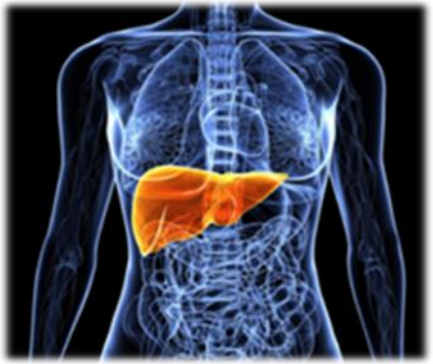
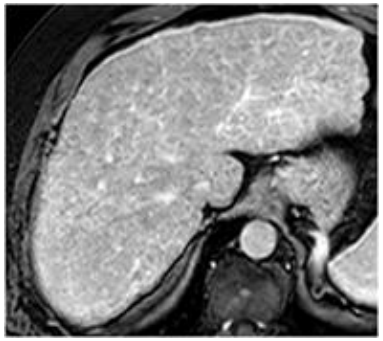
Management of Metabolic Associated Steatotic Liver Disease (MASLD)

Michigan Osteopathic Association
Spring Conference May 16, 2025





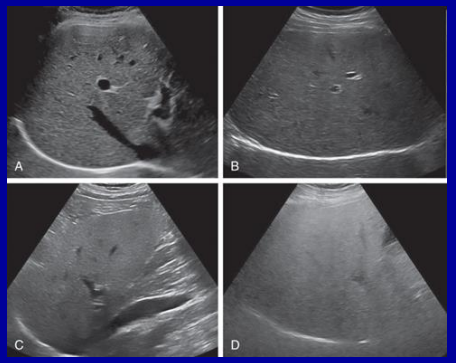
Robert J. Fontana, MD
Professor of Medicine

Robert J. Fontana, MD

- **Research:** Kezar, Takeda, MiroMatrix, Fractyl, NIDDK (DILIN)
- **Consulting:** Moderna, Metsera, MasterSwitch

MASLD in 2025

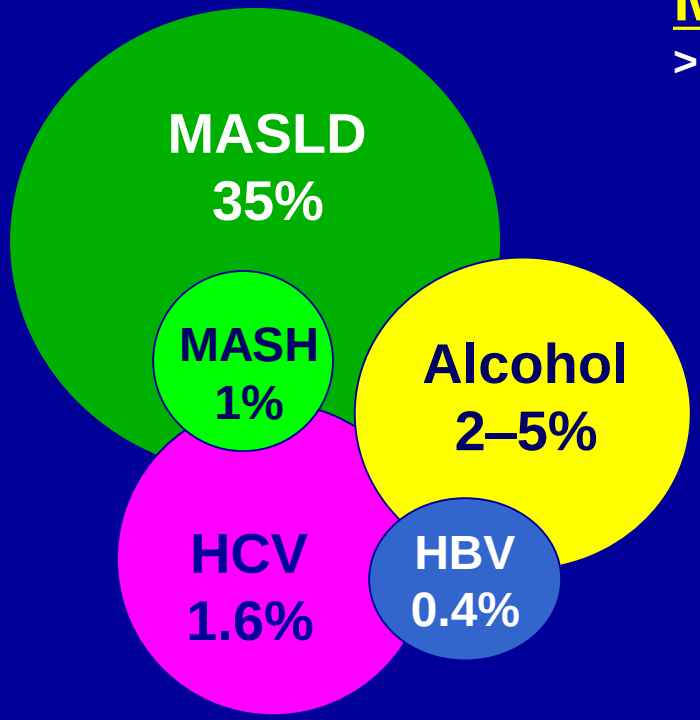
- Epidemiology
  - Diagnosis
  - Staging
- MASLD treatment
  - Lifestyle interventions
  - Resmetirom
- Obesity management
  - GLP-1 RA
- Antifibrotic therapy



US Chronic Liver Disease

Mortality

> 70,000 deaths/yr

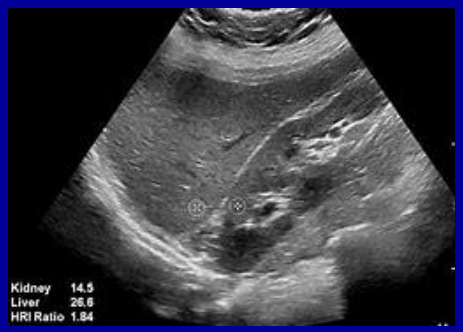


Prevalence

~ 1 million cirrhotics

Metabolic Associated Steatotic Liver Disease

MASLD = Hepatic steatosis on imaging and ≥ 1 cardiometabolic risk factor

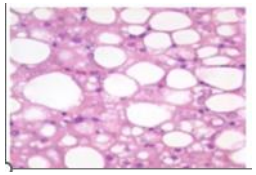


At least 1 out of 5:

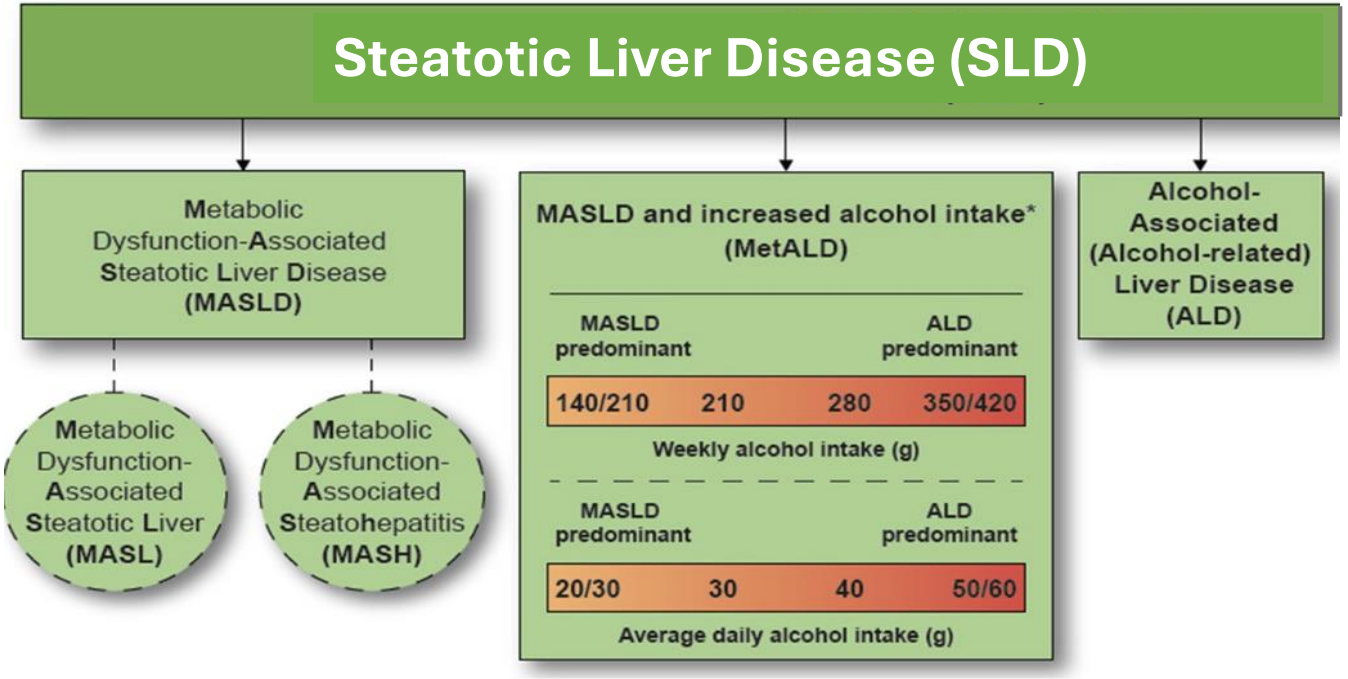
- ☐ BMI ≥ 25 kg/m² [23 Asia] OR WC > 94 cm (M) 80 cm (F) OR ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] OR 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] OR HbA1c ≥ 5.7% [39 mmol/L] OR type 2 diabetes OR treatment for type 2 diabetes
- ☐ Blood pressure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

Exclude: HBV, HCV, iron overload

(Kanwal Hepatology 2024)



MASLD Nomenclature



Rinella M, Hepatology 2023

Prevalence of Steatotic liver disease

(N=7,367 NHANES '17-'20) CAP ≥288 dB/m

SLD
34.2%

MASLD
31.3%

MetALD
2.2%

ALD
0.7%

Cryptogenic or Specific Etiology
0.03%

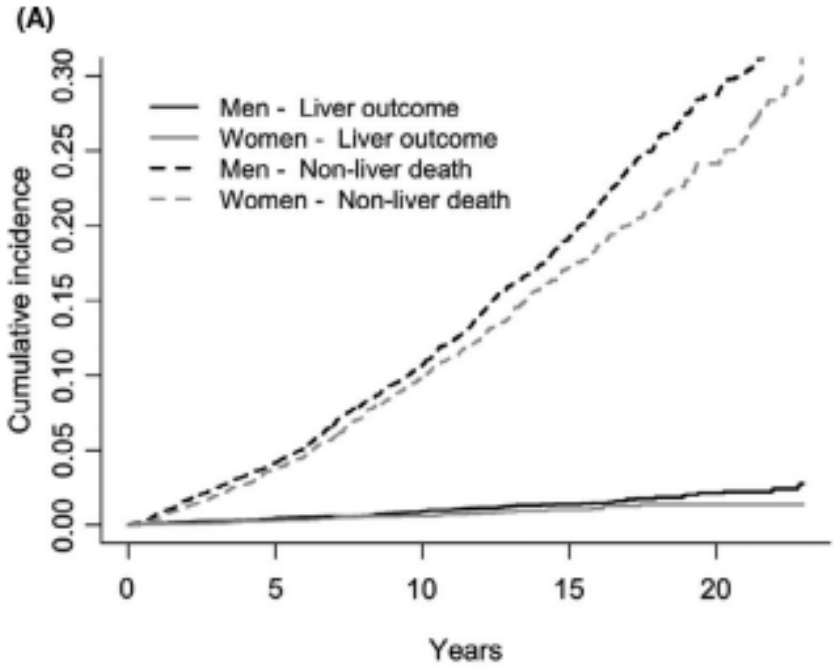
67% some alcohol in past 12 months

% of SLD
92% MASLD
6% MetALD
2% ALD

Lee BP, Hepatology 2024; 79(3);666-673

Risk of liver events in MASLD

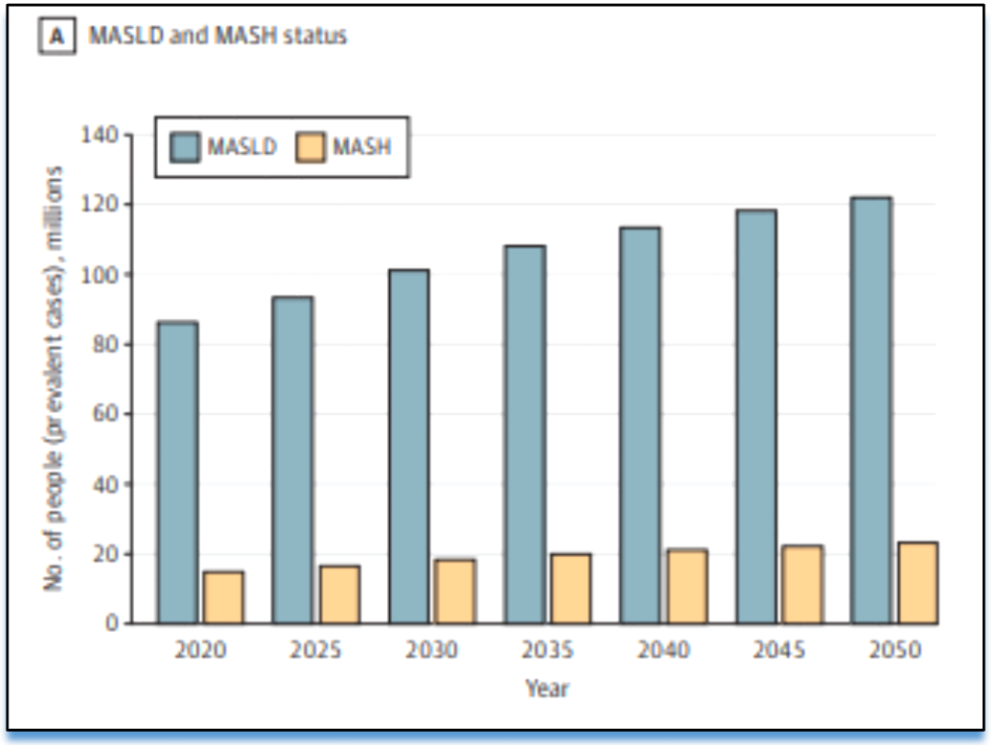
- **Finnish population studies**
  10,993 MASLD patients
- **Liver-related events**
  0.97 per 1,000 person- years
- **Cancer and cardiovascular risk**
  9 -16 times > liver- death



