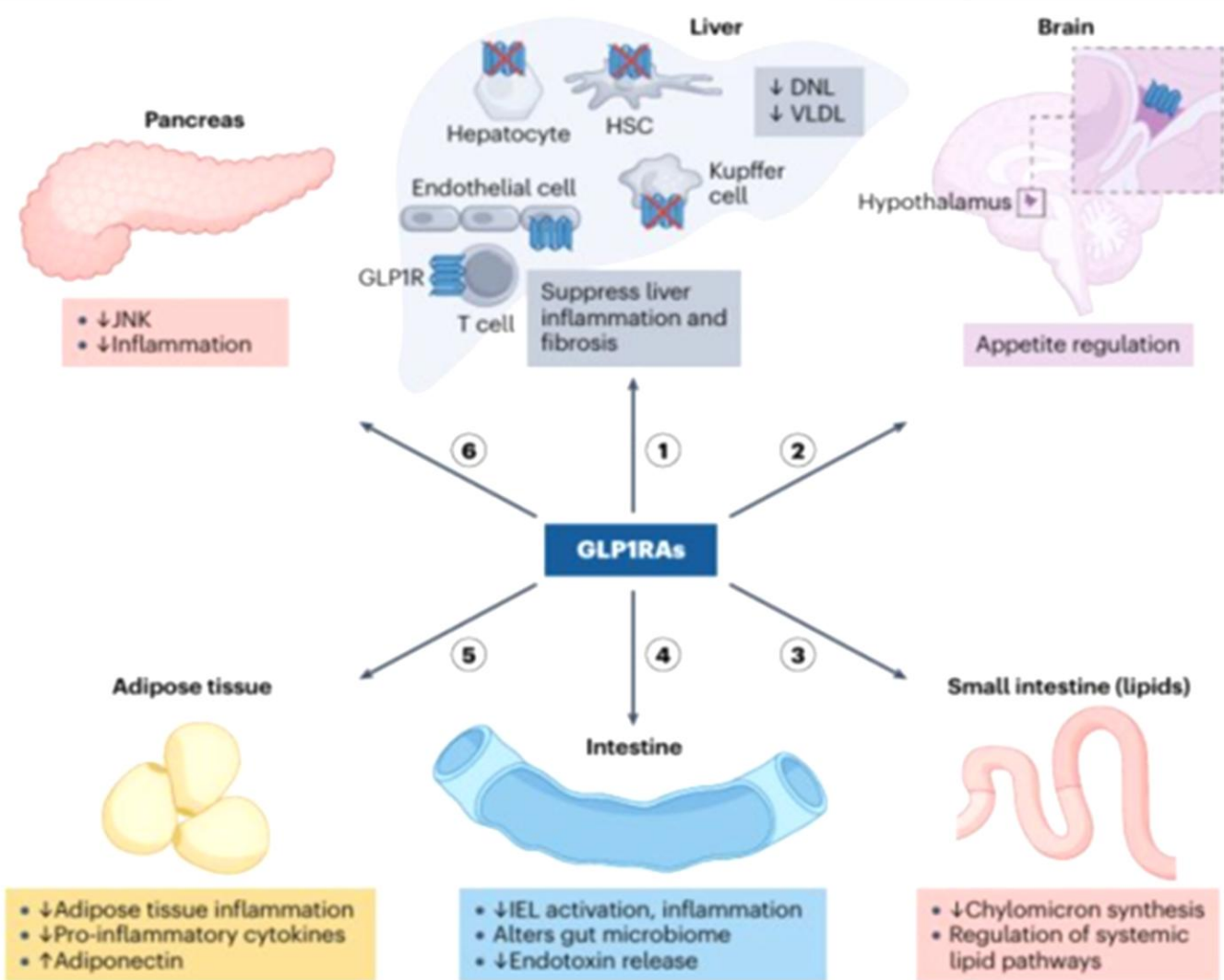
Fibrosis Stage



F0: None
F1: Centrilobular pericellular
F2: Centrilobular and periportal
F3: Bridging
F4: Cirrhosis (compensated)

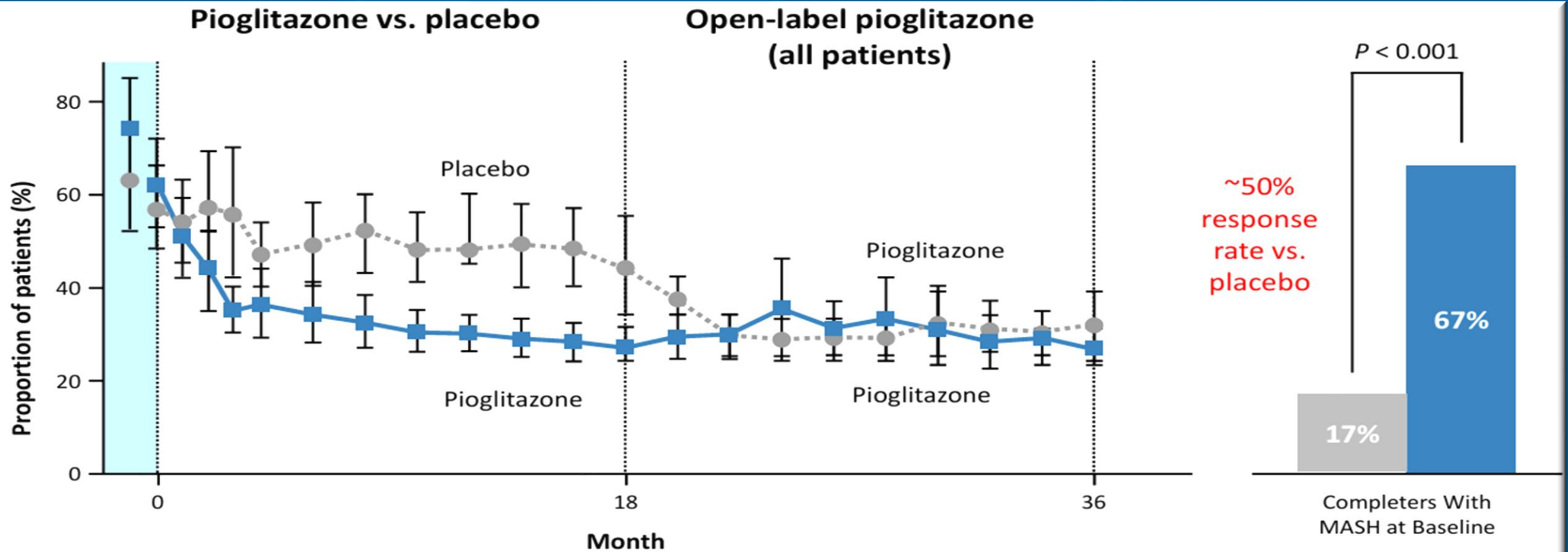


GLP-1 RA Improve MASH Mostly Via Extrahepatic Actions



- ✓ **CNS Appetite Control → Weight Loss ↓ Systemic Inflammation**
- ✓ **↓ Chylomicron Synthesis & Improve Lipid Metabolism**
- ✓ **Bind Gut Immune Cells → Anti-Inflammatory + Microbiome Benefits**
- ✓ **Reduce Adipose & Pancreatic Inflammation**

Plasma ALT & Pioglitazone Compared To Placebo



Cusi K et al, Ann Intern Med 2016;165:305-15.



Pioglitazone & CVDz In MASLD

Medicine®

Systematic Review and Meta-Analysis

OPEN

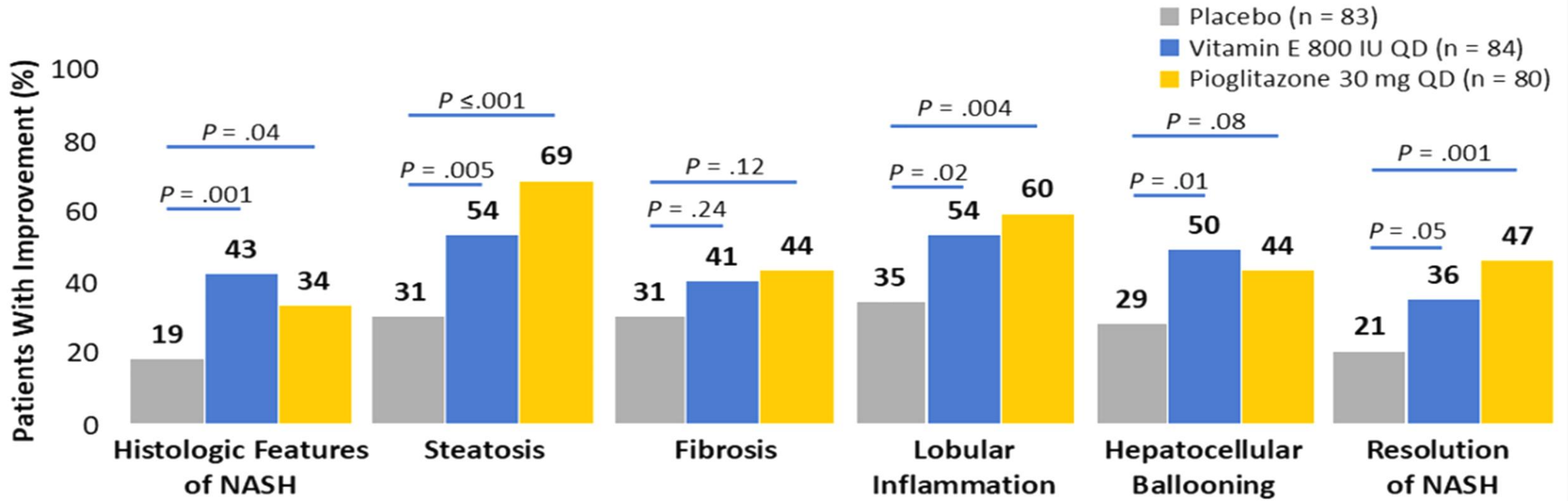
Pioglitazone on nonalcoholic steatohepatitis **A systematic review and meta-analysis of 15 RCTs**

