The Changing Paradigm of Treating MASLD/MASH: At the Crossroads of Hepato-Cardiometabolic Care

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Obesity Medicine Association (OMA) members are physicians, nurse practitioners, physician assistants, and other healthcare providers who take a **comprehensive, evidence-based approach** to treating obesity.

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Disclosures of Conflicts of Interest

Naim Alkhouri, MD, FAASLD, DABOM

Consulting Fees: 89Bio, AbbVie, Boehringer Ingelheim, Echosens, Fibronostics, Gilead, Intercept, Ipsen, Madrigal, NorthSea, Novo Nordisk, Perspectum, Pfizer, Zydus

Research: 89Bio, Akero, Arbutus, AstraZeneca, Better Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Corcept, CymaBay, DSM, Galectin, Genentech, Genfit, Gilead, Healio, Hepagene, Intercept, Inventiva, Ionis, Ipsen, Madrigal, Merck, NGM, Noom, NorthSea, Novo Nordisk, Perspectum, Pfizer, Poxel, Viking, Zydus

Amreen M. Dinani, MD, FRCPC

Consulting Fees: Madrigal Pharmaceuticals, Novo Nordisk

Research: GSK, Hanmi, Inventiva, Liver Cirrhosis Network, Madrigal Pharmaceuticals, NIDDK

Nicholas Pennings, DO, DABOM, MFOMA, FACOFP, FAAFP

Consulting Fees: Abbott

Other: Medifast

Learning Objectives:

After participating in this educational activity, participants should be better able to:

- Summarize the pathophysiologic rationale for using obesity pharmacotherapy in patients with metabolic dysfunction-associated steatotic liver disease (MASLD)/metabolic dysfunction-associated steatohepatitis (MASH)
- Apply recommendations for the treatment of patients with MASLD/MASH with GLP-1 RAs
- Devise a multidisciplinary plan to manage obesity in patients with MASLD/MASH
- Interpret data from clinical trials of emerging liver-directed therapies for MASLD/MASH
- Interpret data from clinical trials of emerging anti-obesity therapies for MASLD/MASH

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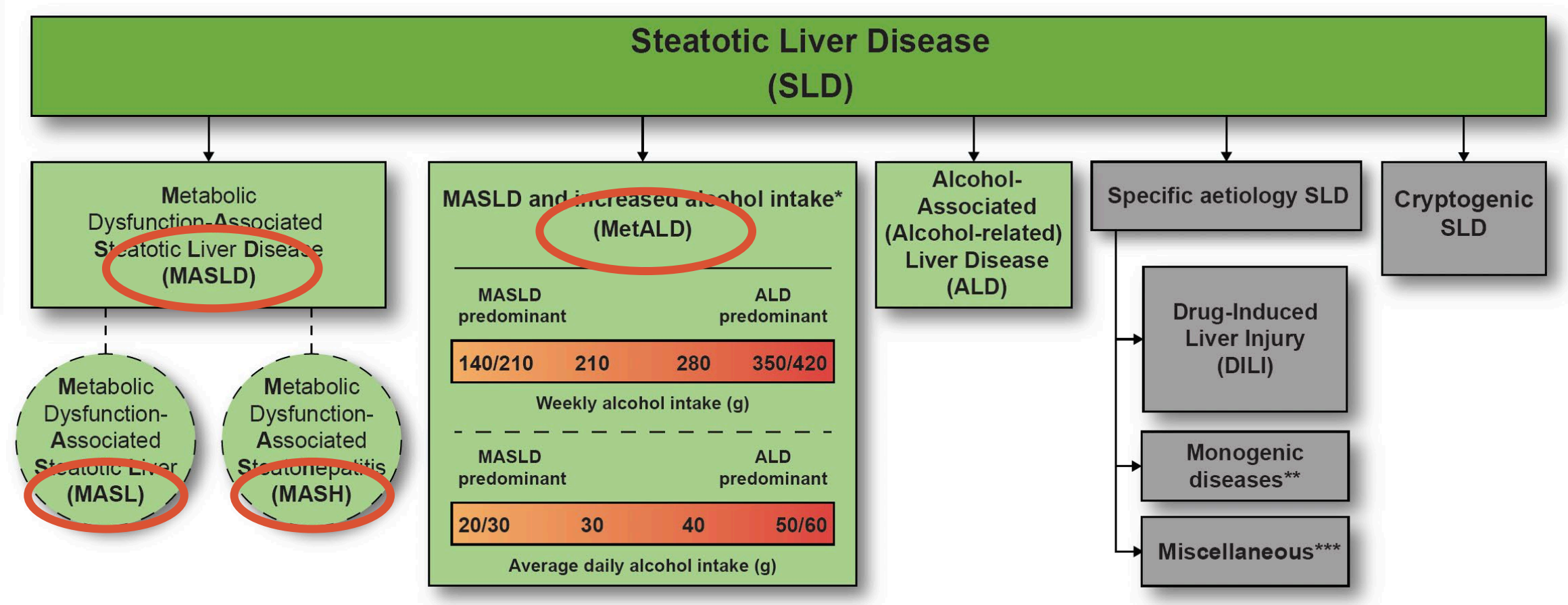
Consensus Nomenclature



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

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Adapted from: Rinella ME, et al. *Hepatology*. 2023;78(6):1966-1986.
Kanwal F, et al. *Hepatology*. 2024;79(5):1212-1219.

In an adult with steatosis in whom other causes of steatotic liver disease have been ruled out, which of the following is needed to confer a diagnosis of MASLD?

- Presence of 1 cardiometabolic risk factor
- Presence of at least 2 cardiometabolic risk factors
- Presence of at least 3 cardiometabolic risk factors
- Presence of all 5 cardiometabolic risk factors

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AASLD. New MASLD Nomenclature. https://www.aasld.org/new-masld-nomenclature

Cardiometabolic Risk Factors: It Only Takes One!

Adult Criteria	Cutoffs & Parameters
BMI	BMI >25 kg/m^2 [23 Asia] **OR** waist circumference >94 cm (M) / 80 cm (F)*
Fasting Serum Glucose	≥100 mg/dL **OR** 2-hour post-load glucose level ≥140 mg/dL **OR** HA1c >5.6% **OR** T2D
Blood Pressure	≥130/85 mmHg **OR** specific antihypertensive drug therapy
Plasma Triglycerides	≥150 mg/dL **OR** lipid-lowering drug therapy
Plasma HDL Cholesterol	≥40 mg/dL (M) / ≥50 mg/dL (F) **OR** lipid-lowering drug therapy

***Or ethnicity-adjusted equivalent**

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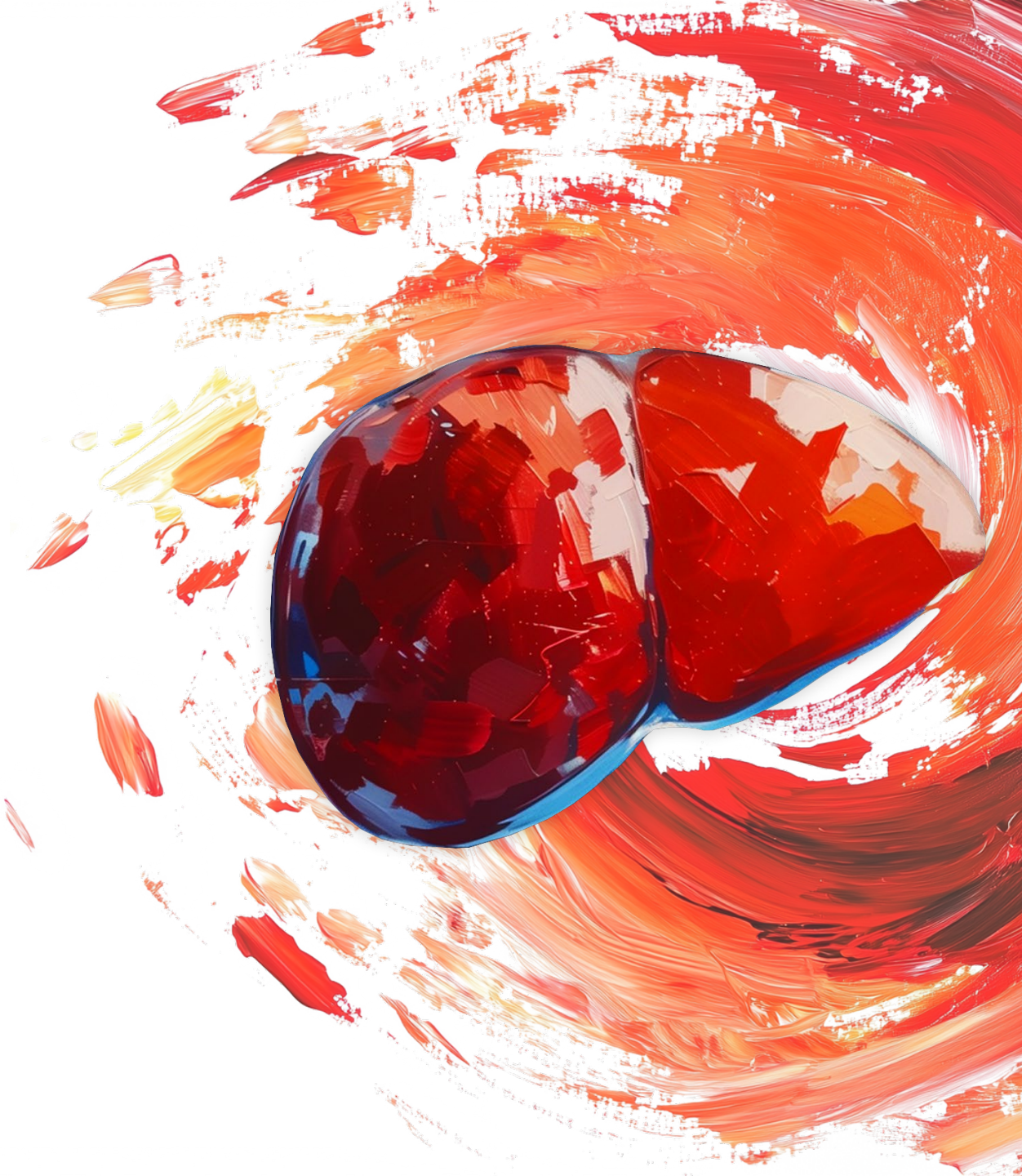
AASLD. New MASLD Nomenclature. https://www.aasld.org/new-masld-nomenclature

Pathophysiology of MASLD/MASH

Nicholas Pennings, DO



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Obesity

A ***chronic, relapsing, and treatable multifactorial, neurobehavioral disease,***

wherein an increase in body fat promotes ***adipose tissue dysfunction*** and ***abnormal fat mass physical forces***

resulting in adverse ***metabolic, biomechanical,*** and ***psychosocial*** health consequences.

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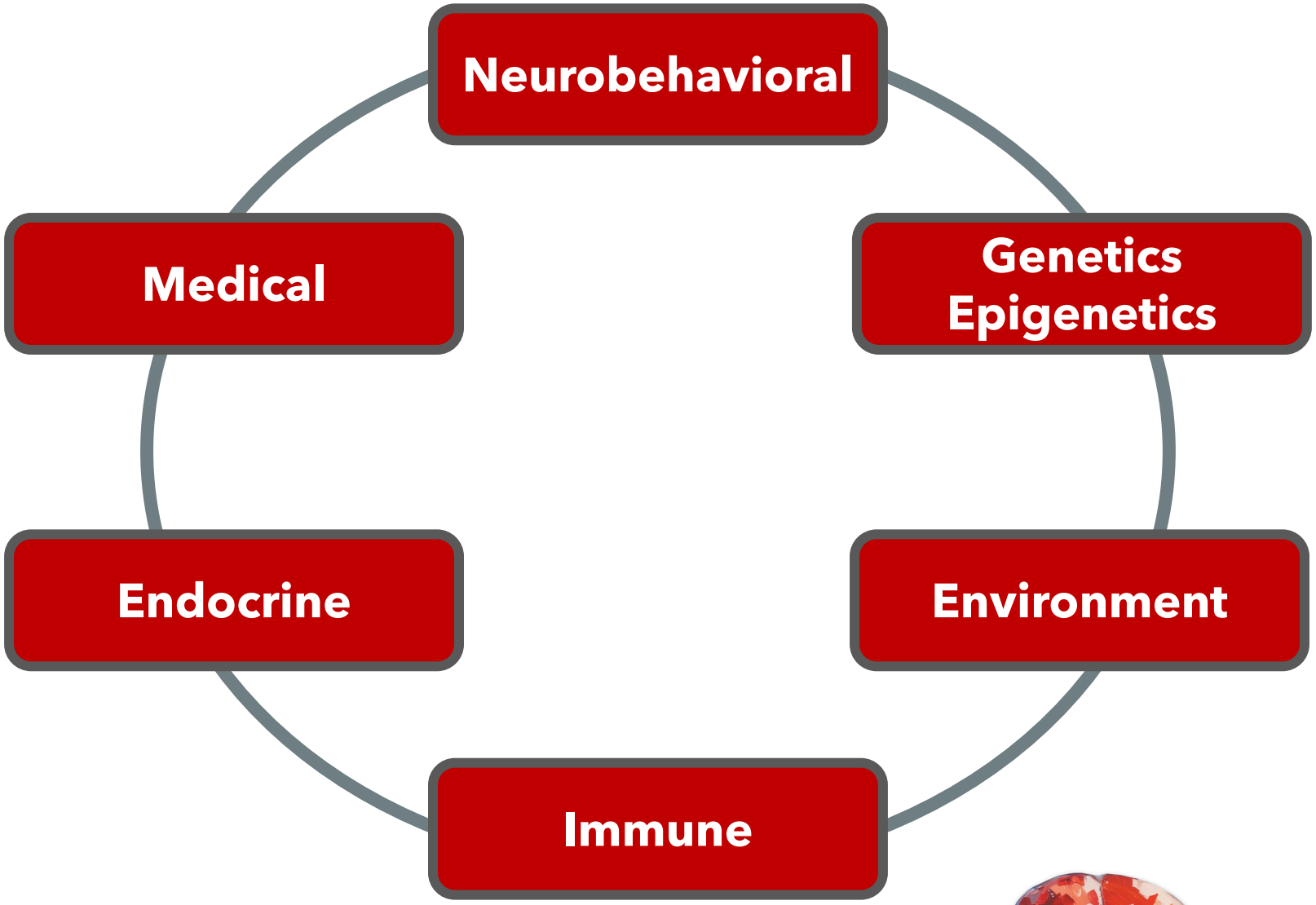
Obesity: A Multifactorial Disease



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Adapted from Obesity Algorithm®, Obesity Medicine Association®

Severity of Obesity: Body Mass Index

Overweight and Obesity Classification BMI (m/kg^2)	Normal weight: 18.5 – 24.9
	Pre-obesity/overweight: 25.0 – 29.9
	Class I obesity: 30.0 – 34.9
	Class II obesity: 35.0 – 39.9
	Class III obesity: ≥40

Different BMI cutoff points may be more appropriate for women vs men, among those of different races and among individuals.

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Adapted from Obesity Algorithm®, Obesity Medicine Association®

Pathogenic Obesity

Deranged endocrine and immune responses

↓

Sick fat syndrome (adiposopathy)

↓

Endocrine/metabolic

Abnormal and pathologic physical forces

↓

Fat mass disease

↓

Biomechanical, structural

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Adapted from Obesity Algorithm®, Obesity Medicine Association®

What BMI Level Triggers MASH?

Adipose Tissue Distribution

Subcutaneous

Metabolically Healthy with Obesity

Visceral + SC Overload

Metabolically ***Un***healthy with Obesity

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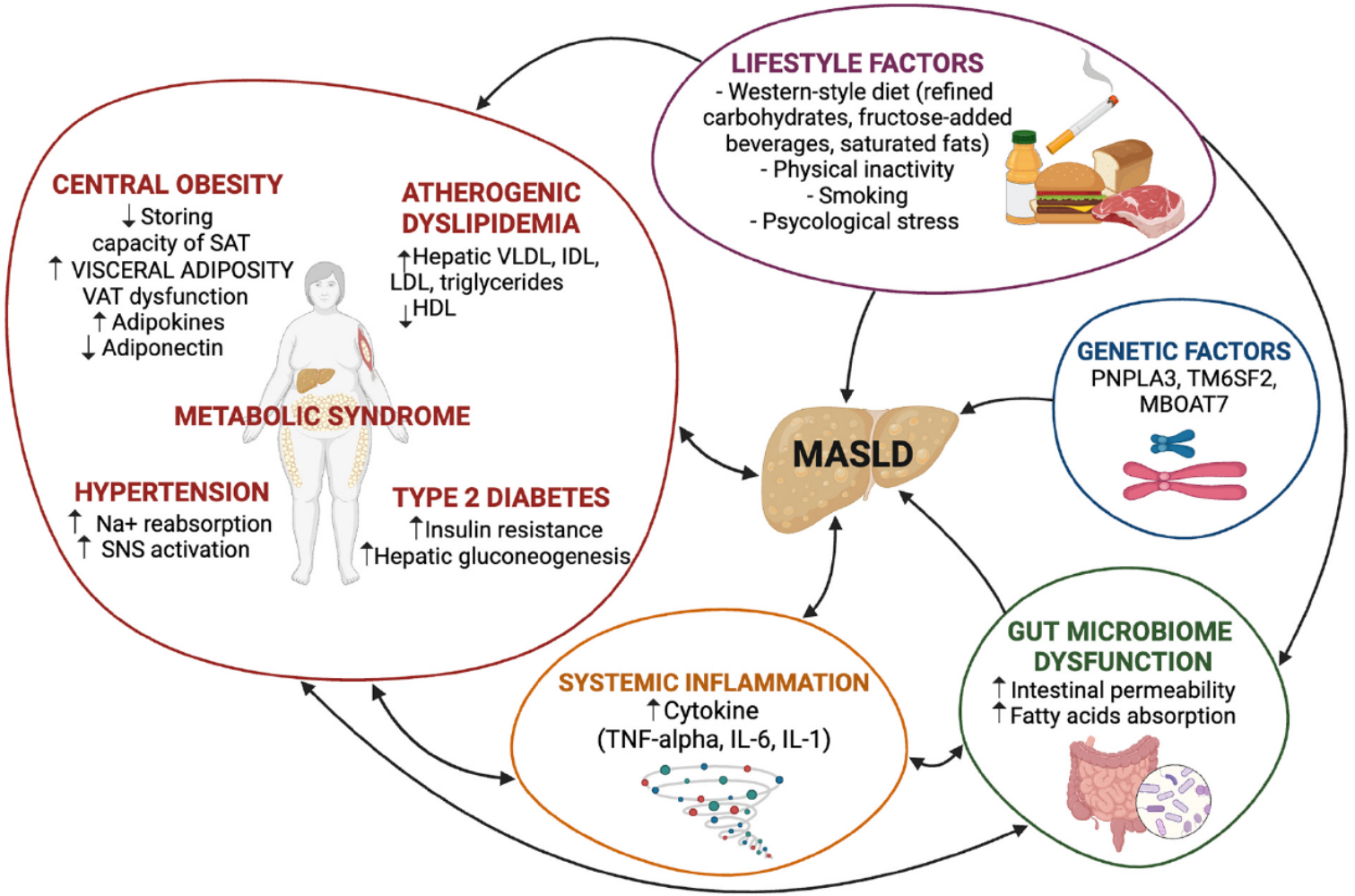
Getting to the Core of SLD: Metabolic Dysfunction



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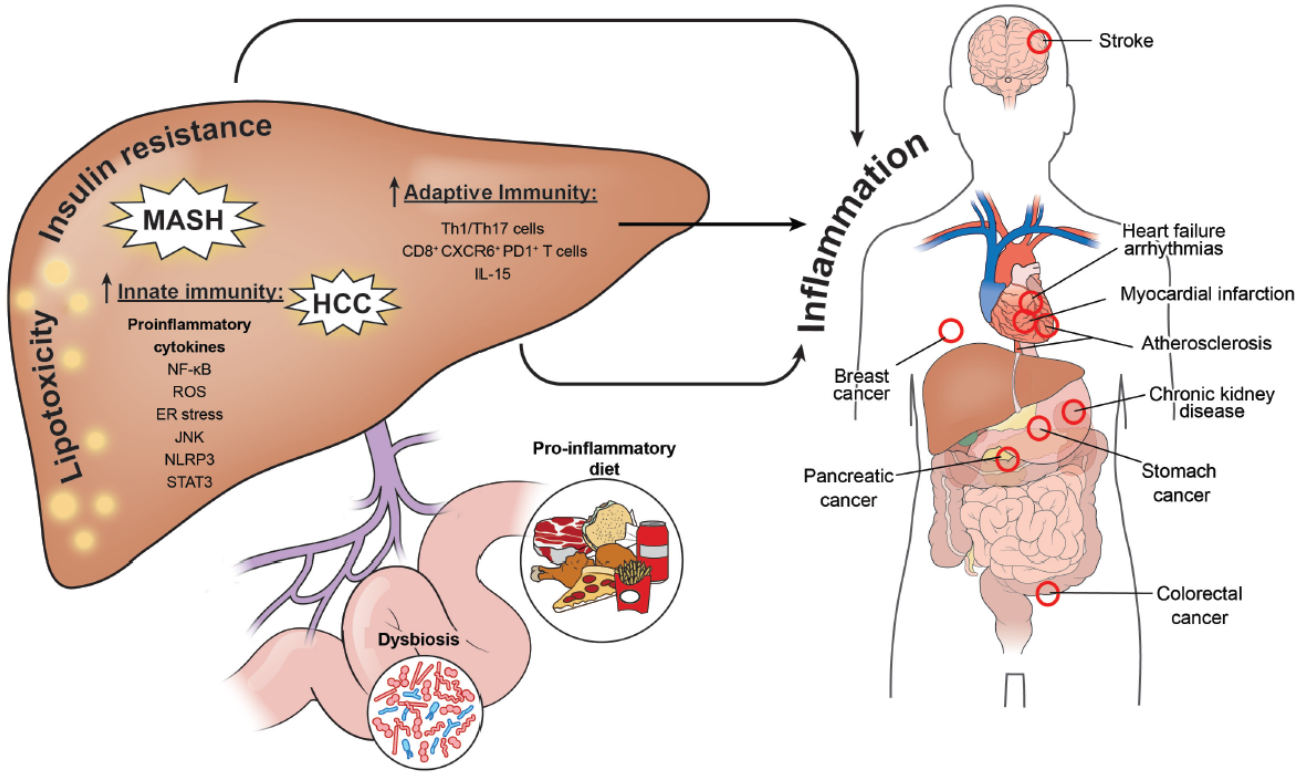
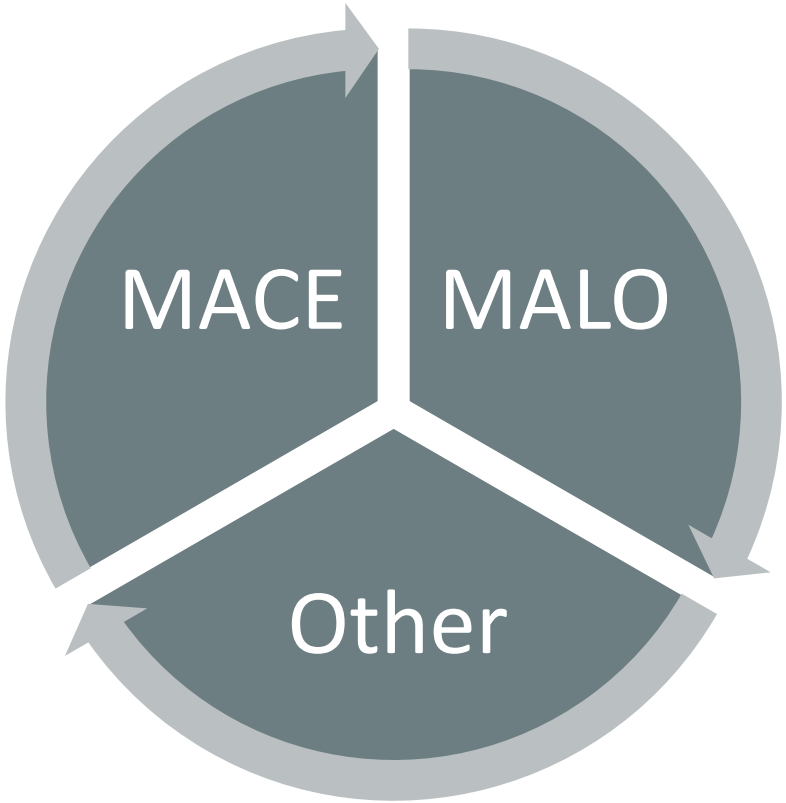
Raggi P, et al. *Atherosclerosis*. 2024;392:117523.