((Mannisto Liver International 2021: 41: 2590)

US MASLD Burden '20-50

↑ MASLD prevalence to 41.4% (122 million)
↑≥ F2 to 11.7 million people

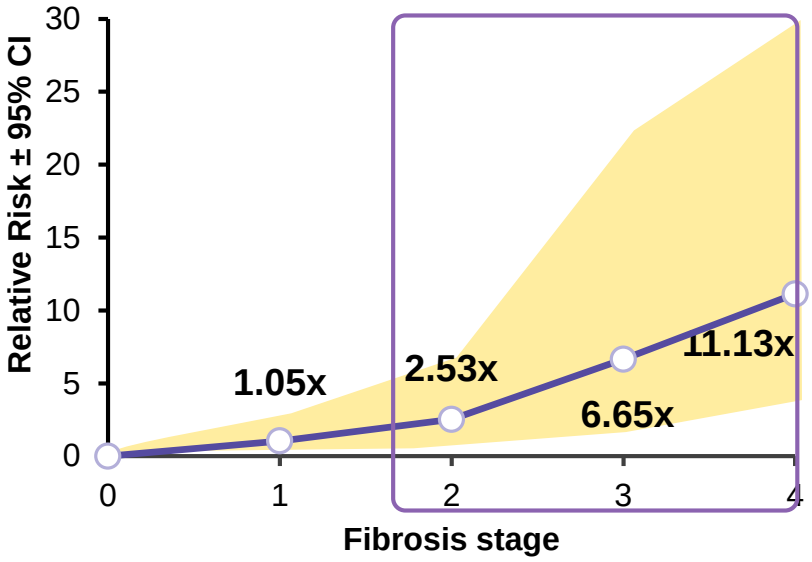


↑ Liver-mortality to 95,000 per yr
↑ HCC by 200% to 22,000 per yr
↑ Liver txp by 400% to 6,700 per yr

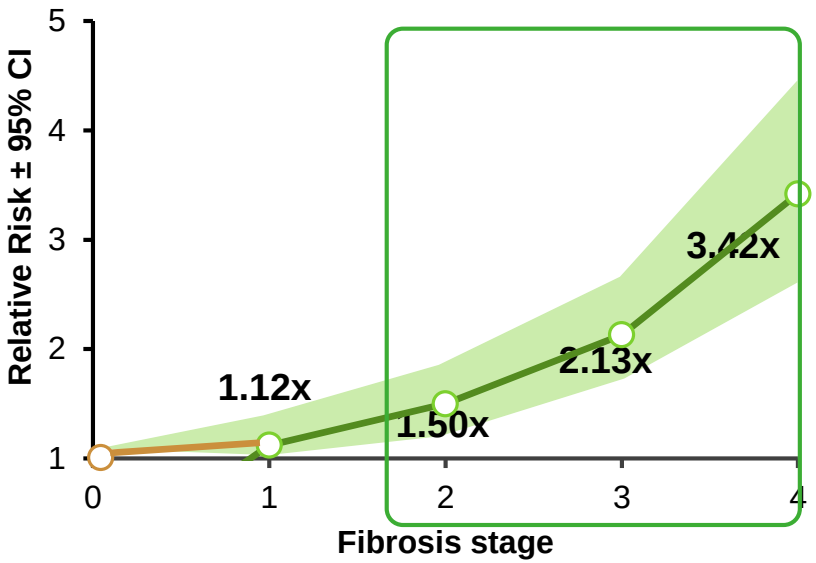
(Le et al, JAMA Open 2025: 8 (1))

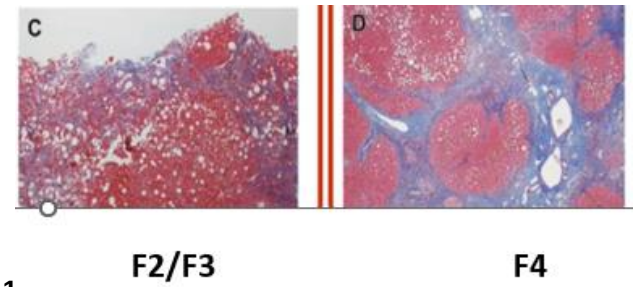
Liver Fibrosis predicts Hepatic and overall Mortality in MASLD

Liver-related mortality
(meta-analysis of 7 studies)



All-cause mortality
(meta-analysis of 8 studies)





(Taylor RS et al. *Gastroenterology*. 2020;158:1611 [illegible].

Non-invasive Screening tests for MASLD

Blood biomarkers

CBC, comprehensive

- FIB-4

Serum ELF panel

Liver imaging

VC transient elastography

- Stiffness & CAP (fat)

MR elastography

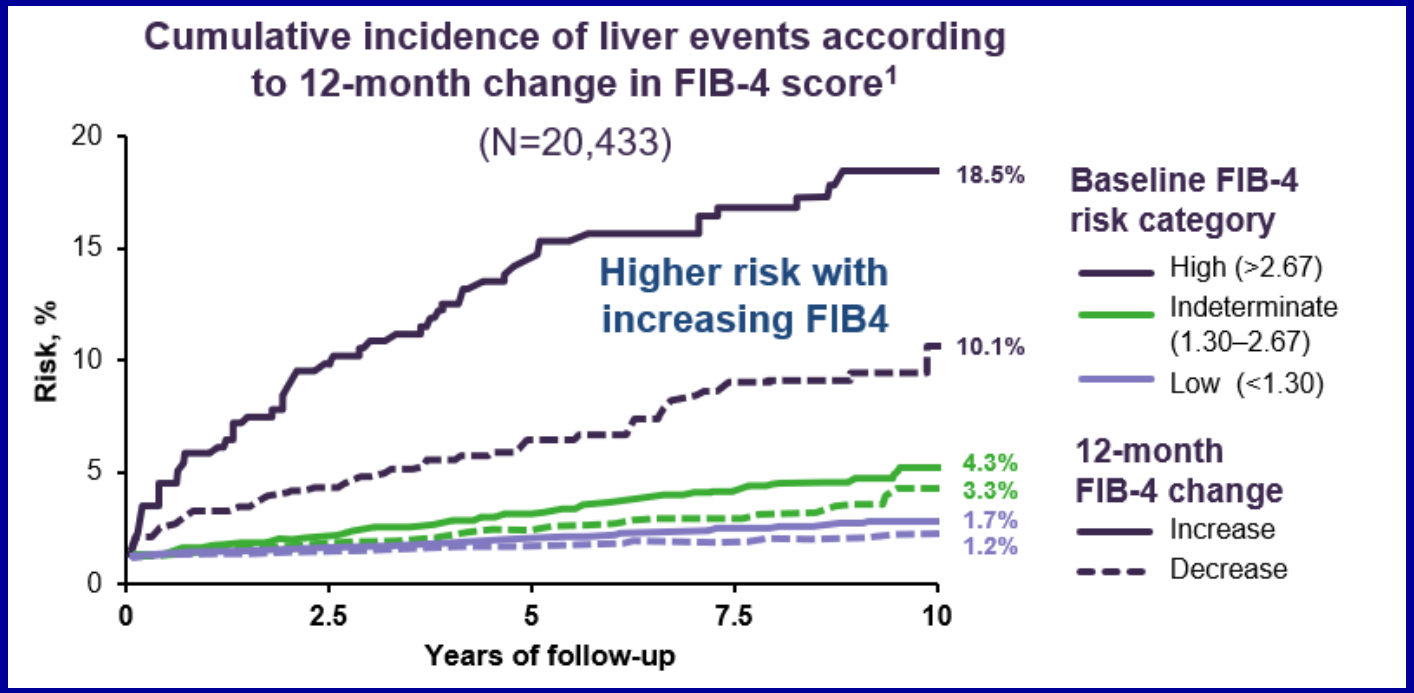
- Stiffness & PDFF (fat)

FIB-4 = (Age * AST)/ (Plat x Sqrt (ALT))

FIB-4 in MASLD

- **To detect F3/ F4 fibrosis**
  - **< 1.3 NPV 95%**
  - **1.3 - 3.2 Intermediate**
  - **> 3.25 PPV 70%**
  - **– If > 65 yrs, cut-off < 2.0 and > 3.25**

EMR embedded



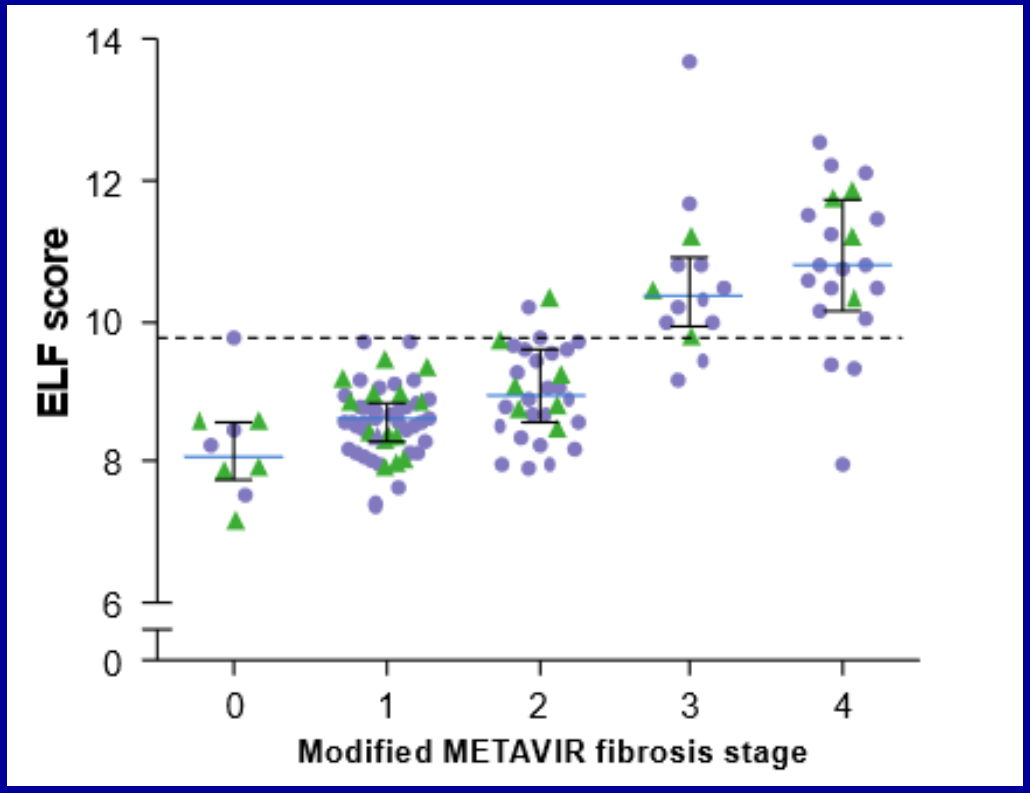
UK cohort

(Anstee Lancet 2023: 36)

Enhanced Liver Fibrosis Panel

- **ELF Panel for F3/F4 ***
  - < 7.7 NPV 85%
  - 7.7- 9.8 Medium
  - ≥ 9.8 PPV 90%

Reference lab ($$)



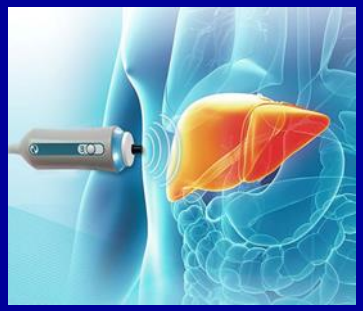
ELF Panel

Hyaluronate, TIMP-1, PIIINP

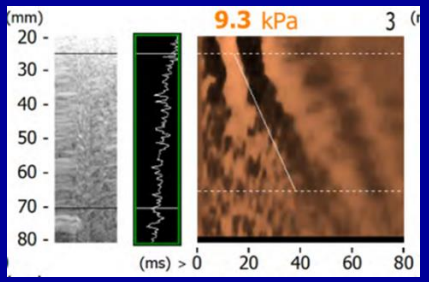
(Fagan Liver Int 2015: 35: 1673)

VCTE (Fibroscan)

- **50 Hz probe (1 x 3 cm core)**
  - **10 minute POC test**



- **Liver stiffness: 4 to 70 kilopascals**
  - **F0/F1 < 8 kPa**
  - **F2/F3 8 – 12 kPa**
  - **> F4 > 12 kPa**