Yan Zhao, Master^{a,b}, Wenli Zhao, PhD^{c,d}, Hongwu Wang, PhD^e, Ye Zhao, PhD^f, Huaien Bu, PhD^g, Hirokazu Takahashi, PhD^{h,*}



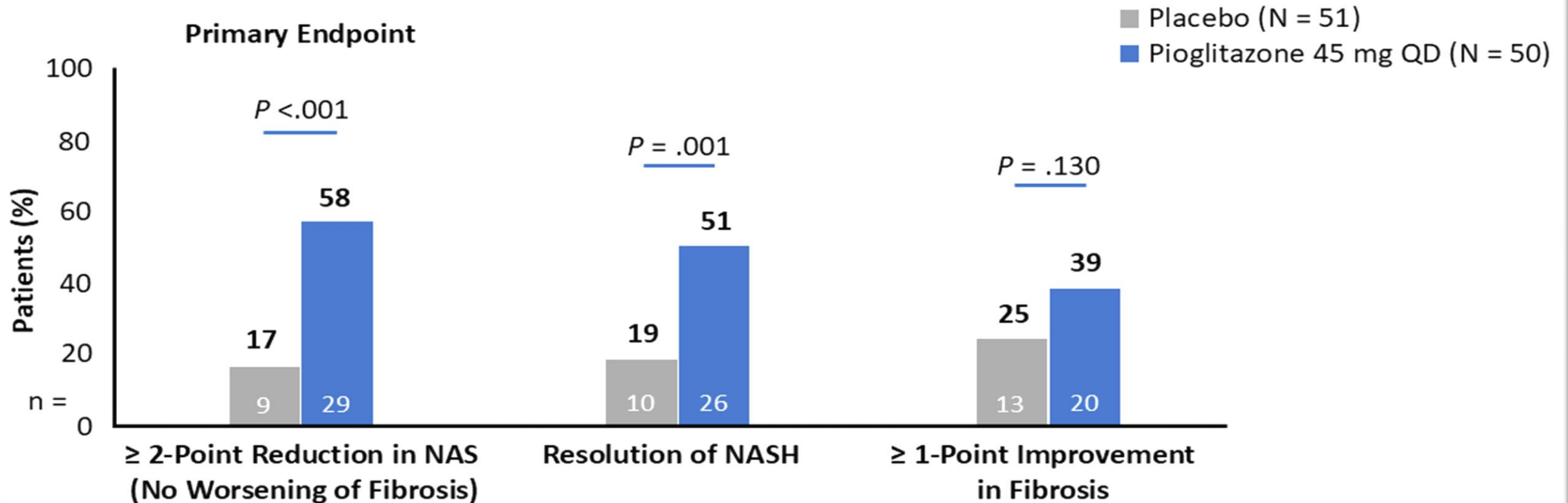
PIVENS: Pioglitazone & Vitamin E In MASH @ 96 Weeks

- Double-blind, placebo-controlled, randomized phase III study in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)



Pioglitazone In MASH With Pre-DM / Diabetes: 18 Month Outcomes

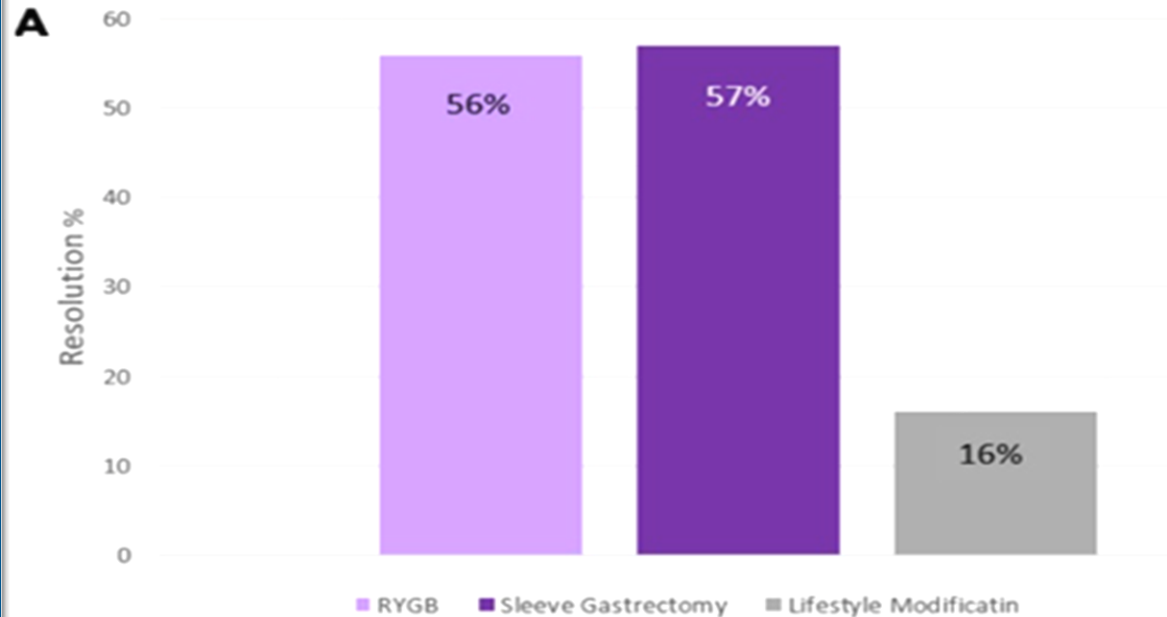
- Randomized, placebo-controlled, double-blind phase IV study of patients with NASH and prediabetes or T2D (N = 101)^[1]



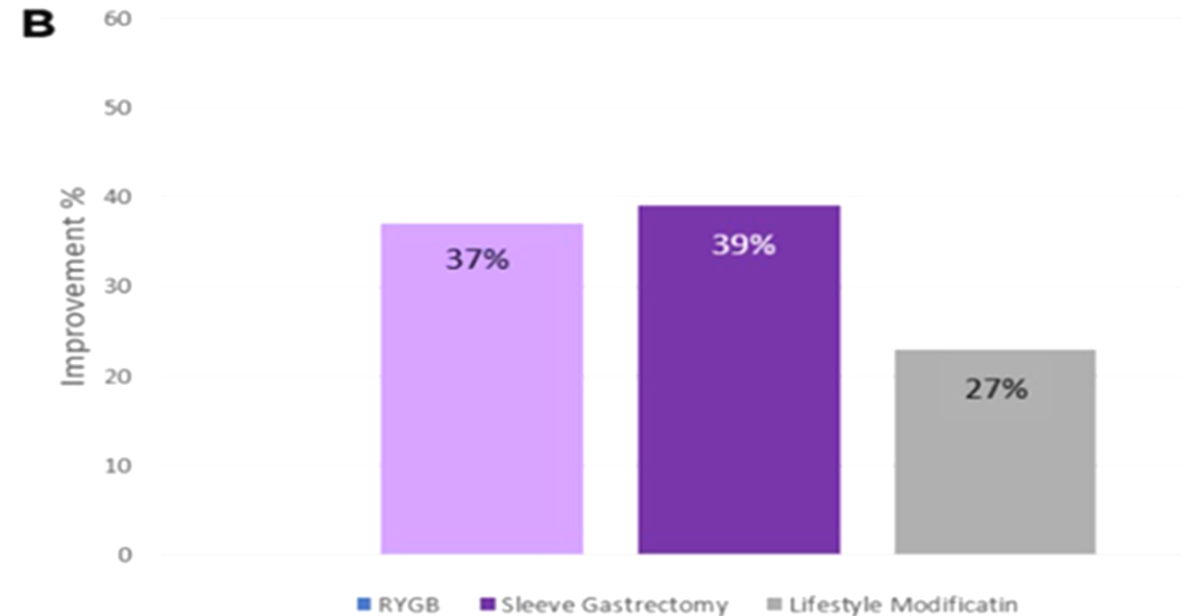
BRAVES Study: Bariatric Surgery Superior To Lifestyle / Medical Treatment In MASH

288 subjects with MASH, randomized 1:1:1 to RNYGB, Sleeve gastrectomy or medical treatment
Medical treatment included vitamin E (Pioglitazone and/or Liraglutide in subjects with T2D)

Resolution of MASH without worsening fibrosis



Improvement in at least one stage of fibrosis without worsening of MASH



1. Aminian. JAMA. 11/11/21. doi:10.1001/JAMA.2021.19569.

2. Verrastro O. et al., *Lancet*. 2023;401:1786-1797



New Emerging Therapies

- ❖ Resmetirom (THR-Beta Agonist)
- ❖ **FDA Approval March 2024**: Indicated In Conjunction With Diet & Exercise Treatment of Adults with:
 - Non - Cirrhotic Non - Alcoholic Steatohepatitis (NASH) With
 - Moderate – To – Severe Liver Fibrosis (F2 – F3)



