North Carolina Society of Gastroenterology
2026 Annual Meeting

MASLD: From Risk Factors to Treatment Strategies

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Joint Providership

American Society for Gastrointestinal Endoscopy

Disclosures

Clinical Trials with Madrigal, Galectin, Hanmi, Sagimet, GSK, Bausch

Consulting with Target RWE, Madrigal, Merck, Mirum, Boehringer Ingelheim

Research support PCORI, NIDDK

I will discuss off label therapies for MASLD

Objectives

As a result of this presentation, physicians/APPs will be able to:

1. *Identify patients at risk for MASLD*
2. *Understand non-invasive assessments of liver disease*
3. *Discuss potential pharmacotherapy for MASLD*

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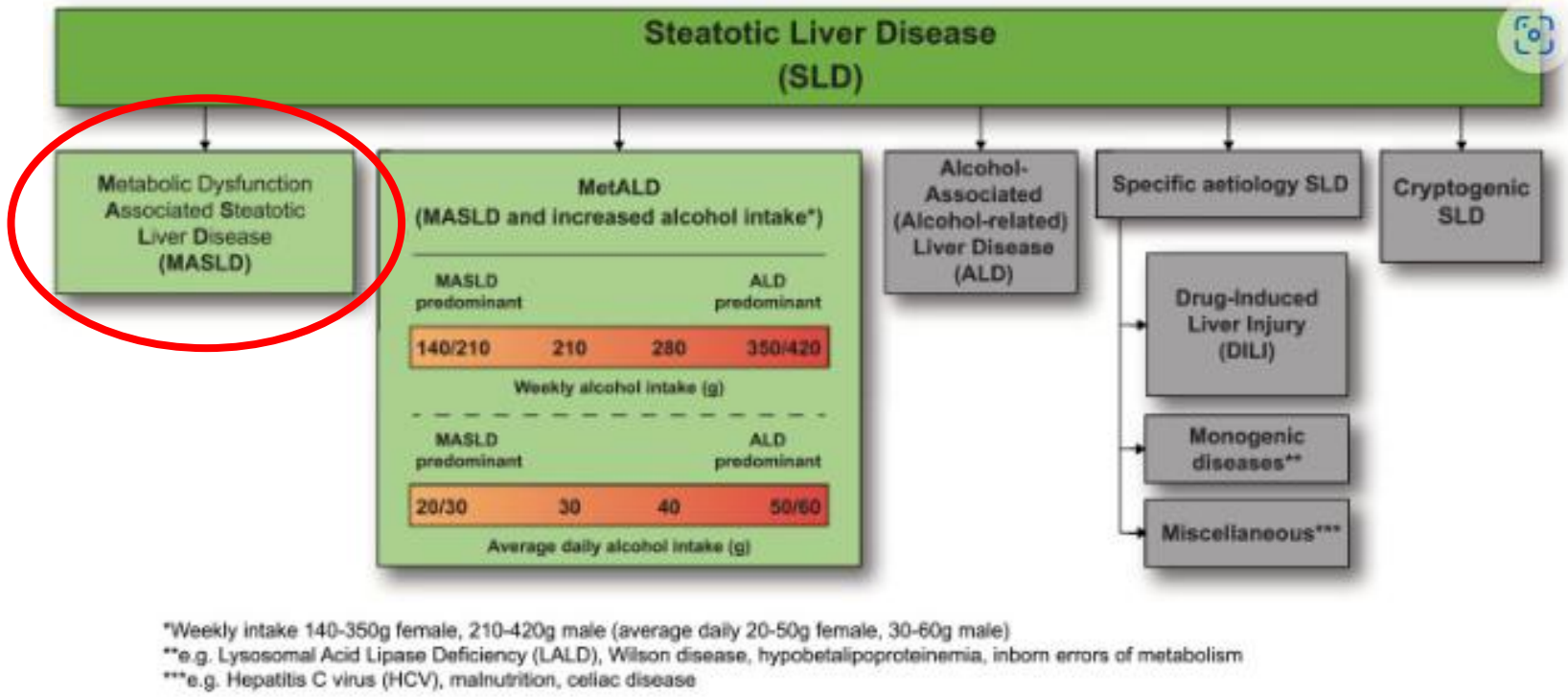
Just when you were getting used to NAFLD…

- June 24, 2023: Several multinational liver societies – ALEH, AASLD and EASL concluded a multi-year consensus conference to rename NAFLD.

- Why?
  - more than a “non” disease
  - ”alcoholic” is stigmatizing
  - ”fatty” is stigmatizing
  - current definition is one of exclusion and doesn’t recognize that multiple liver diagnosis may exist on a background of steatosis
  - Need hepatic steatosis and at least 1 of 5 cardiometabolic criteria



Disclaimer: I will very likely slip up and move back and forth between MASLD/NAFLD and MASH/NASH

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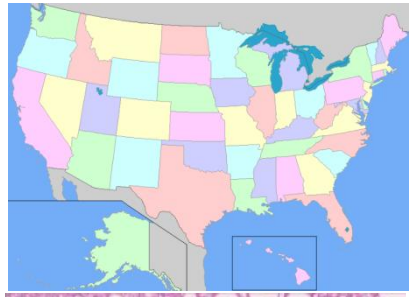
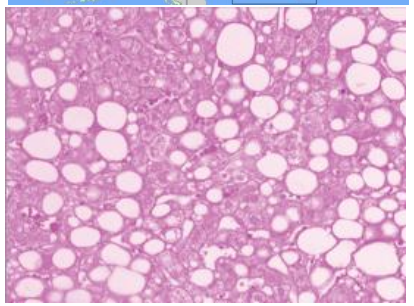
Rinella et al Annals of Hepatology/J Hep/Hep 2023
AASLD MASLD Slide deck 2023

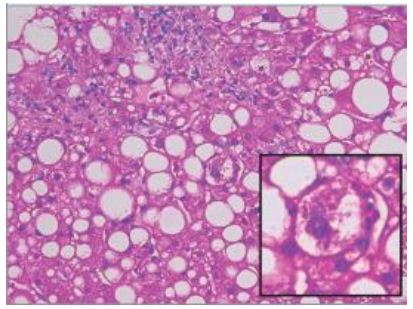
MASLD and MASH are common!



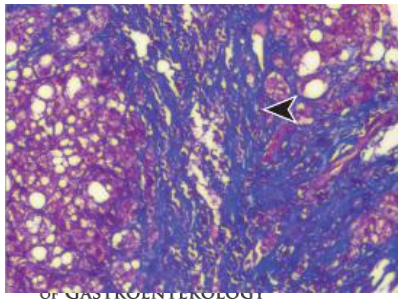
United States population = **325,000,000**



Prevalence of simple steatosis = 30% = **97,500,000**



Patients with Steatosis who progress to MASH = 20% =**19,500,000**



Patients with MASH who progress to cirrhosis = 20% =**3,900,000**

<u>Perspective:</u>

Patients with HCV ~ 4 million

Patients with UC ~ 1 million

Patients with CD ~ 1 million

If only 1% of patients with MASH cirrhosis are listed for OLT, this would be more than double the current size of the national waitlist

Rinella M. JAMA .2015

www.hepchope.com

www.cdc.gov

How to identify patients with MASH for therapy?

- Screening not (yet) recommended for the general population
- High-risk individuals, such as those with T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis
- **Goal is to identify patients with stage 2-3 a.k.a.“at risk MASH” for therapy and those with cirrhosis for screening paradigms**

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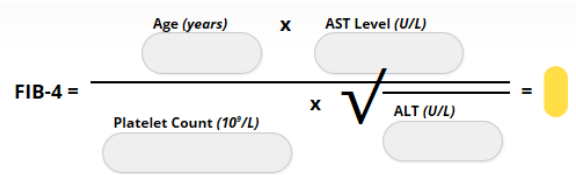
Rinella et al, Hepatology 2023

Non-invasive assessment of disease

- Several clinical prediction scores for assessing severity of disease
  - NAFLD fibrosis score (NFS)

    = 1.675+ (0.037*age) + (0.094*BMI) + (1.13 if DM) + (0.99* AST/ALT)- (0.013*plt) – (0.66*alb)

  - FIB-4



- Both are reasonable to use.
  - Comparable AUROC scores
    - NFS 0.81, FIB-4 0.82
  - Inexpensive
  - On hand held devices
  - Many others with similar accuracy