Metabolic Dysfunction, Inflammation, and Disease





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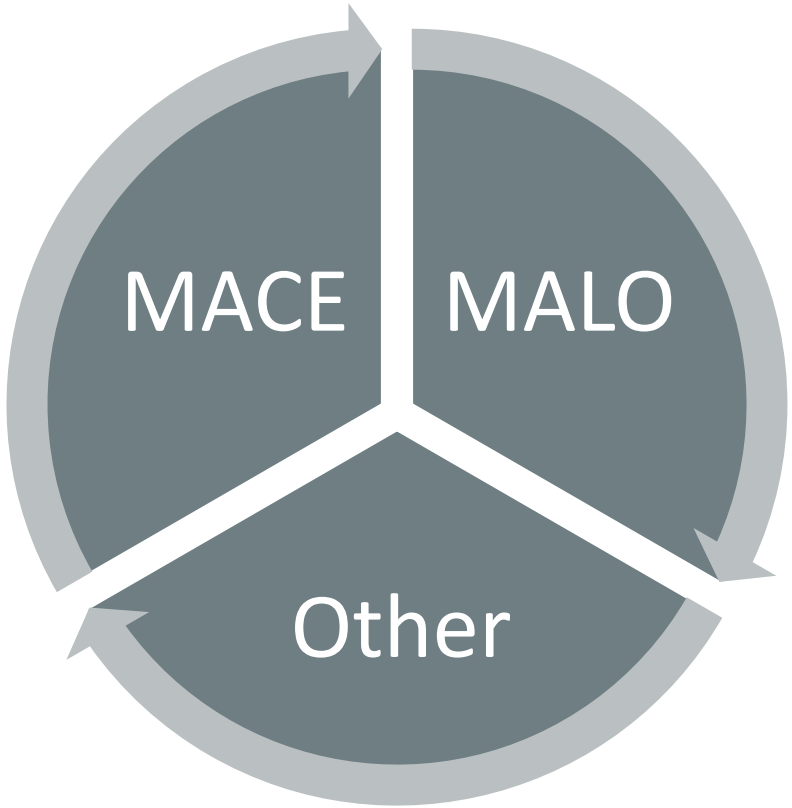
Targher G, et al. *Gut*. 2024;73(4):691-702.

What is the most common cause of death in patients with MASLD?

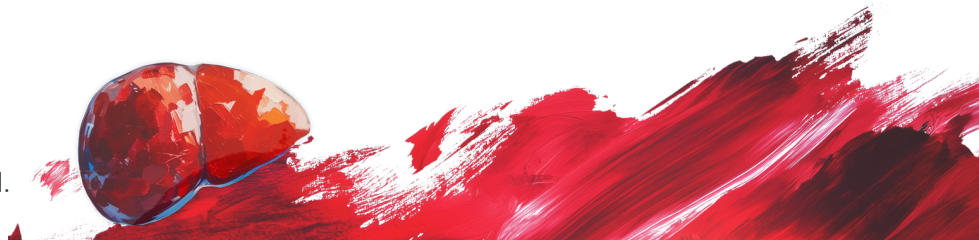
- Cardiovascular disease
- Decompensated cirrhosis
- Extrahepatic cancer
- Hepatocellular carcinoma

MASLD: From Unmitigated Risks to Adverse Events and Outcomes

CVD: the *most common* cause of death



MASH: the *most common* indication for liver transplantation and cause of primary HCC.



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Bilson J, et al. *Diabetes Metab*. 2024;50(1):101506. Finney AC, et al. *Front Cardiovasc Med*. 2023;10:1116861. Schattenberg JM, et al. *Commun Med (Lond)*. 2023;3(1):1. Targher G, et al. *Gut*. 2024;73(4):691-702. Younossi Z, et al. *Hepatol Communic*. 2023;8(1):e0352.

Treating and Managing MASLD/MASH

Goal:

- Prevention of:
  - MACE
  - MALO
  - Extrahepatic cancer
  - Premature death

Strategy:

- Switch from focus on single-modality care to simultaneous treatment and management of multiple comorbidities

Raggi P, et al. *Atherosclerosis*. 2024;392:117523.

Appetite Regulation

Traditional Thinking

- Purposeful behavior
- regulates weight

—

- Calories in & calories out
- Regulates weight

Additional Understanding

- Biology regulates weight

—

- Hormonal response
- regulates weight

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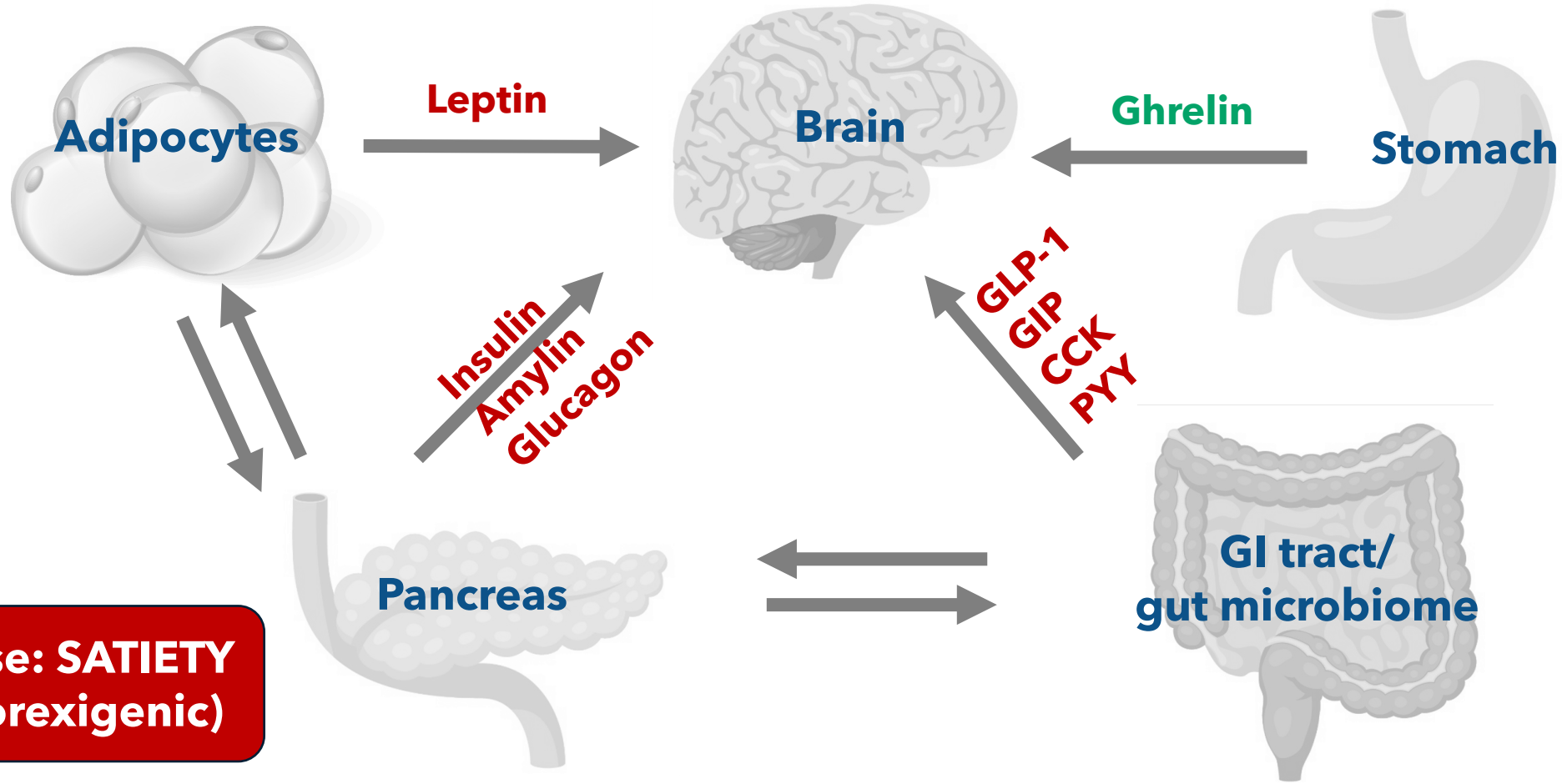
Appetite Regulation

Cause: HUNGER (orexigenic)



Cause: SATIETY (anorexigenic)

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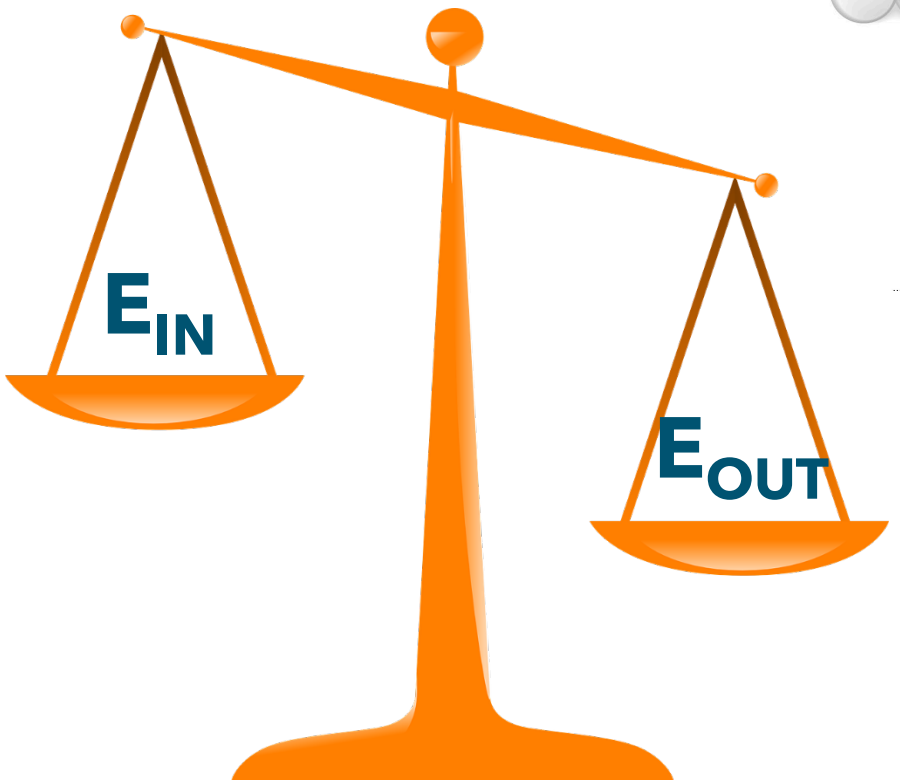
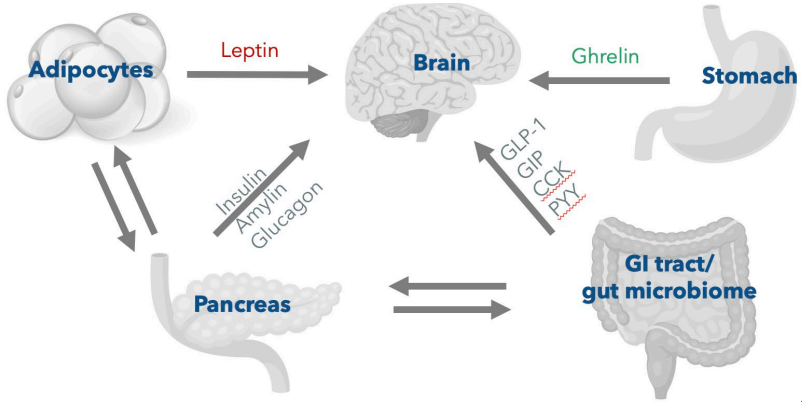
Physiologic Response to Calorie Deficit





↑ Hunger
↓ Satiety

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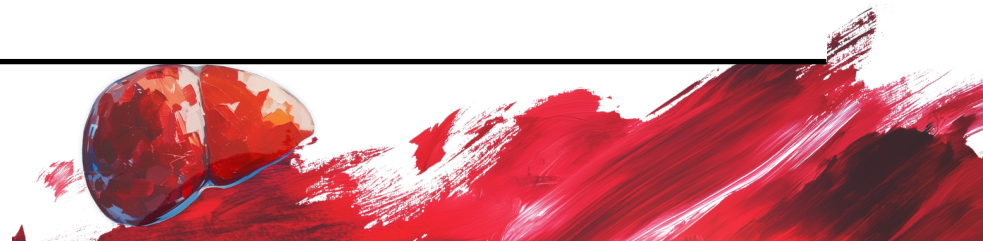
Case 1

Nicholas Pennings, DO

Case 1: A 44-Year-Old White Woman With Class 2* Obesity

Medical Record	Results
Medical history	T2D, HTN, dyslipidemia, abdominal U/S for RUQ pain: fatty infiltrate, no evidence of cholecystitis; family history: obesity and CVD
Current meds	Glyburide 10 mg bid, sitagliptin/metformin 50 mg/1000 mg bid, metoprolol ER 100 mg daily, lisinopril 10 mg daily, atorvastatin 40 mg daily
Social history	Sedentary, denies illicit drug use, drinks occasional glass of wine, smokes cigarettes (1/2 ppd)
Physical exam	BMI: 37.6 kg/m^2, BP: 137/86 mmHg, central adiposity, mild hepatomegaly

***Class 2 obesity: BMI 35 to <40 kg/m^2**



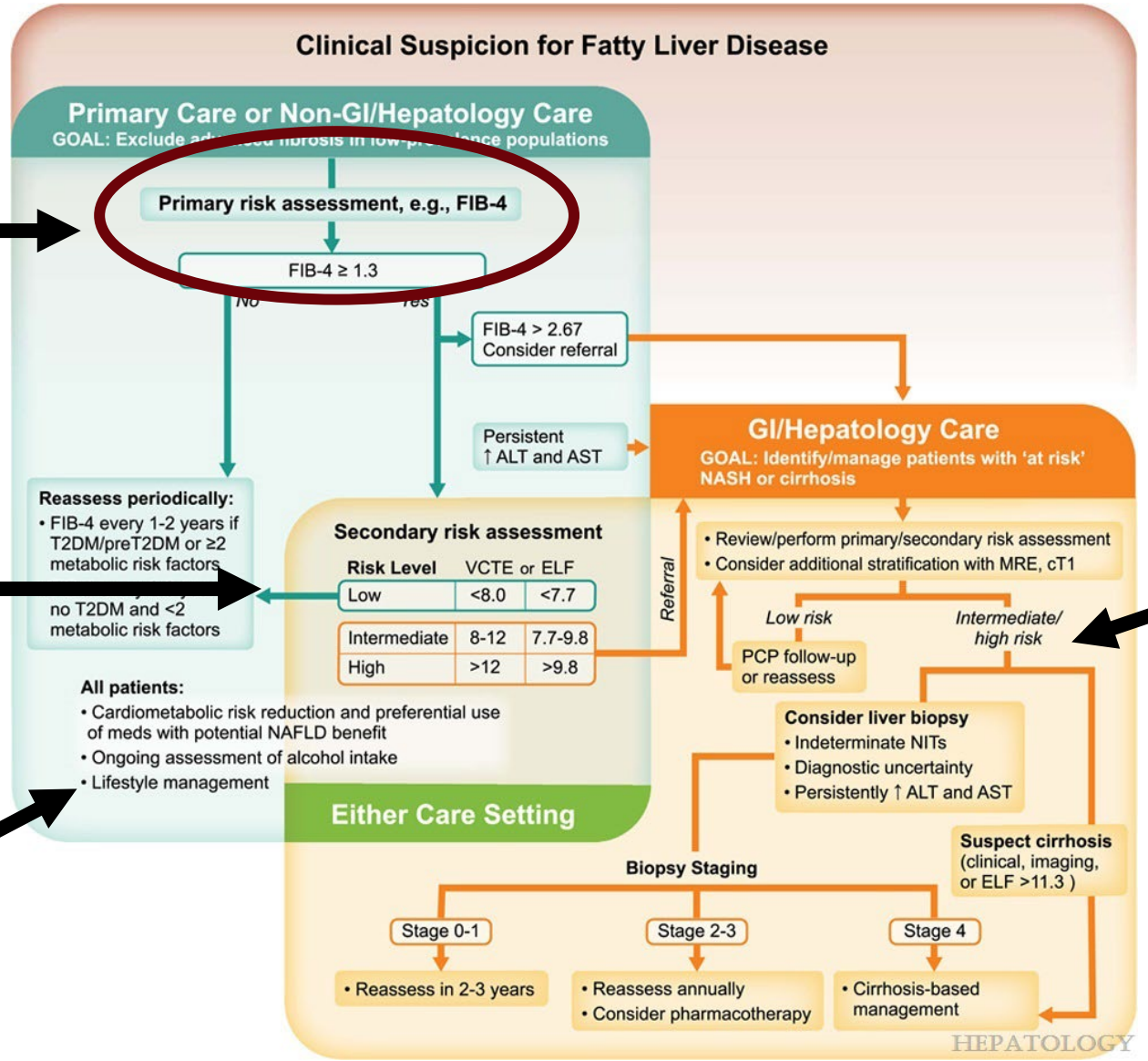
Rule Out Other Causes of Steatotic Liver Disease

- **Medications**: eg, TPN, glucocorticoids, tamoxifen, amiodarone, methotrexate
- **CLD**: eg, alcoholic hepatitis, viral hepatitis, autoimmune disease (eg, PBC, PSC), rare disease (eg, A-1-A deficiency, Wilson disease)
- **HIV**
- **Acquired metabolic disease**: eg, lipodystrophy, cachexia, intestinal bypass surgery

Primary Risk Assessment: FIB-4

Secondary Risk Assessment: VCTE or ELF

Cardiometabolic Risk Reduction



Identify Patients With At-Risk MASH

Rinella ME, et al. Hepatology. 2023;77(5):1797-1835

Effects of Alcohol Use and Cigarette Smoking: A Mandate for Screening

Alcohol[1]

- *"Around 17% of patients with a diagnosis of MASLD have, or will receive, a diagnosis of ALD or AUD at some point in their life course. Such patients have a considerably higher rate of progression to cirrhosis or HCC."*

Tobacco[2]

- *"The combination of tobacco consumption and T2D is associated with a higher prevalence of fibrosis in people with MASLD."*

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1. Nasr P, et al. *Clin Gastroenterol Hepatol*. 2024;22(5):1048-1057.e2. 2. Balogun O, et al. *Hepatol Commun*. 2023;7(11):e0300.

Case 1 (cont'd)

Diagnostic Test	Results
CBC	WBC 5.5 × 10^3/uL, HCT 0.378 (37.8%); platelet ct: 241 G/L
Serum glucose	155 mg/dL, HbA_{1c}: 8.3%
Lipid	TC: 220 mg/dL, HDL: 36 mg/dL, LDL: 88 mg/dL, TG 270 mg/dL
Liver function	ALT: 62 IU/L, AST: 48 IU/L
CMP	BUN: 22 mg/dL, creatinine: 1.1 mg/dL, hsCRP: 5.32 mg/dL
Fibrosis Score	**LSM: 8.6 kPa,** CAP score: 371 dB/m

Case 1 (cont'd)

24-Hour Dietary History	
Breakfast	Sausage biscuit, coffee w/generous amount of flavored creamer
Lunch	Salad w/grilled chicken, ranch dressing, 20 oz soda
Snack	Chips, 20 oz soda
Dinner	Pasta w/meatballs, Italian bread, ice cream, coffee w/generous amount of flavored creamer
Snack	Chips

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Which dietary pattern is most likely to benefit a patient with MASLD? (select all that apply)

- Mediterranean
- DASH
- Ketogenic
- Low fat
- High protein

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You Can’t Out-Exercise the Fork

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Image courtesy of Michael Betel.

What additional pharmacologic therapy would you consider at this time?