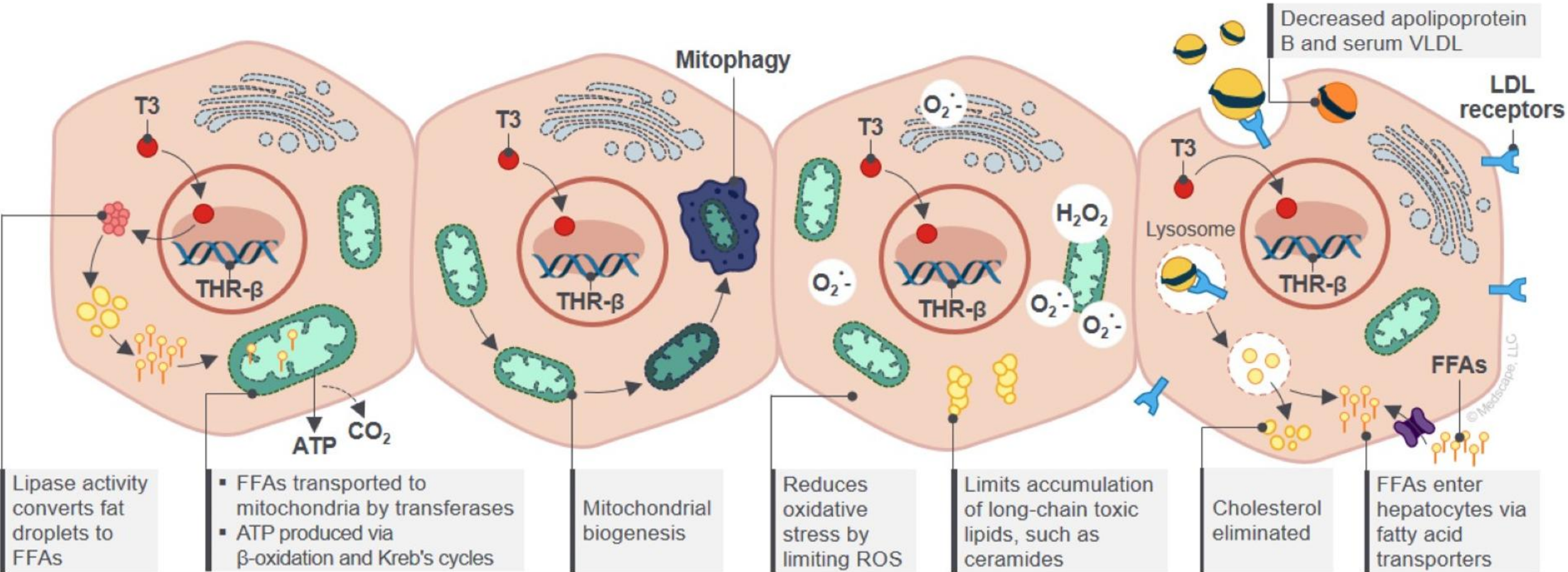
Role THR - Beta In Hepatic Lipid Metabolism

Increases lipophagy
and β -oxidation

Enhances
mitophagy

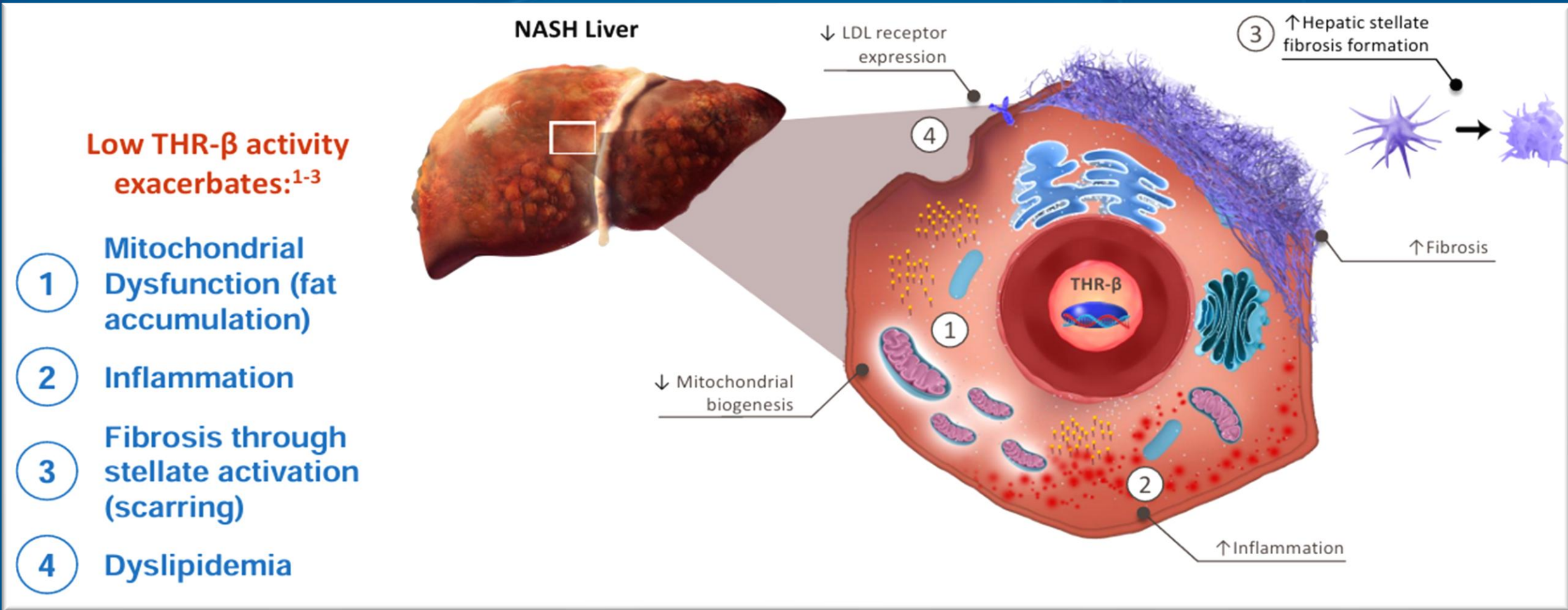
Reduces ROS
and inflammation

Increases
cholesterol clearance



1. Ritter MJ et al., *Hepatology*. 2020;72:742-752.
2. Sinha RA et al., *Nat Rev Endocrinol*. 2018;14:259-269.
3. Taub R et al, *Atherosclerosis*. 2013;230:373-380.
4. Harrison SA et al., *Lancet* 2019;394:2012-2024

Thyroid Hormone Dysfunction Influences Key Pathways Involved In MASLD / MASH

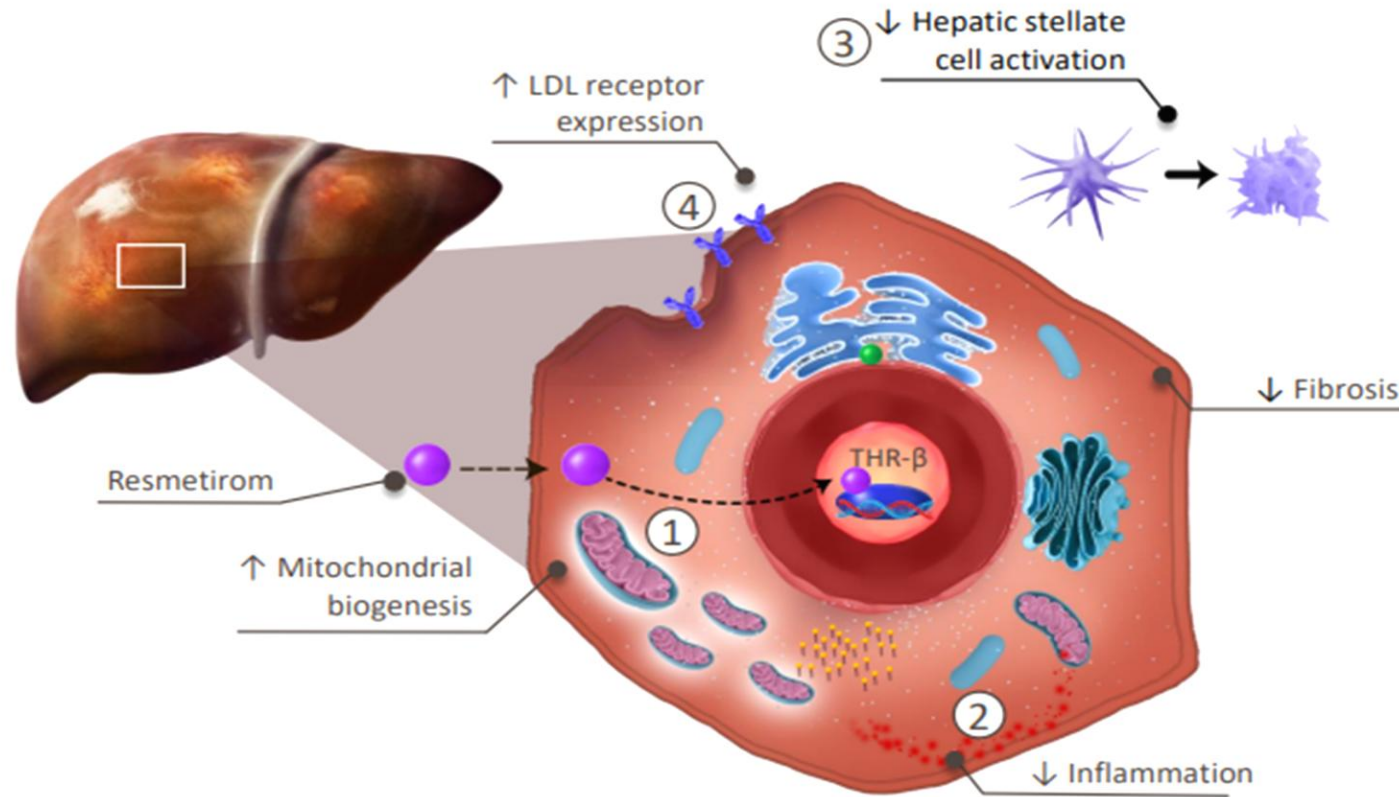


1. Sinha RA, et al. *Nat Rev Endocrinol*. 2018;14:259-269. 2. Karim G, Bansal MB. *touchRev Endocrinol*. 2023;19:60-70. 3. *Proc Natl Acad Sci USA*. 2016;113(24):E3451-E3460



