# Diabetes and Metabolic Associated Steatotic Liver Disease (MASLD) - Evaluation and Treatment

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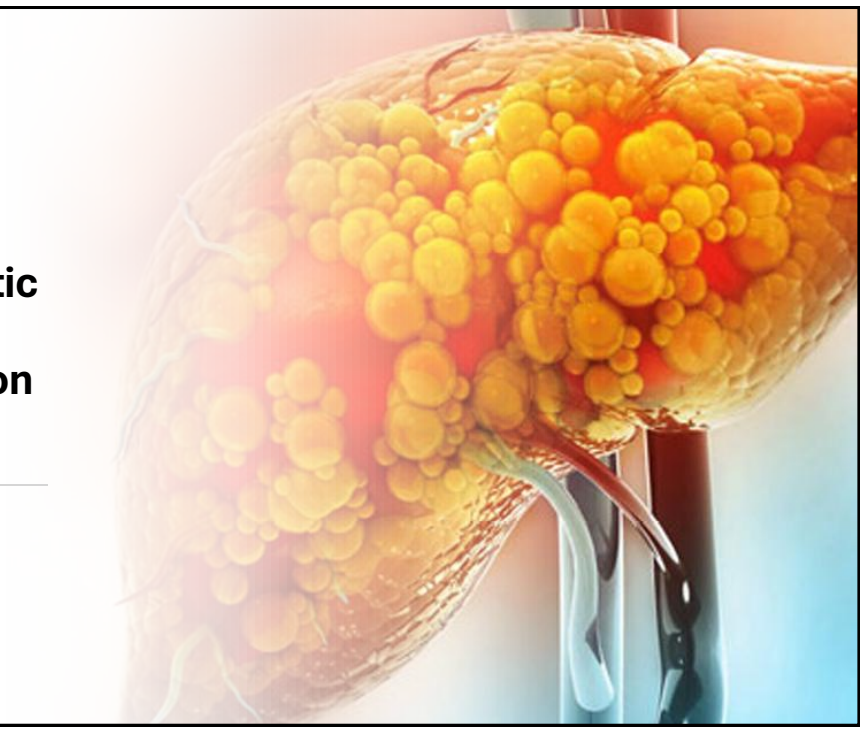

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# Disclosure

Advisory Board: Abbott; Eli Lilly; MannKind; Novo Nordisk

Consultant: Eli Lilly; Novo Nordisk

Research Grant: AbbVie; Bayer Pharmaceuticals; Eli Lilly; Novo Nordisk

Speaker's Bureau: Abbott; Eli Lilly; MannKind; Novo Nordisk

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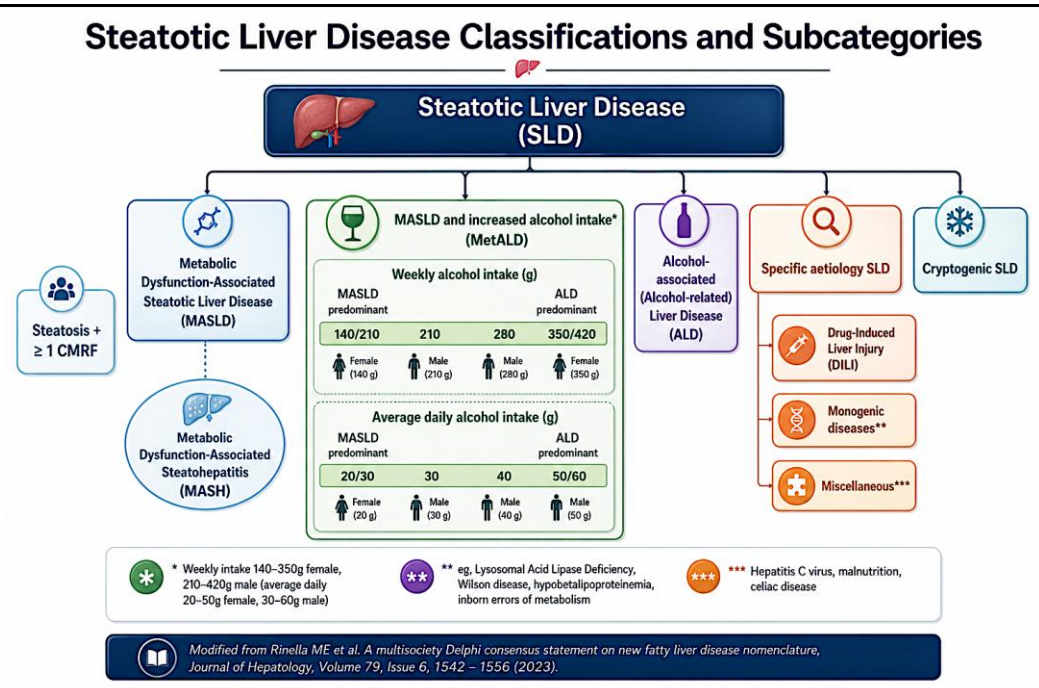