- GLP-1 RA
- Insulin
- Pioglitazone
- SGLT2 inhibitor

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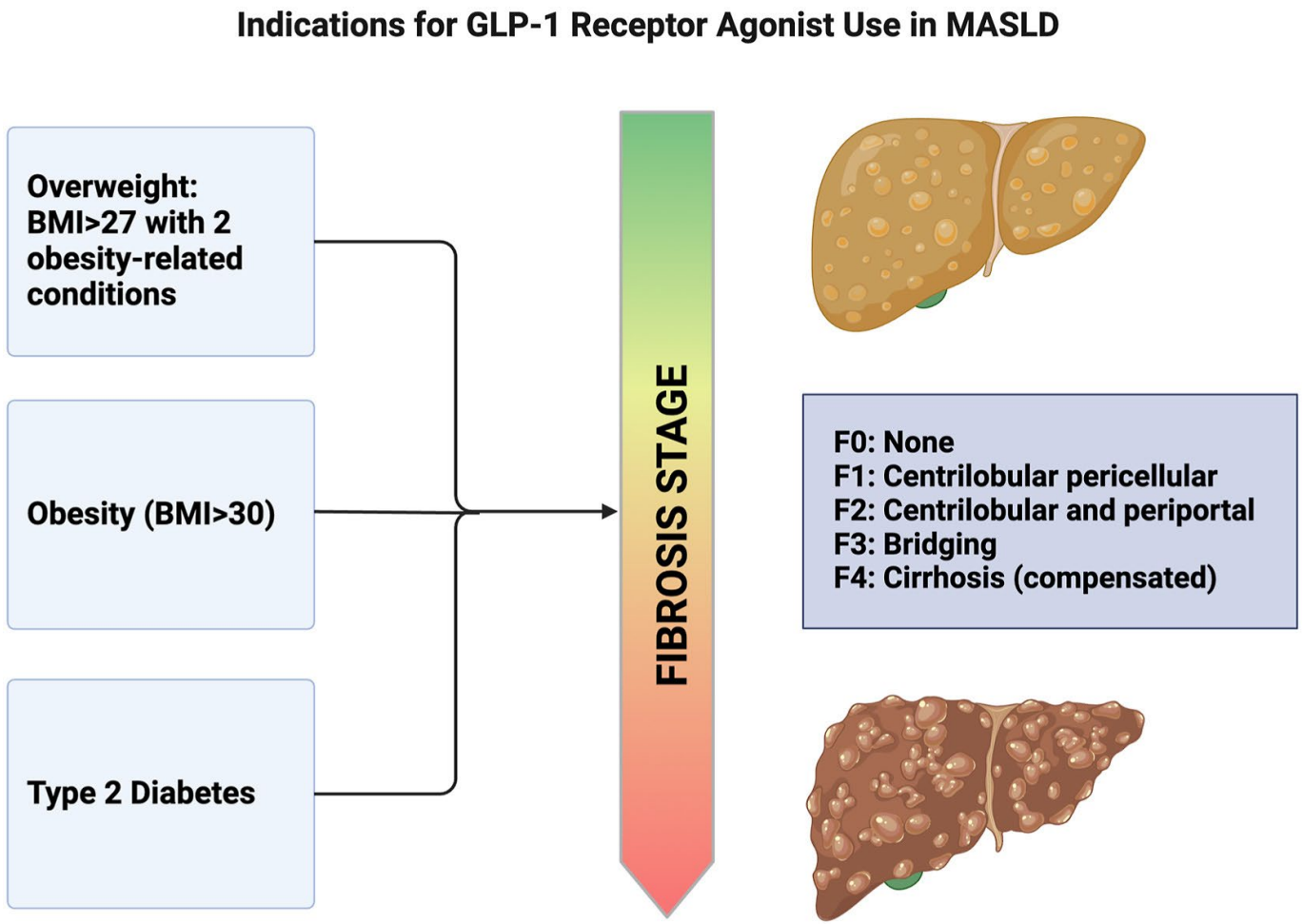
Benefits of GLP-1 RAs in Patients With MASLD



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

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Abushamat LA, et al. *Clin Gastroenterol Hepatol*. 2024;22(8):1565-1574.

Following and Managing the Patient on a GLP-1 RA: A Team Approach

- **Patient education: how GLP-1 RAs work, what to expect:**
  - Patient goals: weight and BMI
  - Weekly SC injection
  - Dose escalation
  - Nutrition, hydration
  - Weight-bearing exercise
  - Managing side effects
  - Duration of use
- **Side effects:**
  - Dyspepsia, nausea, vomiting
  - Constipation, diarrhea
  - Hypoglycemia
  - Dizziness, fatigue, headache
- **Managing side effects:**
  - Decrease dose
  - Assess for sarcopenia
  - Increase protein in diet
  - Prescribe weight-bearing exercise

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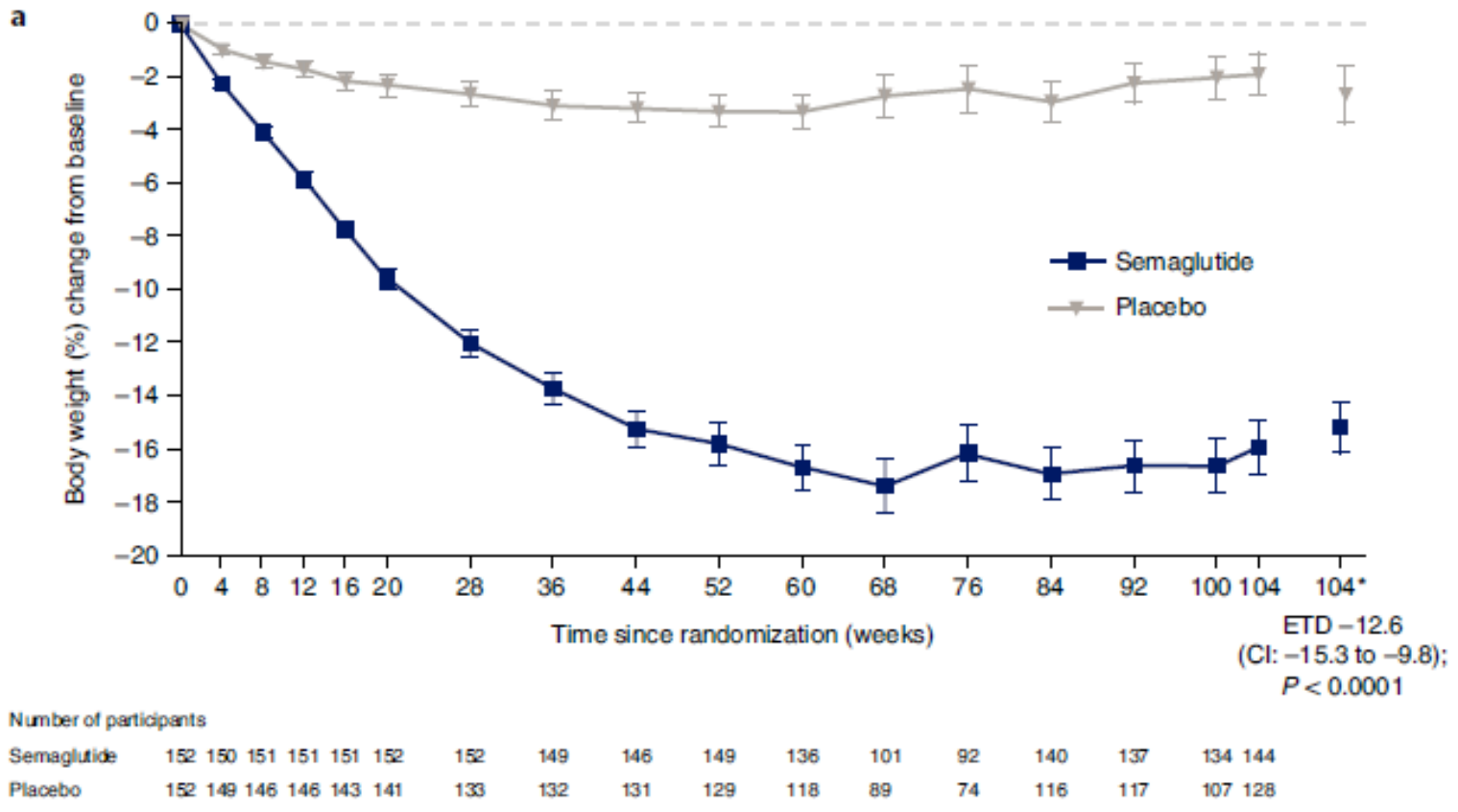
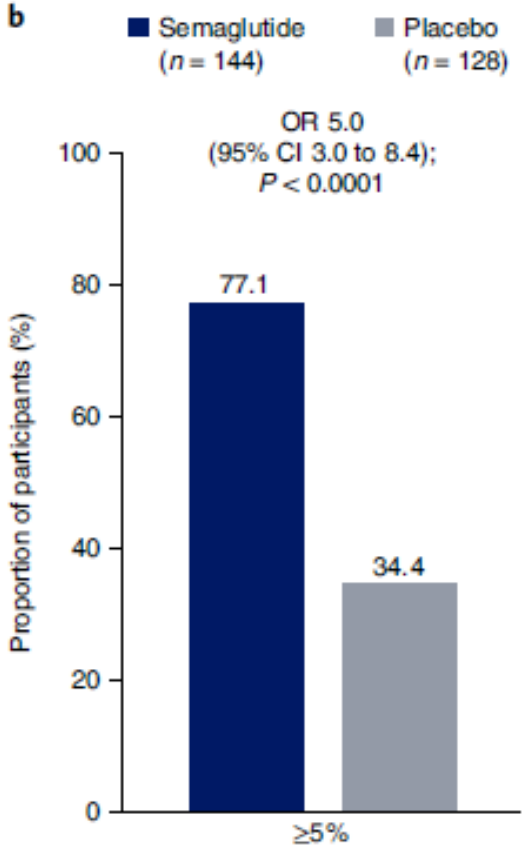
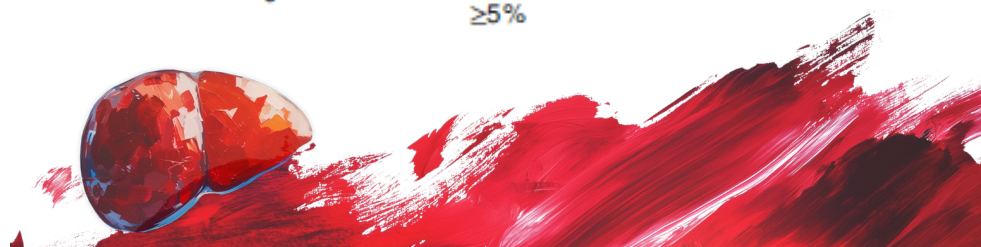
Garvey WT, et al; STEP 5 Study Group. *Nat Med*. 2022;28(10):2083-2091.

Step 5: Sustained Weight Loss With Semaglutide In Adults with Overweight/Obesity Adults and Without Diabetes







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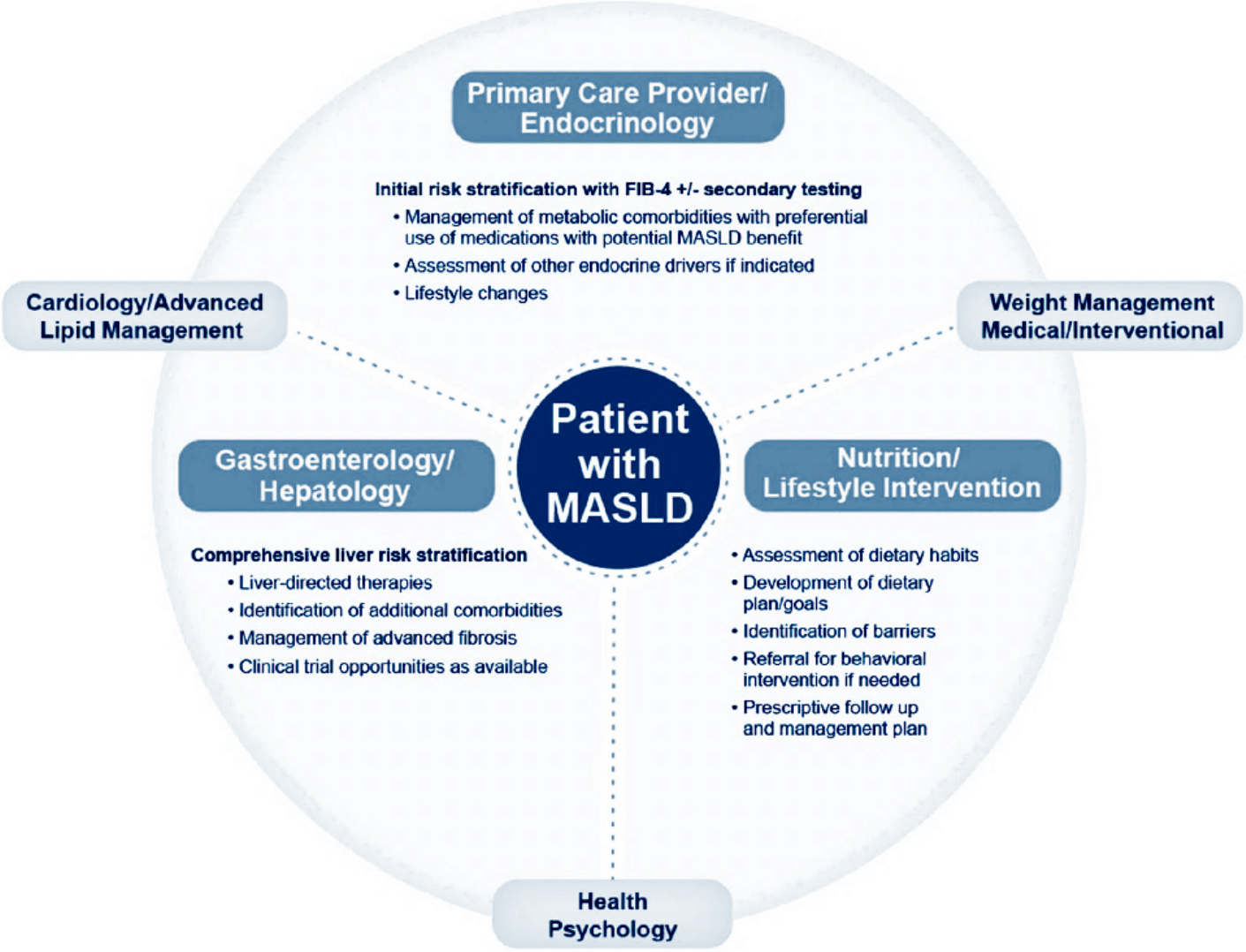
Garvey WT, et al; STEP 5 Study Group. *Nat Med*. 2022;28(10):2083-2091.

Review of Case: A 44-Year-Old White Woman With Class 2 Obesity

- HbA_{1c} = 8.3%
- BMI = 37.6 kg/m^2
- HTN, dyslipidemia
- Smokes cigarettes
- ALT = 62 U/L, AST = 48 U/L
- LSM = 8.6 kPa, CAP = 371 dB/m

Case Conclusion



Treatment Plan:

- Phase out glyburide and add a GLP-1 therapy
- Stop sitagliptin
- Consider an alternative to metoprolol
- Discuss smoking cessation
- Recommend stopping all alcohol consumption
- Develop a healthier dietary plan
- Schedule regular follow-up

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Rinella ME, et al. *Hepatology*. 2023;78(6):1966-1986.

Case 2

Naim Alkhouri, MD

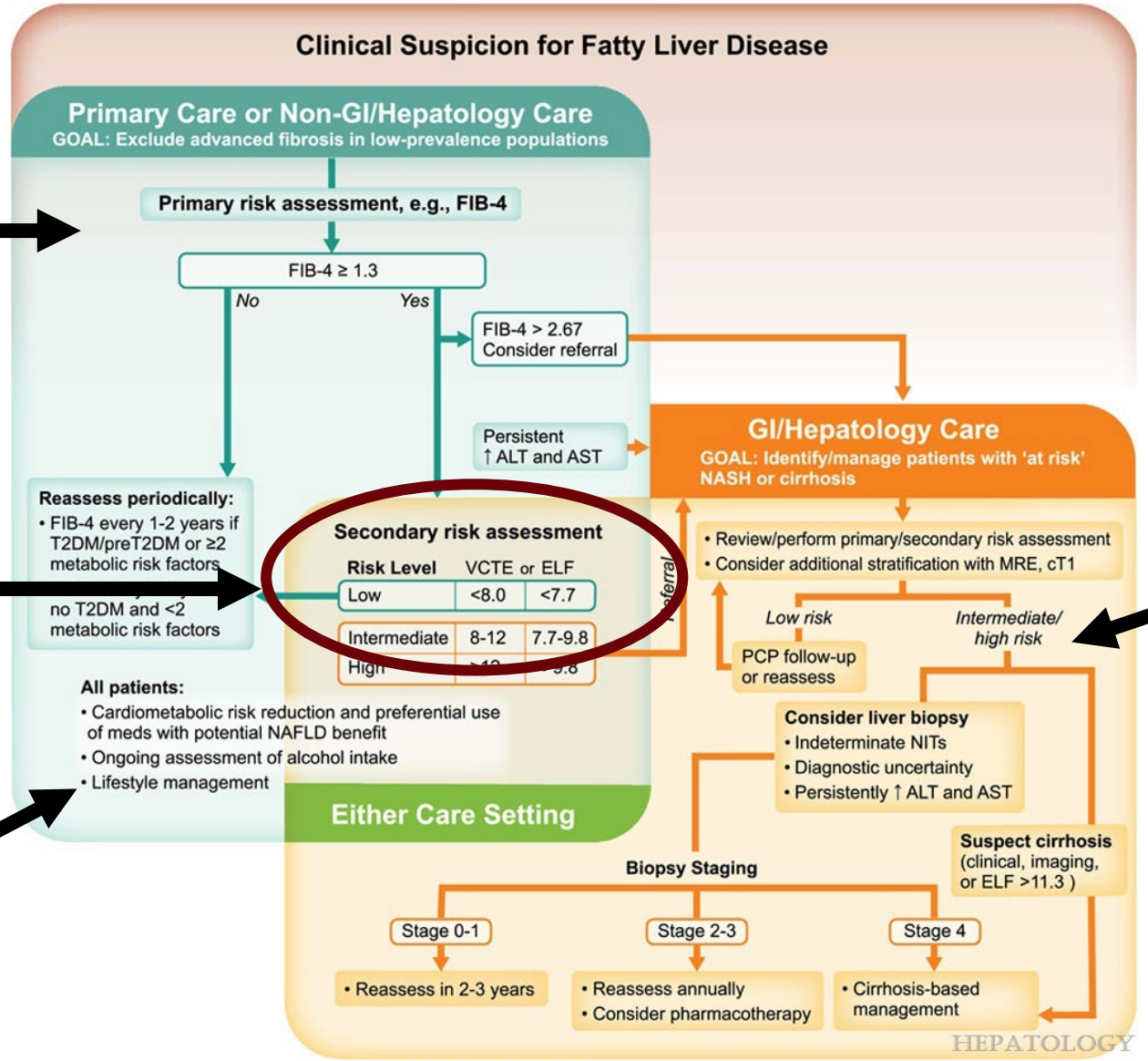
Case 2: A 56-Year-Old Hispanic Woman Referred By Her PCP

Medical Record	Results
Current meds	Atorvastatin 80 mg/day, losartan 50 mg/day
Physical exam	BMI: 42 kg/m^2, BP = 139/84 mmHg
Lab test results	LDLc: 98 mg/dL, HA1c: 6.2%, ALT: 90 U/L, AST: 76 U/L, albumin: 4 g/dL, platelet count: 202,000/µL, FIB4: 2.22
VCTE	**LSM: 10.9 kPa; CAP: 343 dB/m**

Primary Risk Assessment: FIB-4

Secondary Risk Assessment: VCTE or ELF

Cardiometabolic Risk Reduction



Identify Patients With At-Risk MASH

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Rinella ME, et al. Hepatology. 2023;77(5):1797-1835

What additional test would you consider using to assess for at-risk MASH?

- ELF test
- FAST score
- FIB-4 index
- MRI-PDFF

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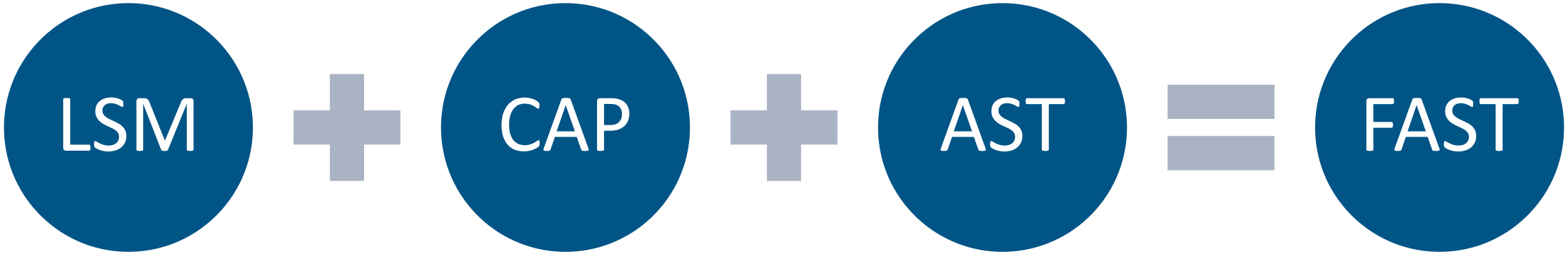
FAST: Score for Identifying At-Risk MASH in Specialty Care

FAST (FibroScan-AST): composite score calculated from LSM, CAP, and AST



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Newsome PN, et al. *Lancet Gastroenterol Hepatol*. 2020;5(4):362-373. Noureddin N, et al. *Hepatology*. 2020;72(6):2228-2230.