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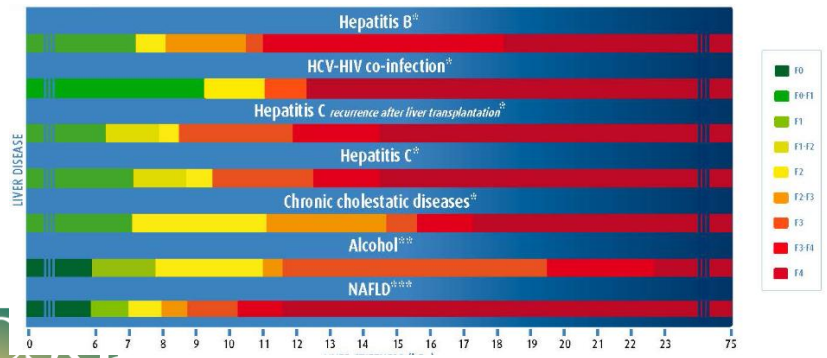
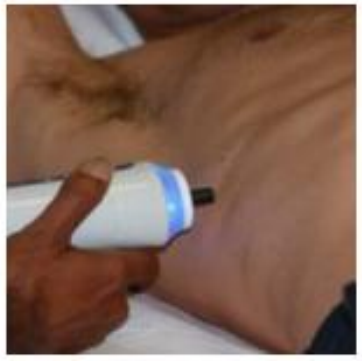
Sterling, Hepatol 2006, Angulo, Hepatol 2007, Angulo, Hepatol 2010, Kim, Radiology 2013

Non-invasive imaging

- Vibration Controlled Transient Elastography (VCTE)
  - Liver stiffness measured in kilopascals and correlated with fibrosis stage, F0-F4
    - Must know disease etiology to interpret score
  - AUROC for F3 or higher disease 0.93 in NAFLD



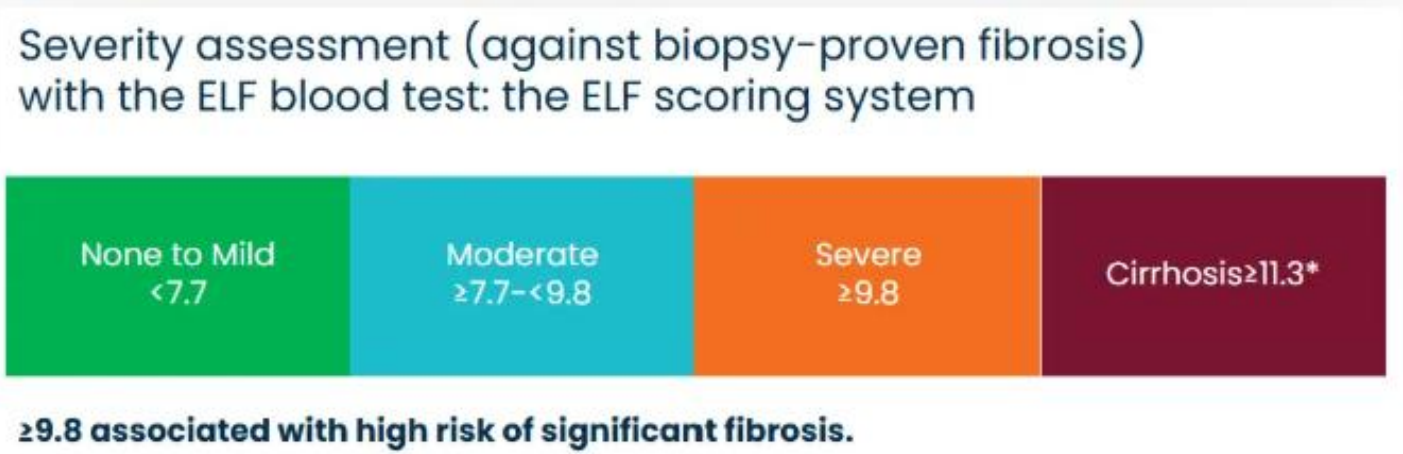
- Controlled Attenuation Parameter (CAP)
  - Steatosis measured in dB/m and correlated with steatosis grade, S0-S3
  - AUROC score for S1 and greater 0.86



Wong, Hepatol 2010, Karlas, J Hepatol 2017

Enhanced Liver Fibrosis test

- The Enhanced Liver Fibrosis (ELF) test is a noninvasive blood test
- Assesses 3 components involved in liver matrix metabolism: hyaluronic acid, procollagen III, and tissue inhibitor of matrix metalloproteinase 1



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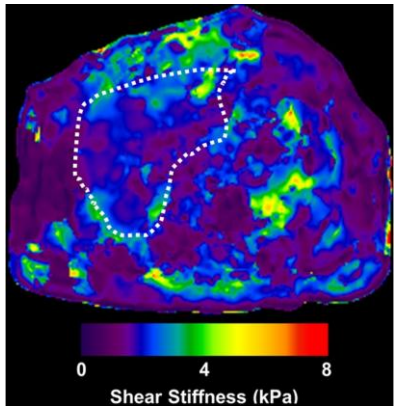
Enhanced Liver Fibrosis (ELF) Test - Nordic Bioscience, accessed Nov 2025

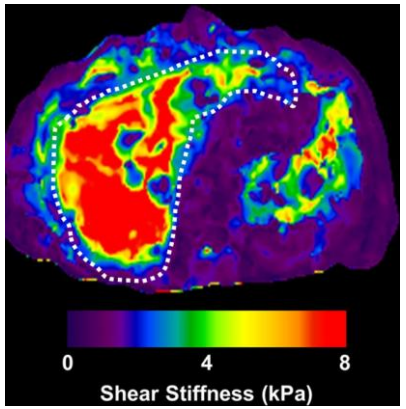
Magnetic Resonance Imaging Technology

- MR-Elastography (MRE) for Fibrosis

- 2D and 3D MRE have AUROC >0.92
- Multiple single center trials show MRE>VCTE



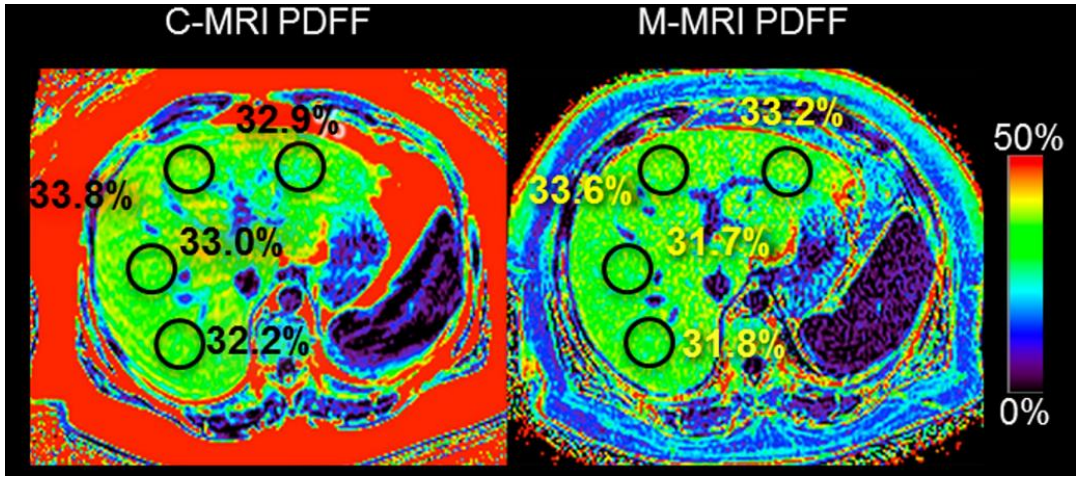
No fibrosis



Advanced fibrosis

- MR-Proton density fat fraction for steatosis (MR-PDFF)

- MR-PDFF>CAP for fat quantification



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Kim, Radiology 2013, Caussy, Hepatology 2018, Hsu, Clin Gastroenterol Hepatol 2018

Liver biopsy not needed in most cases

- Liver biopsy is the referent standard for assessing MASH
  - How reliable is the application of this standard in real world practice?
  - Most pathologists can't agree on grading and staging of disease
- 75-91% concordance between the expert central pathologist diagnosis and TARGET-NASH clinical definition for MASH
  - 1+ CV risk factor
  - Steatosis on imaging
  - Abnormal ALT
- Add a NIT to assess fibrosis stage

Histological Characteristic	Number of Pathology Reports Compared	Weighted Kappa Statistic (95% CI)	Concordance Interpretation
Steatosis	57	0.364 (0.2029, 0.5242)	**Fair**
Lobular Inflammation	29	-0.081 (-0.1847, 0.0220)	**Poor**
Portal Inflammation	31	0.210 (-0.0376, 0.4580)	**Fair**
Hepatocyte Ballooning	26	0.117 (-0.0708, 0.3038)	**Slight**
Fibrosis Stage	69	0.575 (0.4603, 0.6894)	**Moderate**
Scoring System			
NAFLD Activity Score	38	0.237 (0.0591, 0.4150)	**Fair**
Brunt Grade (Inflammation)	26	0.384 (0.1591, 0.6082)	**Fair**
Brunt Stage (Fibrosis)	69	0.590 (0.4775, 0.7019)	**Moderate**

Kim et al APT 2021

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Summary of NIT accuracy for advanced fibrosis in MASH