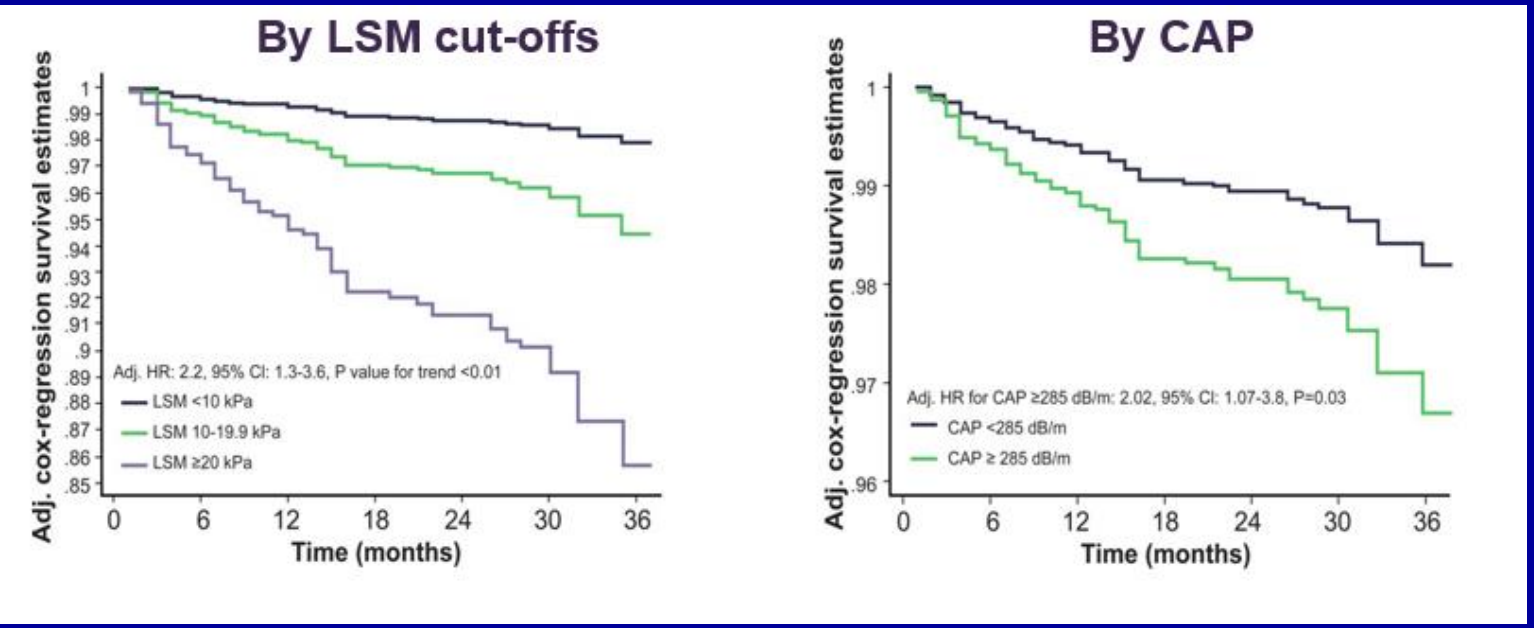
- **False + (Overestimate)**
  - **↑ Bloodflow (eating)**
  - **Alcohol > 2 drinks/d (↑ 3-4 kPa)**

Controlled Attenuation Parameter (CAP)

- **Hepatic steatosis severity**

Normal	< 250 db/m
Mild	250-300 db/m
Mod/ severe	> 300 db/m

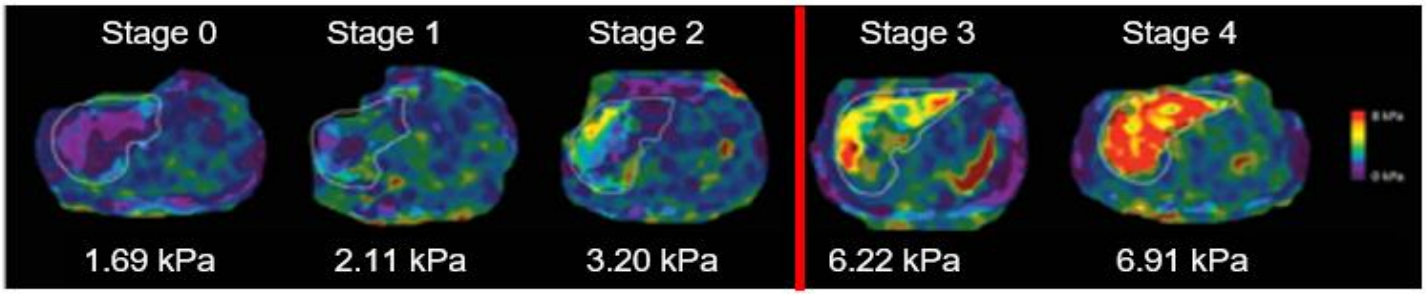
- **CAP can decrease with diet/ weight loss**



NHANES III
4200 adults

(Villar Gomez Hepatology 2023: 77)

Magnetic Resonance Elastography (MRE)



Cutoff for Detecting Advanced Fibrosis	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
MRE stiffness ≥3.64 kPa	0.86 (0.65-0.97)	0.91 (0.83-0.96)	0.68 (0.48-0.84)	0.97 (0.91-0.99)

MRE advantages

↑ Accuracy

No impact of ascites/ BMI

MRE limitations

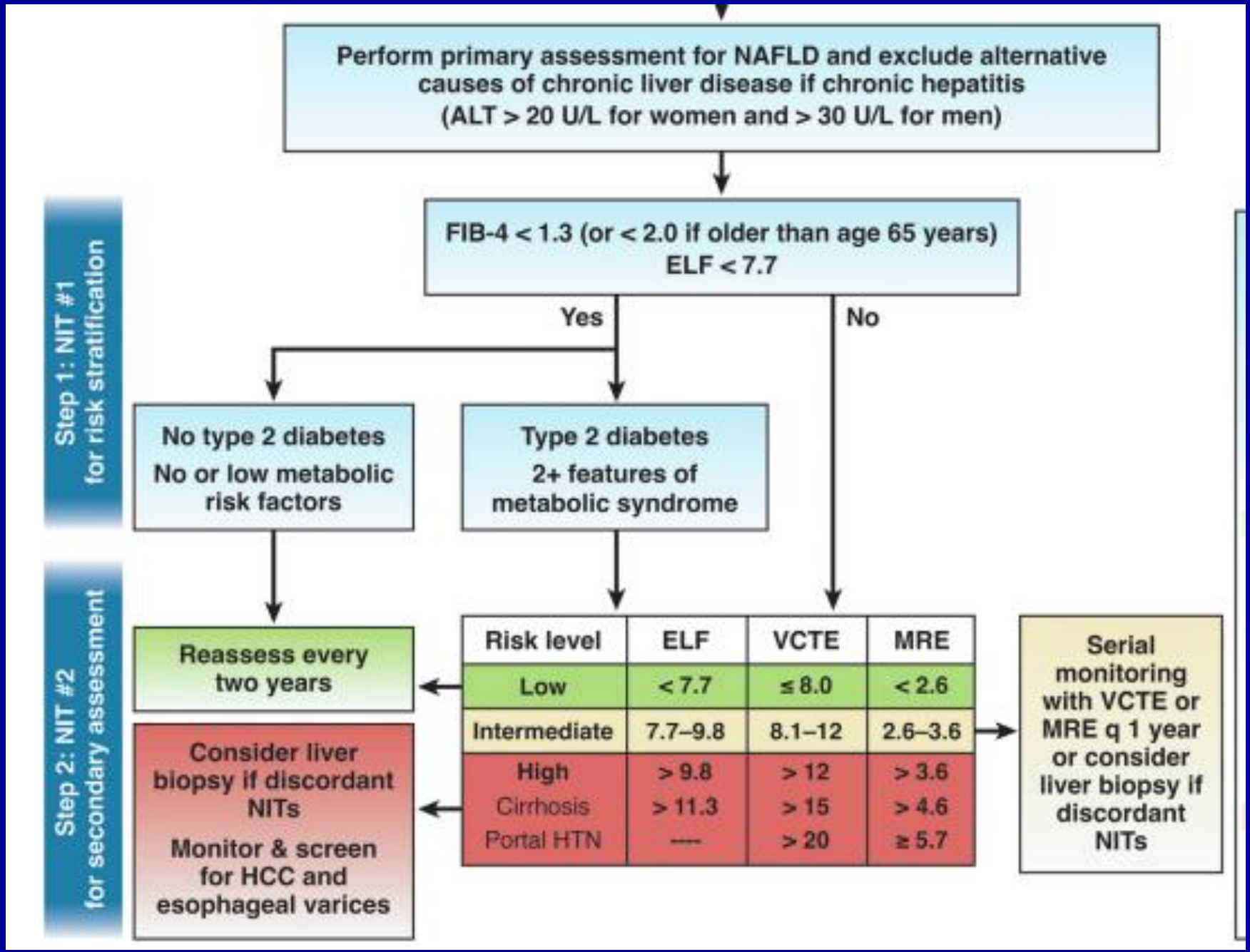
Availability (cost)

MRI- PDFF (0-30%)

Hepatic steatosis

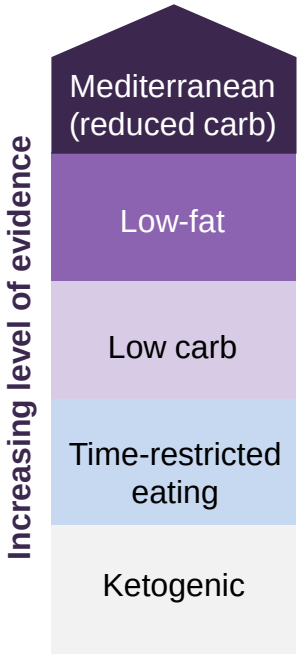
Normal < 5%

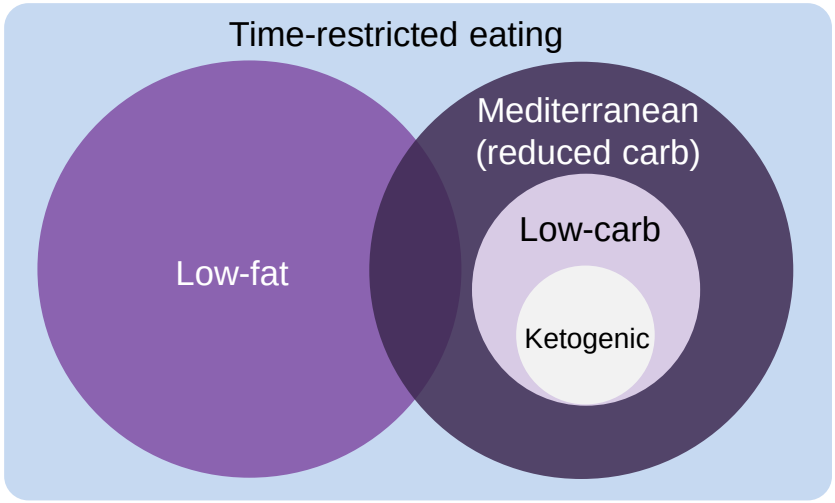
Severe > 20%



(Gastroenterology 2023; 165: 1080)

Type of Diet for MASLD Treatment





All diets should minimize ultra-processed foods and meat, sugary foods and drinks, and saturated fat.

Zelber-Sagi S. *Liver International*. 2022;42:1731-1750.

Intensive Lifestyle intervention MASLD

Paired liver biopsies 1 yr

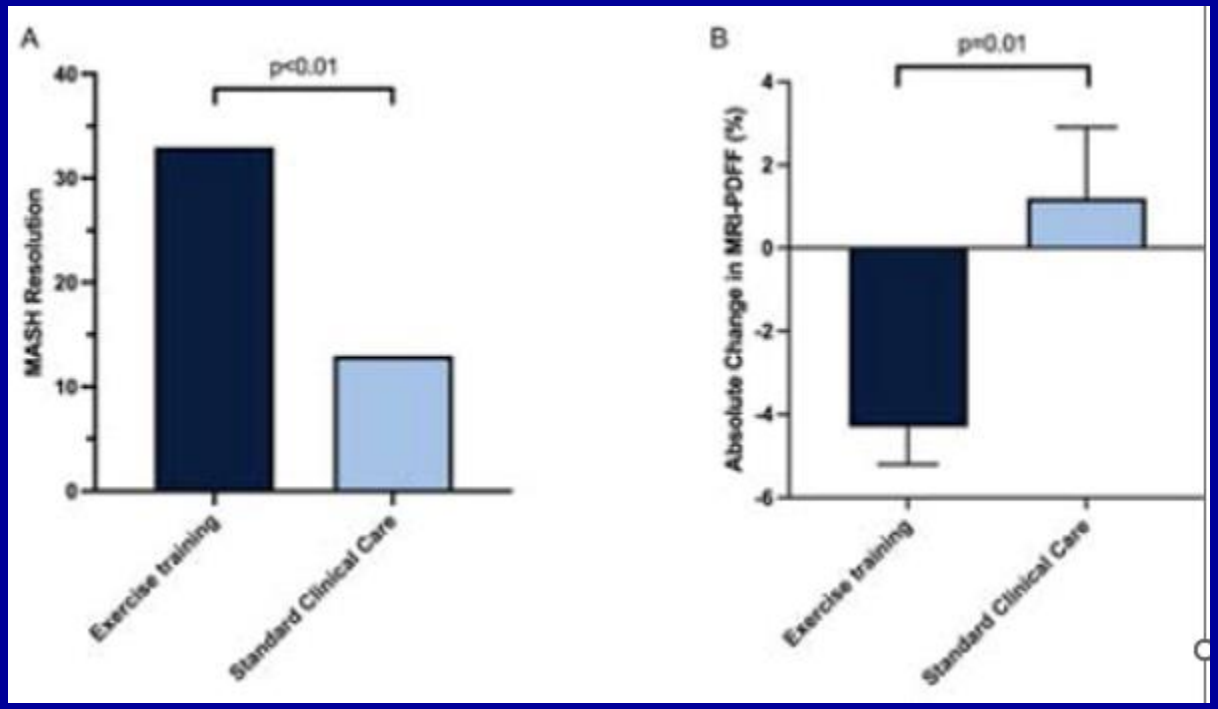
	< 5% WL N= 205 (70%)	5-10% WL N=59 (20%)	> 10% WL N=29 (10%)
Steatosis improved	72 (35%)	41 (69%)	29 (100%)
Lob inflam improved	72 (35%)	46 (94%)	29 (100%)
MASH resolution	21 (10%)	25 (42%)	26 (90%)
Fibrosis			
Regression	33 (16%)	10 (17%)	13 (45%)
Stable	129 (63%)	46 (78%)	16 (55%)
Worsening	43 (21%)	3 (5%)	0 (0%)

Dose dependent impact of weight loss on liver histology

(Vilar-Gomez Gastroenterology 2015)

Exercise improves MASLD even without weight loss !!