Score for Identifying At-Risk MASH in Specialty Care: FAST

Diagnostic Performance Across Derivation and Validation Cohorts[1]	
AUROC	0.80-0.95
Rule-Out (FAST <0.35)	
Sensitivity	0.64-1.00
Specificity	0.35-0.86
NPV	0.73-1.00
Rule-In (FAST ≥ 0.67)	
Sensitivity	0.82-0.99
Specificity	0.25-0.75
NPV	0.33-0.83

FAST for MASH[2]	
	≤0.35: low probability of at-risk MASH → sequential testing for people with high LSM values
Attention to LSM	In the "gray zone" (~30%) → sequential testing with another test
Attention to LSM	**≥0.67:** high probability of at-risk MASH → enroll in MASH clinical trials

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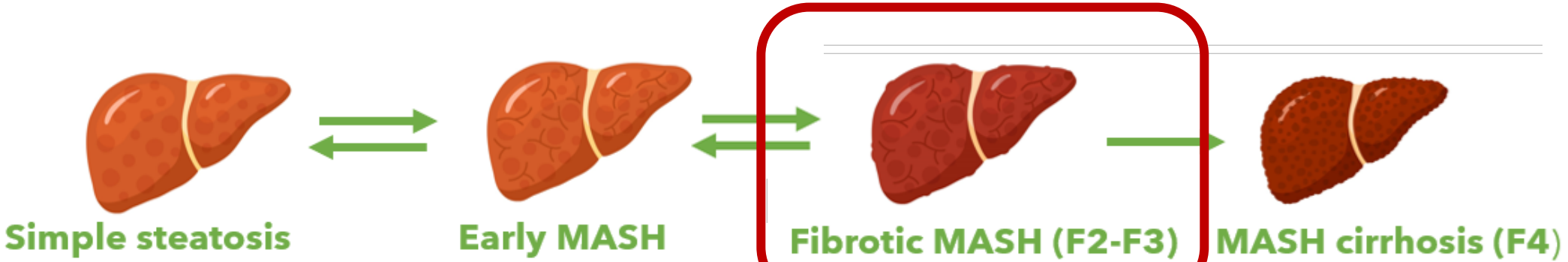
1. Newsome PN, et al. *Lancet Gastroenterol Hepatol*. 2020;5(4):362-373.
2. Noureddin N, et al. *Hepatology*. 2020; 72(6):2228-2230.

Case 2 (cont'd)

Medical Record	Results
Current meds	Atorvastatin 80 mg/day, losartan 50 mg/day
Physical exam	BMI: 42 kg/m^2, BP = 139/84 mmHg
Lab test results	LDLc: 98 mg/dL, HA1c: 6.2%, ALT: 90 U/L, AST: 76 U/L, albumin: 4 g/dL, platelet count: 202,000/µL
VCTE	LSM: 10.9 kPa; CAP: 343 dB/m
FAST	**FAST score: 0.74** → at-risk MASH, significant fibrosis

Medically Complicated Obesity: Target Population for Hepatology Care



At-risk MASH = MASH + ≥F2

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Rinella ME, et al. *Hepatology*. 2023;77(5):1797-1835.

Is a liver biopsy ever indicated when evaluating patients for treatment with resmetirom?

- Yes, when a baseline biopsy was done >12 months ago
- Yes, when there is discordance between 2 current NIT results
- No, NITs should be used instead

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Noureddin M, et al. *Clin Gastroenterol Hepatol*. Published online July 20, 2024.

How would you initiate treatment in this patient?

- Vitamin E
- Resmetirom with lifestyle interventions
- Resmetirom + GLP-1 RA only

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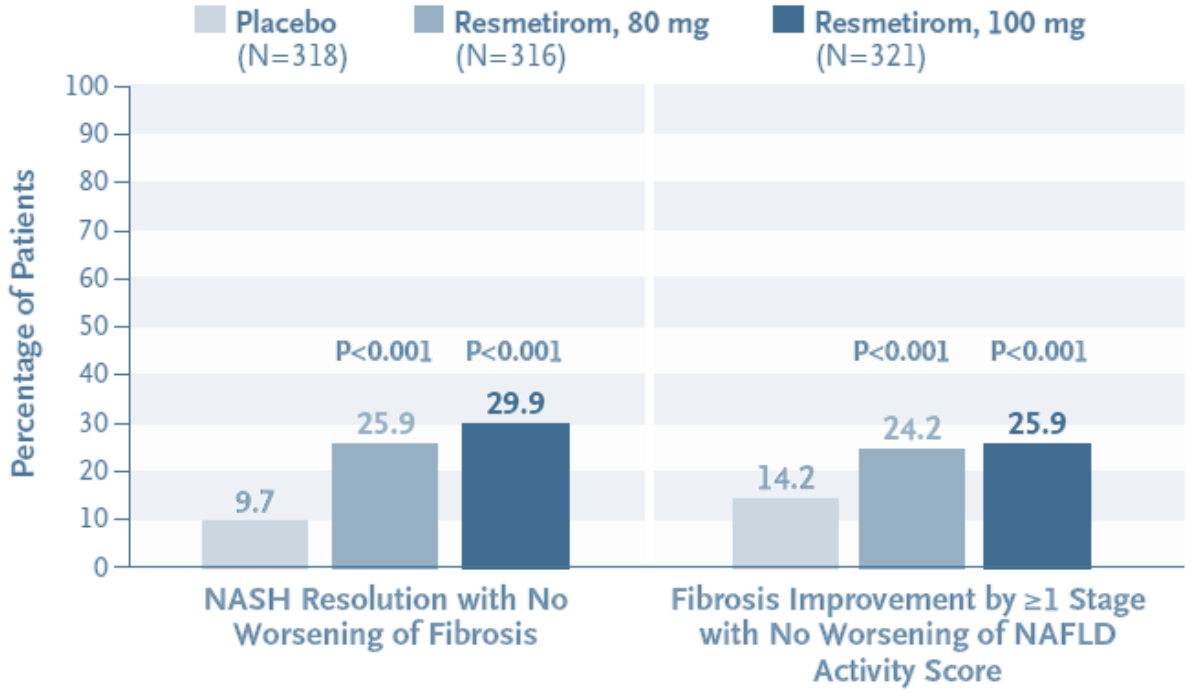
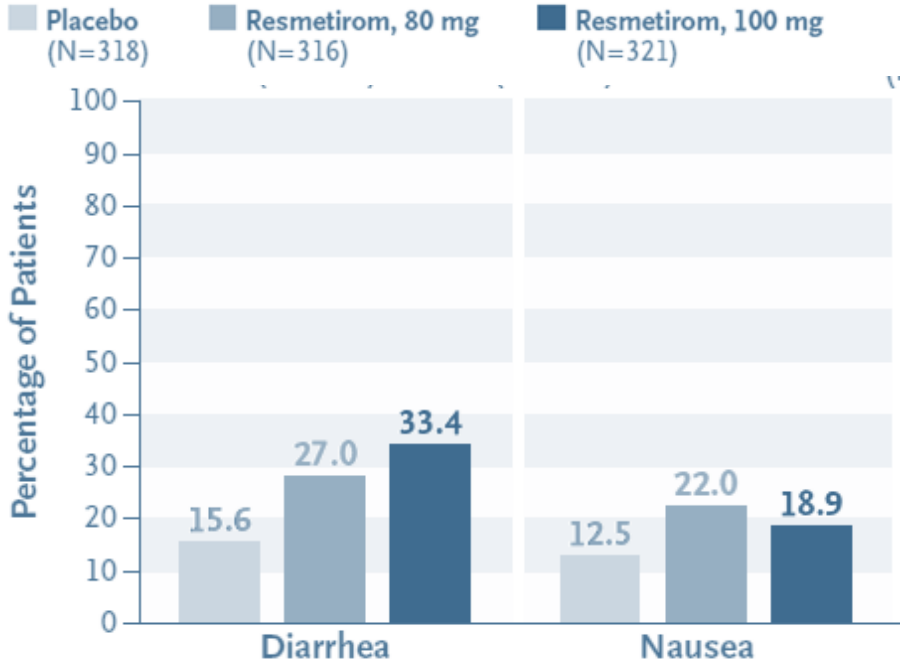
Noureddin M, et al. *Clin Gastroenterol Hepatol*. Published online July 20, 2024.

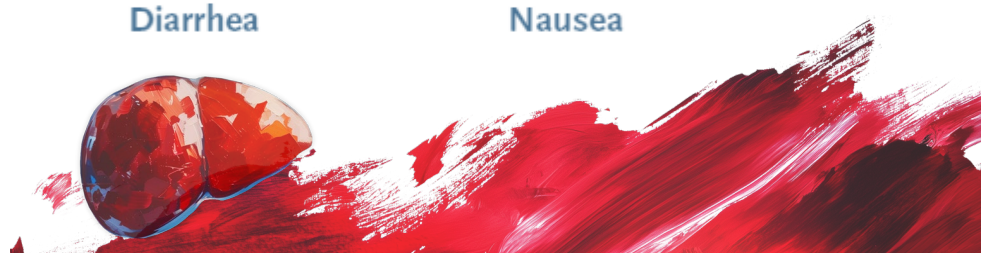
A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH With Liver Fibrosis

Efficacy



Safety





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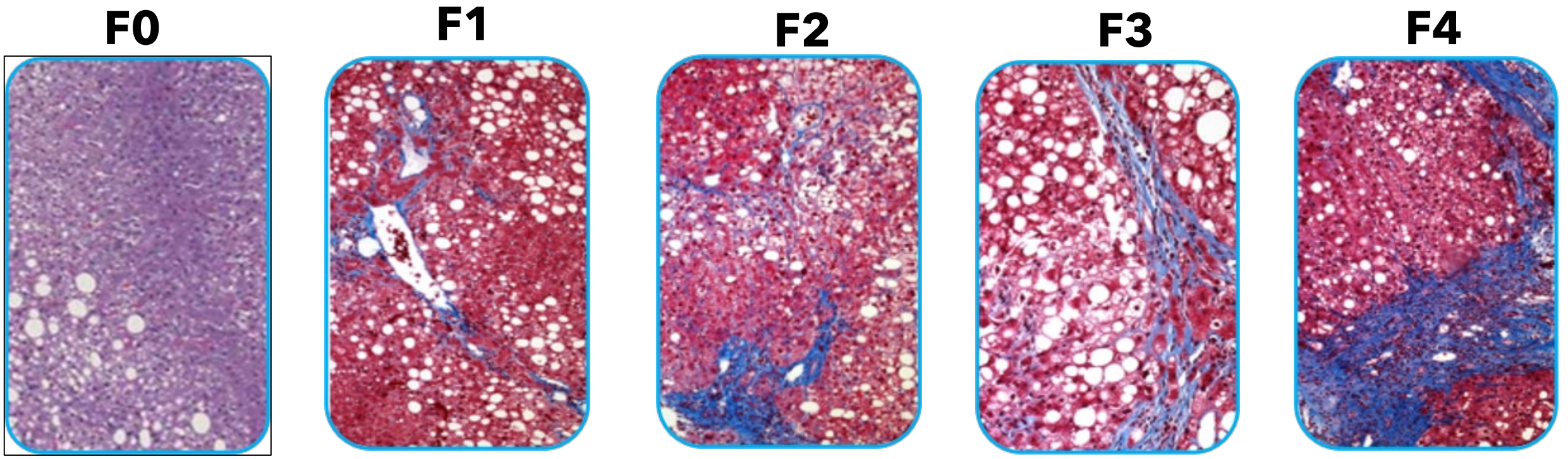
Harrison SA, et al; MAESTRO-NASH Investigators. *N Engl J Med*. 2024;390(6):497-509.

Review of Case: A 56-Year-Old Hispanic Woman Referred by Her PCP

- BMI = 42 kg/m^2
- HbA_{1c} = 6.2%
- ALT = 90 U/L, AST = 76 U/L
- LSM (VCTE) = 10.9 kPa, CAP = 343 dB/m
- ELF score = 9.5
- FAST score = 0.74

Case Conclusion



GLP-1 Therapy/Weight-Loss Strategies + Liver-Directed Therapy

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Use of Incretins for Weight Loss in Patients With MASH

AASLD

Semaglutide* can be considered for its approved indications (T2DM/obesity) in patients with MASH, as it confers a cardiovascular benefit and improves MASH.

EASL

GLP-1 RAs are safe to use in MASH (including compensated cirrhosis) and should be used for their respective indications (T2D and obesity) as their use improves cardiometabolic outcomes.

***Once-weekly SC injection**

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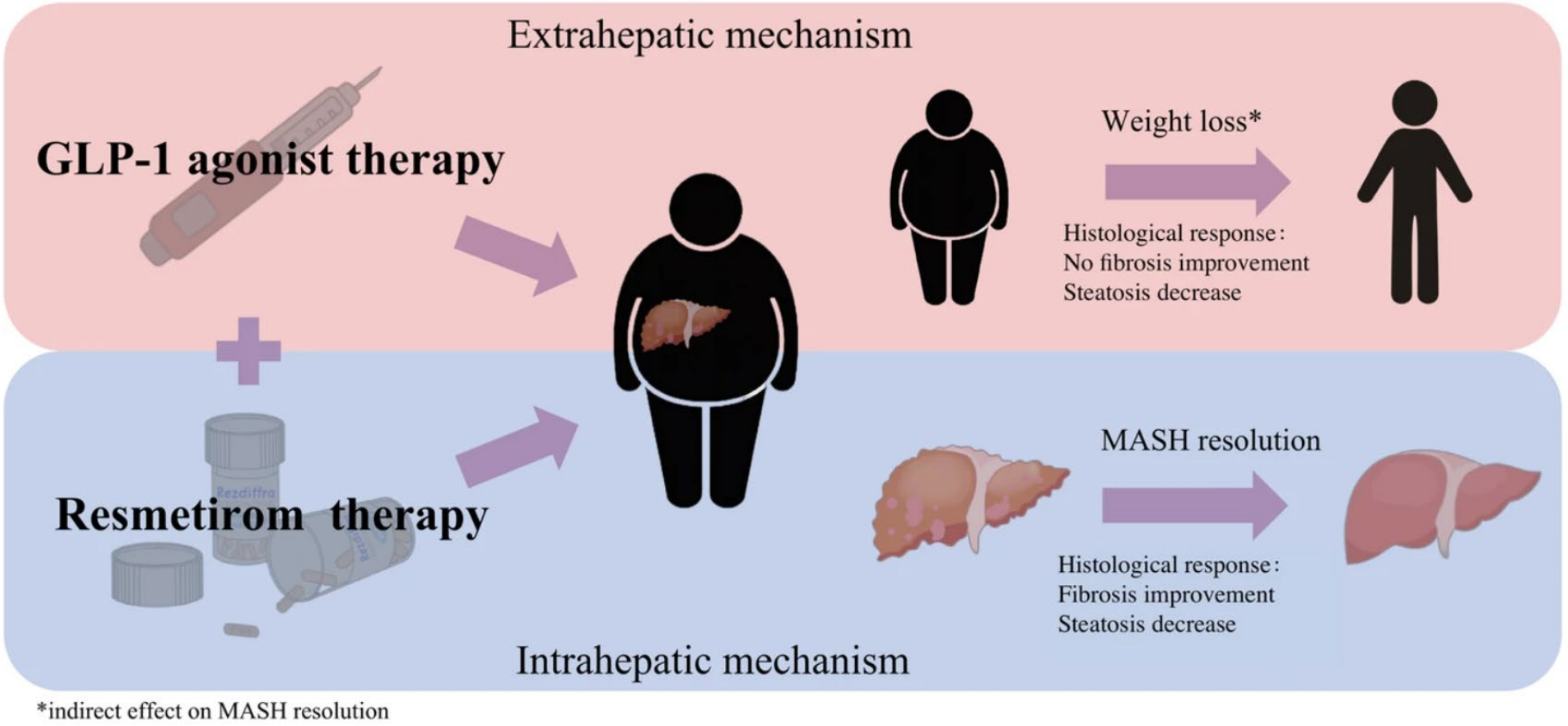
Rinella ME, et al. *Hepatology*. 2023;78(6):1966-1986. EASL. *J Hepatol*. 2024;81(3):492-542.

Combining GLP-1 Agonists With Resmetirom



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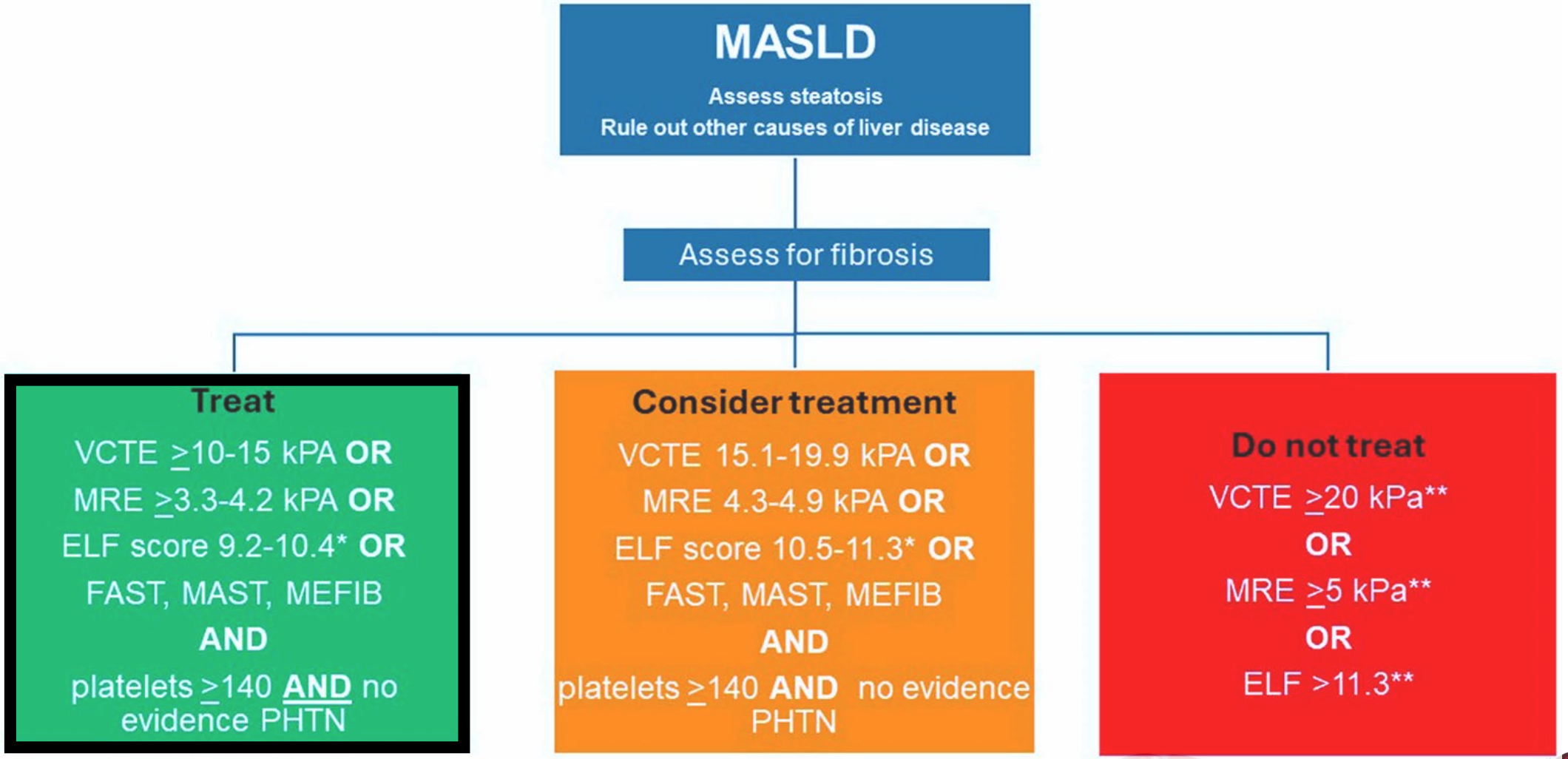
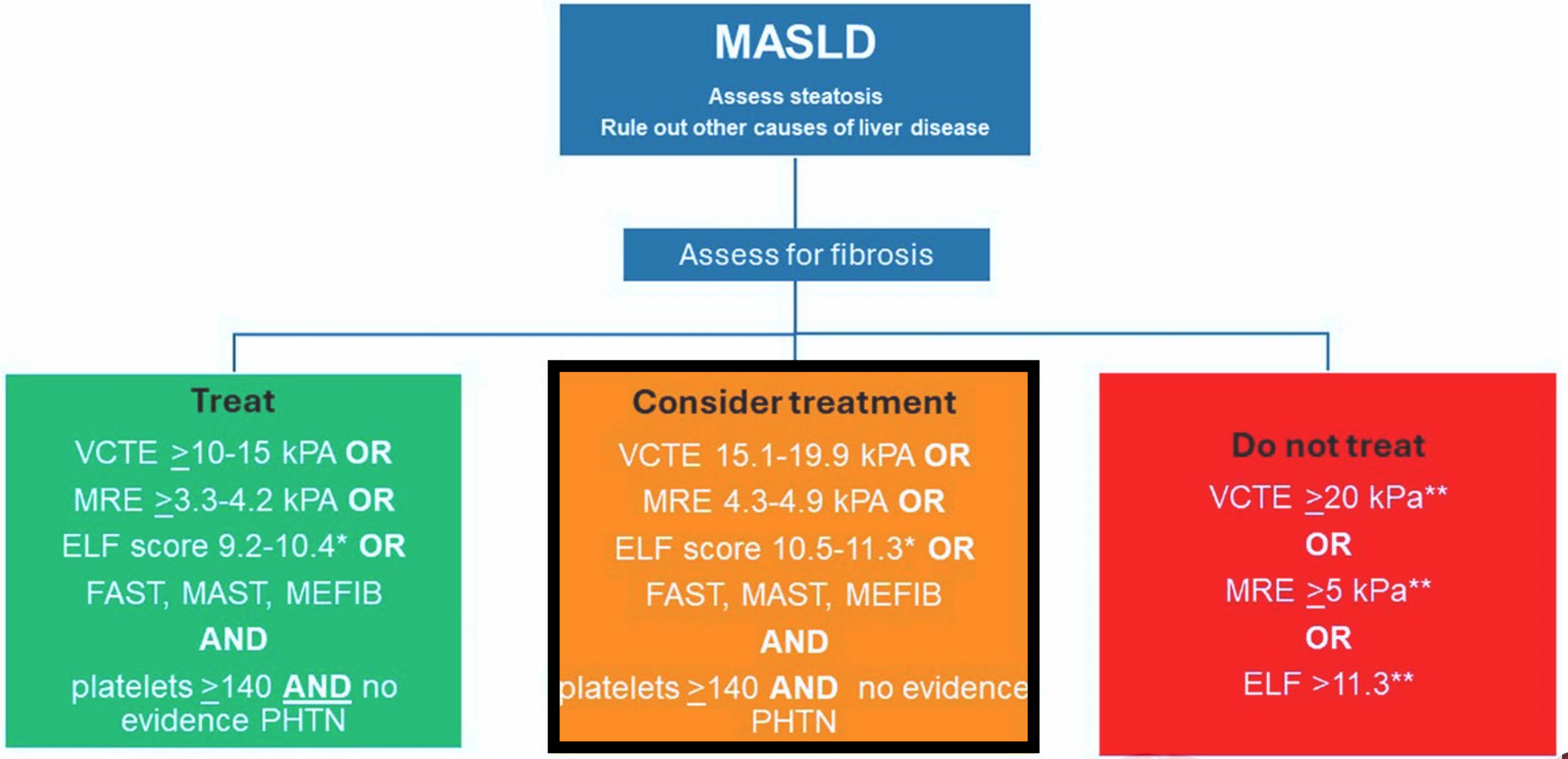
Zhou XD, et al. *npj Gut Liver*. 2024;1(4).