Key Pathways Involved In NASH Pathology

Resmetirom MOA



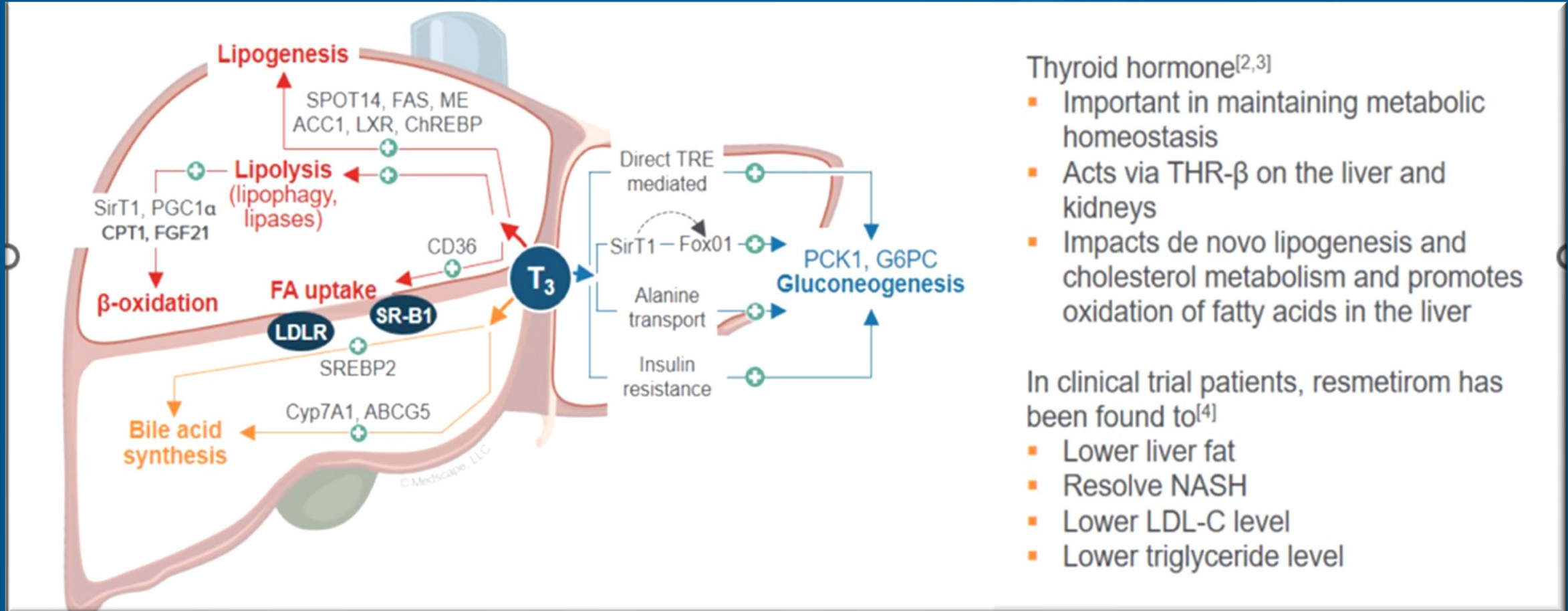
Resmetirom MOA¹⁻⁴

- 1 Mitochondrial biogenesis
- 2 Reduced inflammation
- 3 Reduced activation of hepatic stellate cells → decreased fibrosis
- 4 Increased LDL receptor expression

1. Sinha RA et al., *Nat Rev Endocrinol*. 2018;14:259-269. 2. Alonso-Merlino. *Proc Natl Acad Sci USA*. 2016;113(24):E3451-E3460. 3. Karim G, Basnsal MB. *touchRev Endocrinol*. 2023;19:60-70. 4. Harrison SA. *N Engl J Med*. 2024 Feb 8;390(6):497-509



Resmetirom MOA: THR-Beta Agonist



1. Sinha RA et al., *Trends Endocrinol Metab.* 2014;25:538-545. 2. Ritter MJ et al., *Hepatology.* 2020;72:742-752. 3. Sinha RA et al., *Cell Biosci.* 2016;6:46. 4. Harrison SA et al., *Lancet* 2019;394:2012-2024

Resmetirom PK / PD

Specificity/Selectivity¹⁻⁵

- Liver: Plasma ratio = 10:1
- 18-28x selective for Beta:Alpha
- 99% protein bound
- Half life = 4.5 hours

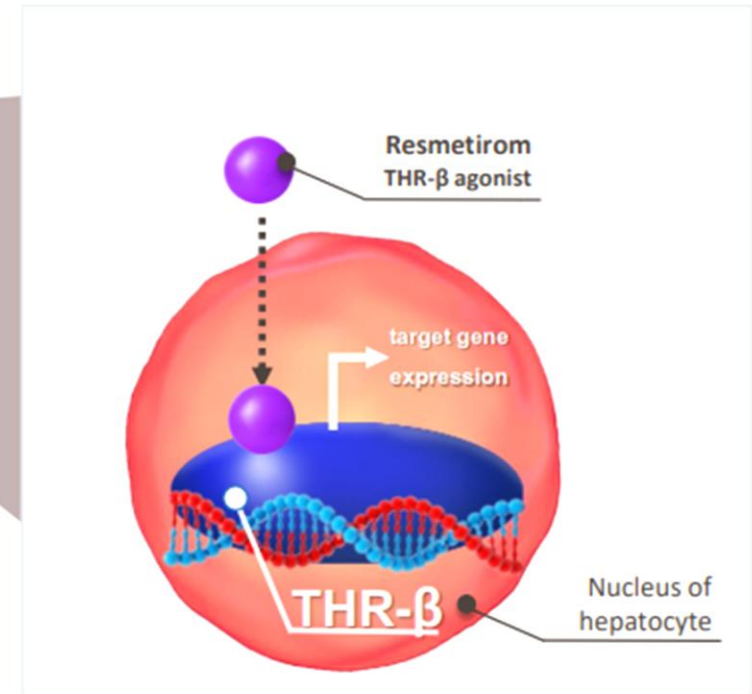
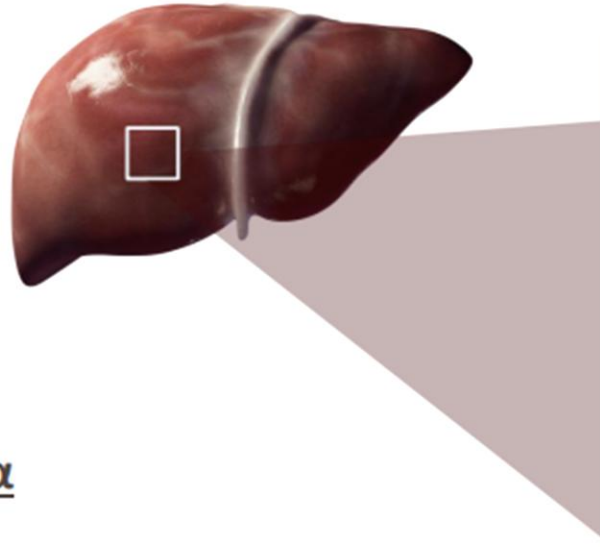
- No observed side effects on THR- α receptor present in:



Bone
(osteoporosis)



Heart
(rate and rhythm)



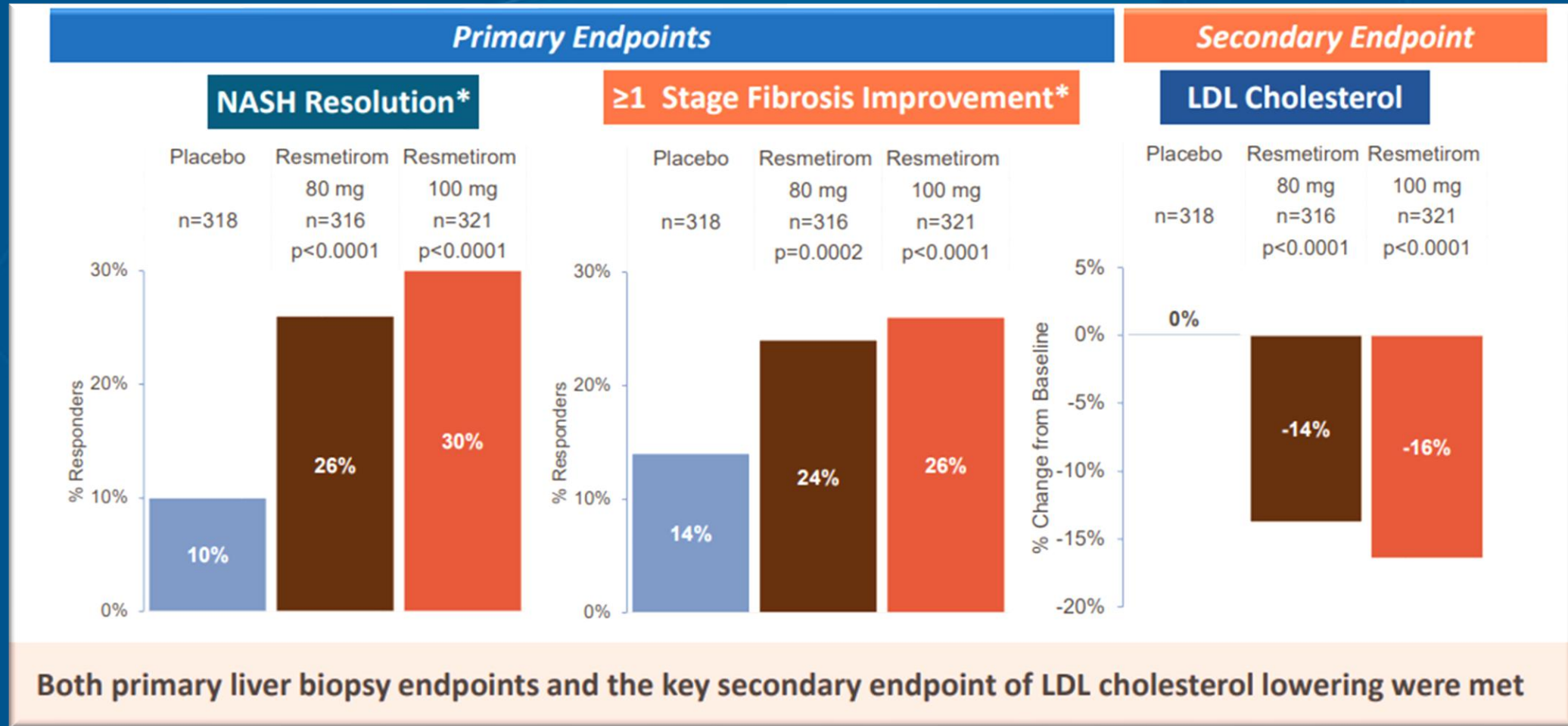
1. Kelly MJ et al., *J Med Chem.* 2014;54:3912-3923. 2. Taub R et al, *Atherosclerosis.* 2013;230:373-380. 3. Harrison SA et al., *Lancet* 2019;394:2012-2024. 4. Harrison SA et al., *Hepatol Commun.* 2021;5:573-588. 5. Harrison SA et al., *N Engl J Med.* 2024 Feb 8;390(6):497-509