150 min/wk mod exercise vs SOC x 20 wks
Age = 52 BMI = 34 39% Diabetes



No weight loss in either group but 24% ↓ALT with exercise (improved MRI-PDFF)

(J Stine Hep Commun 2025)

MASLD Medications

Liver vs systemic target

Agent	Liver Target	Body weight	Hyperlip	Insulin resist
Thyroidβ agonist	+++	-	+	-
Incretin agonist GLP-1	-	+++	+	+
GIP-1	-	+++	+	+
GCK	+++	+++	+	+
FGF-21 agonist	++	+	++	+

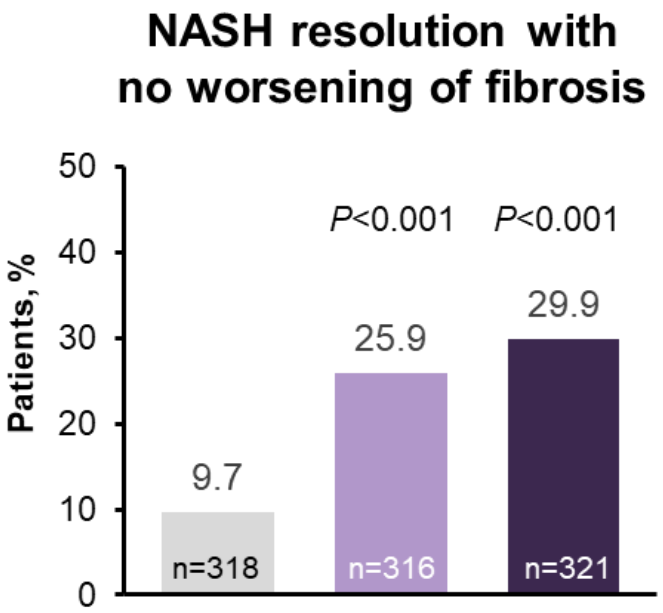
Resmetirom for Non-cirrhotic MASH

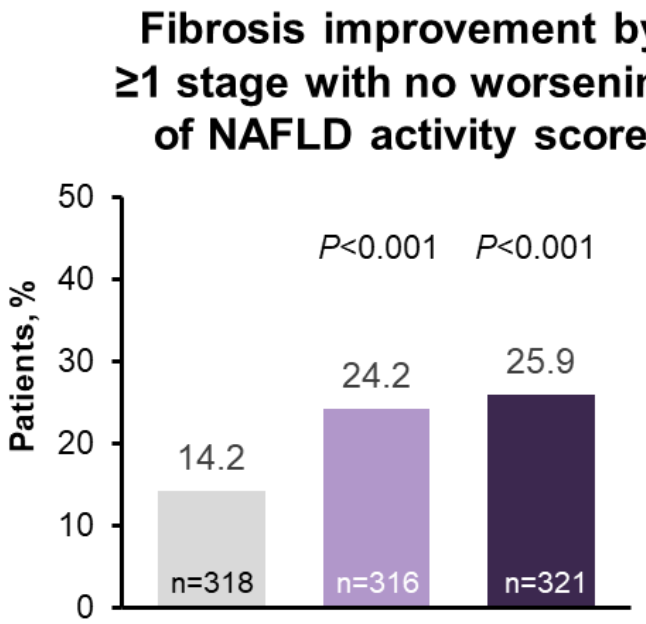
- **Thyroid hormone receptorβ (THR) agonist**
  - **Reduces hepatic steatosis**
    - **Stimulates mitochondria, lipophagy**
    - **↑ hepatic processing LDL (↓ serum)**
    - **Inhibits lipogenesis**
  - **No impact on THR α receptor**

- **80 – 100 mg per day x 12 mon**

(Chen et al Hepatology 2024)

MAESTRO Phase 3 study





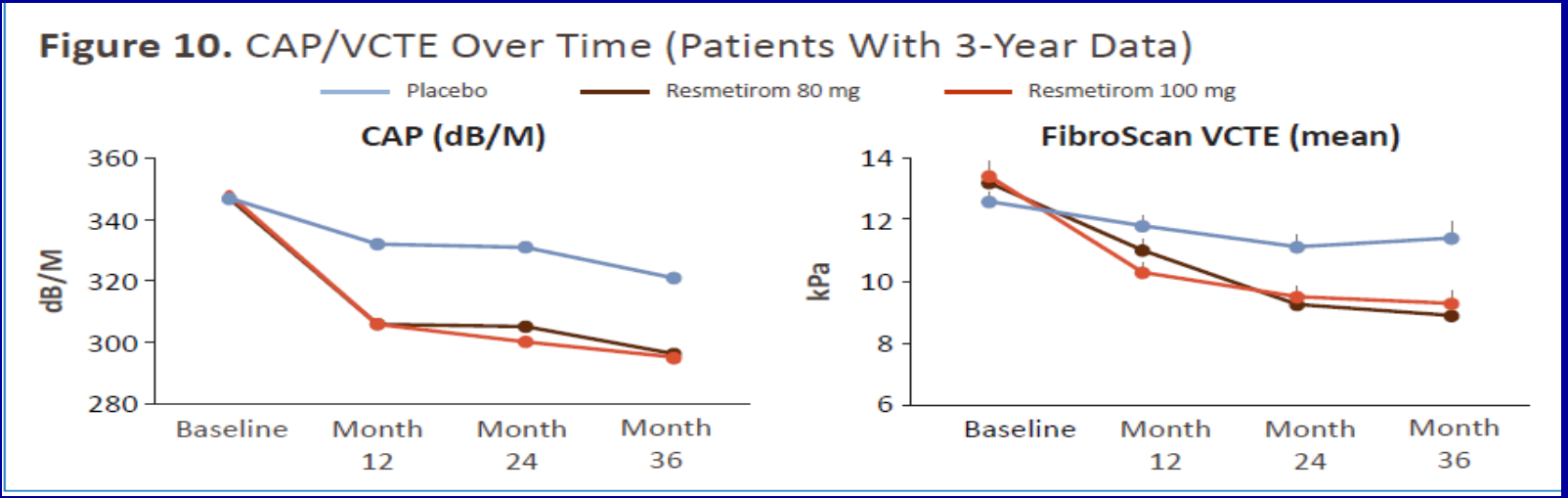
Placebo Resmetirom 80 mg Resmetirom 100 mg

(Harrison NEJM 2024: 390: 497)

Resmetirom in MASLD

- **WHO:** F2 or F3 by NIT or biopsy
  - Baseline VCTE > 8 kPa (MRE > 3.2 kPa)
    - No cirrhosis
      - VCTE > 20, varices, decompensation
    - Contraindicated in PBC, AIH, PSC
      - < 40 mg atorvastatin < 20 mg rosuvastatin
      - Similar efficacy +/- GLP-1
- **How:** 80 or 100 mg per day
  - Labs at mon 3, 6, 12
    - GI AE in 20-30% (< 3 mon)
  - Mon 12: Repeat NIT for response

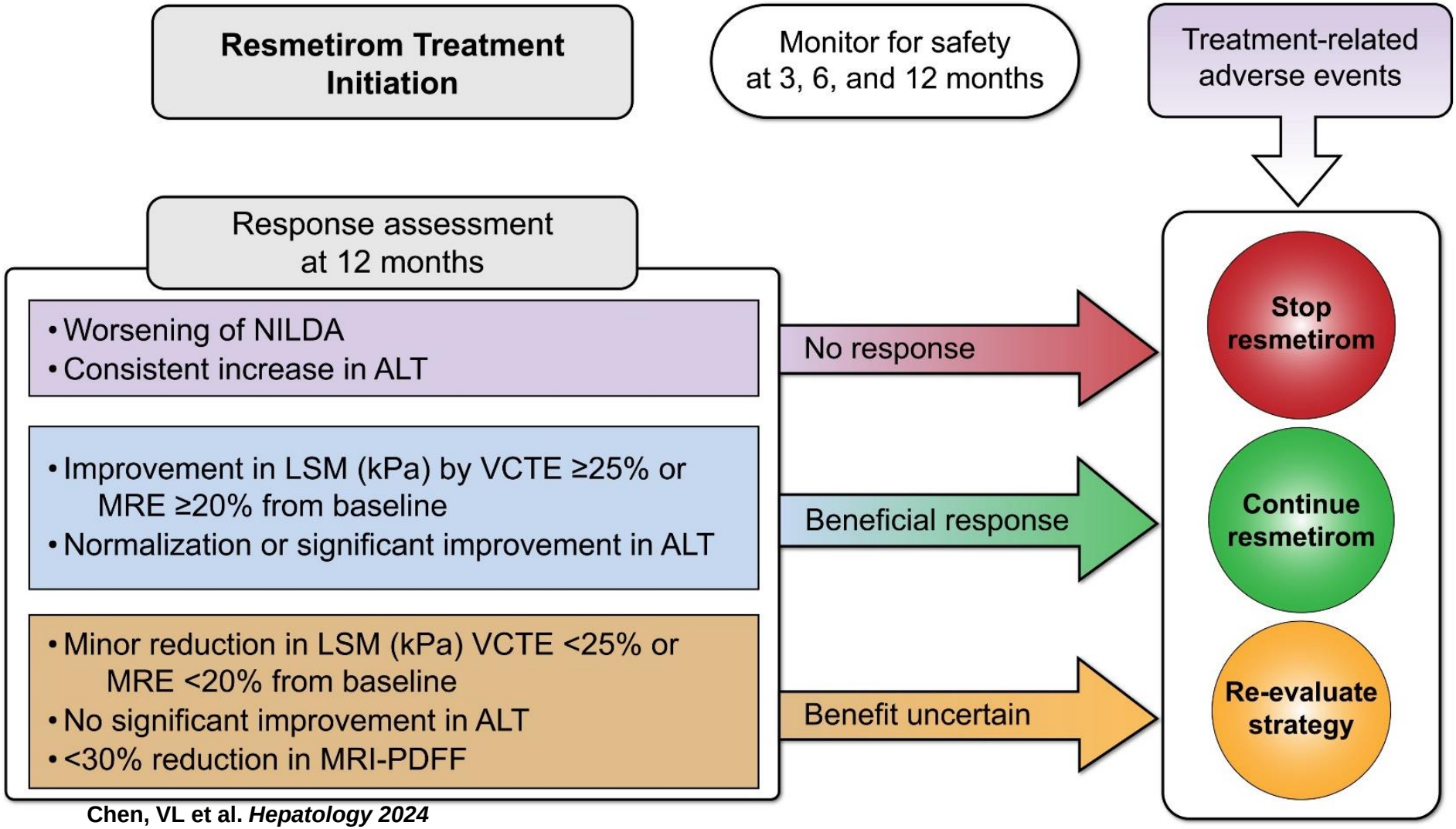
Resmetirom response at 3 years



Year 1 MRI- PDFF ↓ > 30% strongly associated with NASH resolution and fibrosis improvement

(Nouredin #3212 AASLD 2024)