Resmetirom: Treat



Noureddin M, et al. *Clin Gastroenterol Hepatol*. Published online July 20, 2024.

Resmetirom: Consider Treatment



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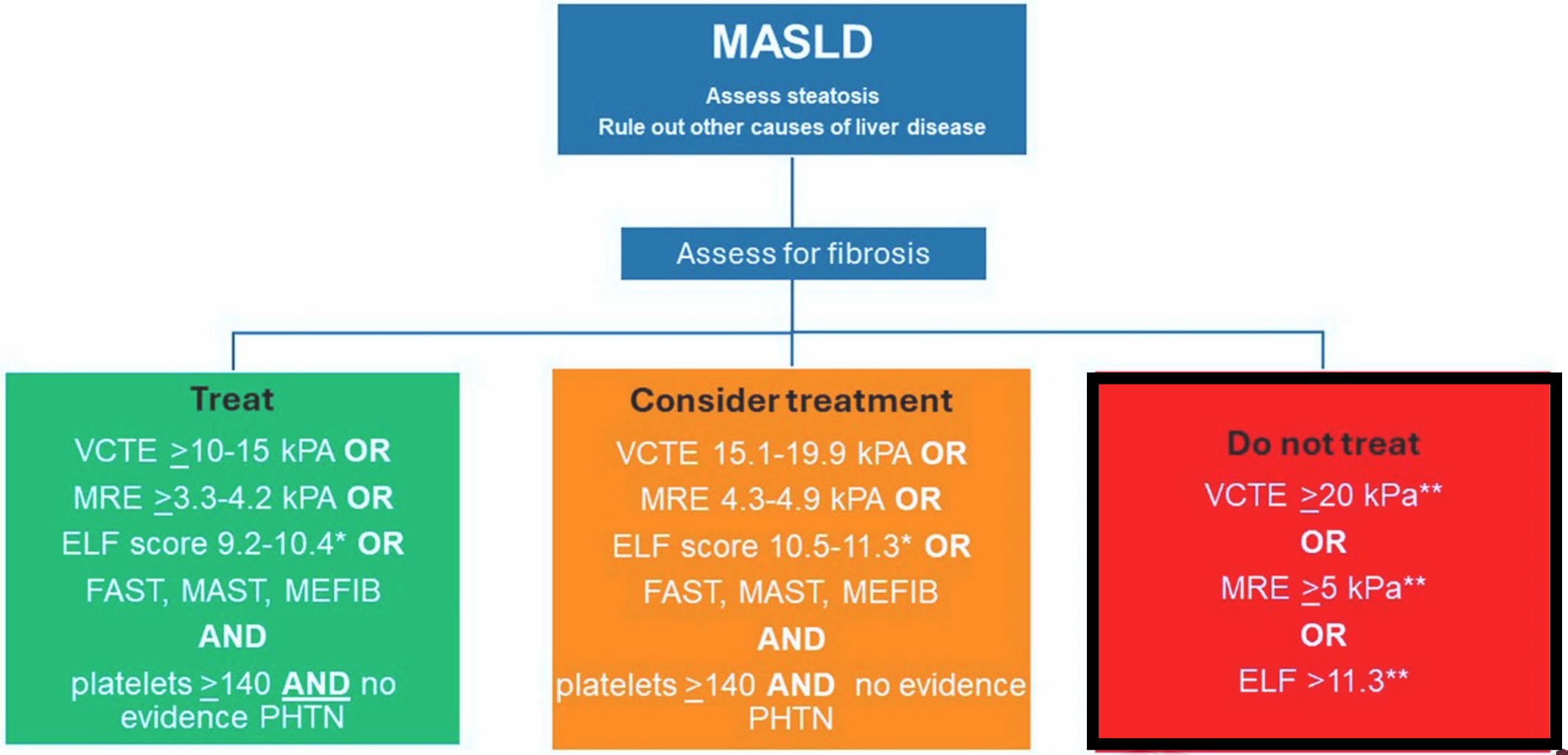
Noureddin M, et al. *Clin Gastroenterol Hepatol*. Published online July 20, 2024.

Resmetirom: Do Not Treat



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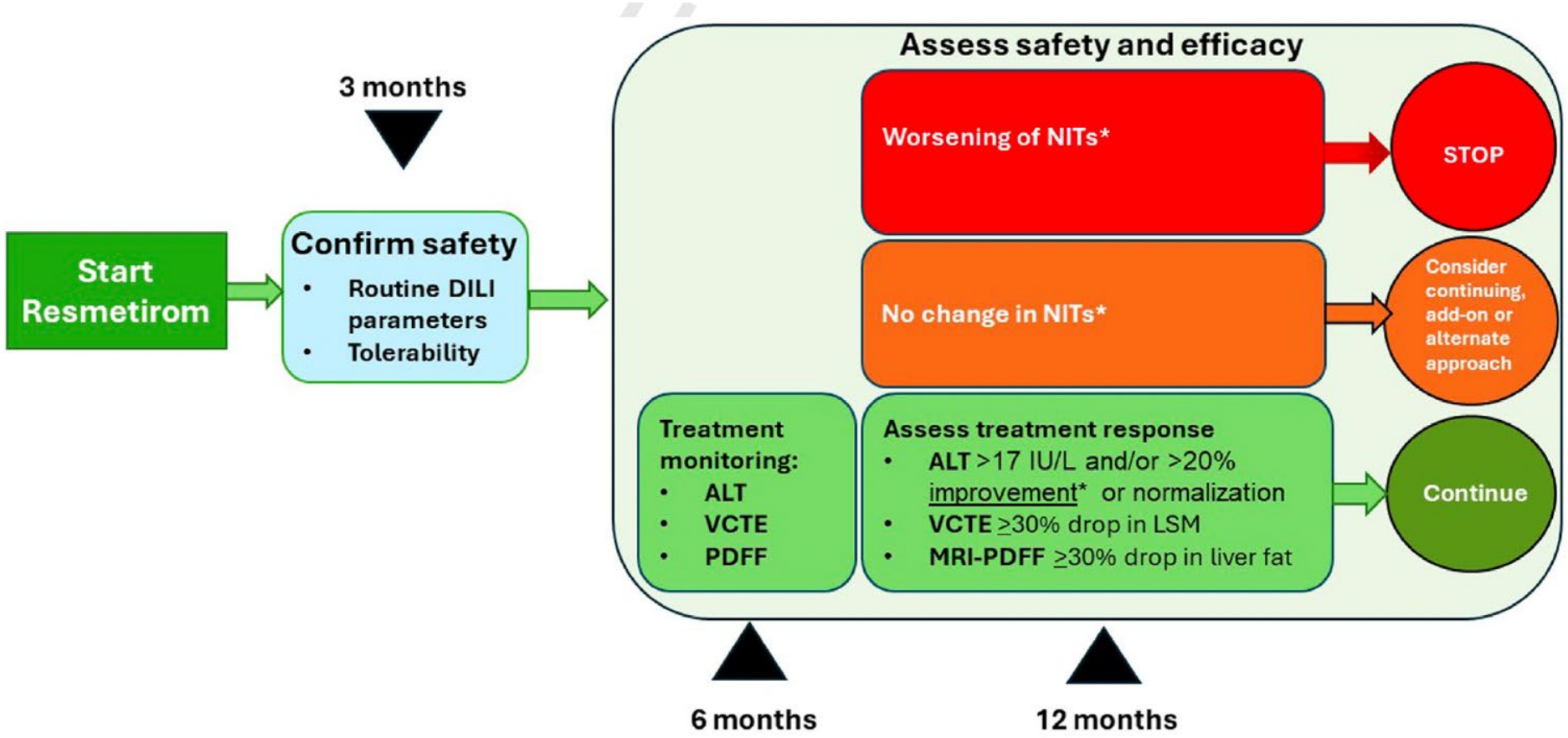
Noureddin M, et al. *Clin Gastroenterol Hepatol*. Published online July 20, 2024.

Treatment With Resmetirom: From Start to Finish



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Noureddin M, et al. *Clin Gastroenterol Hepatol*. Published online July 20, 2024.

Case 3

Amreen Dinani, MD

Case 3: A 60-Year-Old Black Man With MASH

Medical Record	Results
Medical History	Fatigue, loss of appetite
Current meds	Metformin 1000 mg BID, sitagliptin 100 mg daily (T2D diagnosed at age 54)
Physical exam	BP: 152/86 mmHg, BMI: 34 kg/m^2, bilateral LEE, no visible stigmata of CLD, alert and oriented
Lab test results	LDLc: 95 mg/dL, HA1c: 6.9%, ALT: 66 U/L, AST: 76 U/L, albumin 3.5 g/dL, platelet count: 147,000/µL

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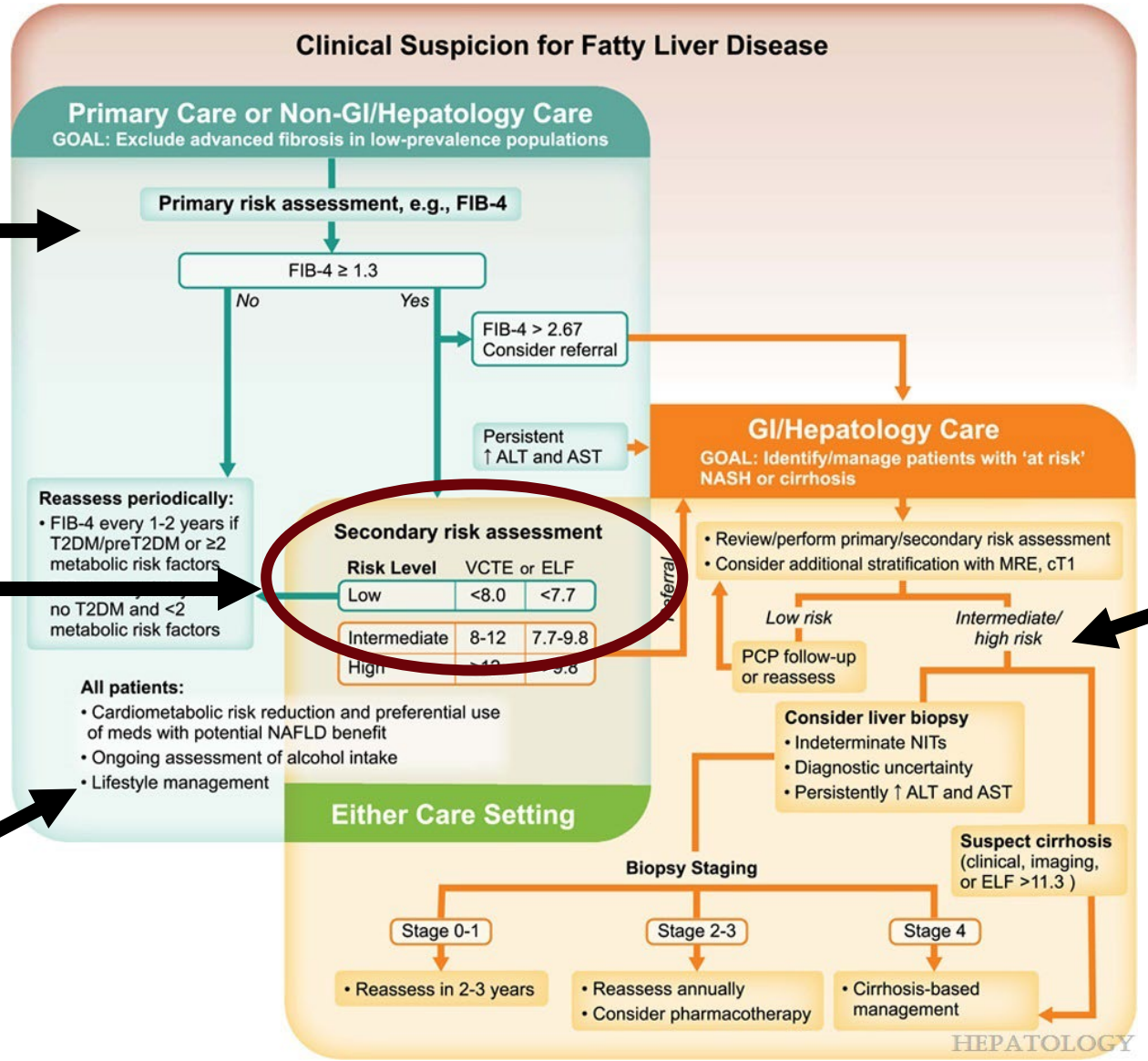
Primary Risk Assessment: FIB-4

Secondary Risk Assessment: VCTE or ELF

Cardiometabolic Risk Reduction



Identify Patients With At-Risk MASH

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Rinella ME, et al. Hepatology. 2023;77(5):1797-1835

Case 3 (cont'd)

Medical Record	Results
NITs	abdominal US: nodular liver, splenomegaly **FIB-4: 3.82**

What test(s) would you order to confirm the patient has CSPH?

- CT scan
- ELF
- FIB4+
- MRI
- VCTE + platelet count

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Brol MJ, et al. *Curr Hepatology Rep*. 2023;22:206-215.

Case 3 (cont'd)

Medical Record	Results
VCTE	21.1 kPa, CAP: 302 dB/m
Platelet count	147,000/µL

What would you do next?

- Initiate a non-selective beta-blocker
- Initiate resmetirom
- Initiate a diet based on intermittent fasting

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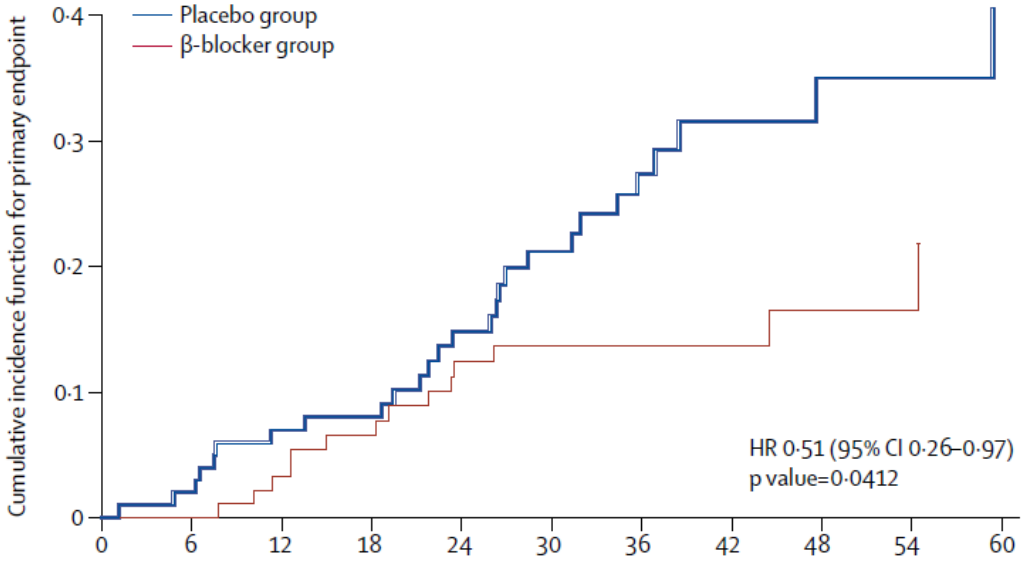
Beta-Blocker Therapy to Prevent Decompensation

A



Patients at risk											
β blockers	100	96	87	80	69	60	48	31	20	15	7
Placebo	101	99	94	86	72	59	42	26	19	13	6
Primary outcome (deaths)											
β blockers		1 (1)	3 (1)	4 (2)	5 (2)	1 (1)	0	0	1 (1)	0	1
Placebo		2 (2)	5 (1)	1	6 (2)	5 (1)	4 (3)	2 (1)	1 (1)	0	1
Censoring events											
β blockers		3	6	3	6	8	12	17	10	5	7
Placebo		0	0	7	8	8	13	14	6	6	6

Baveno VII: A clinically significant decrease in LSM (associated with substantially reduced risk of decompensation and liver-related death) is **a decrease of ≥20% associated with LSM <20 kPa or any decrease to a LSM <10 kPa**.

SAEs: syncope and bradyarrhythmia occurred in 6 patients (four in the β-blockers group); none were fatal

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Villanueva C, et al. *Lancet*. 2019;393(10181):1597-1608.

Would you treat this patient with resmetirom?

- Yes
- No
- Unsure

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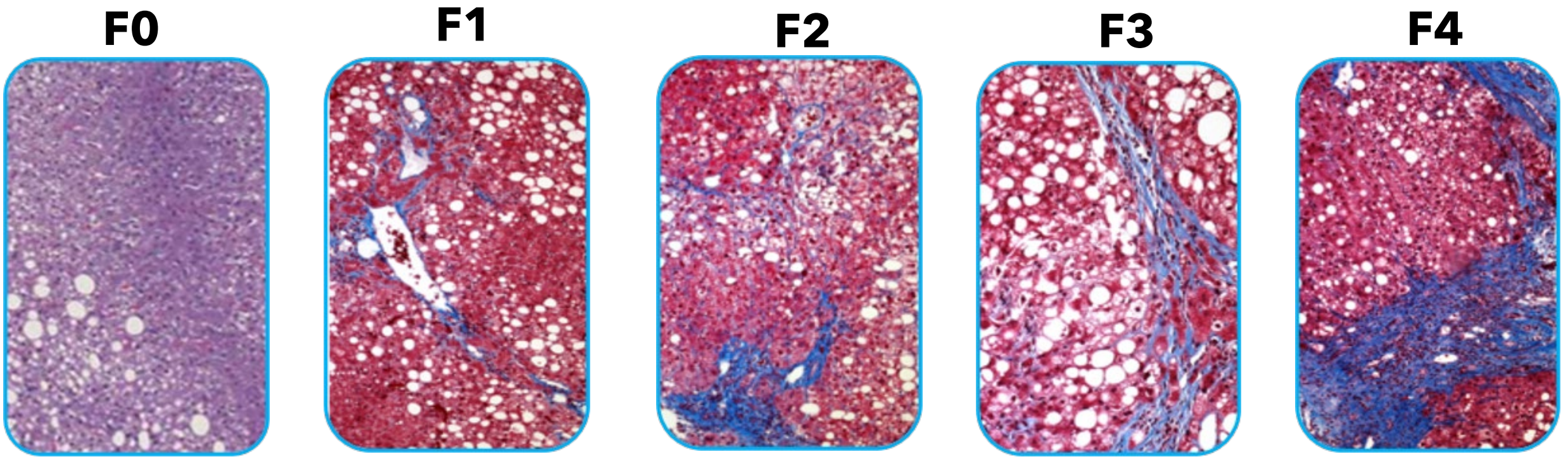
Case Conclusion



GLP-1 Therapy/Weight-Loss Strategies + Liver-Directed Therapy

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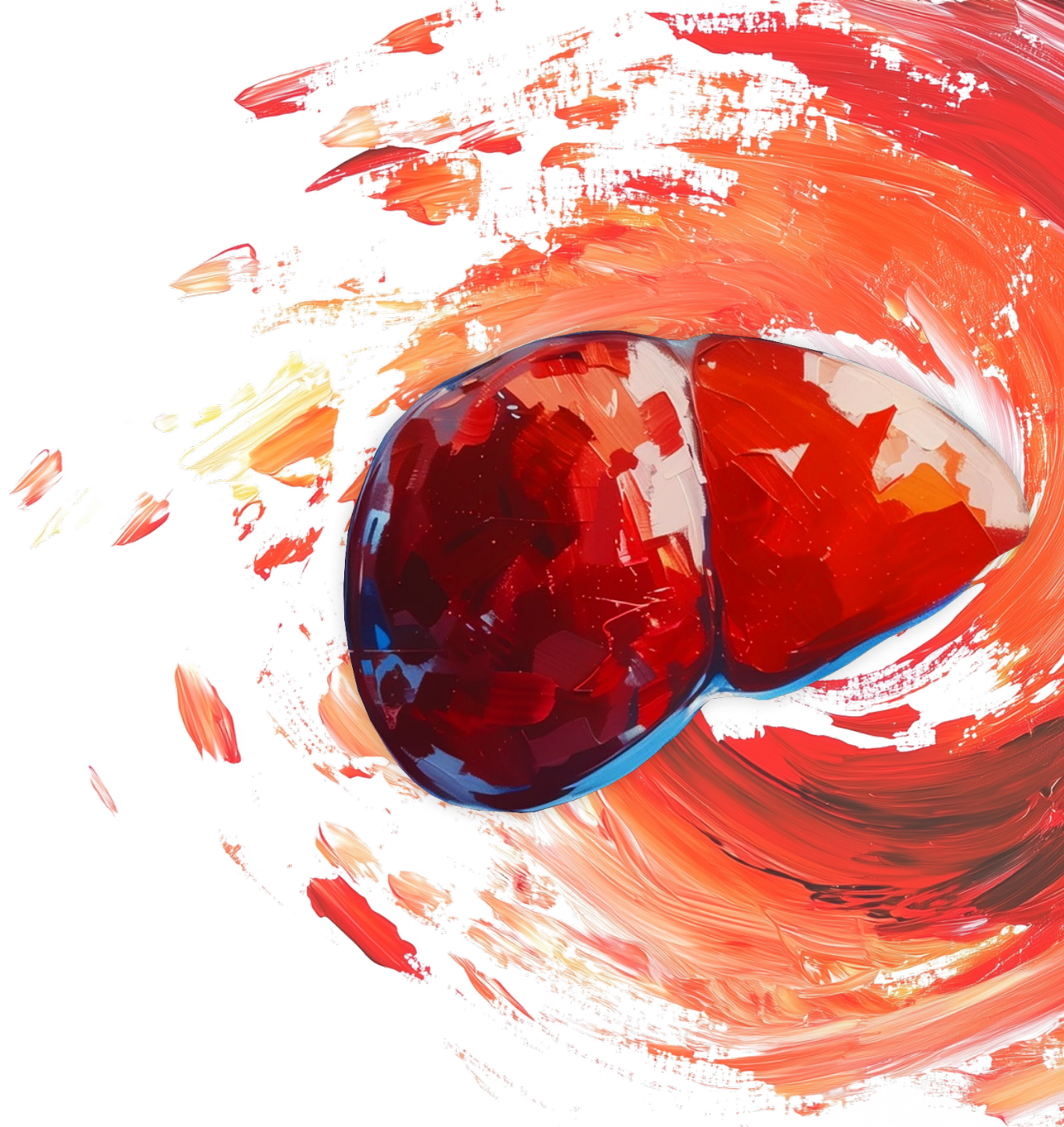
Looking Forward: What's in the Pipeline?