		Test	AUROC	Lower Cut-off to Rule Out AF	Sensitivity for Lower Cut-off	Upper Cut-off to Rule in AF	Specificity for Upper Cut-off
Noninvasive Serum-based Tests	Simple	Fibrosis-4 (FIB-4)[1]	0.78	<1.3	82%	≥2.67	93%
		NAFLD Fibrosis Score (NFS)[1]	0.74	<-1.455	89%	≥0.676	89%
		AST/Platelet Ratio Index (APRI)[2]	0.76	<0.57	90%	>0.84	65%
	Proprietary	Enhanced Liver Fibrosis (ELF™)[3,4]	0.86[b]	<7.7	85%	≥9.8	90%
		FibroSure®[5]	0.83	≤0.31	84%	>0.58	87%
Noninvasive Imaging		Vibration-Controlled Transient Elastography (eg, FibroScan®)[6]	0.93	<7.9 kPa	91%	≥9.6 kPa	92%
		Magnetic Resonance Elastography (MRE)[7]	0.93[c]	<2.97 kPa	85%	>3.62 kPa	83%
Invasive Histological Test		Liver Biopsy[8]	0.87	≤F2	85%	≥F3	89%

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Courtesy Intercept educational series 2023

Potential costs for NITs

- **Fibroscan**
  - Self-Pay (No Insurance):
    - $200 - $500 on average in the U.S., with some clinics charging $299 or around $350
  - Higher End:
    - Some providers or hospitals might charge $1,000 or more, especially in urban areas or for bundled services
- **ELF**
  - The price varies, but it can cost ~ $155 depending on the provider and location
- **MRE**
  - The cost varies, but Medicare reimbursement for a standalone procedure is approximately $240.02. Other sources indicate a higher average cost of around $566.80
- **MRI PDFF**
  - $400-1500 depending on bundling

Liver biopsy: total costs (including doctor, facility, and lab) to potentially range from $1,500 to over $4,000

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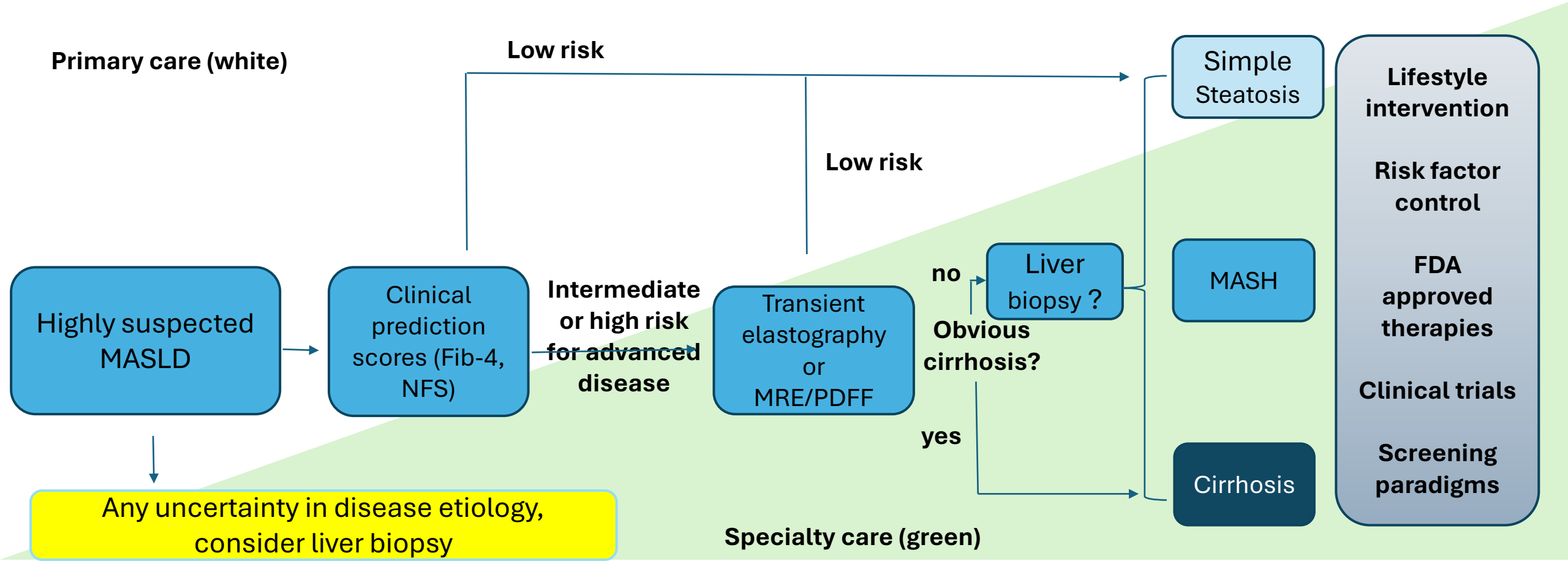
Google AI, accessed December 2025

Diagnosis and evaluation algorithm



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Barritt, AASLD Postgraduate Course 2018

First in disease state therapy

The NEW ENGLAND JOURNAL of MEDICINE

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

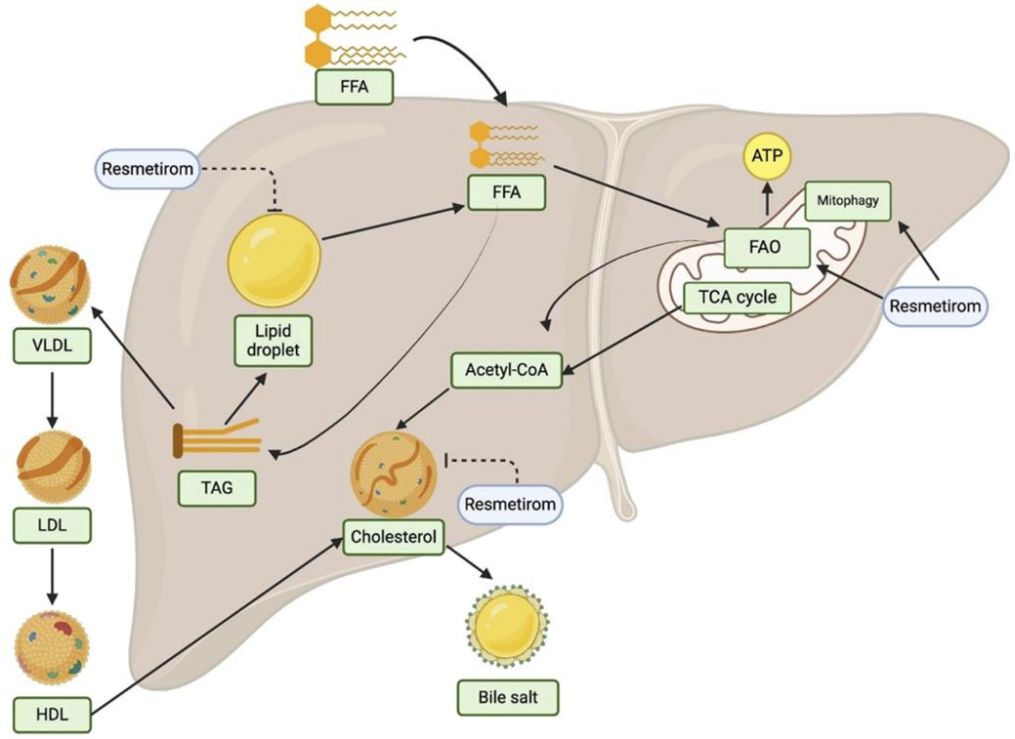
A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*

- Interim analysis of an ongoing, phase 3, multinational, double blind, randomized, placebo-controlled trial assessed the efficacy and safety of resmetirom in adults with biopsy-confirmed NASH and liver fibrosis.