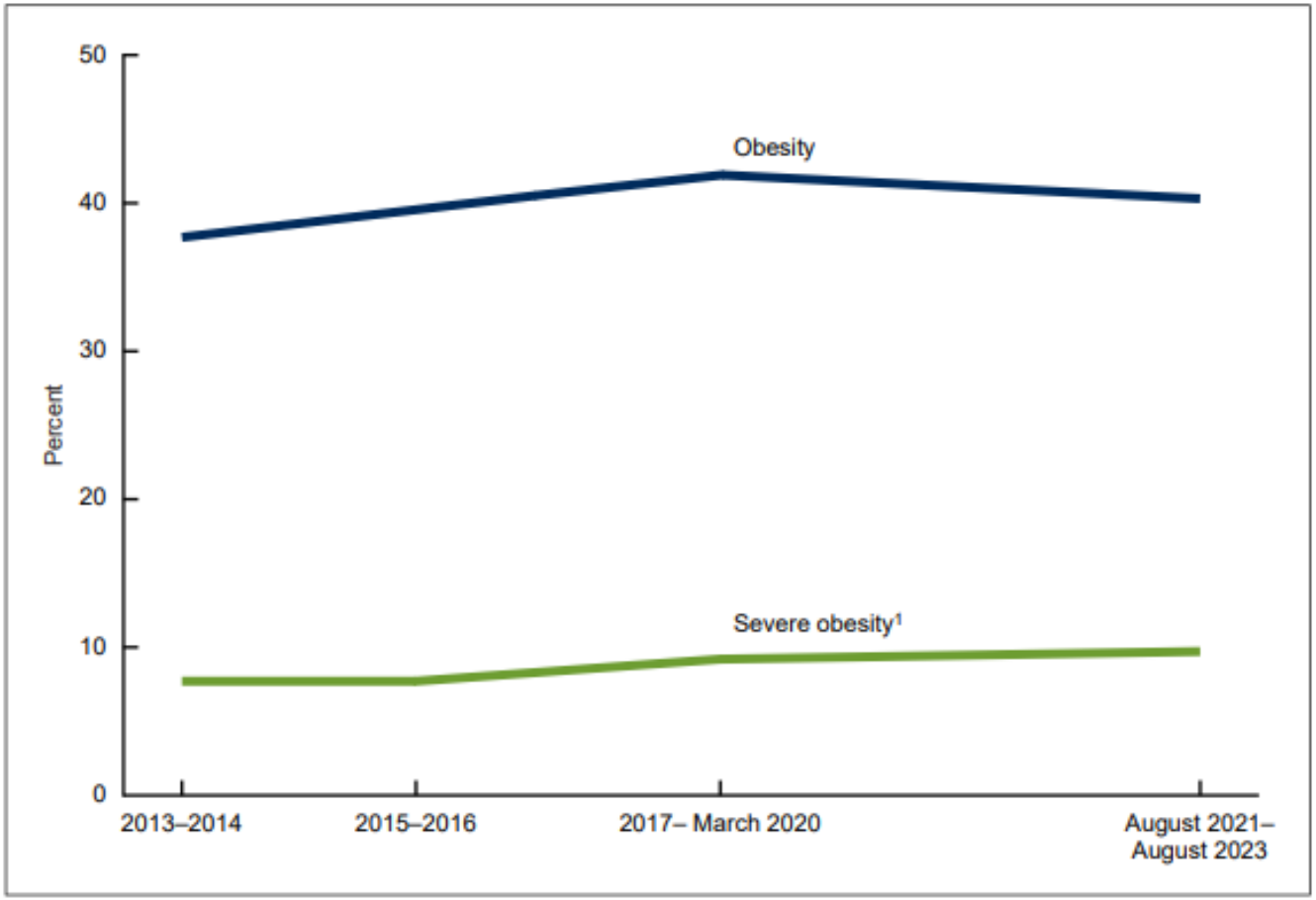
2024 AASLD Practice Guidance



Chen, VL et al. *Hepatology 2024*

Obesity in the US

Figure 4. Trends in age-adjusted obesity and severe obesity prevalence in adults age 20 and older: United States, 2013–2014 through August 2021–August 2023



[1]Significant linear trend ($p < 0.05$).
NOTE: Estimates are age adjusted by the direct method to the U.S. Census 2000 population using the age groups 20–39, 40–59, and 60 and older.
SOURCE: National Center for Health Statistics, National Health and Nutrition Examination Survey, 2013–2014 through August 2021–August 2023.

(NCHS Data Brief No 508: 2024)

Weight loss Approaches

Drugs

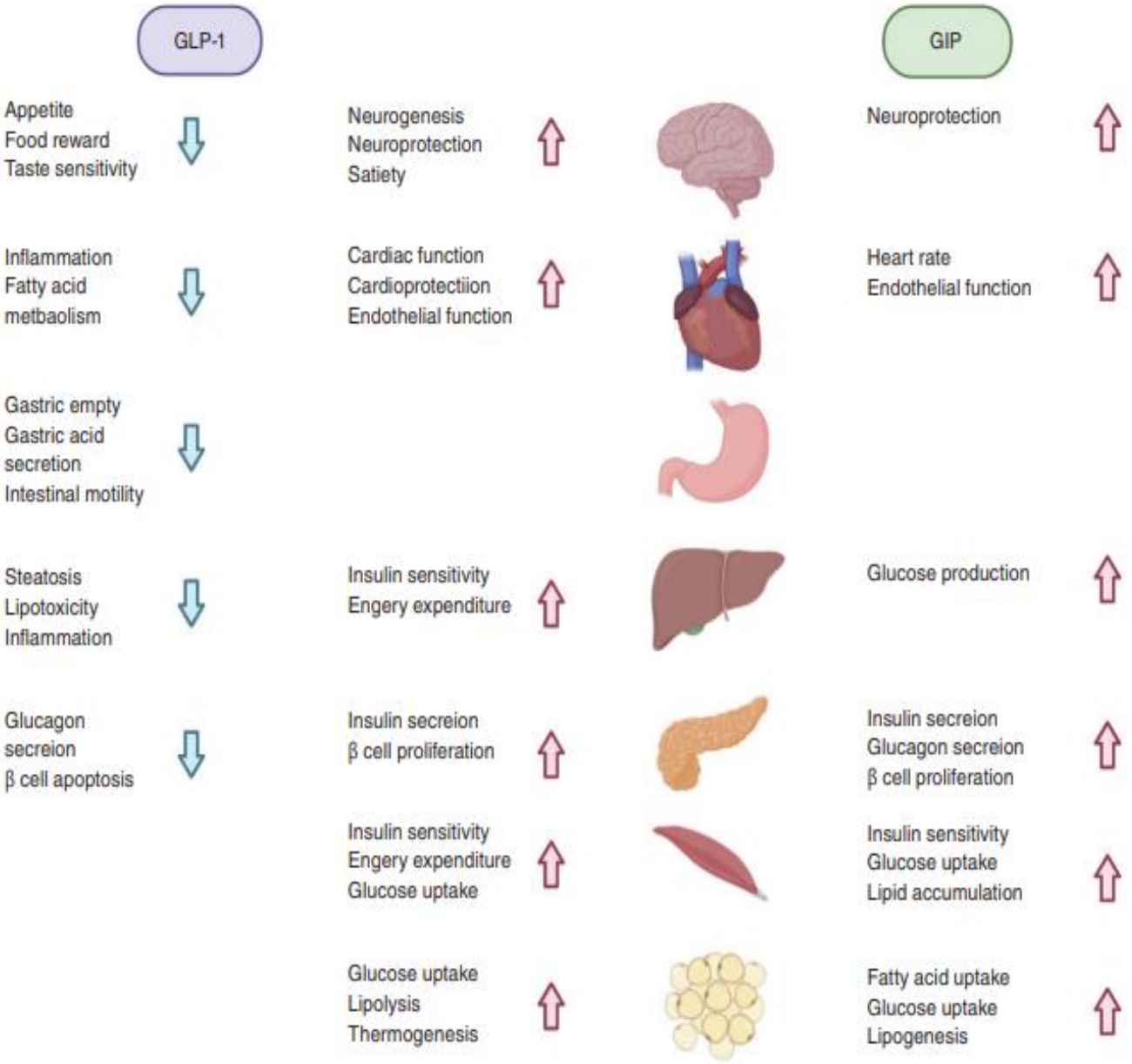
- Orlistat
- Phentermine
- Naltrexone/ buproprion
- Liraglutide
- Semaglutide
- Tirzepatide

Endoscopy

- Gastric balloon
- Sleeve gastroplasty
- DMR
- Electroporation

Surgery

- Roux-enY
- Sleeve gastrectom



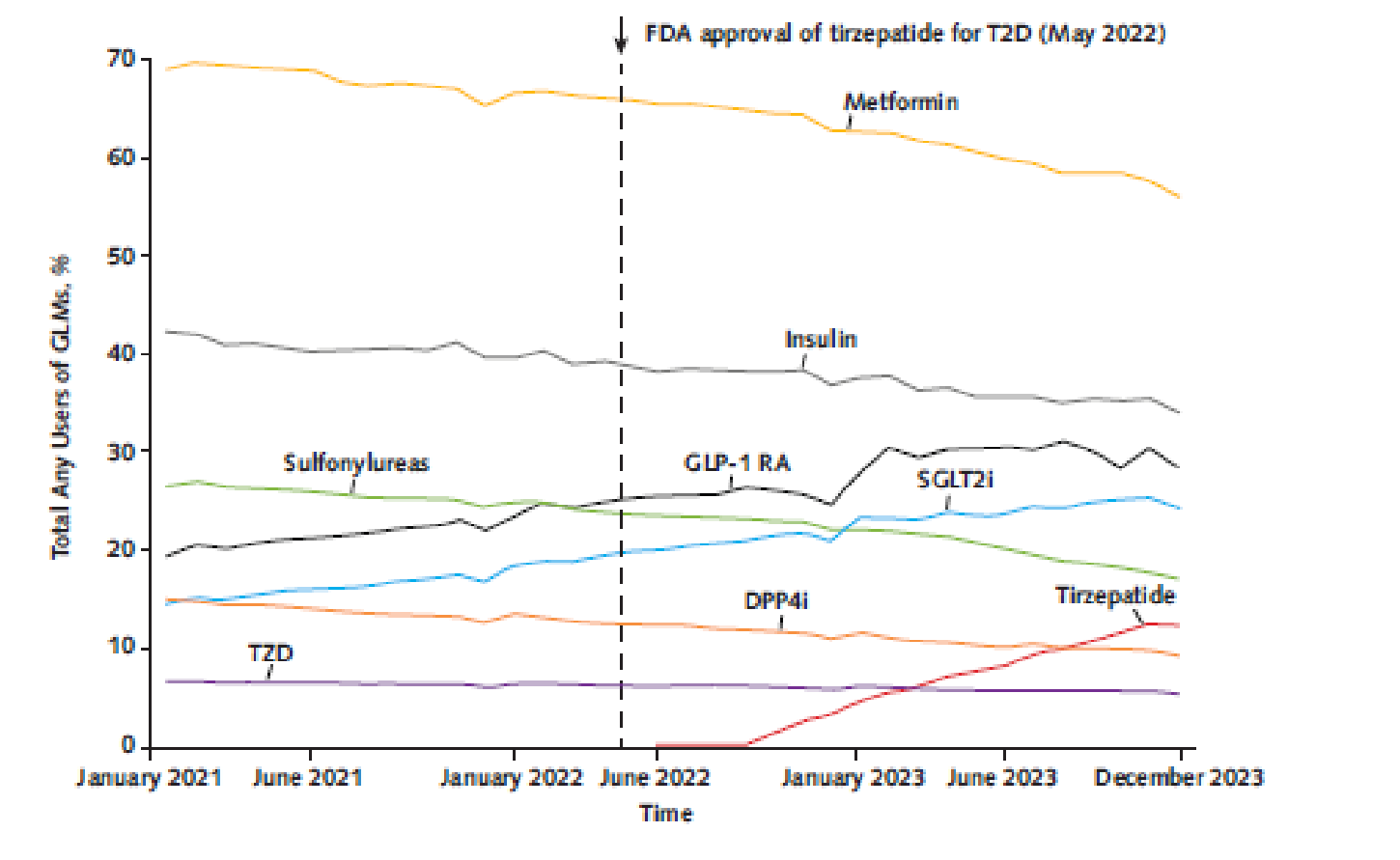
Incretin hormones

- Plietropic effects
- Not liver targeting

(Ren Clin & Molc Hepatology 2024)

Diabetes Medication use in US

Optum Database Age= 65



(Ostrominski Ann Intern Med 2025)