Amreen Dinani, MD



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Drug Candidates in Phase 3 Clinical Trials

PROGRAM	MOA
Resmetirom	**THR-β** oral
Lanifibranor	**PAN-PPAR** oral
Efruxifermin	**FGF21** injectable
Pegozafermin	**FGF21** injectable
Semaglutide	**GLP1-RA** injectable
Survodutide	**Glucagon/GLP-1 receptor dual agonist** injectable

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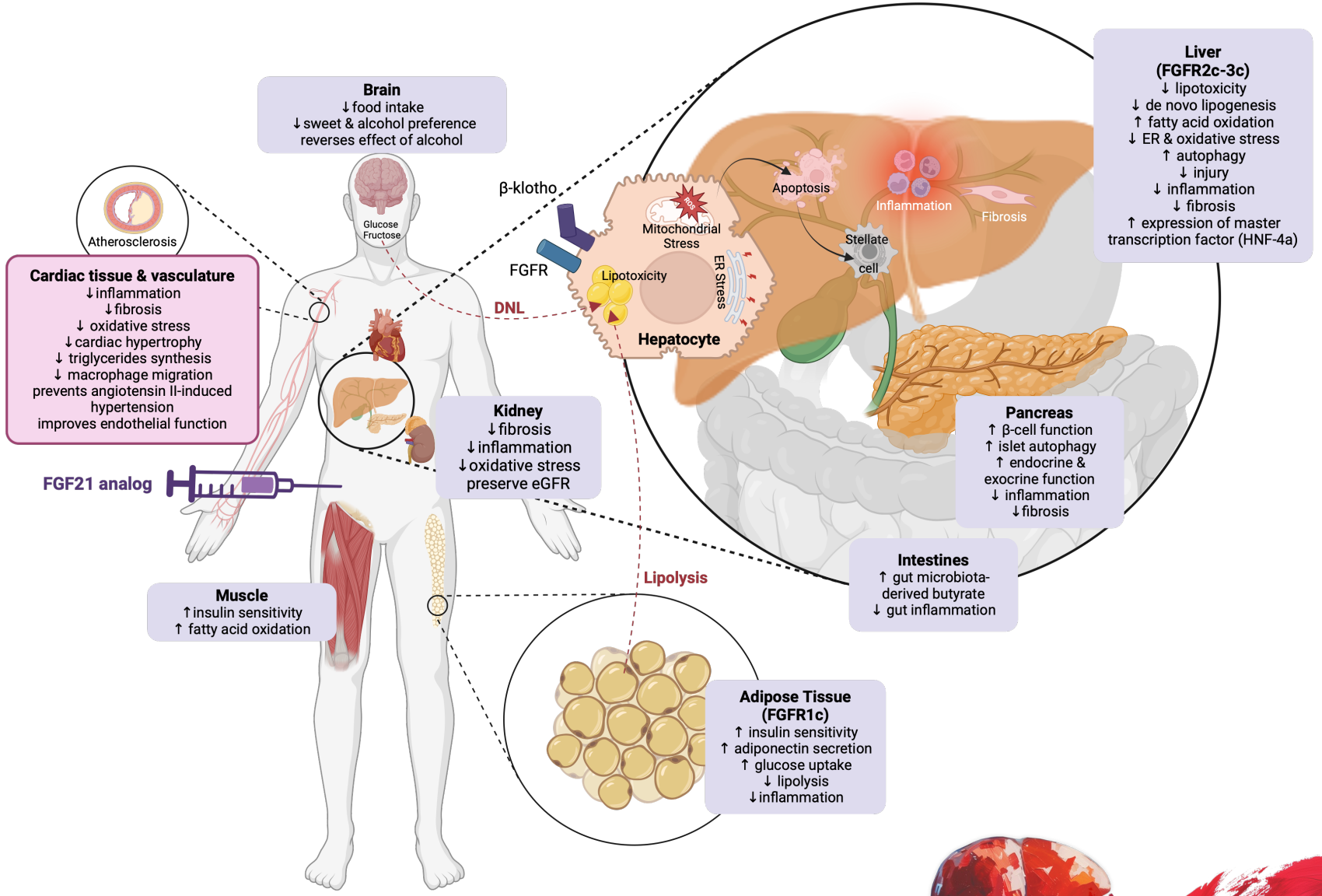
Pleotropic Actions of FGF-21



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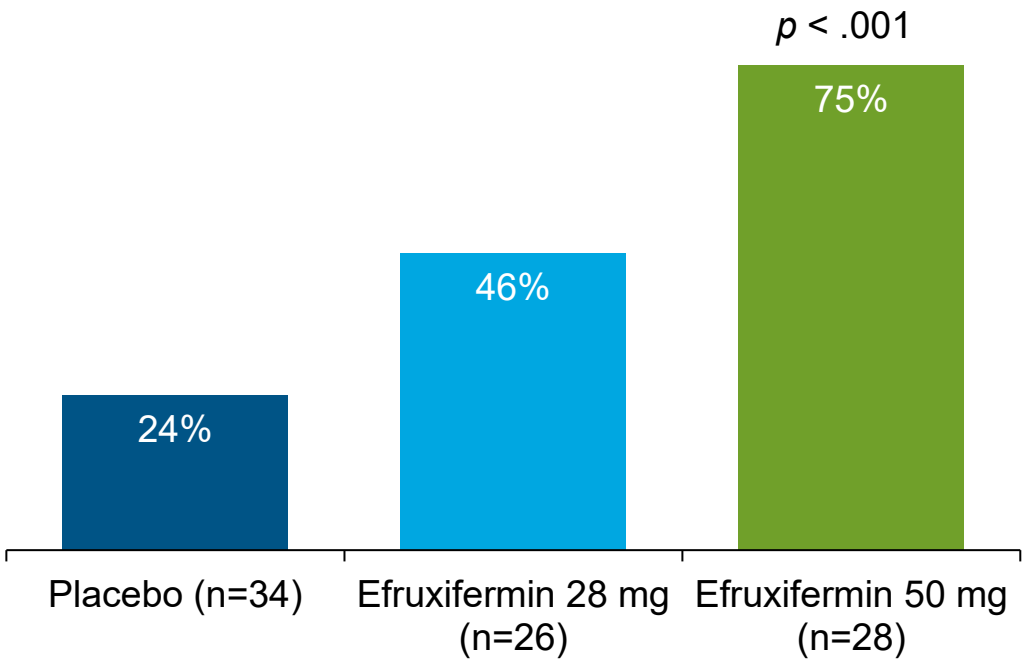
Harrison SA, et al. *J Hepatol*. 2024 Sep;81(3):562-576

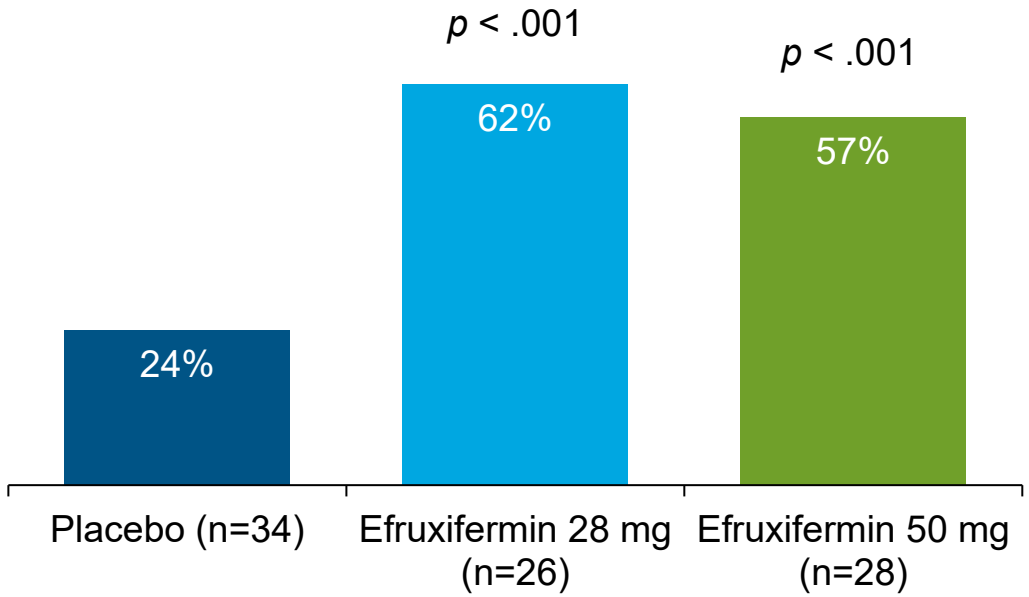
Efruxifermin: Phase 2b HARMONY Trial

Efruxifermin is a long-acting FGF21 analog

Primary Endpoint: Fibrosis Improvement
Efruxifermin 50mg Dose Achieved Statistical Significance
Week 96



Key Secondary Endpoint: NASH Resolution
Both Efruxifermin Doses Achieved Statistical Significance
Week 96



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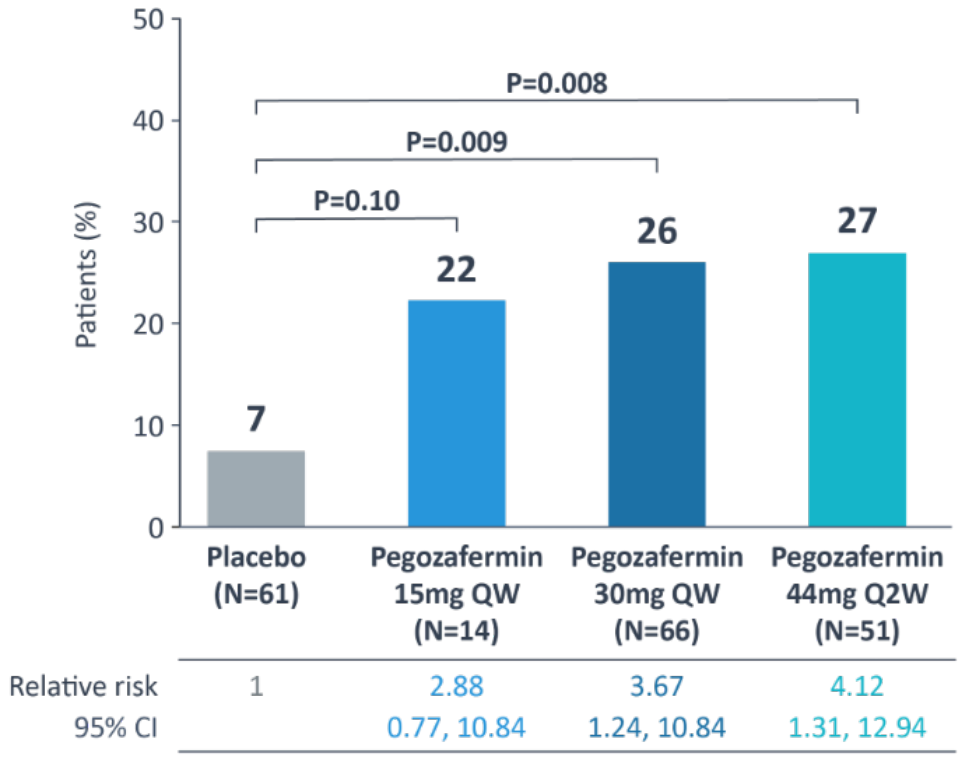
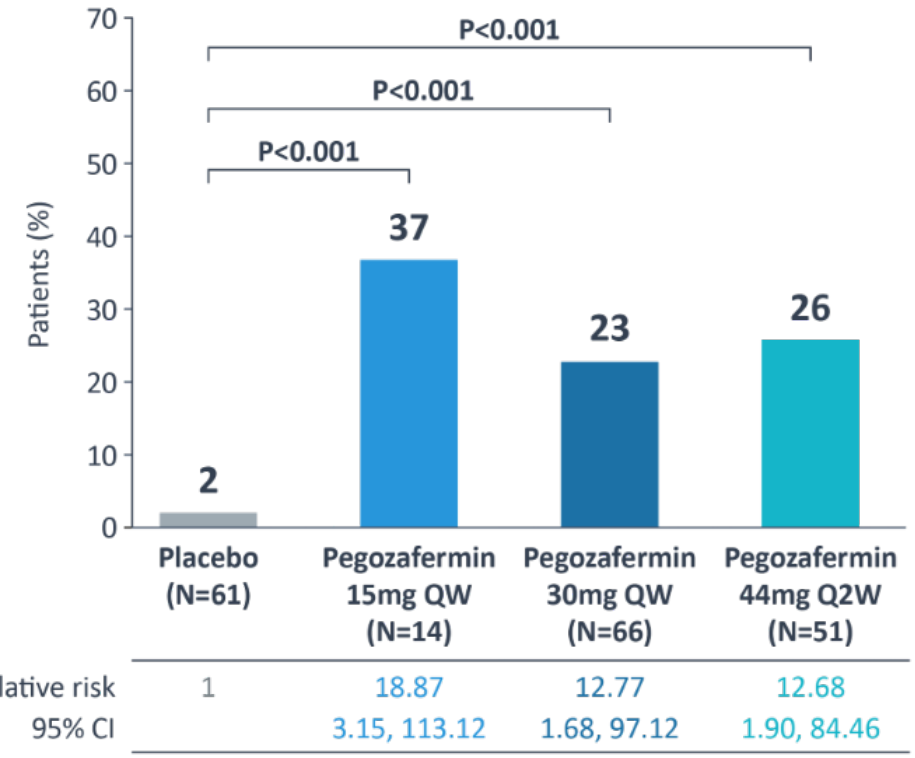
Phase 2b HARMONY study. https://www.biospace.com/article/releases/akero-therapeutics-reports-statistically-significant-histological-improvements-at-week-96-in-phase-2b-harmony-study/

Pegozafermin: ENLIVEN, Phase 2b Results





Safety: nausea, diarrhea

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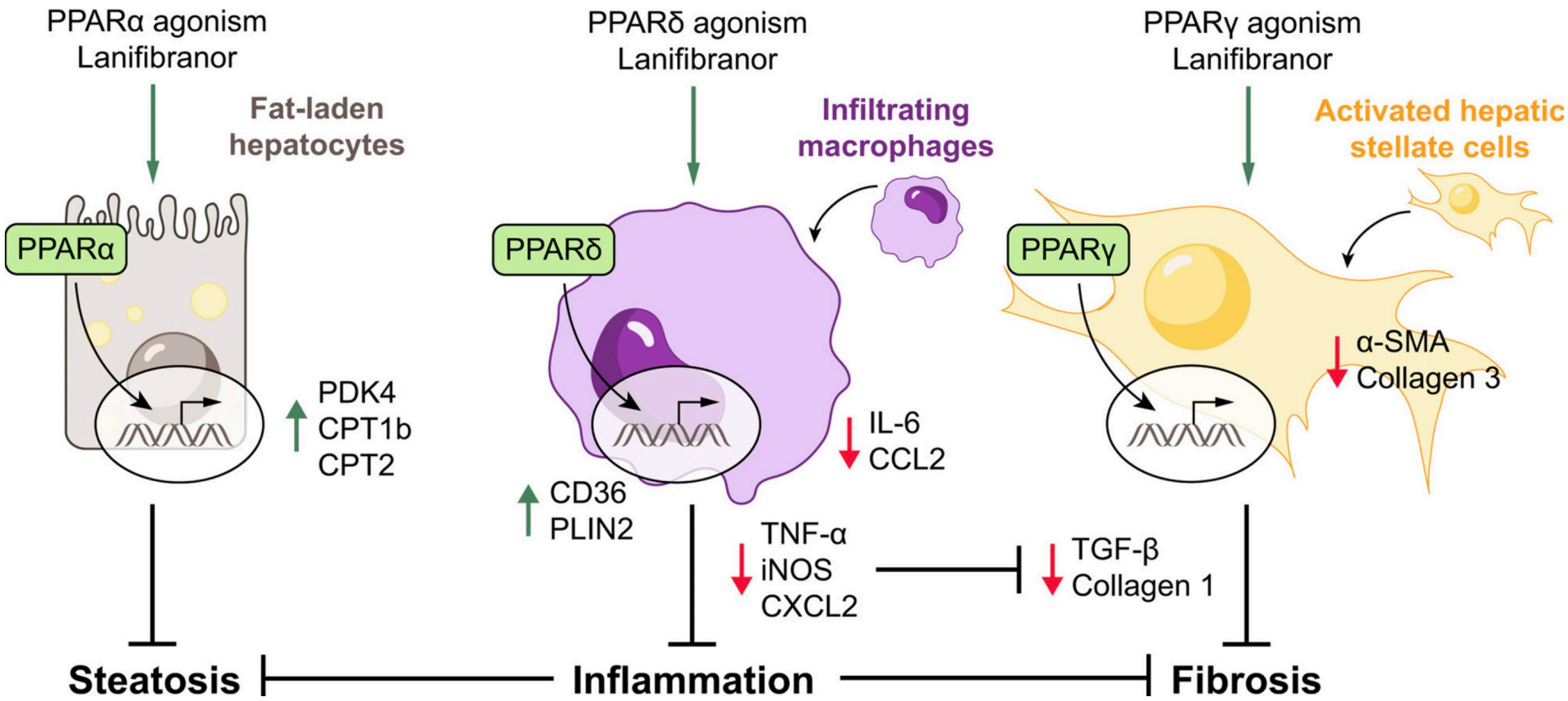
Loomba R, et al. *N Engl J Med*. 2023;389(11):998-1008.

Impact of PPAR Agonism on NASH



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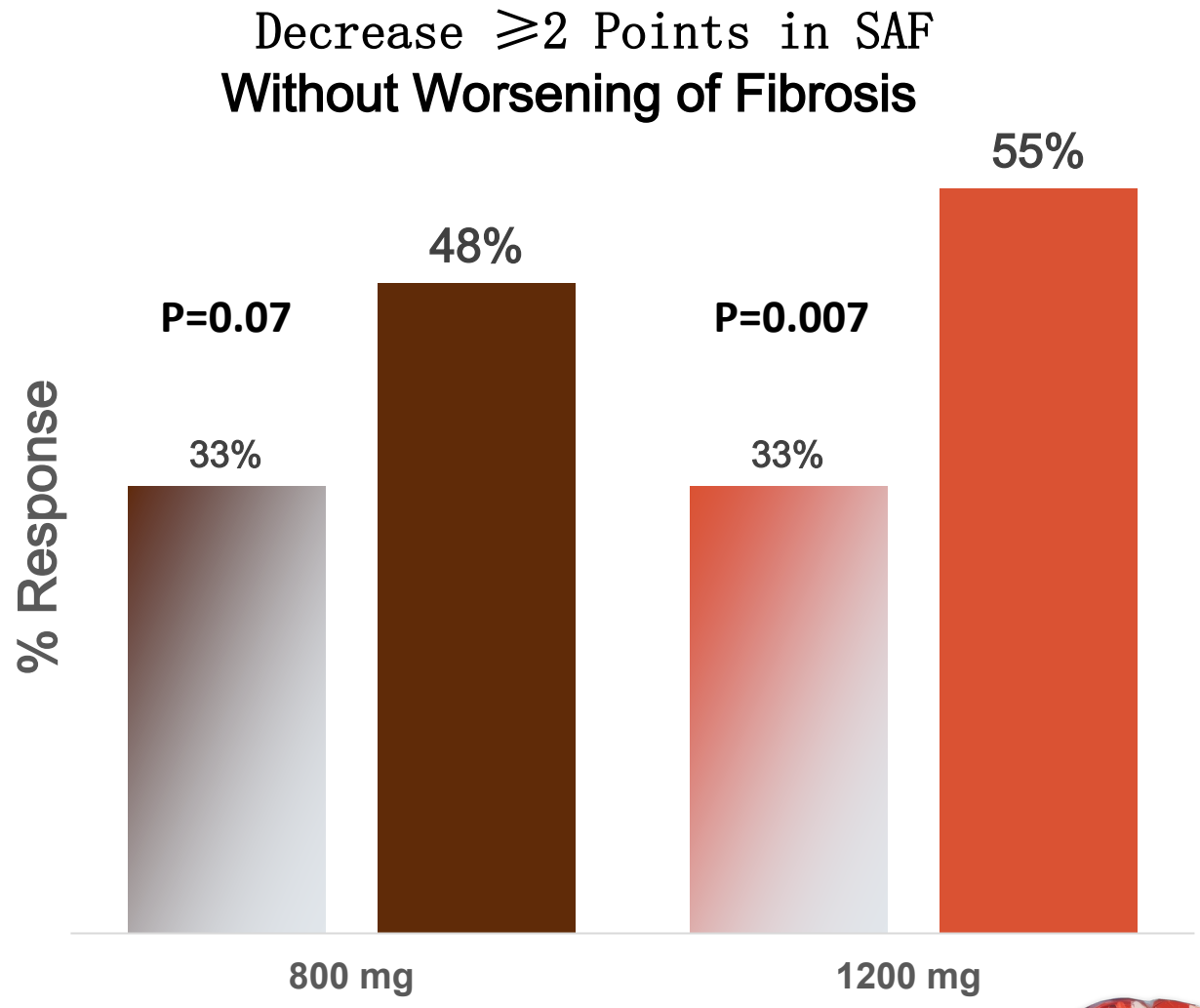
Lefere S, et al. *J Hepatology*. 2020;73(4):757-770.