Harrison et al NEJM 2024

THB responsible for regulation of multiple metabolic pathways



Barritt and Stine AJG 2024

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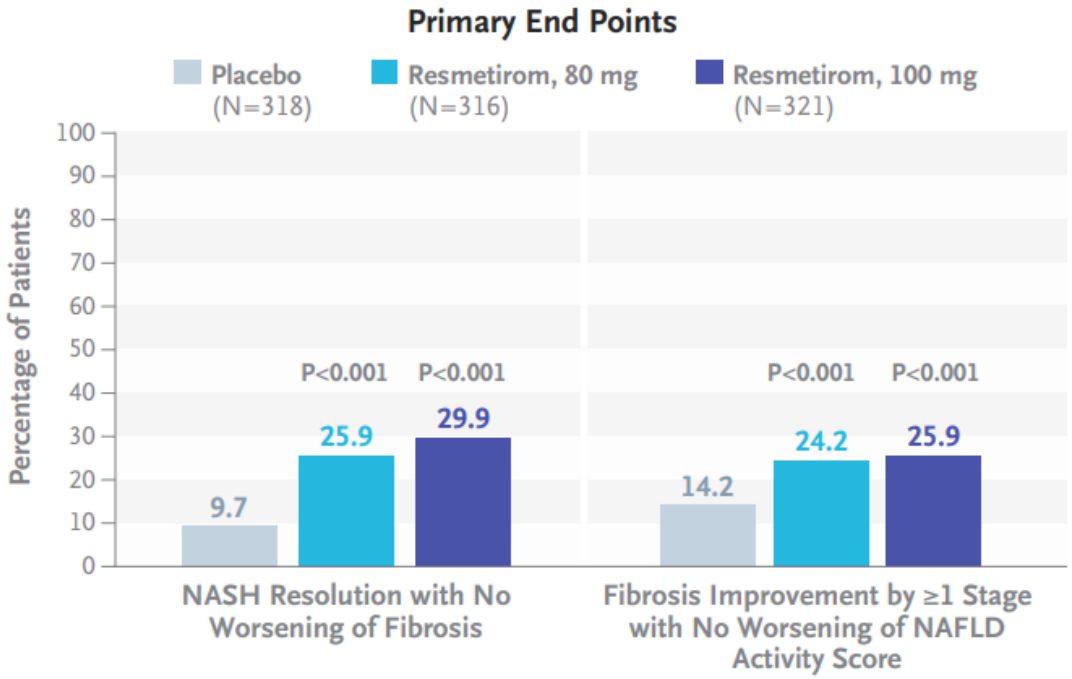
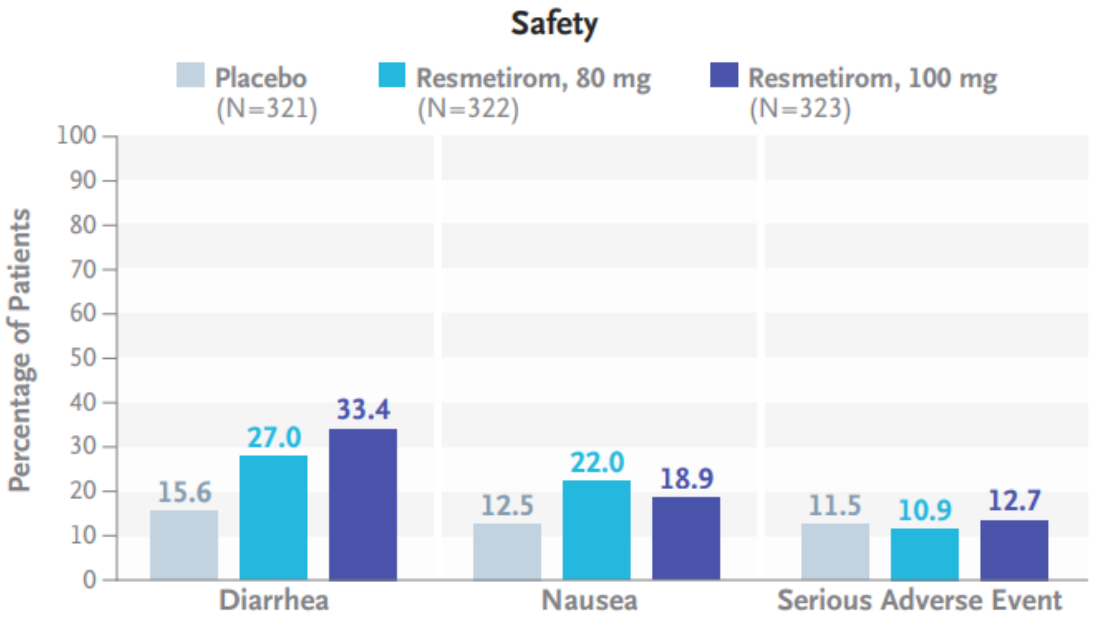
Results- safety and efficacy





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Harrison et al NEJM 2024

Secondary end points

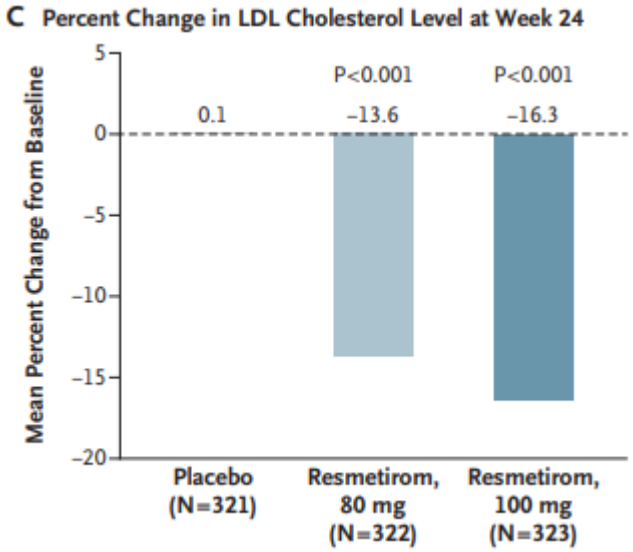

Table 3. Key Secondary and Other Secondary End Points (Primary Population).*

Measurement	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)	Difference between Resmetirom, 80 mg, and Placebo (95% CI)†	Difference between Resmetirom, 100 mg, and Placebo (95% CI)†
	least-squares mean percent change from baseline			*percentage points*	
LDL cholesterol level at wk 24‡§	−13.6±1.7	−16.3±1.7	0.1±1.7	−13.7 (−17.5 to −10.0)¶	−16.4 (−20.1 to −12.6)¶
Apolipoprotein B level at wk 24§	−16.8±1.3	−19.8±1.3	0.39±1.3	−17.2 (−20.0 to −14.4)	−20.2 (−22.9 to −17.4)
Triglyceride level at wk 24§‖	−22.7±4.0	−21.7±4.3	−2.6±4.1	−20.1 (−28.3 to −11.8)	−19.1 (−27.8 to −10.3)
Lipoprotein(a) level at wk 24§**	−30.4±3.8	−35.9±4.0	−0.84±3.5	−29.5 (−37.6 to −21.5)	−35.1 (−43.5 to −26.6)
MRI-PDFF at wk 52	−35.4±2.8	−46.6±2.8	−8.7±2.7	−26.7 (−32.9 to −20.6)	−37.9 (−44.2 to −31.7)
Alanine aminotransferase level at wk 48††	−26.6±3.7	−33.2±3.9	−6.9±3.8	−19.7 (−27.7 to −11.6)	−26.3 (−34.5 to −18.1)
Aspartate aminotransferase level at wk 48††	−22.1±3.9	−28.3±3.9	−2.9±3.8	−19.3 (−27.2 to −11.3)	−25.4 (−33.5 to −17.4)
γ-Glutamyltransferase level at wk 48††	−25.0±5.5	−31.9±6.3	3.3±5.2	−28.3 (−37.3 to −19.3)	−35.2 (−45.5 to −25.0)

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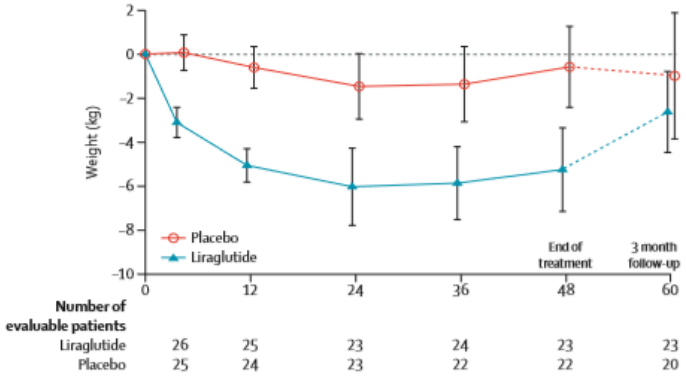
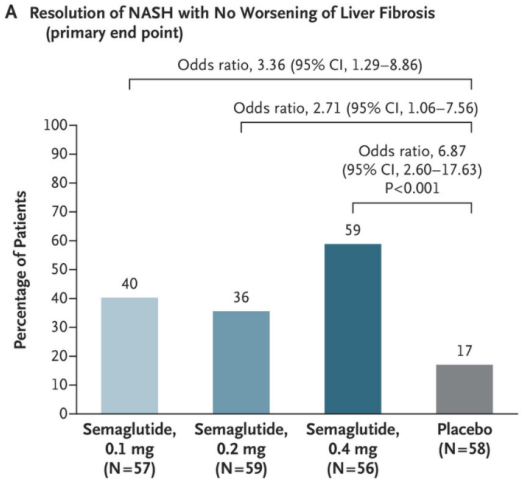
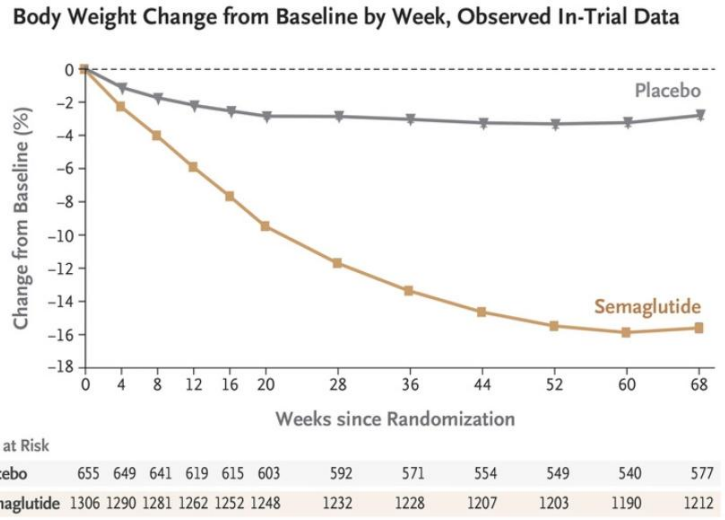
Harrison et al NEJM 2024