Obesity Medication use in US

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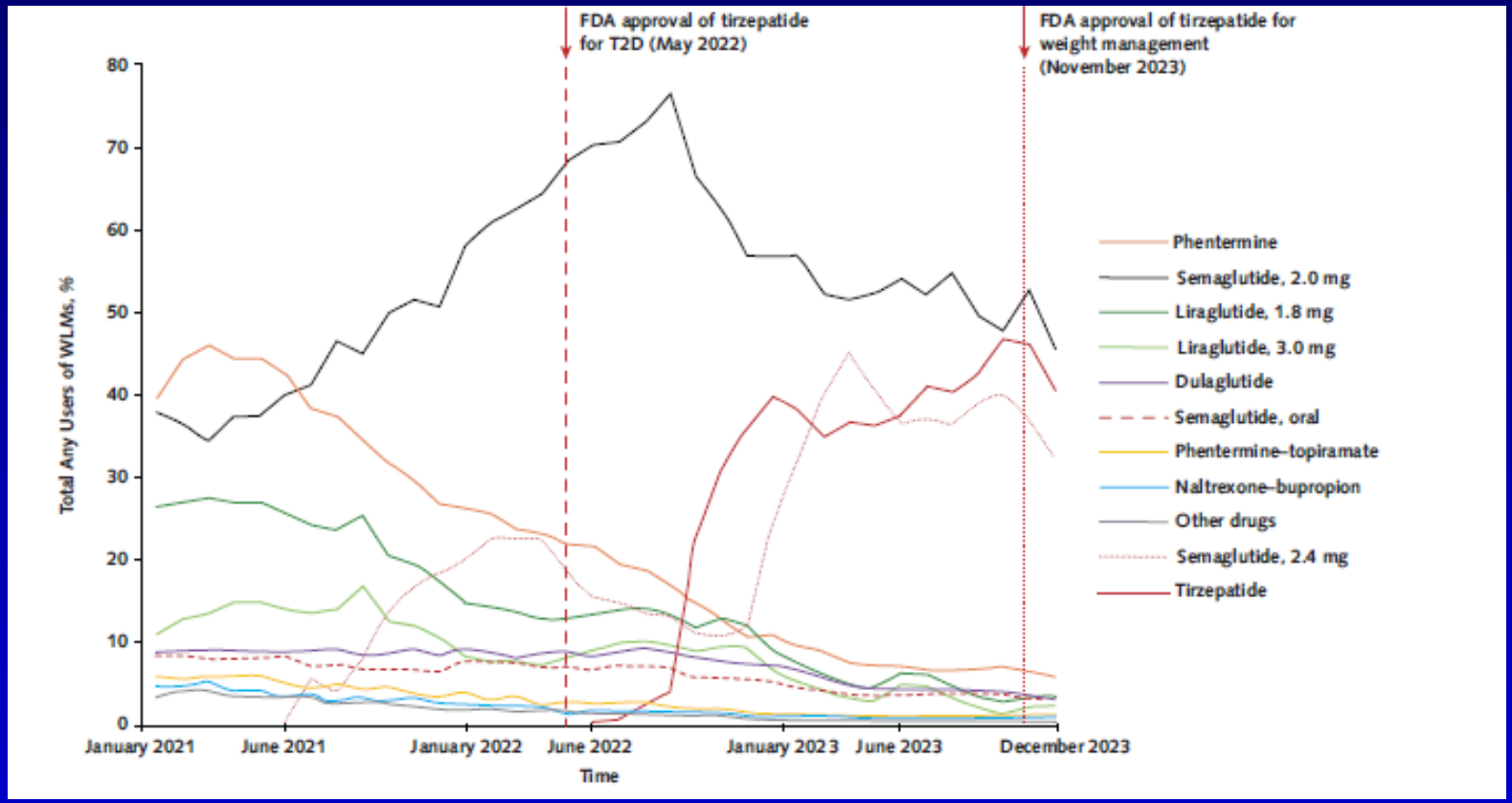
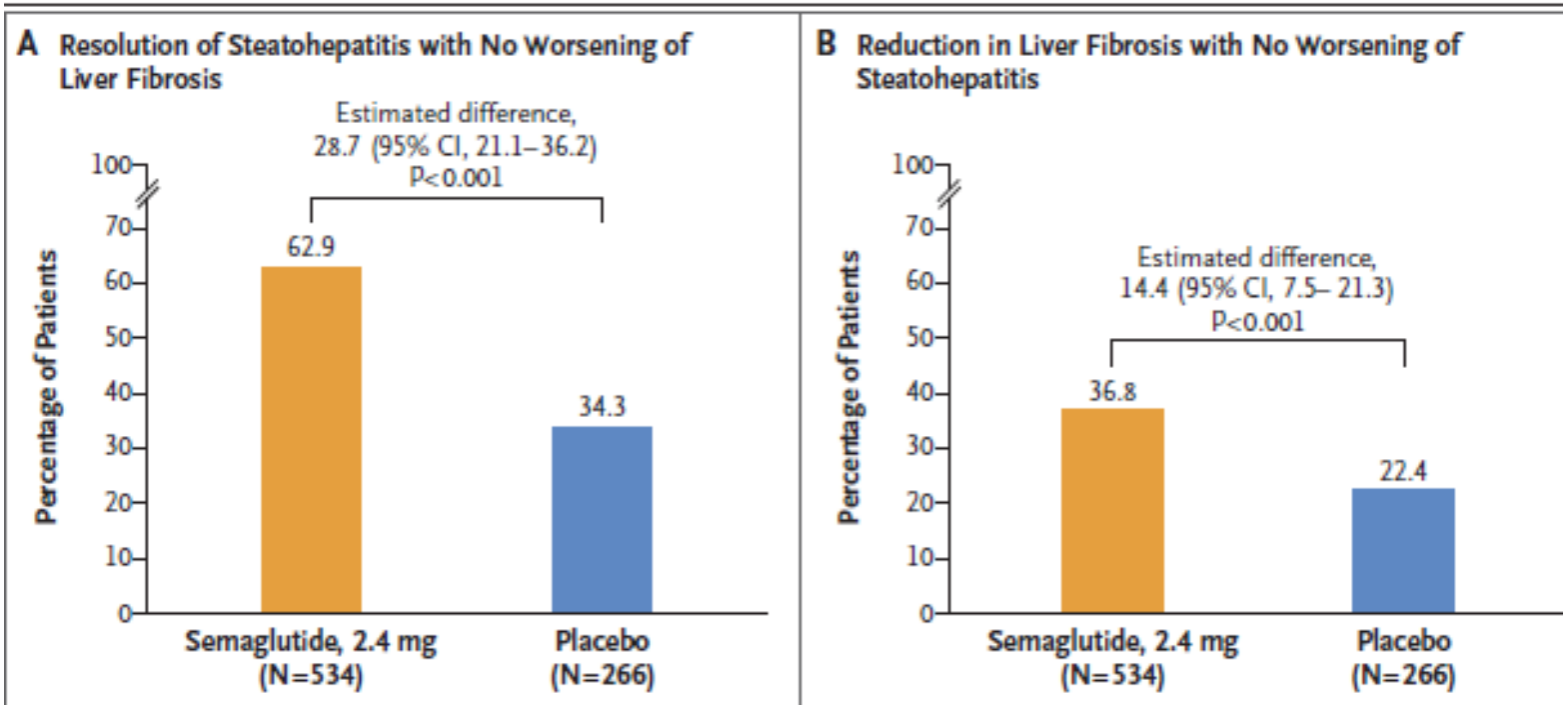


(Ostrominski Ann Intern Med 2025)

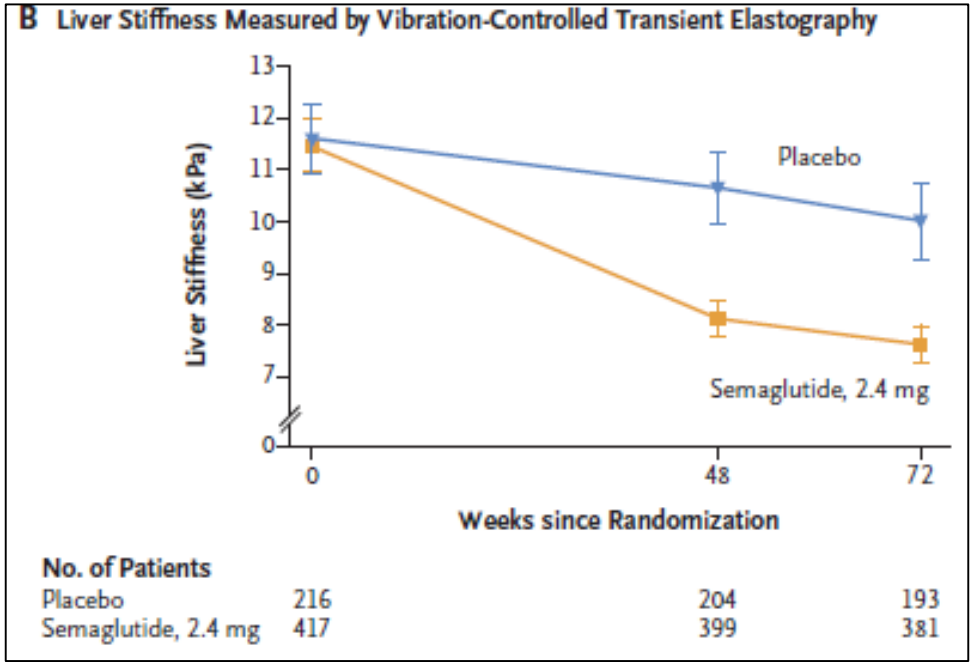
Semaglutide x 72 wks: Essence Trial

1200 F2/F3 MASH



(Sanyal NEJM 2025)

Semaglutide: Essence Trial

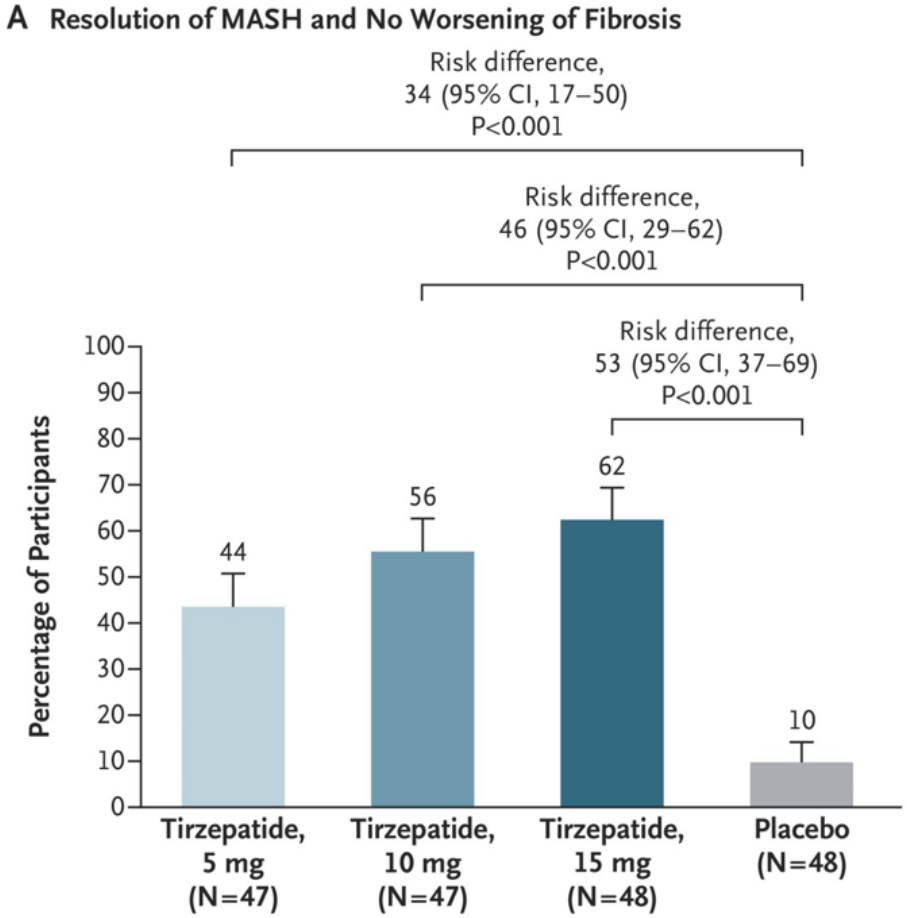


	Semaglutide	Placebo	p
Weight loss (%)	- 10 %	- 2.1 %	< 0.001
CRP (mg/dl)	- 53	- 20	< 0.001
LDL (mg/dl)	- 6.1	- 4.1	< 0.001

(Sanyal NEJM 2025)