MAESTRO Clinical Development Program

MAESTRO clinical trials are intended to provide a comprehensive data set in patients with NASH

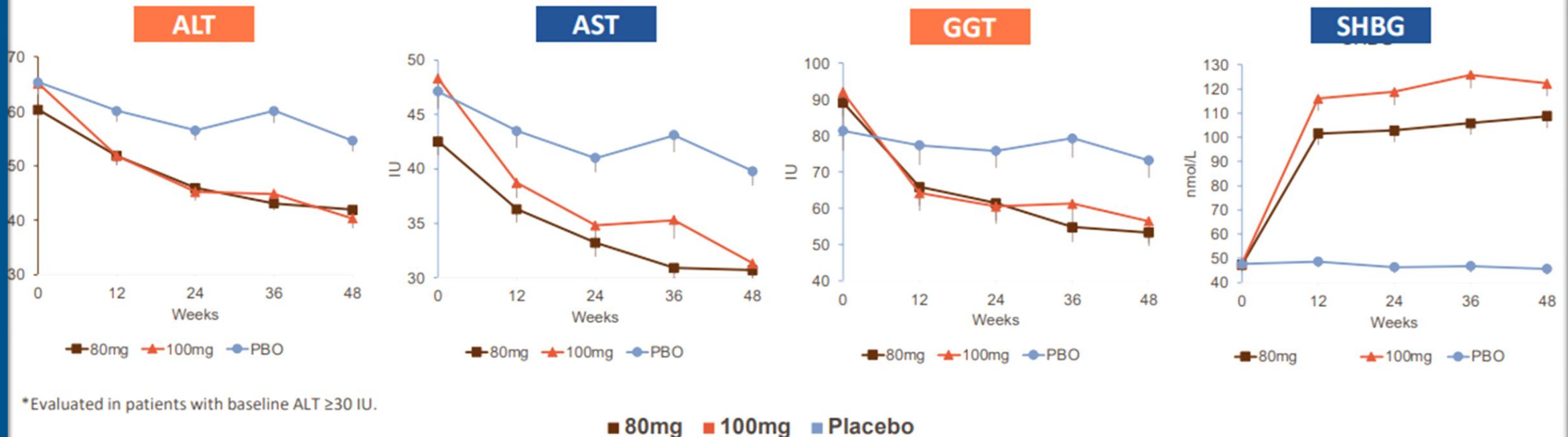
			
MAESTRO NAFLD-1	MAESTRO NAFLD-OLE	MAESTRO NASH	MAESTRO NASH OUTCOMES
Safety & tolerability as measured by incidence of Adverse Events (AE)	Safety & tolerability as measured by incidence of AEs (Extension to MAESTRO-NAFLD-1)	NASH resolution and/or fibrosis improvement on liver biopsy and composite clinical events	Event-driven trial evaluating progression to hepatic decompensation in patients with well-compensated NASH cirrhosis
52 weeks	52 weeks	52 weeks biopsy (completed) 54 months clinical outcomes	~36 months
~1200 patients (Completed)	~700 patients (Ongoing)	~1700 patients (Ongoing)	~700 patients (Recruiting)

Biopsies At Baseline & Week 52



Change From Baseline Liver Enzymes & SHBG

- Reduction of liver enzymes relative to placebo, both percentage change and absolute reduction
- Associated with the neutral biomarker SHBG that increased in proportion to resmetirom target engagement (exposure)



Trends Observed Non-Invasive Tests After Resmetirom Use

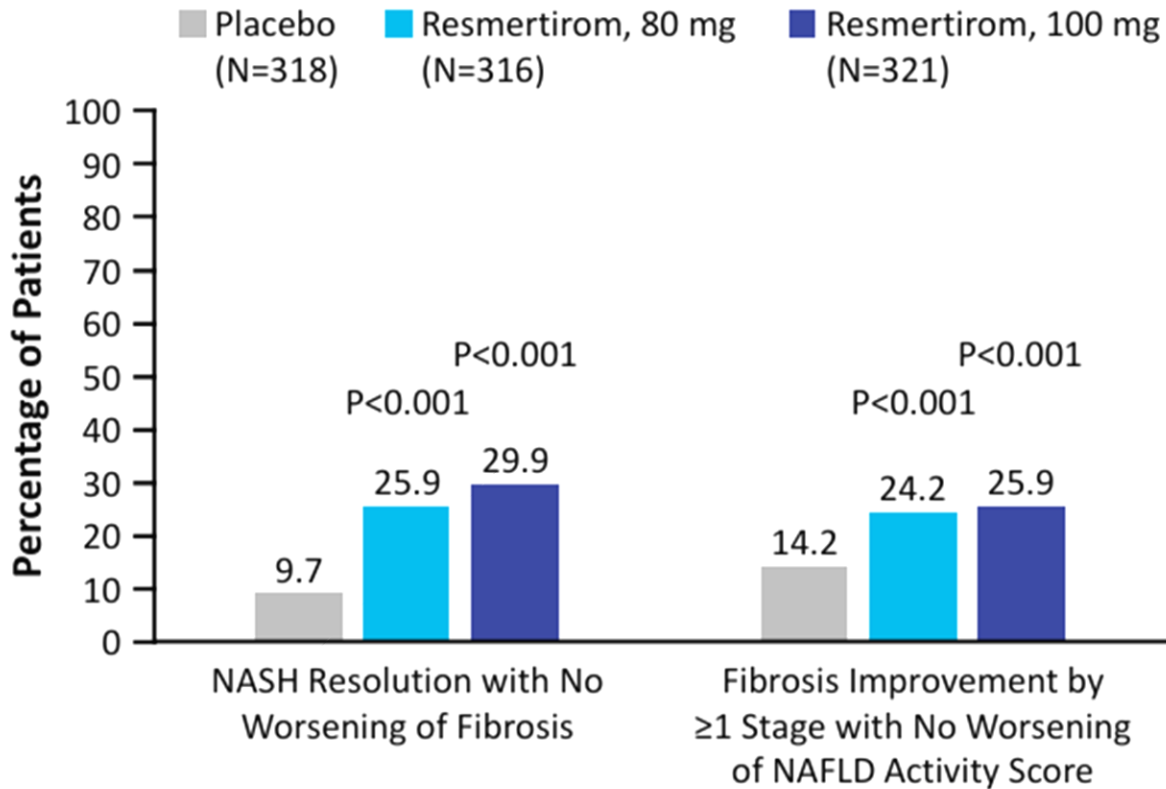
MAESTRO-NASH

Test type	Steatosis and inflammation marker (NASH resolution)	Fibrosis marker
MRI-PDFF % liver fat	↓	
Fibroscan CAP	↓	
Liver volume	↓	
Liver enzymes	↓	↓
ELF		↓
MRE kPa		↓
Fibroscan LSM		↓