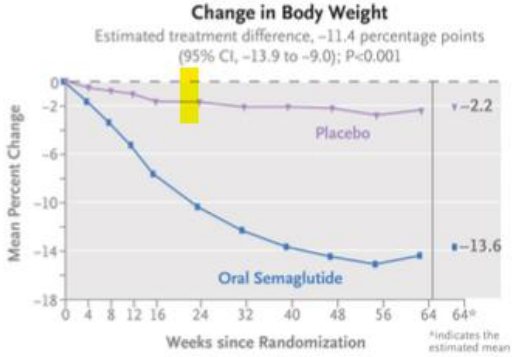
Glucagon-like peptide 1 receptor agonists for MASH?

- Liraglutide
  - Resolution of NASH in 9/23 (39%) liraglutide vs. 2/22 (9%) placebo p=0.019
  - Secondary outcomes showed improvements in weight and ALT
- Semaglutide in NASH- phase 2
  - NASH resolution semaglutide 0.4mg (59%) vs placebo (17%)
  - Fibrosis improvement not different than placebo
  - 13% weight loss vs 1% placebo
- Semaglutide in obesity
  - 15% weight loss after 68 weeks vs 2% in placebo
    - 86% achieved 5% loss, 69% achieved 10% loss, 50% achieved 15% or more weight loss
- Oral semaglutide
  - 25mg po led to ~14% weight loss vs 2% placebo in 64 weeks









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Armstrong et al Lancet 2016; Newsome et al NEJM 2021; Wilding et al NEJM 2021; Barritt et al APT 2022; Wharton et al NEJM 2025

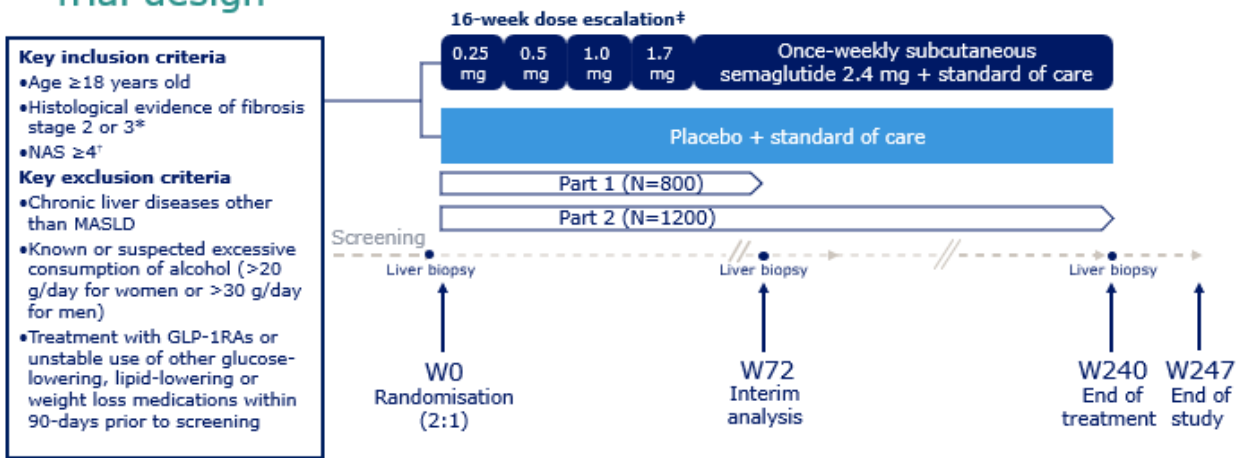
Phase 3 Semaglutide – ESSENCE trial

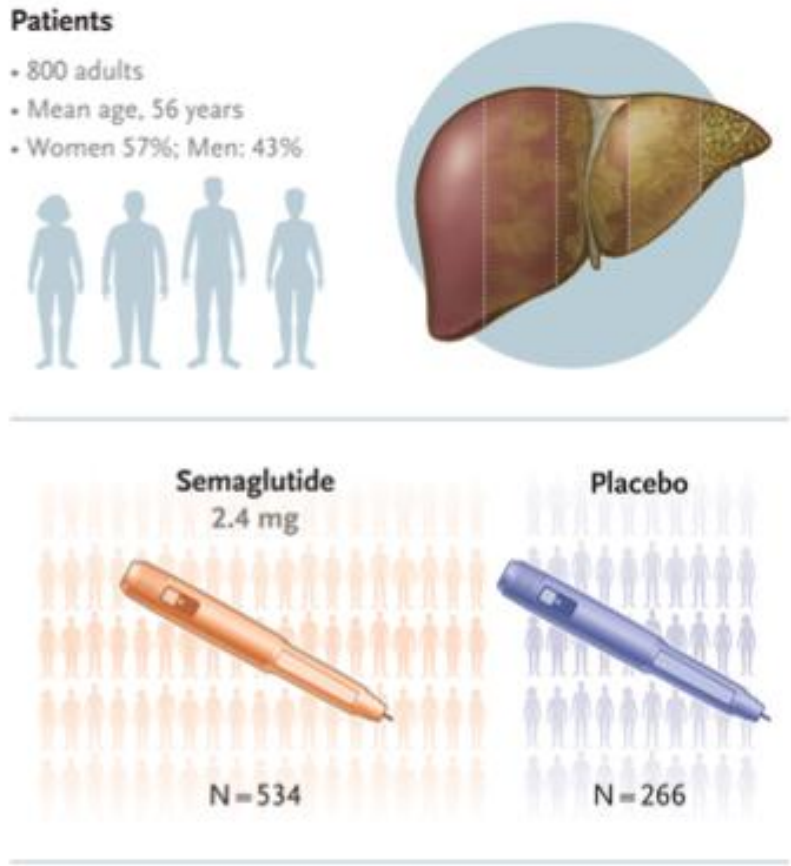
The NEW ENGLAND JOURNAL of MEDICINE

Semaglutide in Metabolic-Related Steatohepatitis

A Research Summary based on Sanyal AJ et al. | 10.1056/NEJMoa2413258 | Published on April 30, 2025

Methods
Trial design





- Phase 3 study was 72 weeks compared to phase 2 study which was only 52 weeks in duration
- FDA approved 18 August 2025 for stage 2-3 MASH