Tirzepatide SYNERGY study

5, 10, 15 mg/ wk vs PBO x 52 wks

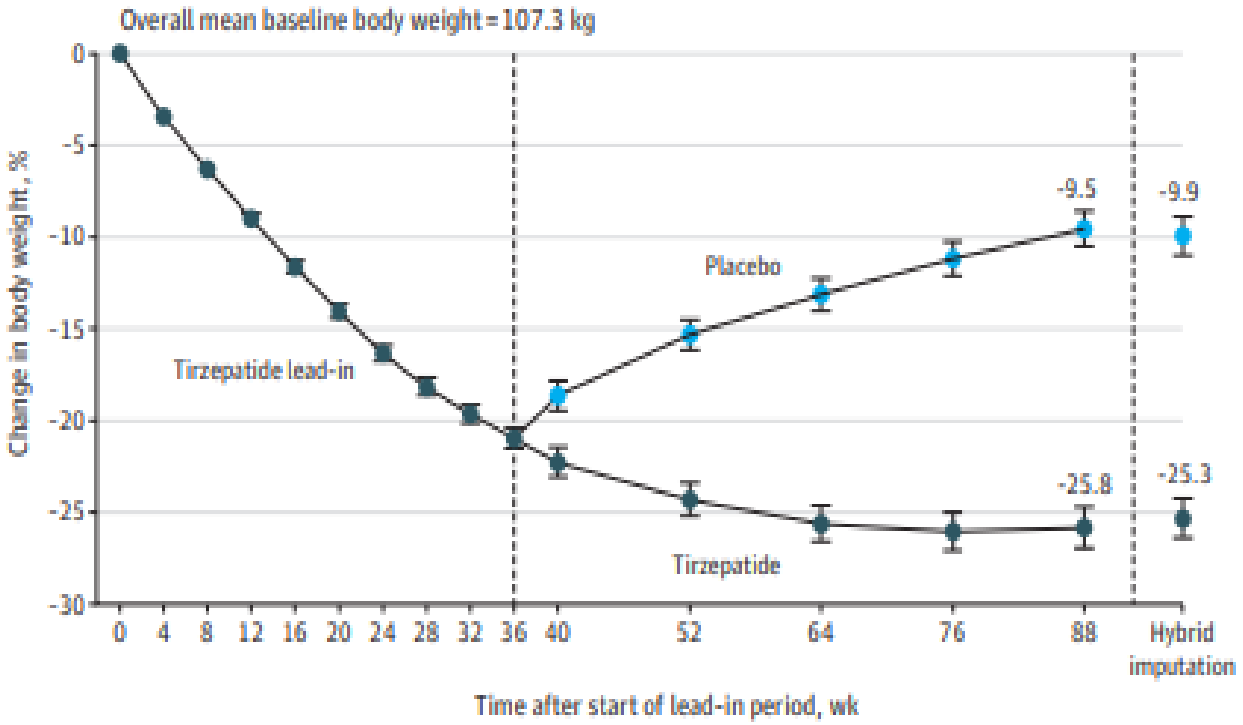


2° Efficacy

15% Med wt loss
Improved AST/ALT
Trend to ↓fibrosis
↓ 55% MRI PDFF

(Loomba NEJM 2024: 391: 299)

Weight regain GLP-1/ GIP discontinuation



Other issues

20% early D/C

1% pancreatitis

↑ Med thyroid cancer

Unclear

? ↓ Lean muscle mass

(Aronne JAMA 2024;331: 38)

GLP-1/ GIP in Clinical Practice

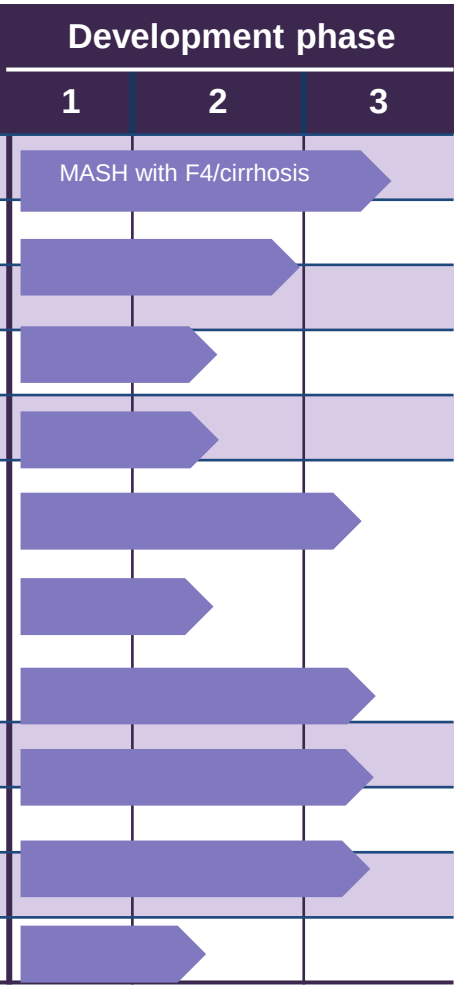
- **Semaglutide** (0.2 to 2.4 mg/wk) *
  - Approved: NIDDM, obesity, CKD, CVD
- **Tirzepatide** (2.5 to 15 mg/wk) *
  - Approved: NIDDM, obesity, sleep apnea

- **Obesity**
  - **Not covered** Blue Cross MI nor MEDICARE (4/25)
  - Self-pay: **$500**/month manufacturers

* Contraindicated: Pancreatitis, MEN II, med thyroid cancer

MASH Therapies in Development in 2025

Class	Agent	Description	Development phase
THR-β agonists	Resmetirom	THR-β agonist	MASH with F4/cirrhosis
	VK2809	THR-β agonist	
GLP-1R agonists	Semaglutide	GLP-1 agonist	
	Tirzepatide	Dual GLP1 and GIP agonist	
	Survodutide	Dual GLP-1 and GCG agonist	
	Pemvidutide	Dual GLP-1 and GCG agonist	
FGF21 agonists	Efruxifermin	FGF-21 agonist	
	Pegozafermin	FGF-21 agonist	
PPAR agonist	Lanifibranor	Pan PPAR	
FASN inhibitor	Denifanstat		



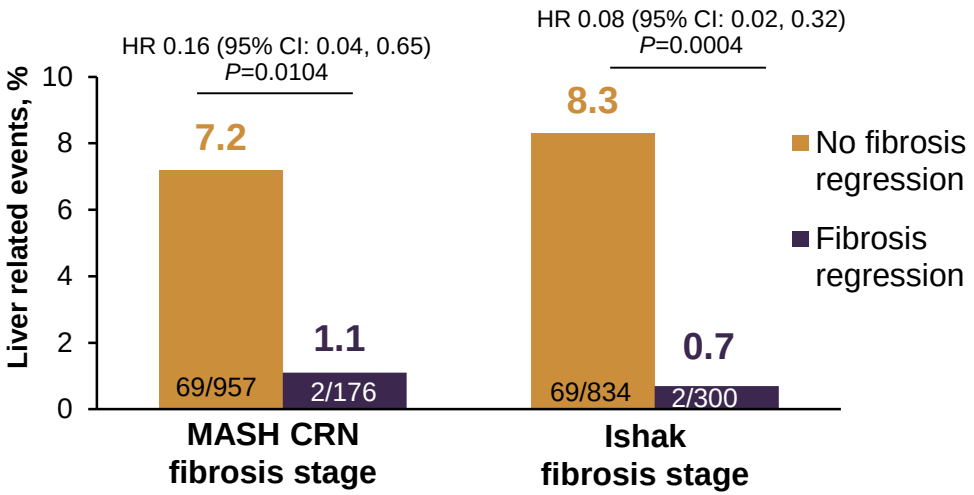
FASN, fatty acid synthase; FGF-21, fibroblast growth factor-21; GCG, glucagon receptor agonist; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide; PPAR, peroxisome proliferator-activated receptor.

National Library of Medicine. Accessed August 21, 2024. www.clinicaltrials.gov

Fibrosis Regression Leads to Improved Clinical Outcomes in MASH Cirrhosis

- MASH cirrhosis (STELLAR-4 and simtuzumab clinical trials)
  - Regression: Any reduction in fibrosis (MASH CRN or Ishak)
  - Liver-related events: ascites, portal hypertension, hemorrhage, HE, MELD >15, LT and death
- In MASH-cirrhosis, regression observed **in 16% over 48 weeks**

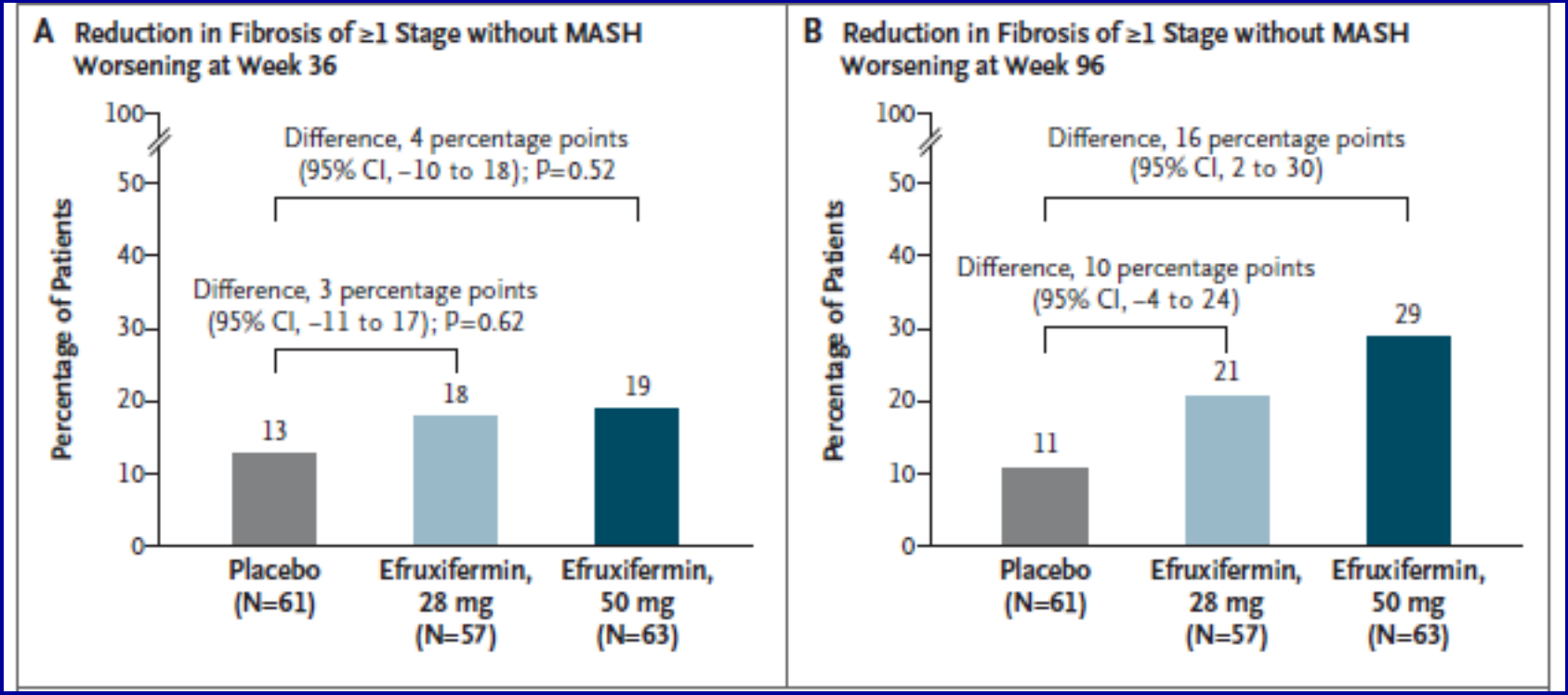
Fibrosis regression and liver-related events in MASH cirrhosis



Sanyal AJ et al. *Hepatology*. 2022;75(5):1235-1246.

FGF-21 Bivalent SQ agonist

181 MASH cirrhosis



Efficacy: Improved liver stiffness, ALT, triglycerides, HDL, LDL vs PBO
Safety: Reduced BMD, 3 decompensation events
Phase 3: Efruxifermin 50 mg/wk vs PBO (5 years)

(Noureddin NEJM 2025)

MASLD Management in 2025

- Hepatic steatosis in ~35% of Americans
  - Assess disease severity (fibrosis) with Serum biomarkers (FIB-4, ELF) & liver elastography (VCTE, MRE)
  - Quantitate hepatic steatosis (MRI PDFF, CAP)
- Lifestyle modifications for ALL
  - Goal: 5 to 10% weight loss
- Resmetirom approved for F2/F3 MASH
  - MASH resoln 29% vs 10% at 1 yr
  - GLP-1 (GIP-1) RA MASH resoln 60% vs 30% wk 72
- FGF-21 analogues show promise in MASH cirrhosis
  - Anti-fibrotic & dyslipidemic effects
  - Slow improvement (5 year trials)

Thank YOU !!!