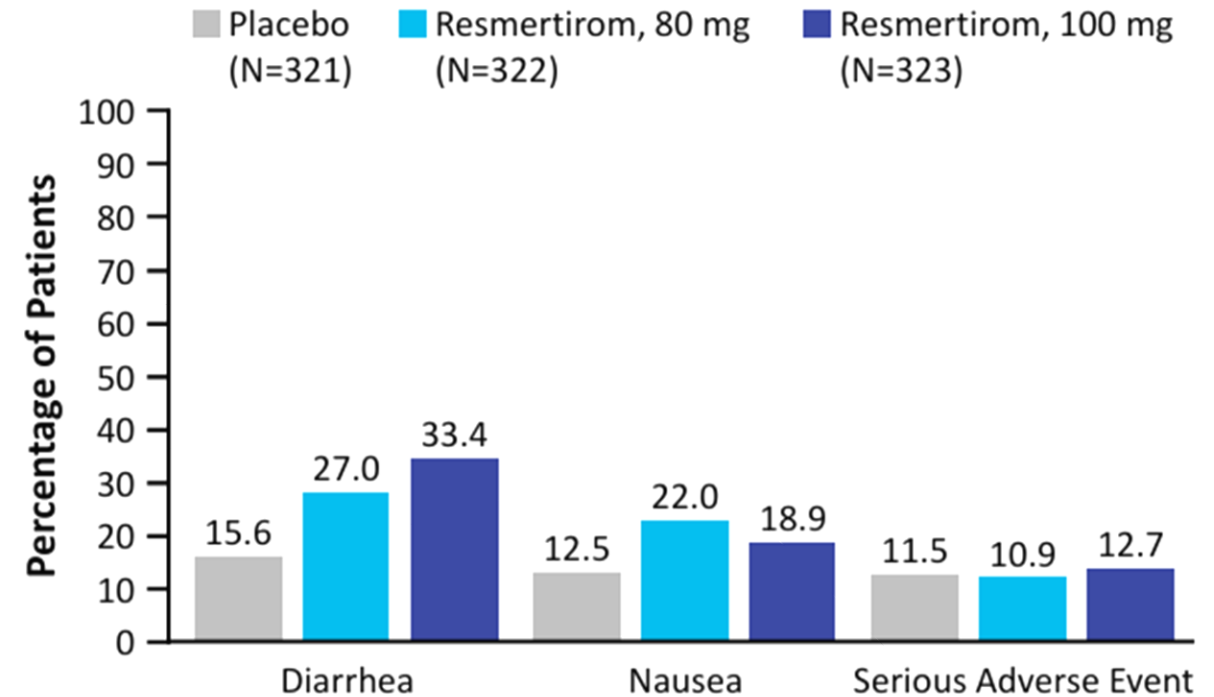


MAESTRO-NASH Trial: Resmetirom

Primary End Points



Safety



In March 2024, the US FDA approved resmetirom for the treatment of adults with noncirrhotic NASH with moderate to advanced liver fibrosis, to be used along with diet and exercise

Resmetiron: Broad Response



**50% Resmetiron Rx
Patients Showed
Either NASH
Resolution Or
Fibrosis
Improvement**



**> 70% Patients
Achieved
> 30% Reduction
In Non-Invasive
Test Results
(MRI – PDFF)**



**> 80% Resmetiron
Rx Patients
Achieved Fibrosis
Reversal Or No
Fibrosis
Progression**

Common Adverse Events With Resmiteron

Adverse Reaction	Placebo (n = 294) n (EAIR)	Resmetirom 80 mg (n = 298) n (EAIR)	Resmetirom 100 mg (n = 296) n (EAIR)
Diarrhea	52 (14)	78 (23)	98 (33)
Nausea	36 (9)	65 (18)	51 (15)
Pruritus	18 (4)	24 (6)	36 (10)
Vomiting	15 (4)	27 (7)	30 (8)
Constipation	18 (4)	20 (5)	28 (8)
Abdominal pain	18 (4)	22 (5)	27 (7)
Dizziness	6 (1)	17 (4)	17 (4)

Adverse reactions leading to discontinuation:

- Resmetirom 100 mg (8 per 100 PY), 80 mg (5 per 100 PY) vs placebo (4 per 100 PY)
- Diarrhea and nausea were the most common causes of treatment discontinuation



✓ Emerging Agents: Where Are We Headed?

Calorie Excess

GLP-1 RA

Semaglutide

Liraglutide

Dulaglutide

GIP/GLP-1 Agonist

Tirzepatide

AOM

Phentermine/
Topiramate

Bupropion/
Naltrexone

SGLT2i

Dapagliflozin

Empagliflozin

Canagliflozin

Surgery

Sleeve
Gastrectomy

Gastric Bypass

ER Stress

Lipotoxicity

Mitochondrial Dysfunction

FXR Agonists

Obeticholic acid

Tropifexor

SCD1 Inhibitor

Aramchol

THR-β Agonist

Resmetirom

ACC Inhibitor

Fircostat

Inflammation

Cholesterol Toxicity

Multifunctional

THR-β Agonist

Resmetirom

PPAR Agonists

Pioglitazone

Lanifibranor

Saroglitazar

FXR Agonists

Obeticholic acid

Tropifexor

Fibrosis

Multiple MOAs

Simtuzumab

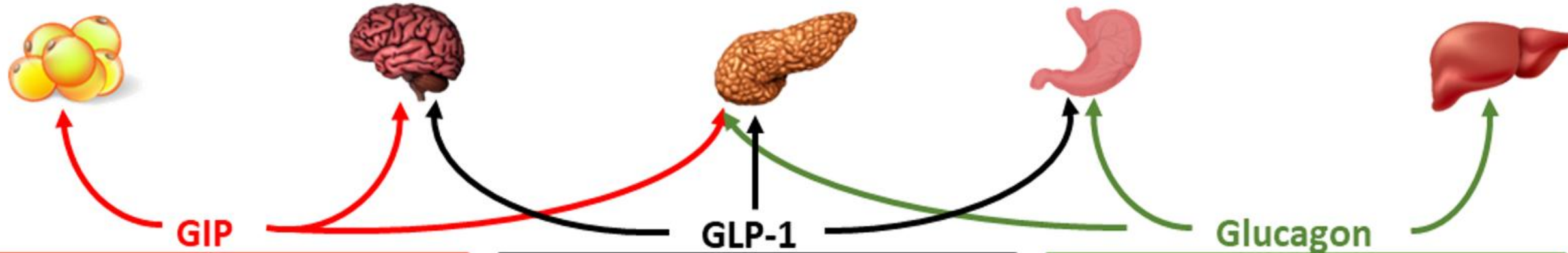
CCR2/5

BMS 986263

Vitamin E

Triple Agonists GLP-1 / GIP / Glucagon Receptor

In Clinical Development For Obesity



Adipose:

- ↑ insulin sensitivity
- regulation of lipid metabolism

CNS:

- ↓ appetite
- energy expenditure?

Islets:

- ↑ insulin secretion
- ↑ glucagon secretion

CNS:

- ↓ appetite

Islets:

- ↑ insulin secretion
- ↓ glucagon secretion

Stomach:

- delayed gastric emptying

CNS:

- ↑ energy expenditure , ↓ appetite

Islets:

- ↑ insulin secretion

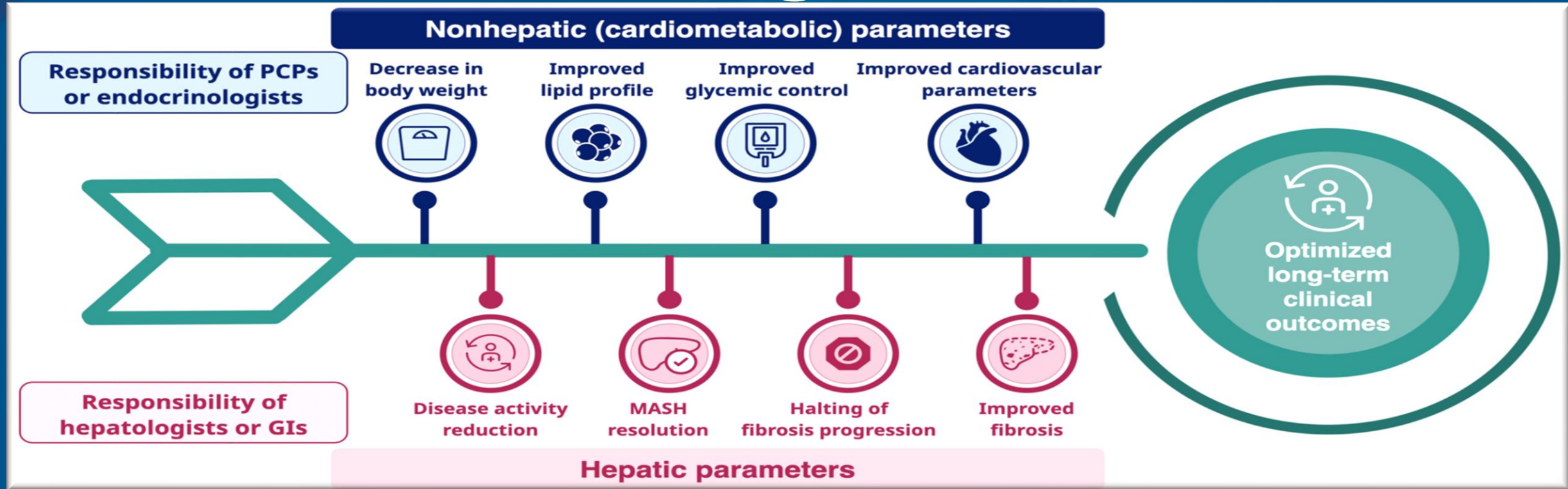
Stomach:

- Delayed gastric emptying

Liver:

- ↑ glycogenolysis/gluconeogenesis
- ↑ hepatic glucose output
- ↑ fatty acid oxidation
- ↑ amino acid catabolism