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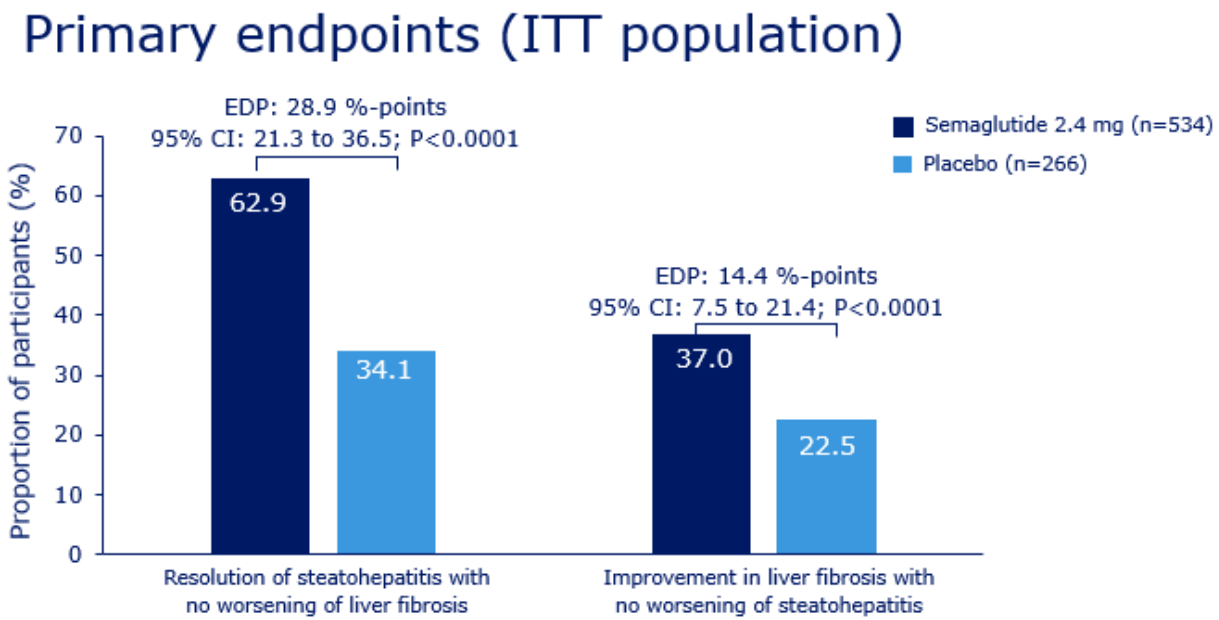
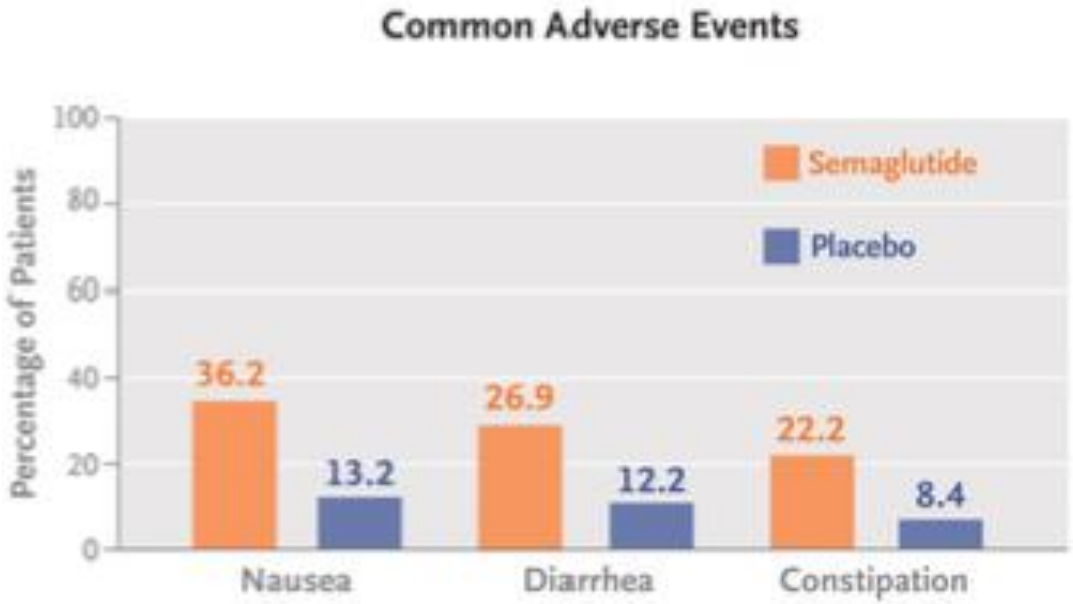
Sanyal NEJM 2025

Results- safety and efficacy





- Non-invasive tests (VCTE, ELF, PRO-C3) all show fibrosis regression
- Improved multiple CV risk factors

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Sanyal NEJM 2025

Incretin targets

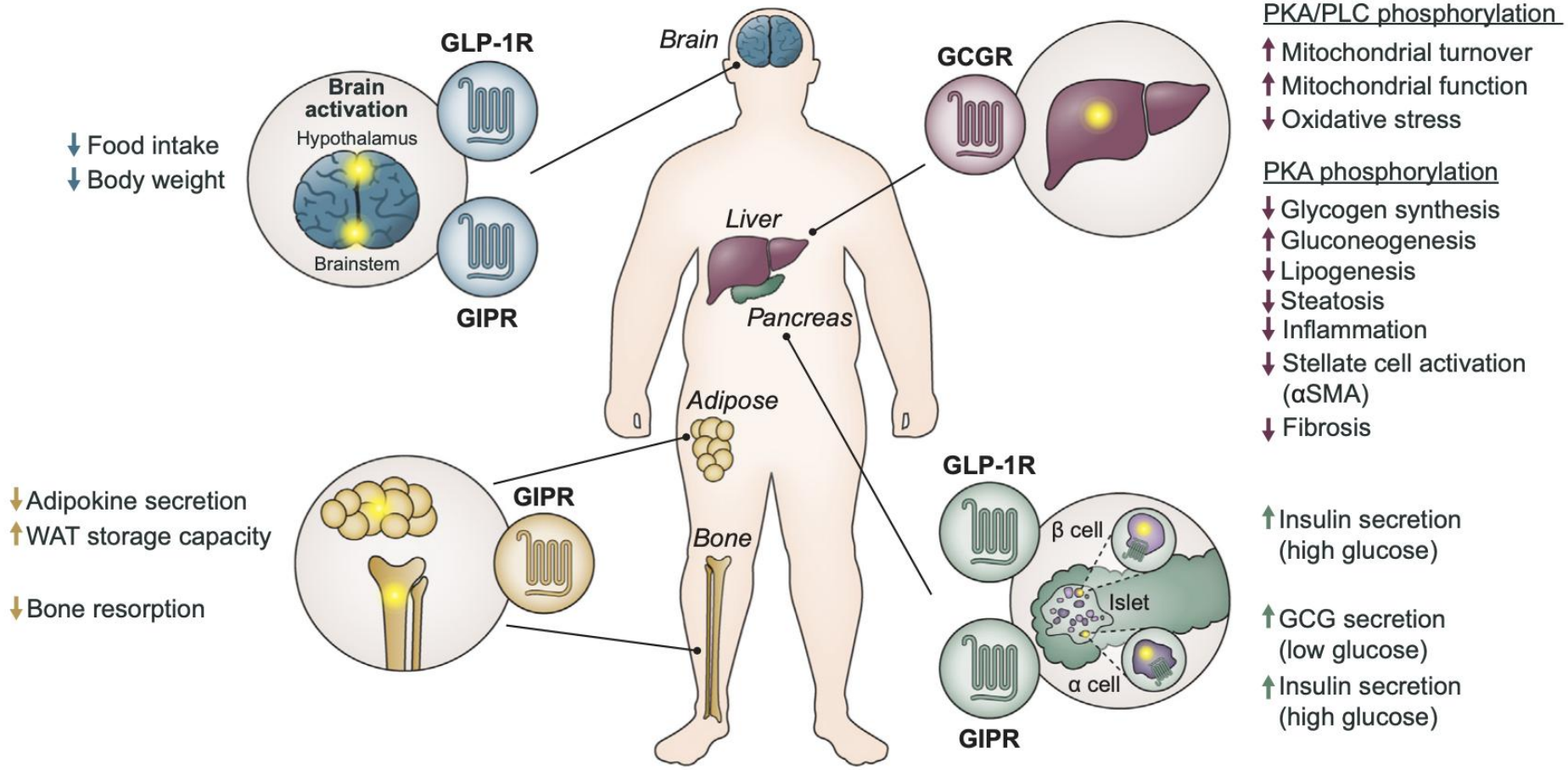

Fig. 1. The major modes and sites of action of the relevant incretin hormones/receptor agonists are detailed. GCG, glucagon; GCGR, glucagon receptor; GIPR, glucose-dependent insulinotropic peptide receptor; GLP-1R, glucagon-like peptide 1 receptor; WAT, white adipose tissue.