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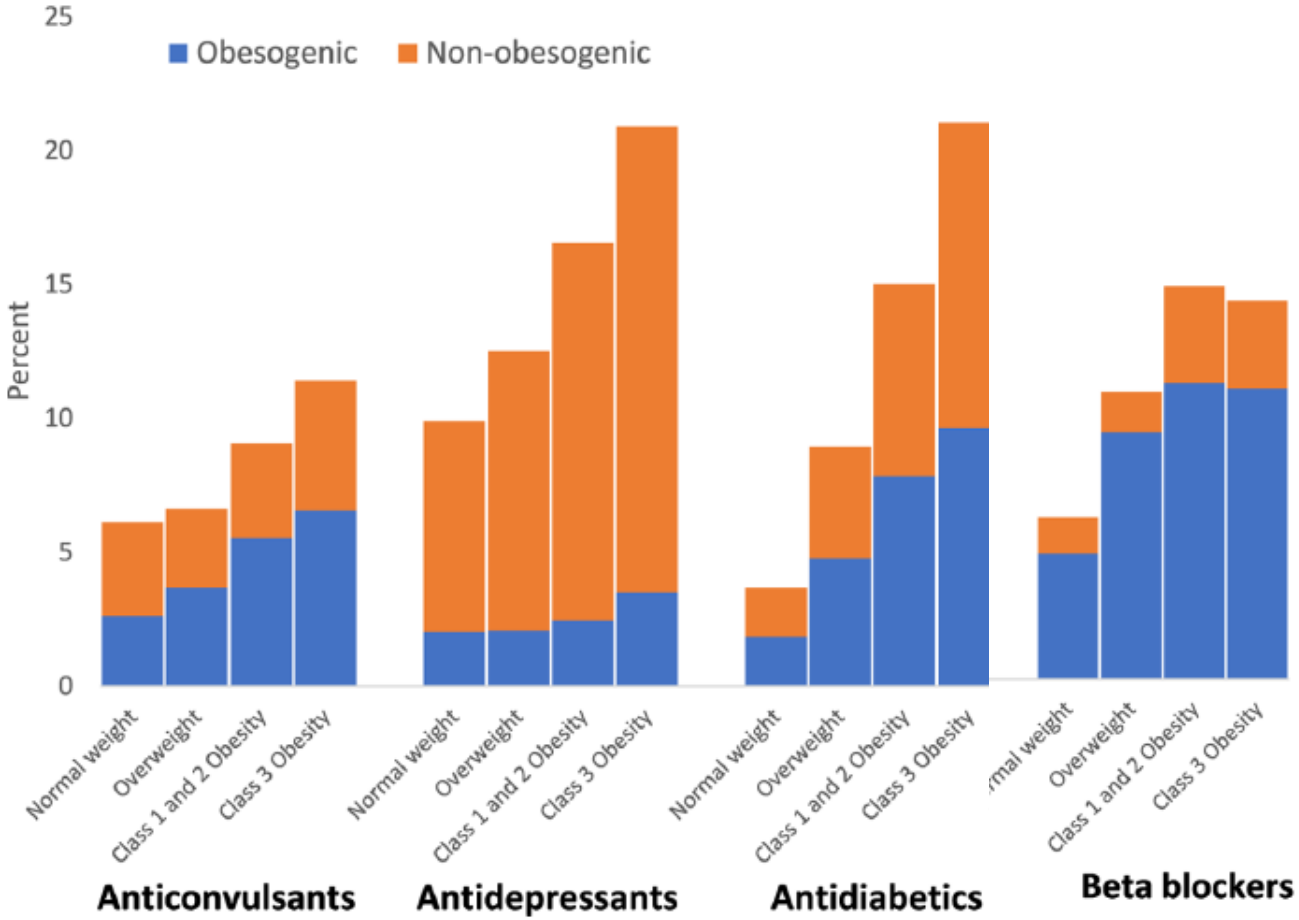
Obesogenic drug use in the US

20% of Americans NHANES '98-'18



Beta blockers

- Propranolol
- Atenolol
- Metoprolol

Antidiabetes

- Glipizide
- Glyburide
- Metformin
- Pio, rosiglitazone
- Insulin

Carbamazepine, valproate
Gabapentin, pregabalin

Paroxetine, amitriptyline
Mirtazipine, nortryptiline

(Hales Obesity 2022: 30: 229)

MASLD Cirrhosis Phase 3 Trials

Compound	Mechanism	End Points
Resmetirom (Oral)	THR-B Agonist	Liver related outcomes
Efruxifermin (SQ)	FGF21 analogue	Liver related outcomes Histology
Pegozafermin (SQ)	FGF21 analogue	Liver related outcomes Histology
Survodutide (SQ)	GCGR/ GLP-1R dual agonist	Liver related outcomes

Resmetirom: Phase 3 Safety Summary

Adverse events >10% in any group

	Resmetirom 80 mg (n=322) %	Resmetirom 100 mg (n=323) %	Placebo (n=321) %
Diarrhea	**27.0**	**33.4**	**15.6**
Covid-19	21.4	16.7	20.6
Nausea	**22.0**	**18.9**	**12.5**
Arthralgia	14.9	10.8	12.5
Back pain	10.9	8.4	11.8
Urinary tract infection	10.2	8.4	8.4
Fatigue	10.2	8.0	8.7
Pruritus	8.1	11.5	6.9
Vomiting	8.7	10.8	5.3

NOTE: Increases in mean ALT and AST (<1.5x baseline) were observed in the first 4 weeks after initiating resmetirom treatment. Values returned to baseline ~8 weeks after initiating treatment.

(Harrison SA et al. *N Engl J Med*. 2024 Feb 8;390(6):497-509)

MASLD Clinical trials 2025

	Phase	Date
Thyroid-β agonists (Oral)		
Resmetirom	3	1/28
VK2809 (ASC41)	2	6/25
GLP-1 agonists		
Semaglutide *	3	6/25
Tirzepatide * (GLP/GIP)	2	6/24
Survodutide (GLP/GCG)	2	6/24
Pemvidutide (GLP/ GCG)	2	6/26
PPARα agonists (Oral)		
Lanfibranor *	3	9/26
Saroglitazar	2	7/25
SGLT2 inhibitors		
Dapagliflozin *	3	4/24
FGF21 analogues		
Pegbelferim	2	9/21
Efruxifermin	3	5/24

(Huttasch Metabolism 2024: 157)

* FDA approved

Lifestyle Modifications in MASLD

Weight loss goals (TBW %)

Steatosis: ≥5%

- **MASH & Fibrosis: ≥10%**
- **Target: 7-10% WL**

Diet

- **Restrict saturated fat, starch, added sugar**
- **Mediterranean diet**
- **Total calories**
- **Limit ultra-processed food intake**
- **Avoid sugar-sweetened beverages**
- **> 3 cups of coffee (+/- caffeinated) daily**

Physical activity

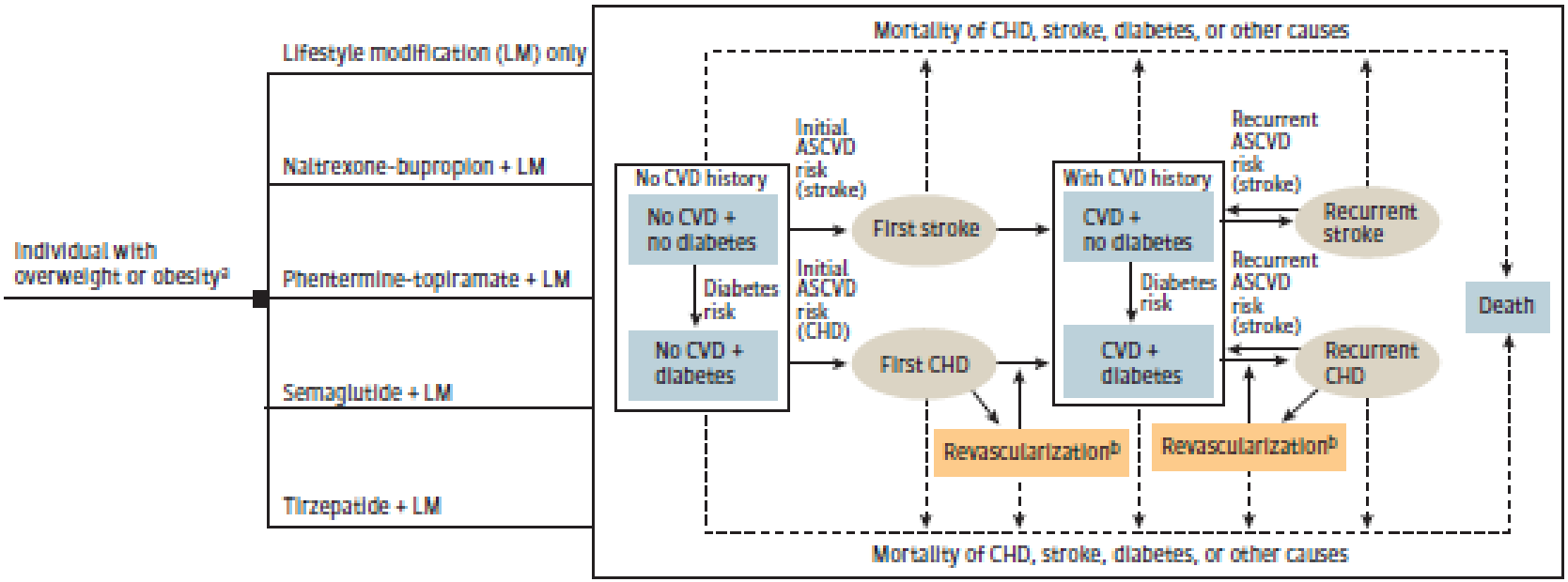
- **Structured exercise tailored to the patient's preferences**
- **Increase activity to the extent possible**
- **Swimming, walking (FIT-BIT)**
- **Exercise can reduce hepatic fat content**

Rinella et al. *Hepatology.* 2023; Tacke et al. *J Hep* 2024; 81(3):492-542; Cusi et al. *Endocrine Practice* 2022;28(5):528-62.

Obesity Meds Cost-effectiveness

126 million Americans (NHANES ‘20)

BMI = 34.7 Age=48 yrs 85% Co-morbidity



(Hwang JAMA Health For 2025: 6)

Cost-effectiveness of Obesity Meds

	Tirzepatide	Semaglutide	Naltrexone-bupropion	Phenteramine- topamax
Annual cost	$12,718	$16,188	$3,598	$2,786
↓ DM cases	20.8%	19.2%	11.5%	8.3%
↓ CVD cases	10.6%	8.3%	2.5%	4.6%
Incremental QALY gained	35%	25%	6%	14%
ICER	$197,023	$467,676	Cost- saving	$85,200

GLP-1/ GIP are NOT COST EFFECTIVE
Greatest ↓mortality if co-morbidity
If Tirzepatide $4334/yr or Semaglutide $1522/yr then cost-effective

(Hwang JAMA Health 2025; 6)

Lifestyle interventions in MASLD x 1 yr

> 5% WL ↓hep steatosis/inflam > 10% WL↓ fibrosis

Table 2. Improvement of Histologic Outcomes Across Different Categories of Weight Loss at the End of Treatment

Variables	Overall (n = 293)	WL <5 (n = 205)	WL = 5–6.99 (n = 34)	WL = 7–9.99 (n = 25)	WL ≥10 (n = 29)	*P* value
Weight loss, %	3.8 ± 2.7	1.78 ± 0.16	5.86 ± 0.09	8.16 ± 0.22	13.04 ± 6.6	—
Resolution of steatohepatitis[a]	72 (25)	21 (10)	9 (26)	16 (64)	26 (90)	<.01
NAS improvement[b]	138 (47)	66 (32)	21 (62)	22 (88)	29 (100)	<.001
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<.001
Steatosis improvement[c]	142 (48)	72 (35)	22 (65)	19 (76)	29 (100)	<.001
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<.001
Lobular inflammation improvement	147 (50)	72 (35)	24 (71)	22 (88)	29 (100)	<.001
Change from baseline	−0.49 ± 0.15	−0.29 ± 0.05	−0.53 ± 0.22	−1.32 ± 0.09	−1.21 ± 0.11	<.001
Ballooning improvement[c]	115 (39)	54 (26)	14 (41)	21 (84)	26 (90)	<.001
Change from baseline	−0.45 ± 0.17	−0.24 ± 0.04	−0.41 ± 0.13	−1.12 ± 0.13	−1.34 ± 0.08	<.001
Fibrosis status[d]						<.01
Regression	56 (19)	33 (16)	6 (18)	4 (16)	13 (45)	
Stabilized	191 (65)	129 (63)	25 (74)	21 (84)	16 (55)	
Worsened	46 (16)	43 (21)	3 (8)	0 (0)	0 (0)	
Change from baseline	−0.01 ± 0.02	0.09 ± 0.07	−0.02 ± 0.03	−0.17 ± 0.12	−0.86 ± 0.20	<.001*
Portal inflammation improvement[c]	44 (15)	27 (13)	3 (9)	5 (20)	9 (31)	.049
Change from baseline	0.02 ± 0.02	0.06 ± 0.01	0.09 ± 0.03	−0.07 ± 0.01	−0.31 ± 0.08	<.01**
NAS status						<.001
NAS ≤2	119 (41)	48 (23)	20 (59)	22 (88)	29 (100)	
NAS 3–4	79 (27)	74 (36)	2 (6)	3 (12)	0 (0)	
NAS ≥5	95 (32)	83 (41)	12 (35)	0 (0)	0 (0)	

(Vilar-Gomez Gastroenterology 2015)

Resmetirom 2 year data

(EASL 2025)