Lanifibranor: Phase 2b Results



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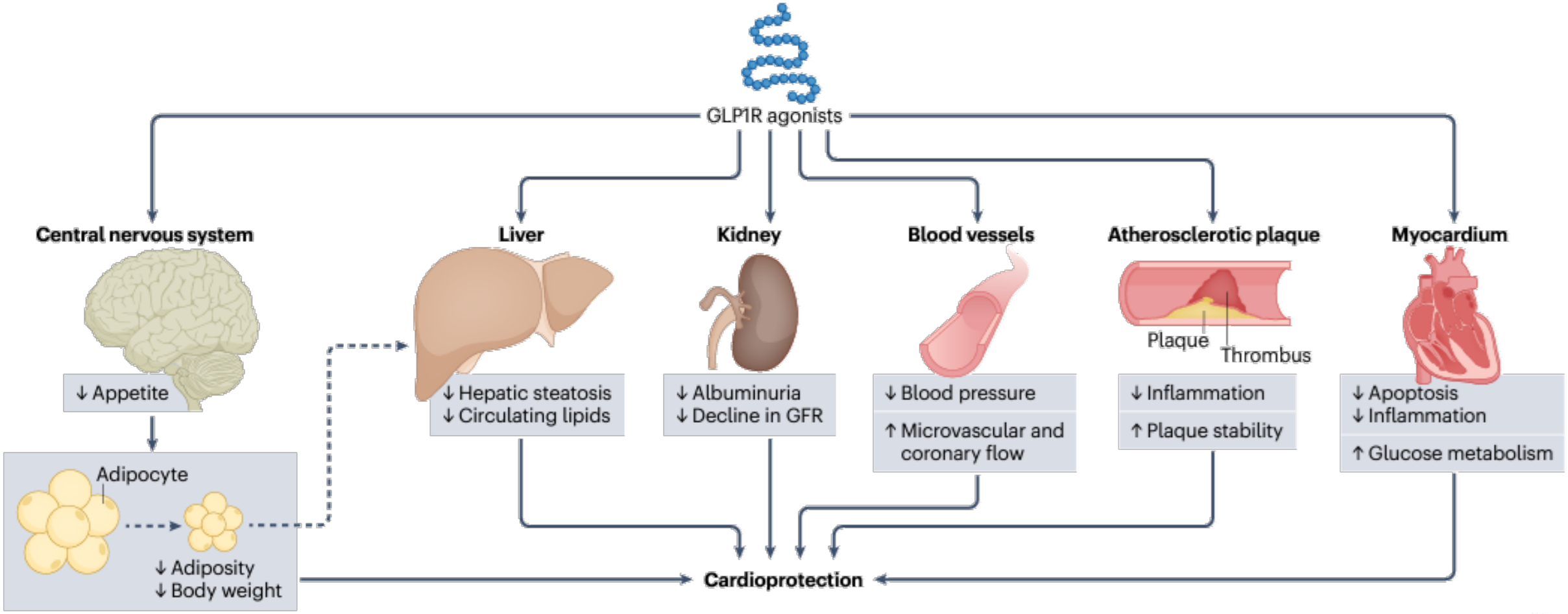
Francque SM, et al. *N Eng J Med.* 2021 Oct 21;385(17):1547-1558.

Pleotropic Effects of GLP-1



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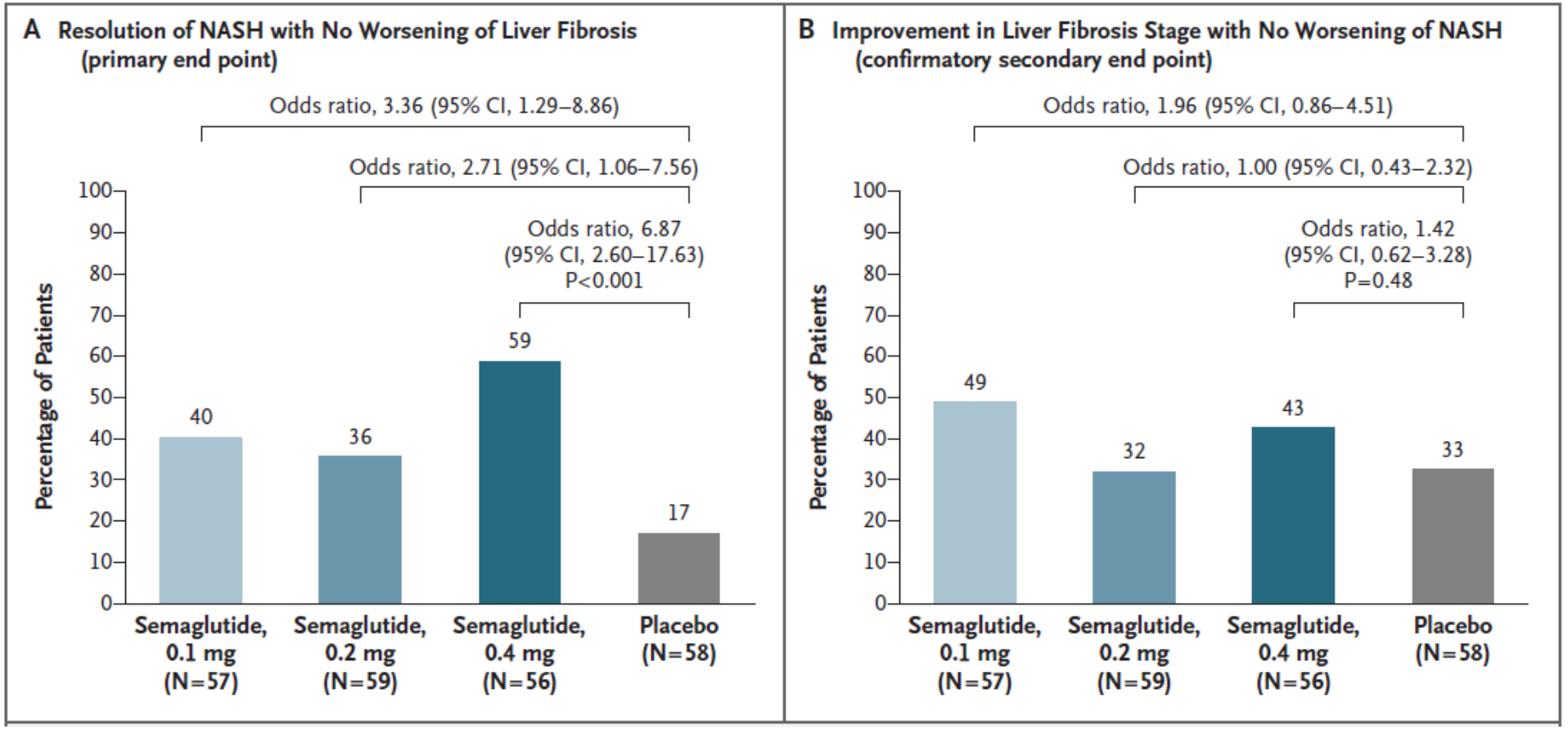
Ussher JR and Drucker DJ. Nature Rev Cardiol. 2023;20:463-474.

Emerging Incretin Targets

Target	Drug
GLP-1	Semaglutide (ph 3)
GLP-1 + GIP	Tirzepatide (ph 2a)
GLP-1 + glucagon	Cotadutide (ph 2), efinopegdutide (ph 2a), survodutide (ph 3)
GLP-1 + GIP + glucagon	Retatrutide (ph 2a)

Semaglutide: Phase 2 Results



Safety: GI disorders most common semaglutide-related AEs: nausea, vomiting, constipation, abdominal pain

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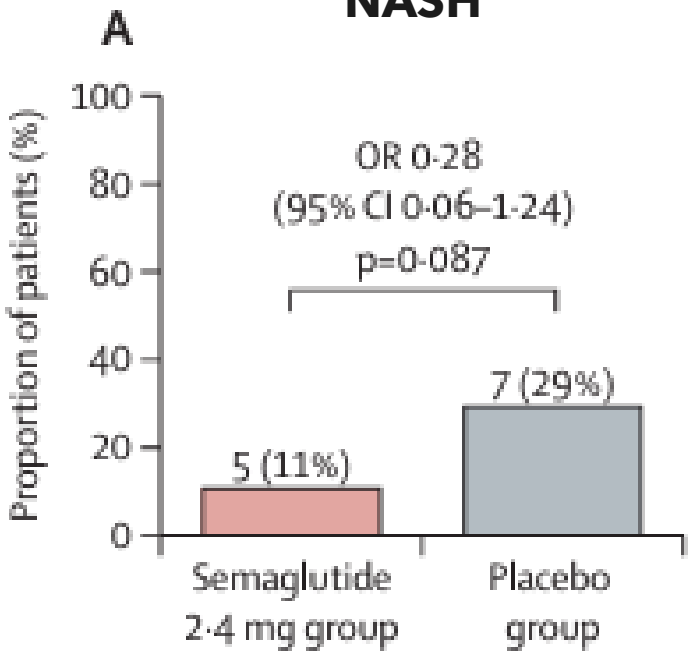
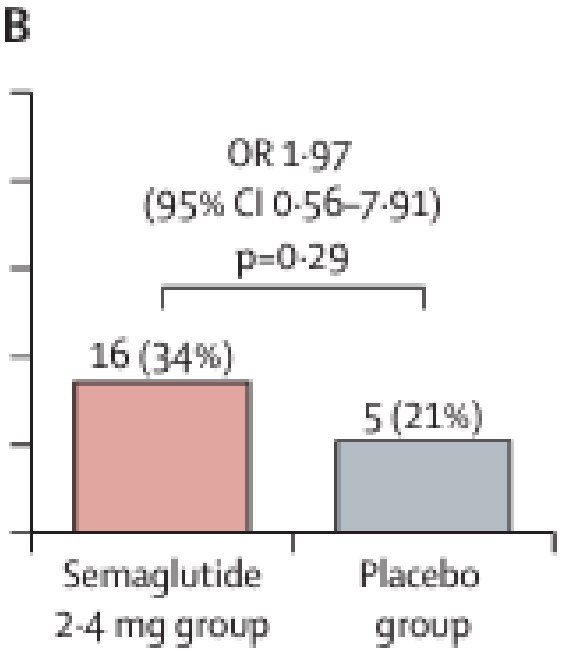
Newsome PN, et al. N Engl J Med. 2021;384:1113-1124.

Semaglutide*: NASH-Related Cirrhosis, Phase 2 Clinical Trial

Improvement in Fibrosis and No Worsening of NASH



Resolution of NASH at 48 Weeks



Efficacy: In patients with NASH and compensated cirrhosis, semaglutide* did not significantly improve fibrosis or achievement of NASH resolution vs PBO

Safety: GI-related, no deaths

***GLP-1 agonist, once-weekly SC injection.**

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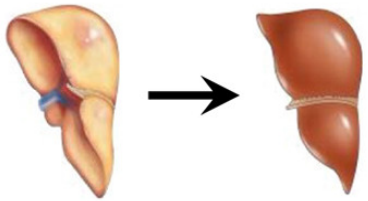
Loomba R, et al; NN9931-4492 Investigators. *Lancet Gastroenterol Hepatol*. 2023;8(6):511-522.

Efruxifermin + Semaglutide: Phase 2b Clinical Trial Results

Administration of once-weekly efruxifermin, for 12 weeks, to patients with type 2 diabetes and MASH with fibrosis (F1–F3) receiving a stable GLP1-RA:

50 mg efruxifermin (n=21)

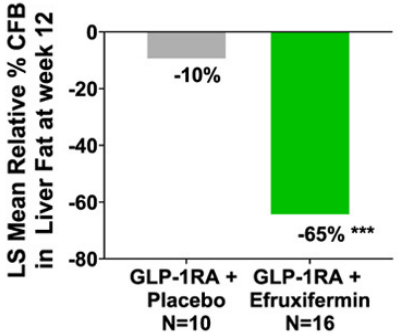
vs placebo (n=10)



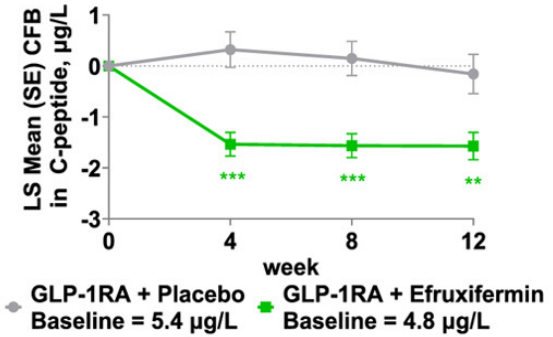
Improved liver and metabolic health:

Safety: mild-to-moderate GI events, no TRAEs

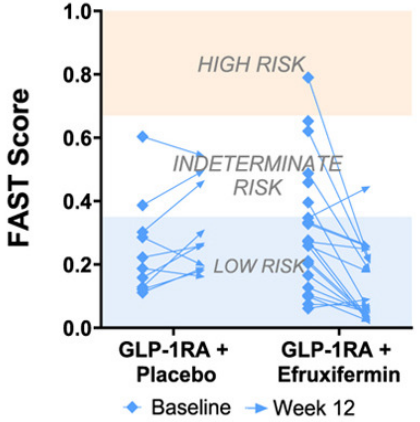
Decreased liver fat



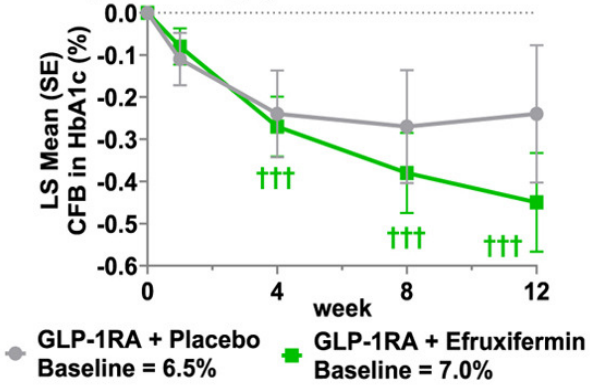
Improved insulin sensitivity



Reduced risk of MASH progression



Improved glycemic control



Clinical Gastroenterology and Hepatology

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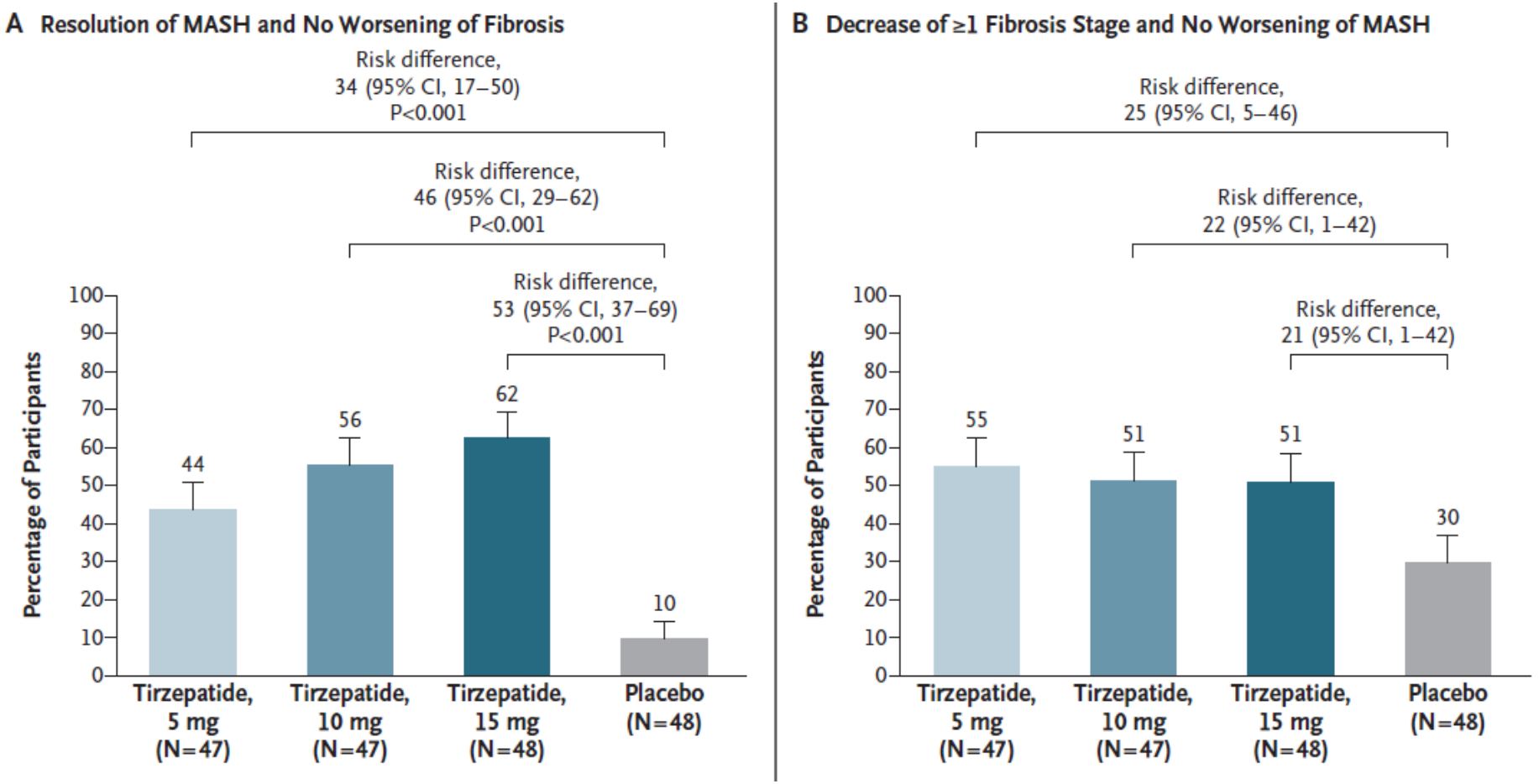
Harrison SA, et al. *Clin Gastroenterol Hepatol*. Published online March 4, 2024. doi:10.1016/j.cgh.2024.02.022

Tirzepatide*: SYNERGY-NASH, Ph 2b Clinical Trial



Safety: mild-to-moderate GI events

***Dual agonist: GLP-1/GIP**

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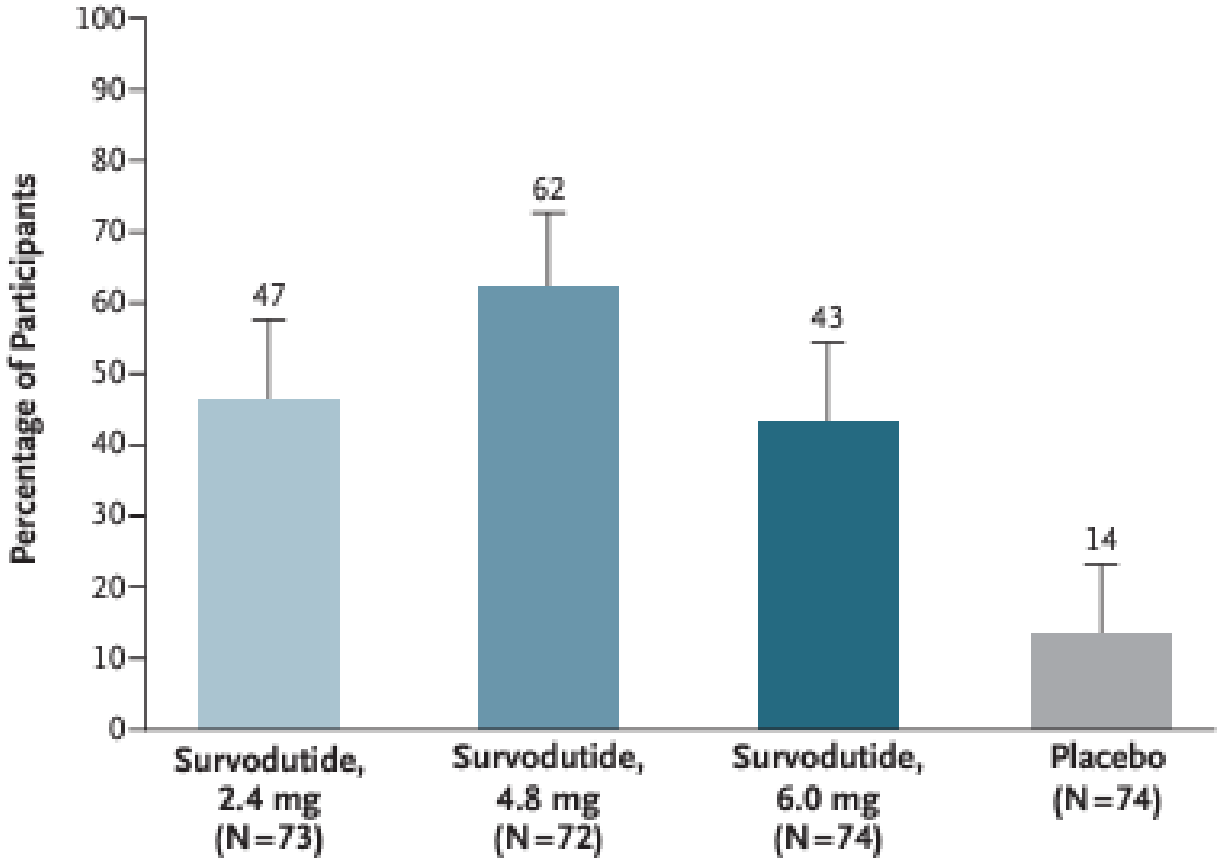
Loomba R, et al; SYNERGY-NASH Investigators. *N Engl J Med.* 2024;391(4):299-310.