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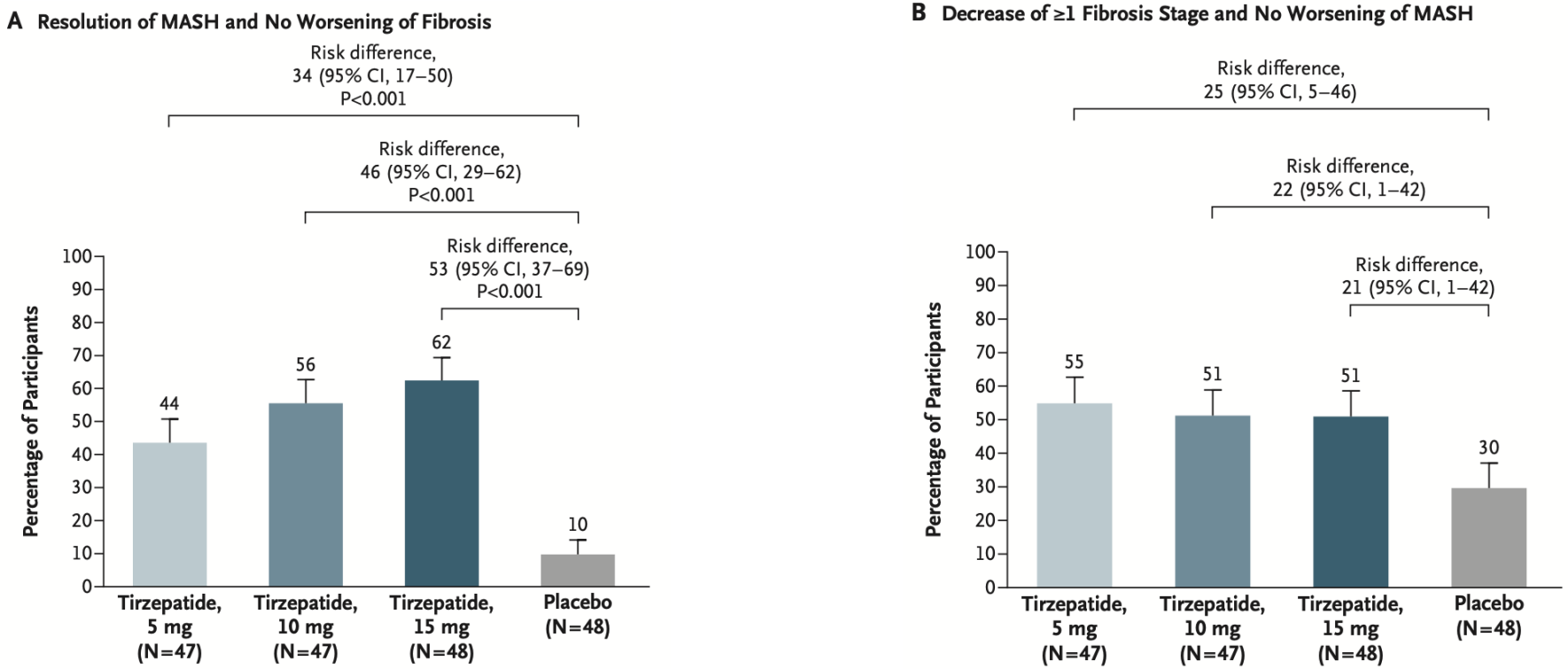
Newsome et. al. J Hepatol, 2023

GLP1 + GIP: Tirzepatide for MASH

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*



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Loomba et al NEJM 2024

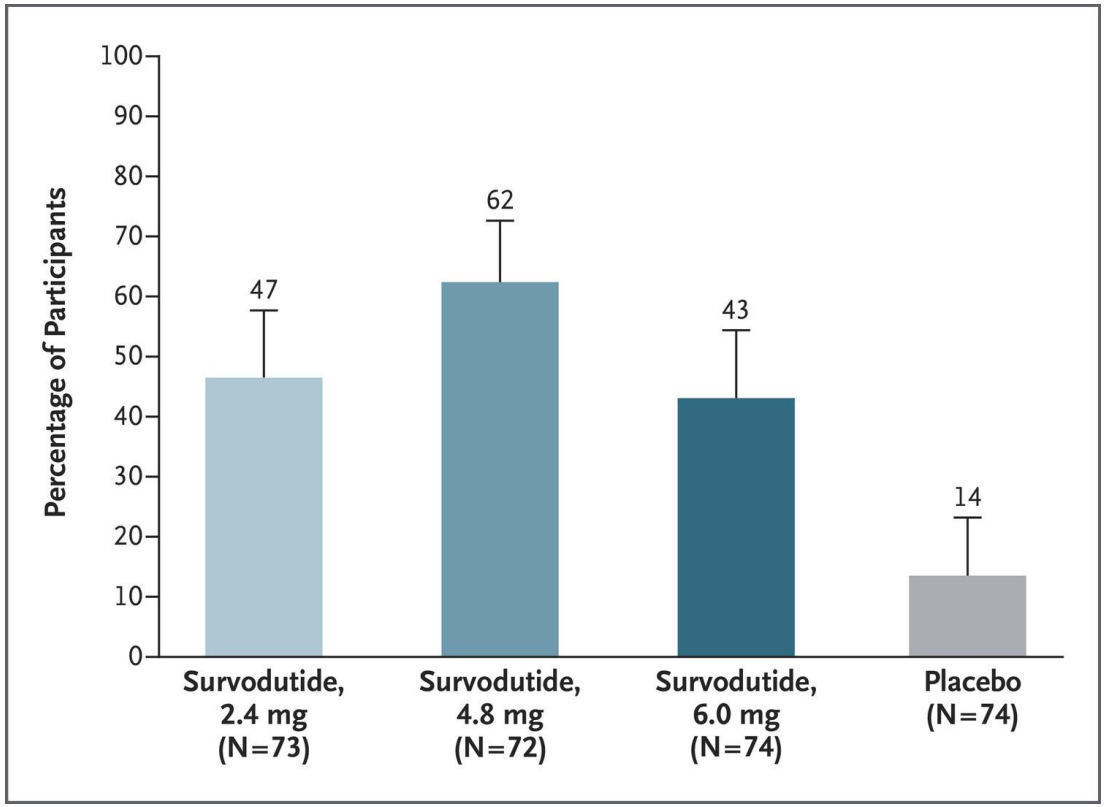
GLP1 + GCGR: Survodutide for MASH

ORIGINAL ARTICLE

A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

Arun J. Sanyal, M.D., Pierre Bedossa, M.D., Ph.D., Mandy Fraessdorf, Ph.D., Guy W. Neff, M.D., Eric Lawitz, M.D., Elisabetta Bugianesi, M.D., Quentin M. Anstee, Ph.D., F.R.C.P., Samina Ajaz Hussain, M.D., Philip N. Newsome, M.B., Ch.B., Ph.D., Vlad Ratziu, M.D., Azadeh Hosseini-Tabatabaei, Pharm.D., Ph.D., Jörn M. Schattenberg, M.D., Mazen Noureddin, M.D., M.H.Sc., Naim Alkhouri, M.D., and Ramy Younes, M.D., Ph.D., for the 1404-0043 Trial Investigators*

- Planned treatment analysis:
  - 47-62% improved MASH without worsening of fibrosis



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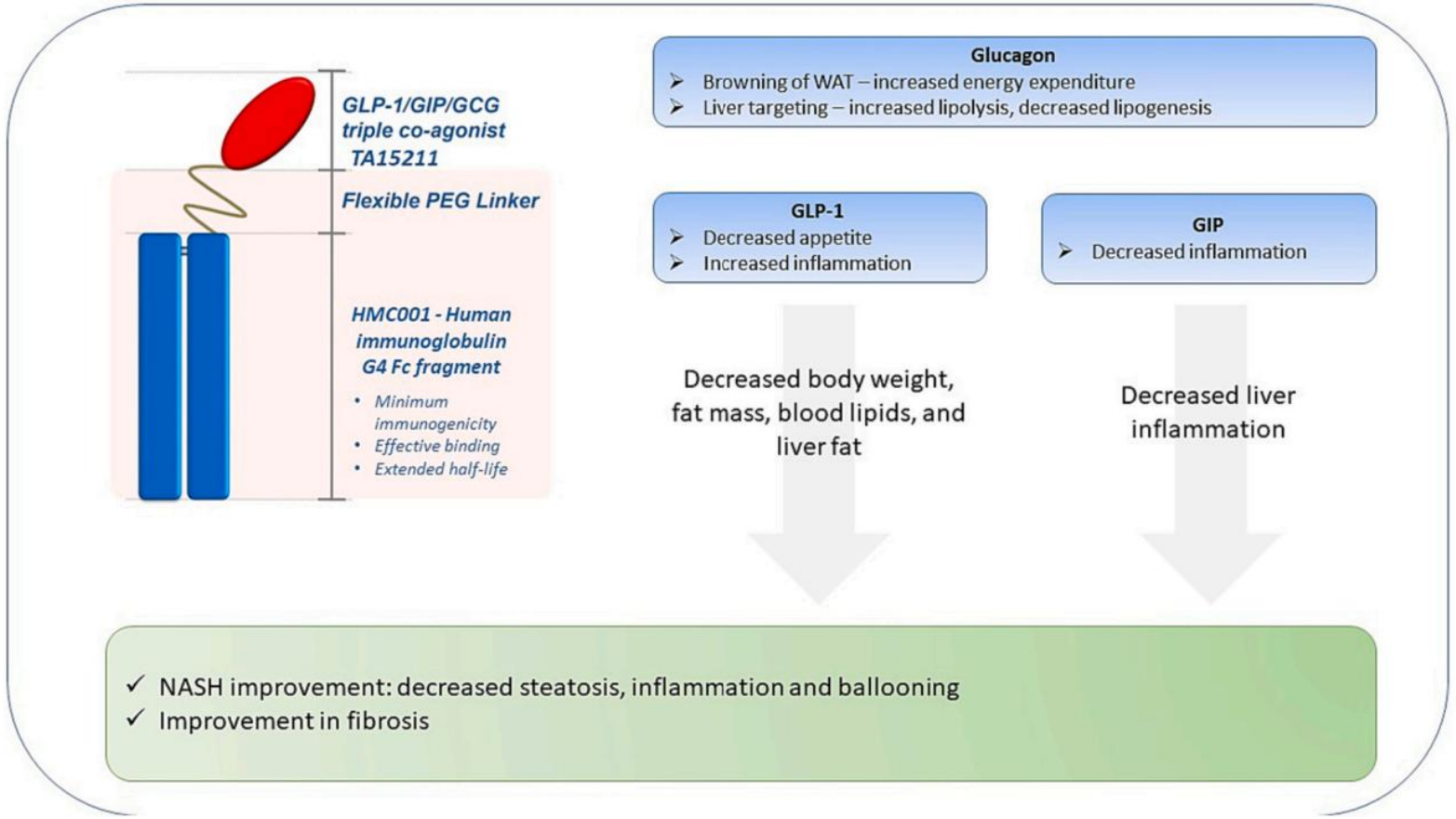
Sanyal et al NEJM 2024