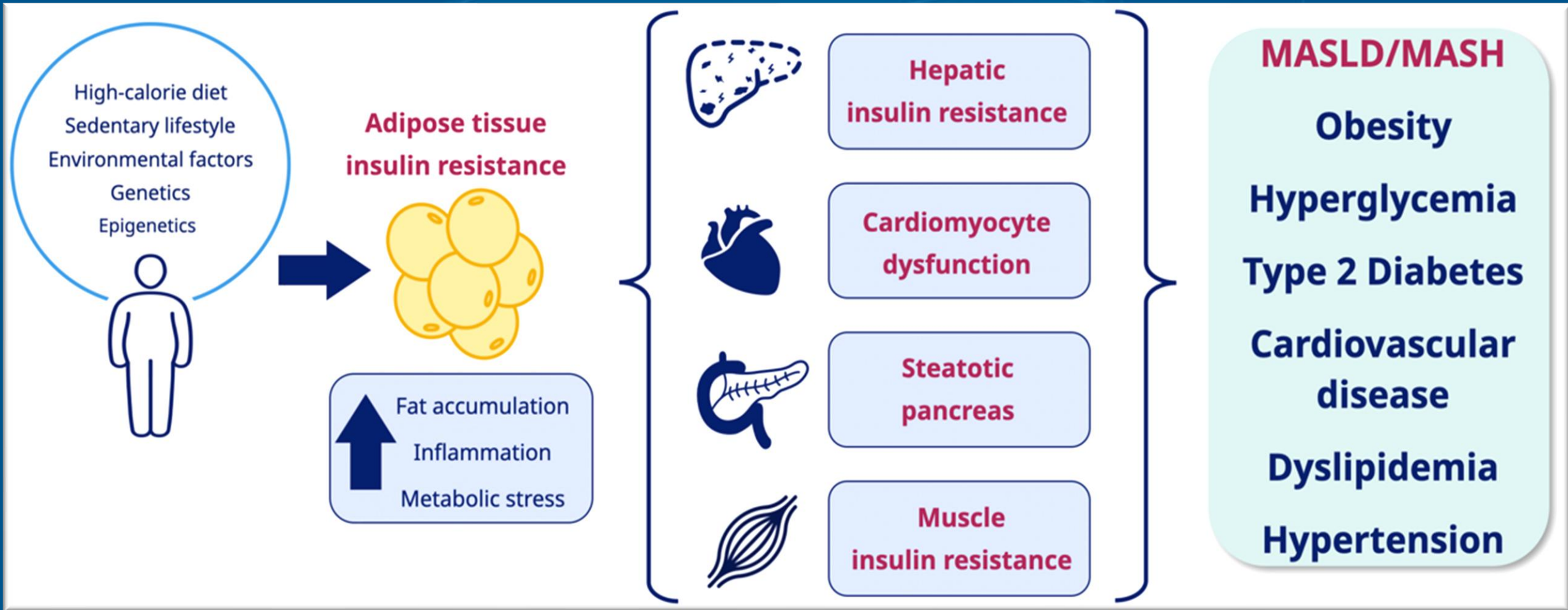
Take Home Message: Call To Action



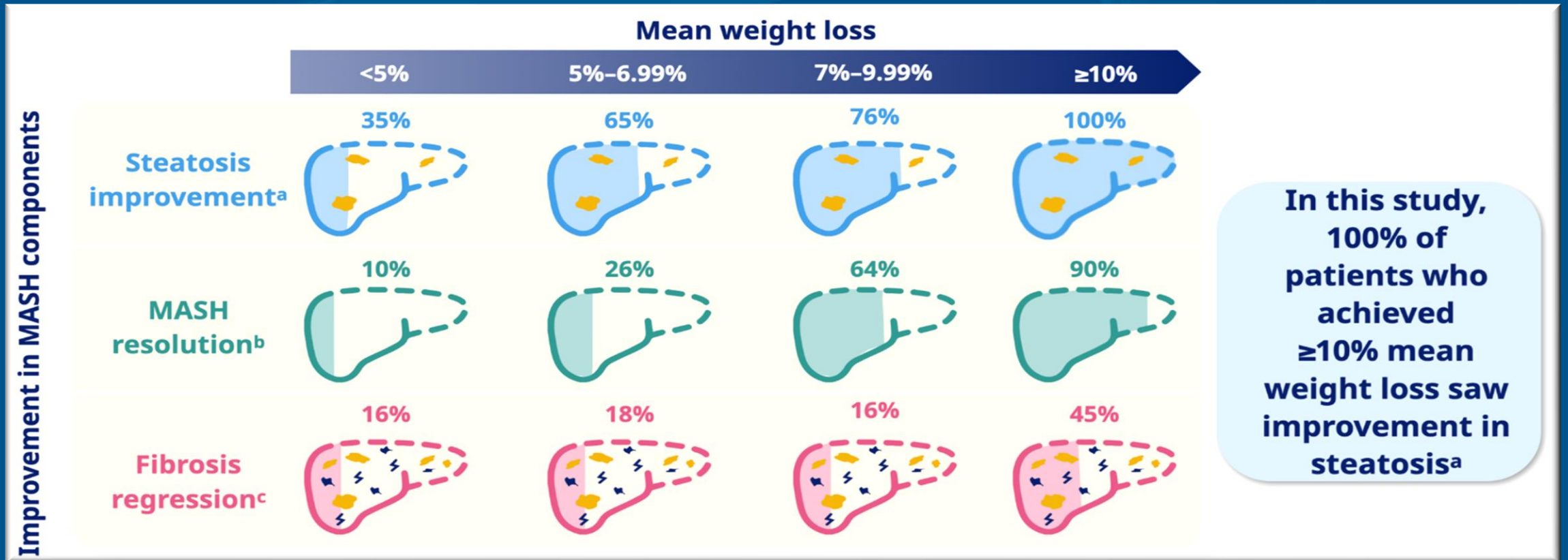
The Need For Multi-Disciplinary Teams

- PCP, Diabetologist / Diabetes Care Team, Hepatologist Rx Comorbidities ASAP
- Treat Obesity / T2DM GDMT and if Appropriate Liver Directed Rx to Reduce MALO / CVDz / Malignancy

Questions ?



Questions ?



Vilar-Gomez E et al. *Gastroenterology* 2015;149(2):367-378
Aminian A et al. *JAMA*. 2021;326(20):2031-2042



Questions ?

- What Is Most Accurate Regarding The Use of Statins In Patients With MASLD & MASH?
 - A. They Are Generally Safe For The Prevention & Reduction Of Cardiovascular Disease
 - B. They Are Contraindicated In This Population
 - C. They Can Only Be Used In Patients With Cirrhosis
 - D. They Cannot Be Used If Patients Have Decompensated Cirrhosis

Researchers Have Determined Statins Are Safe & Recommended For 1*/2* Prevention CVDz. Ample Evidence: Reduction All-Cause Mortality / Cancer Mortality. Statins Potentially Prevent Development Progression of HCC. #1 COD = CVDz / Non-Hepatic Cancers. AASLD – ‘Statins: Safe & Recommended Across Dz Spectrum Including Compensated Cirrhosis. Limited Data With Decompensated Cirrhosis’



Questions ?

◀ What Is The Most Common Arrhythmia Associated With MASLD?

- A. Atrial Fibrillation
- B. Atrial Flutter
- C. Ventricular Fibrillation
- D. Ventricular Tachycardia

CVDz Most Common COD. MASLD Strongly Ass'd With Various CV Complications: ASCVDz, Heart Dz, Heart Failure, & Arrhythmias. AFib Particularly Common in MASLD



Questions ?

- ❖ Which Test For New – Onset Diabetes Is Most Appropriate For Patients With Cirrhosis Due To MASLD?
 - A. A1c Measurement
 - B. Fasting Blood Sugar Measurement'
 - C. Random Blood Glucose Test
 - D. Oral Glucose Tolerance Test

2 Hour Postprandial 75 – Gram Oral GTT Found To Outperform FBS, A1c In Patients With Cirrhosis. A1c Especially Susceptible To Inaccuracy d/t Changes In Erythrocyte Turnover, Hemolysis Caused By Splenomegaly, Impaired Erythropoiesis d/t Bone Marrow Suppression & Repeated Blood Transfusions



Questions ?