Survodutide*: Phase 2 Clinical Trial

Histologic Improvement in MASH, No Worsening of Fibrosis



Primary Endpoint After 48 Weeks of Planned Treatment

Efficacy: Survodutide was associated with significant improvement in MASH with no worsening of fibrosis ($P < 0.001$)

Safety: AEs (nausea, diarrhea, vomiting) more common with study drug vs placebo; SAEs equally common

***Dual agonist: GLP-1/GCG**

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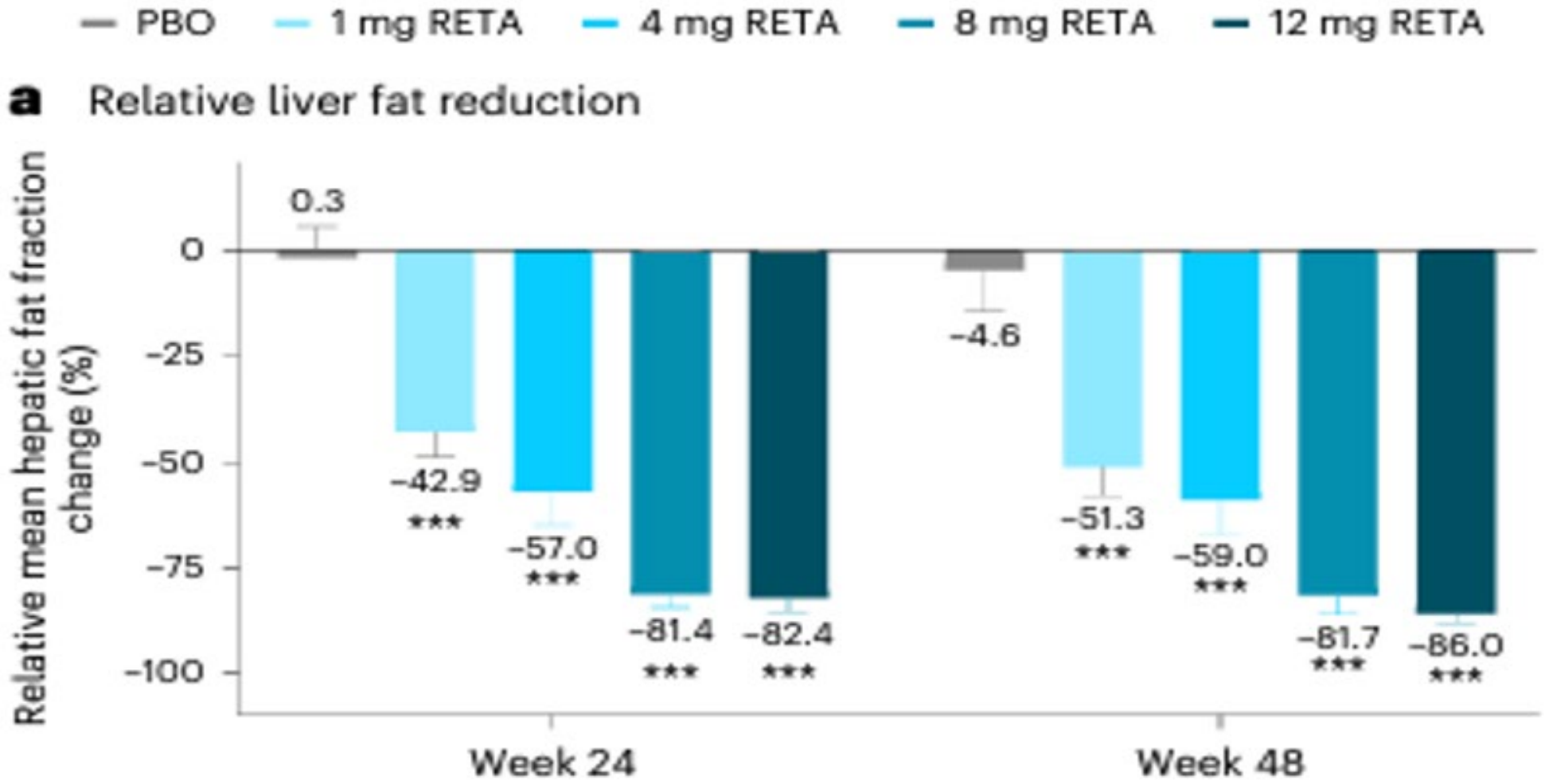
Sanyal AJ, et al; 1404-0043 Trial Investigators. *N Engl J Med*. 2024;391(4):311-319.

Retatrutide*: Phase 2a Clinical Trial



***Triple agonist: GLP-1/GIP/GCG**
********P < 0.001 versus PBO**

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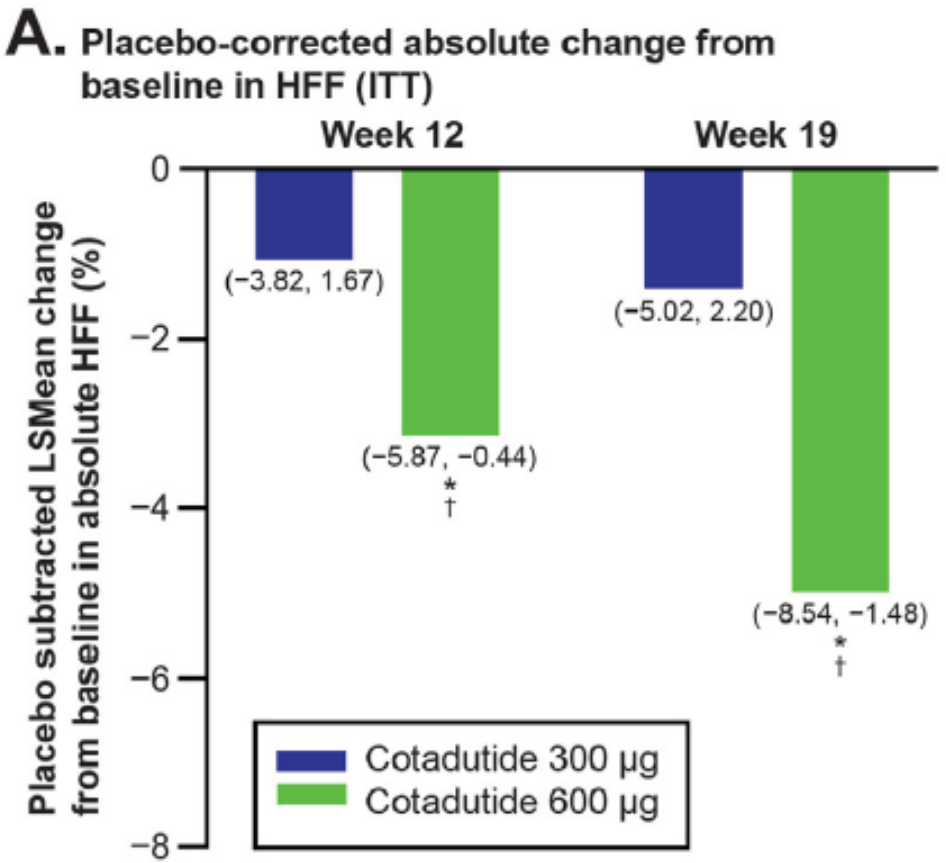
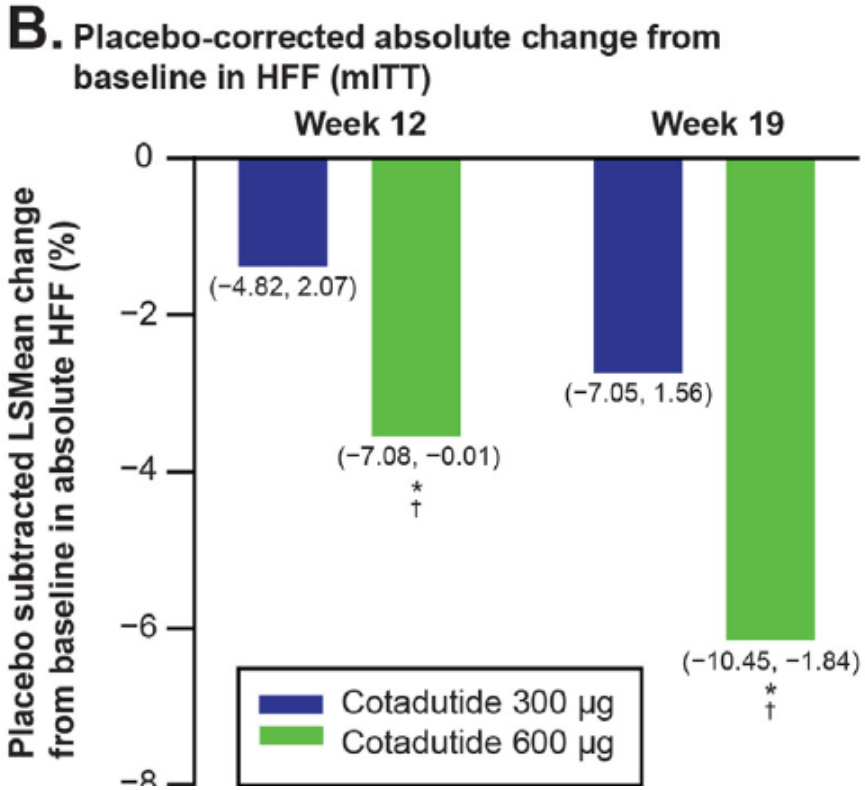
Sanyal AJ, et al. *Nat Med*. 2024;30(7):2037-2048.

Cotadutide*: PROXYMO, Phase 2 Results



Safety: AEs mostly mild to moderate GI symptoms



***Dual agonist: GLP-1/GCG**

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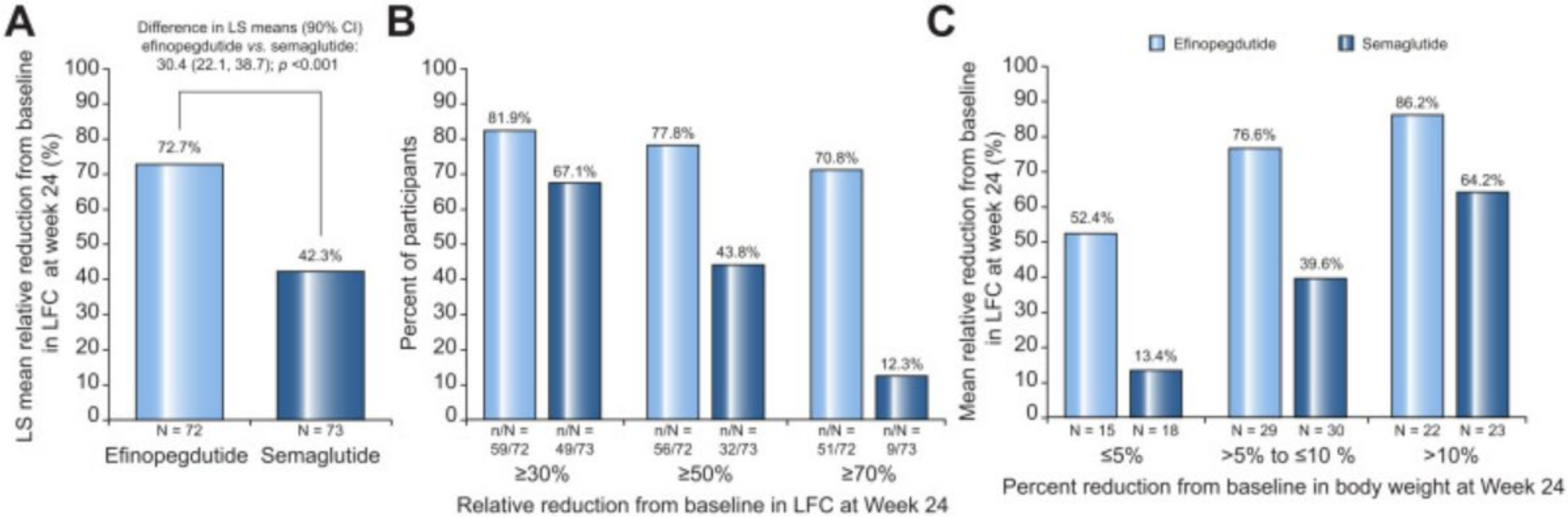
Shankar SS, et al. Clin Gastroenterol Hepatol. 2024;22(9):1847-1857.e11.

Efinopegdutide* (MK-6024): Phase 2a Results

Difference in Liver Fat Content



***Dual agonist: GLP-1/GIP/glucagon**

Safety: incidence of GI TRAEs slightly higher with efinopegdutide vs semaglutide

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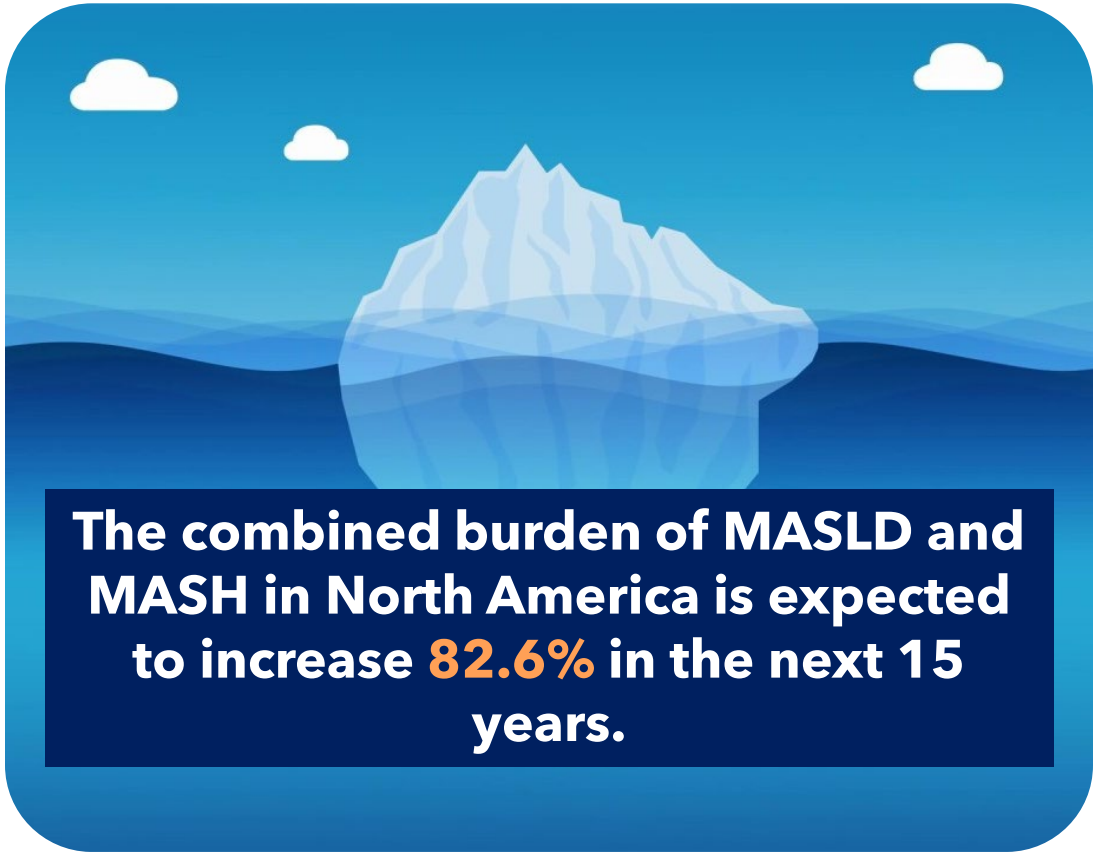
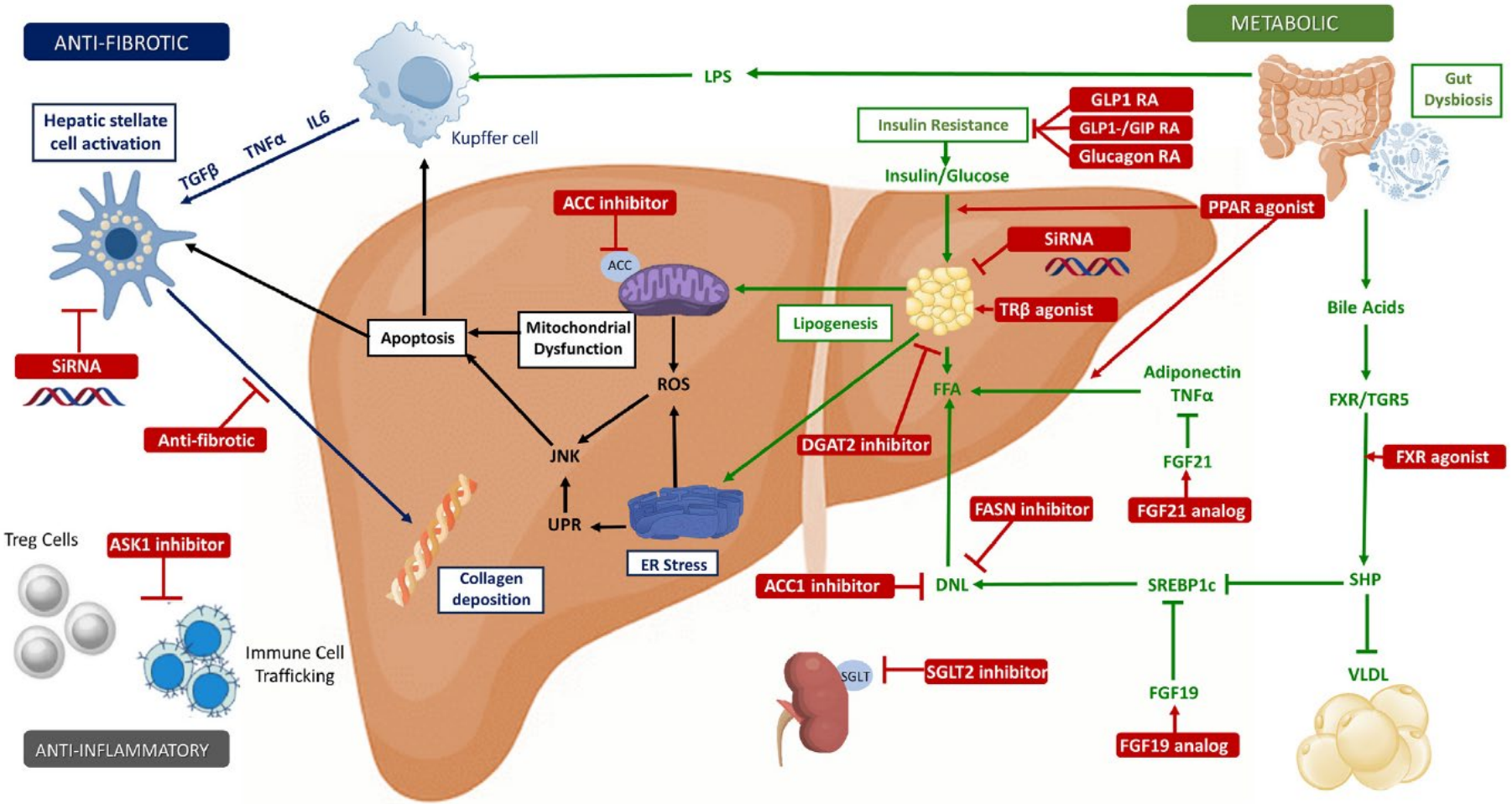
Romero-Gómez M, et al. *J Hepatol*. 2023;79(4):888-897.

At Least 2 Million Adults With High-Risk MASH in the US: NHANES 2017–2018



Vilar-Gomez E, et al. *Clin Gastroenterol Hepatol*. 2023;21(1):115-124.e7.
Younossi ZM, et al. *J Clin Exp Hepatol*. 2023;13(3):454-467.

Potential Therapeutic Targets for MASH



Tincopa MA, et al. Cell Metab. 2024 Jun 4;36(6):1430.

Concluding Remarks

Naim Alkhouri, MD

Nicholas Pennings, DO

Amreen Dinani, MD

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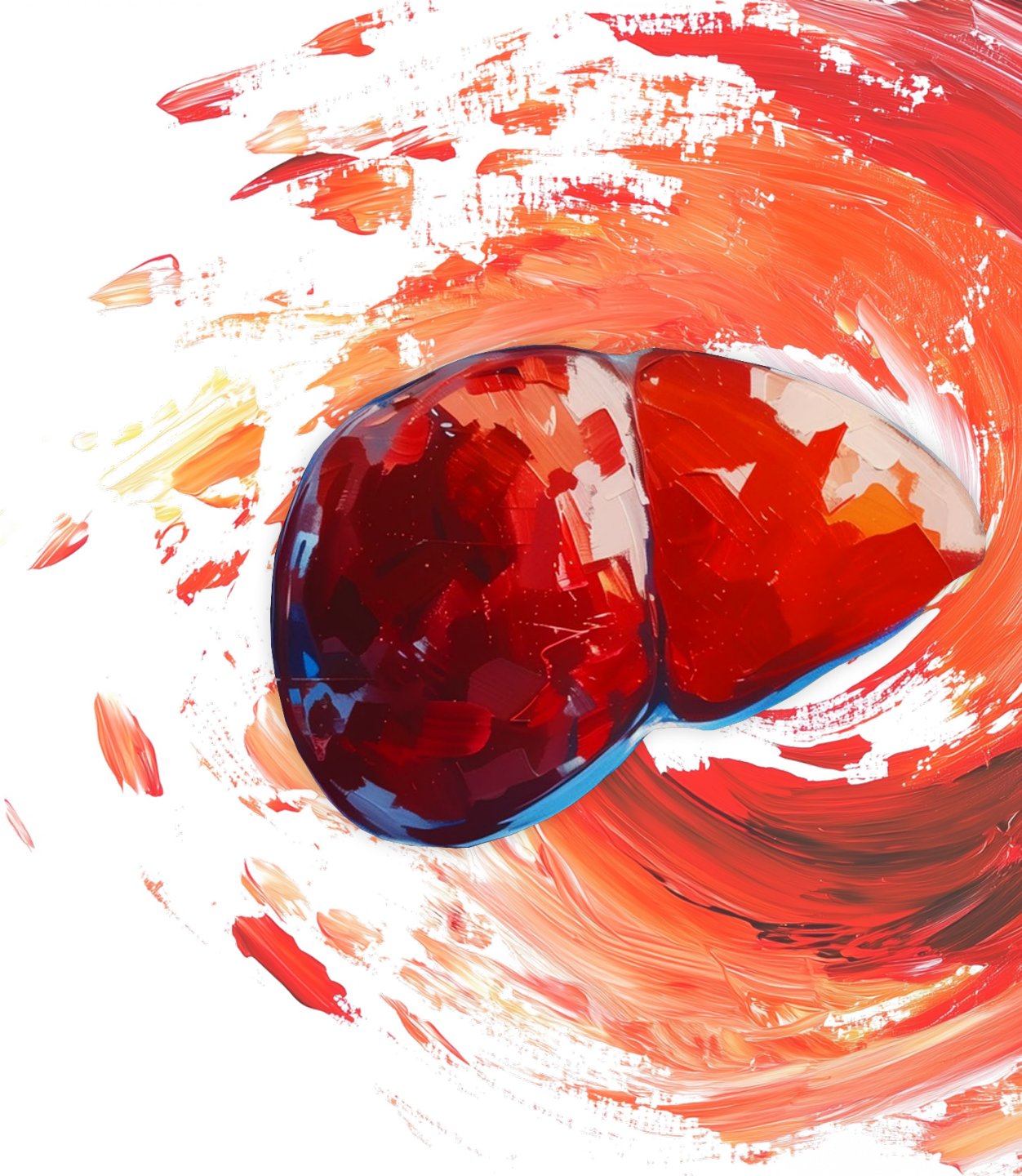

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