Triple incretin agonists ?!? GLP1 +GIP +GCGR

- Several combination GLP1/GIP/GCGR in development
- Key is getting the right ratio among the receptors to maximize efficacy and reduce side effect profile



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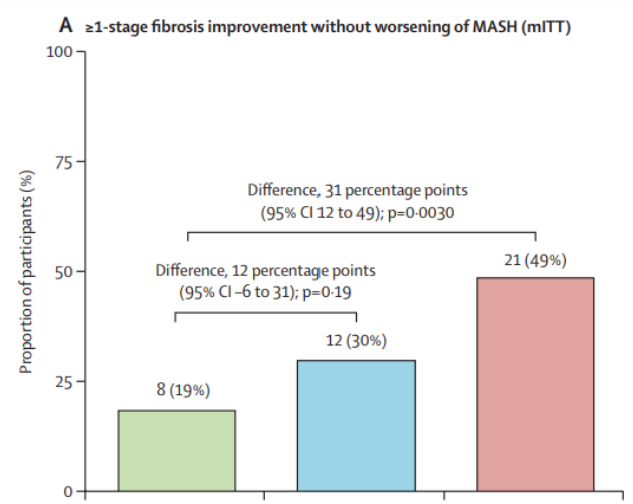
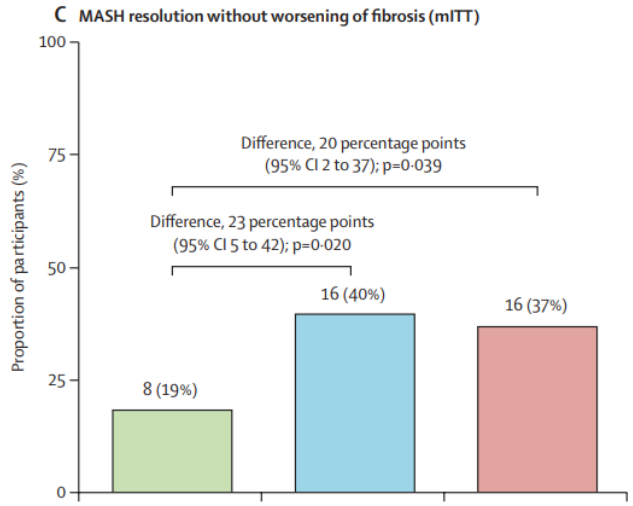
Abdelmalek Contemp Clin trials 2023

Fibrosis Growth Factor Analogues

- **Efruxifermin**

- 96 week phase 2b study of 128 patients with stage 2-3 MASH
- Weekly injection



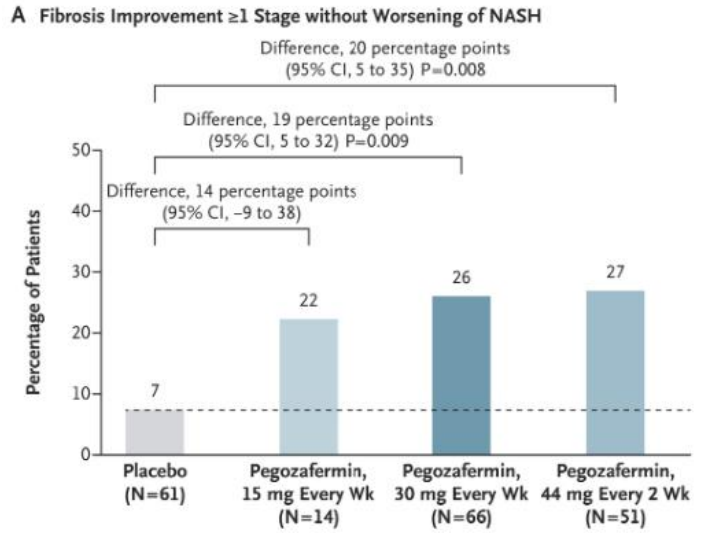


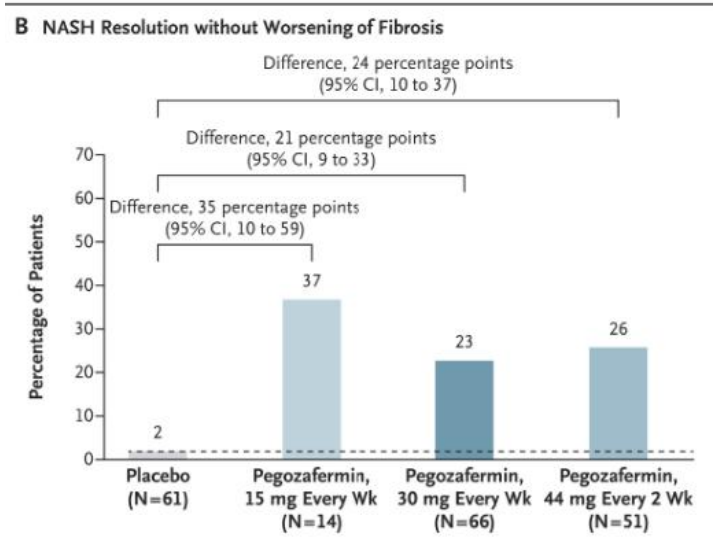
Noureddin et al. Lancet 2025

- **Pegozafrmin**

- 24 week phase 2b study of 22 patients with stage 2-3 MASH

- Weekly or bi-weekly injections





Loomba et al NEJM 2023

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Peroxisome proliferator-activated receptor

A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH

Francque SM et al. DOI: 10.1056/NEJMoa2036205

- Phase 2b RCT of 247 subjects with NASH without cirrhosis
- 2 doses of Lanifibrabor vs placebo
- Used Steatosis, Activity, Fibrosis (SAF-A) score (0-4)
- 1* outcome decrease by 2 or more points

Decrease of ≥2 Points in SAF-A Score and No Worsening of Fibrosis

	Lanifibranor	Placebo	Risk Ratio (95%CI)	P Value
Lanifibranor, 800 mg	48%	33%	1.45 (1.00–2.10)	P=0.07
Lanifibranor, 1200 mg	55%	33%	1.69 (1.22–2.34)	P=0.007

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Francque et al NEJM 2021

Summary

- NIT are reasonable to identify patient who may benefit from pharmacotherapy for MASH
- Lifestyle intervention and risk factor control (not discussed today) are critical for all patients with MASLD
- FDA has approved resmetirom and semaglutide for stage 2-3 MASH
- Multi-incretin therapies, FGF-21, and pan-PPAR drugs show promising phase 2 data

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CME/MOC Question:
(multiple choice – list 4 answers to choose from)

- A 48 year old sedentary woman with dyslipidemia has steatosis on imaging. Her VCTE (Fibroscan) is 10.0 kPa with a CAP of 290 and interpreted as Stage 3 fibrosis with significant steatosis. Her ALT is 60 with a HGB A1C of 5.2 and a BMI of 27. PETH is negative. Viral and AIH markers are negative.
- **In addition to lifestyle intervention, which is the next best step?**

- A. Liver biopsy
- B. pharmacotherapy with resmetirom or semaglutide
- C. pharmacotherapy with tirzepatide
- D. pharmacotherapy with pioglitazone

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CME/MOC Answer

- A. Liver biopsy – incorrect. The patient has a reasonable clinical diagnosis of MASH with an NIT showing stage 3 fibrosis. Liver biopsy is unnecessary unless there is additional clinical concern for an alternative diagnosis
- **B. pharmacotherapy with resmetirom or semaglutide – Correct – Resmetirom and semaglutide are FDA approved for stage 2-3 fibrosis. The choice of which drug should come down to individualized clinical factors and discussion with the patient**
- C. pharmacotherapy with tirzepatide – incorrect – while FDA indicated for diabetes and obesity, this person is only overweight with a normal A1C. While phase 2 clinical trials are promising, it is not yet FDA approved for the apriori indication of MASH. Without diabetes or obesity, it is not clear if the patient will have the same benefit from this MOA
- D. pharmacotherapy with pioglitazone – incorrect- in patients without diabetes this medication did not show benefit in the PIVENS trial and is not FDA approved for MASH

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Bansal et al Hepatology 2025, Barritt et al AGJ 2025, Loomba et al NEJM 2024, Sanyal et al NEJM 2010

Thank you!

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