PRACTICE GUIDELINE

AASLD Practice Guideline
and management

– D. Every 5

**Patients at low risk for MASH with
advanced fibrosis at initial assessment (FIB-4 <1.3)**

**Prediabetes, T2D, or ≥2 metabolic risk factors
(eg, obesity, dyslipidemia, hypertension)**

Yes

No



**Repeat FIB-4
every 1–2 years**



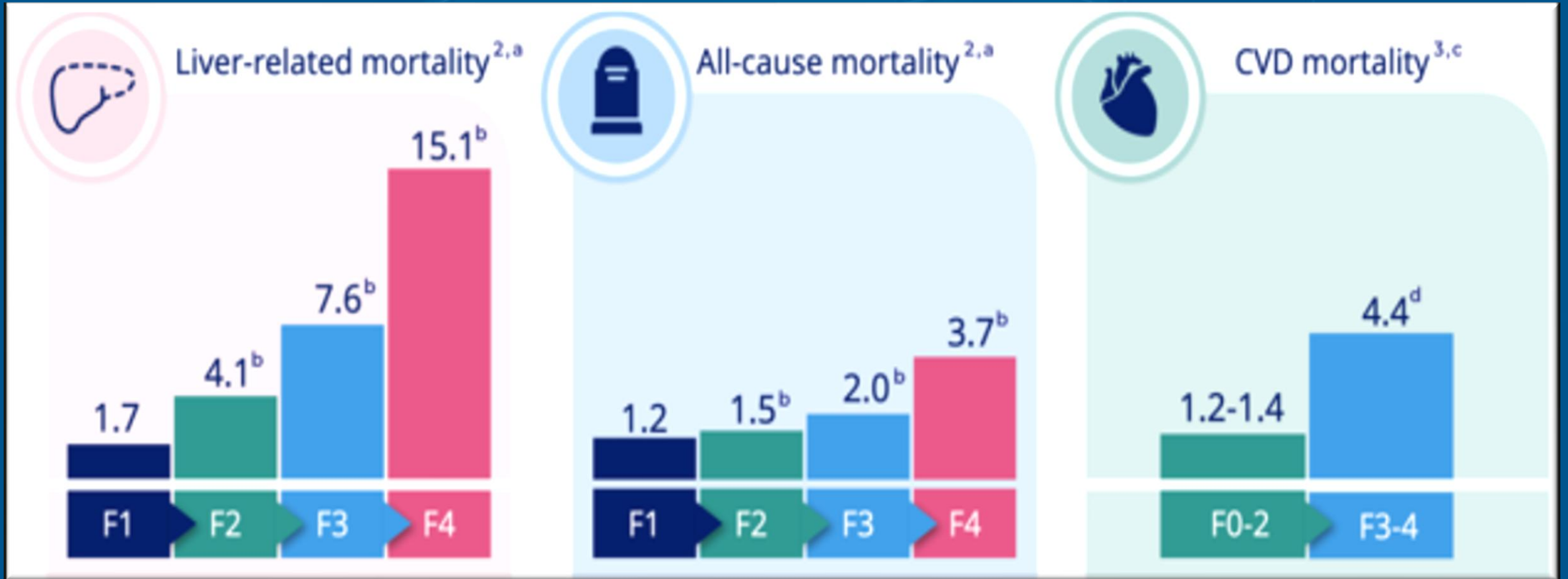
**Repeat FIB-4
every 2–3 years**



ment
ase

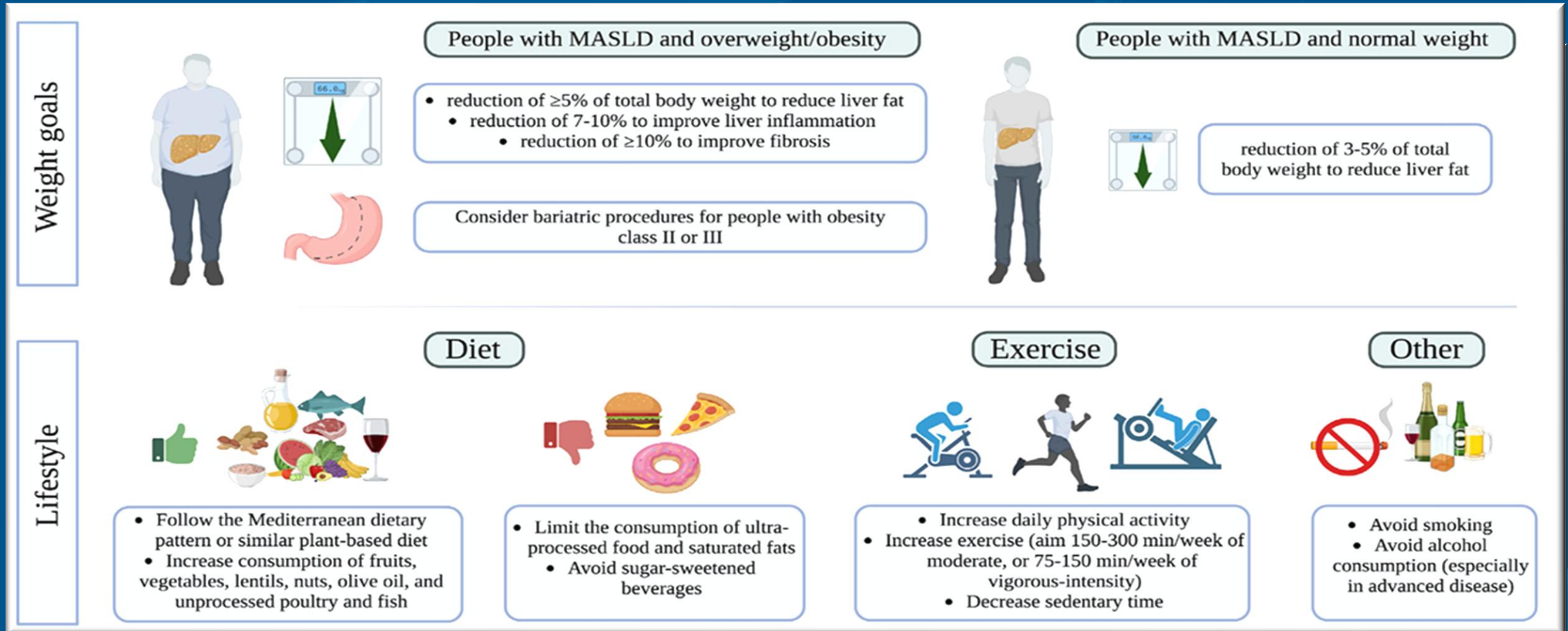


Questions ?



1. Rinella ME et al., *Hepatology* 2023;77(5):1797-1835.
2. Ng CH et al. *Clin Gastroenterol Hepatol*. 2023;21(4):931-939.
3. Ekstedt M et al. *Hepatology*. 2015;61(5):1547-1554.
4. Shroff H et al. *Curr Hepatol Rep*. 2020;19(3):315-326

ADA Recommendations: MASLD Treatment Algorithm



Guideline-based Management of MASH in the Primary Care Setting

Screening

Recommended in adults with:

Cardiometabolic and other risk factors, including:^a

T2D
Pre-diabetes
Insulin resistance

Obesity

Aged >50 years
>Mild alcohol intake^b
Family history of cirrhosis



Hepatic steatosis



Persistently elevated liver enzymes

Alina Allen et al.,

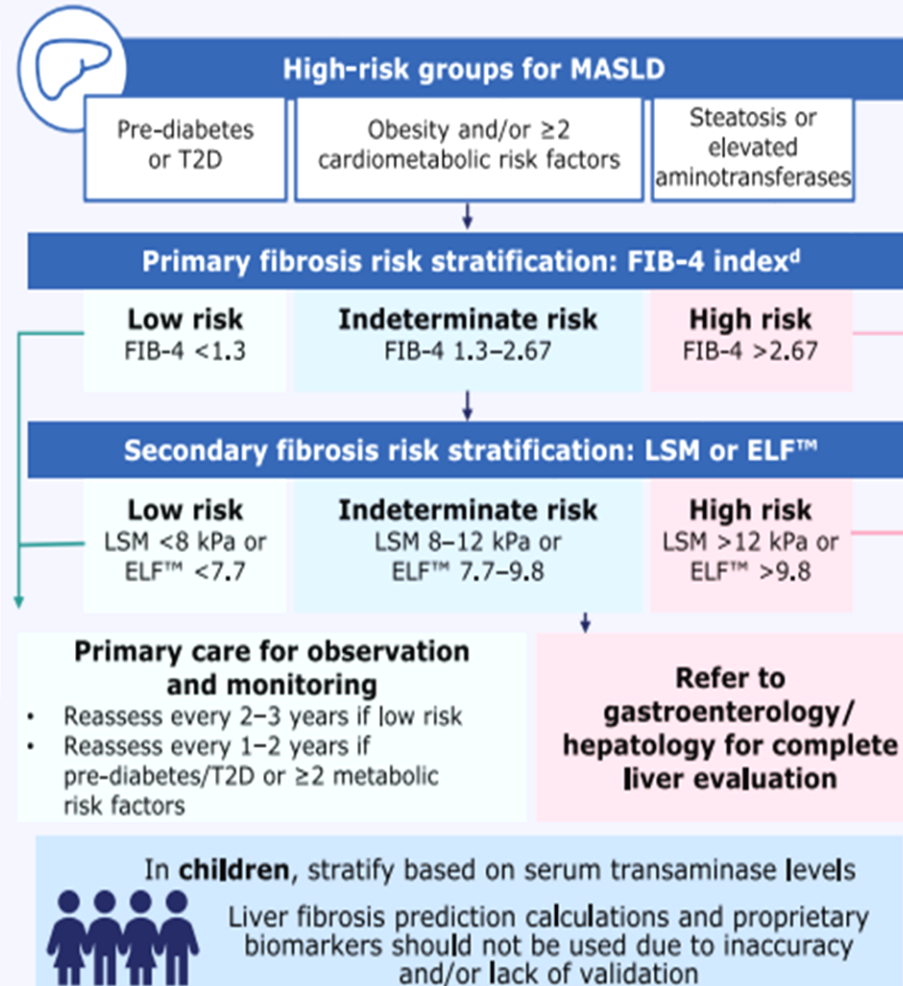
Recommended in children with:

T2D, Obesity, PCOS^c, T1D

Medicine, 136(3), 229-245, DOI:10.1080/00032548.2024.2325332

Not recommended

Risk Stratification



Management

Lifestyle interventions



Healthy diet
(e.g. Mediterranean)



Physical activity



Avoid excess alcohol intake

Weight loss targets

$\geq 10\%$
preferred

(minimum goal of $\geq 5\%$)



Bariatric surgery

Consider in appropriate individuals with clinically significant fibrosis^e and obesity with comorbidities



Pharmacotherapy

MASH + T2D
GLP-1RAs^f and/or pioglitazone

MASH (no T2D)
Consider vitamin E

MASH + obesity
AOM^f adjunct to lifestyle intervention

CVD risk reduction



Manage comorbidities according to current standards of care

Statins
safe and recommended^g

**Any
Questions?**



“Traditional Wisdom is Short on Wisdom and Long on Tradition”

Mark Twain

“We Can’t Solve Problems Using the Same Kind of Thinking We Used When We Created Them.”

Albert Einstein



F3

Detection of Advanced Fibrosis				
Serum	FIB-4	≥2.67	<1.3	- No added cost¹⁻³ - Not accurate in aged <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 laboratory⁴ - Cost
Imaging	VCTE	≥12 kPa	< 8 kPa	Point of care⁵
Imaging	MRE	≥3.63 kPa	<2.55 kPa	MRE LSM ≥3.63 kPa (associated with advanced fibrosis, AUROC of 0.93)

F4

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^{5,8}
Serum	ELF	≥11.3	<7.7	ELF ≥11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis⁴
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 kPa⁵
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^{7,8}