Modified from Rinella ME et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature, Journal of Hepatology, Volume 79, Issue 6, 1542 - 1556

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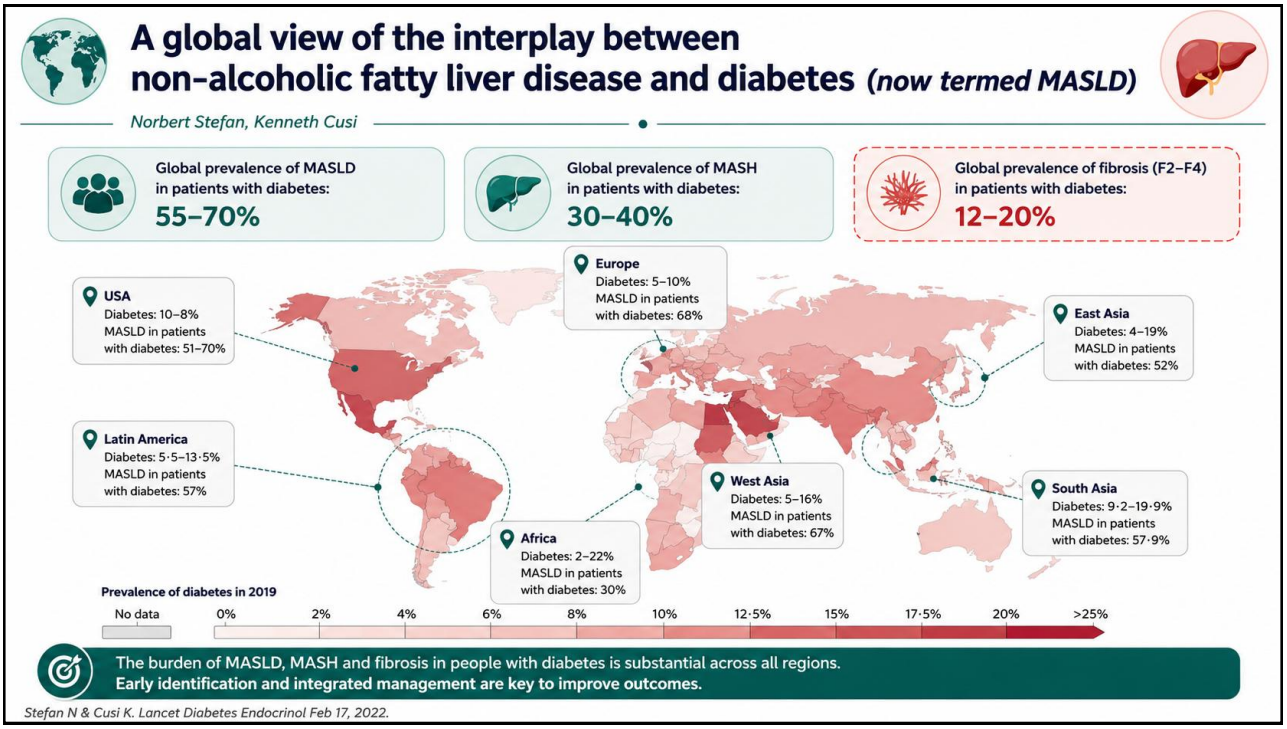
A global view of the interplay between non-alcoholic fatty liver disease and diabetes (now termed MASLD)
Norbert Stefan, Kenneth Cusi
Global prevalence of MASLD in patients with diabetes: 55–70%
Global prevalence of MASH in patients with diabetes: 30–40%
Global prevalence of fibrosis (F2–F4) in patients with diabetes: 12–20%
USA
Diabetes: 10–8%
MASLD in patients with diabetes: 51–70%
Europe
Diabetes: 5–10%
MASLD in patients with diabetes: 68%
East Asia
Diabetes: 4–19%
MASLD in patients with diabetes: 52%
Latin America
Diabetes: 5·5–13·5%
MASLD in patients with diabetes: 57%
West Asia
Diabetes: 5–16%
MASLD in patients with diabetes: 67%
South Asia
Diabetes: 9·2–19·9%
MASLD in patients with diabetes: 57·9%
Africa
Diabetes: 2–22%
MASLD in patients with diabetes: 30%
Prevalence of diabetes in 2019
No data
0% 2% 4% 6% 8% 10% 12·5% 15% 17·5% 20% >25%
The burden of MASLD, MASH and fibrosis in people with diabetes is substantial across all regions.
Early identification and integrated management are key to improve outcomes.
Stefan N & Cusi K. Lancet Diabetes Endocrinol Feb 17, 2022.

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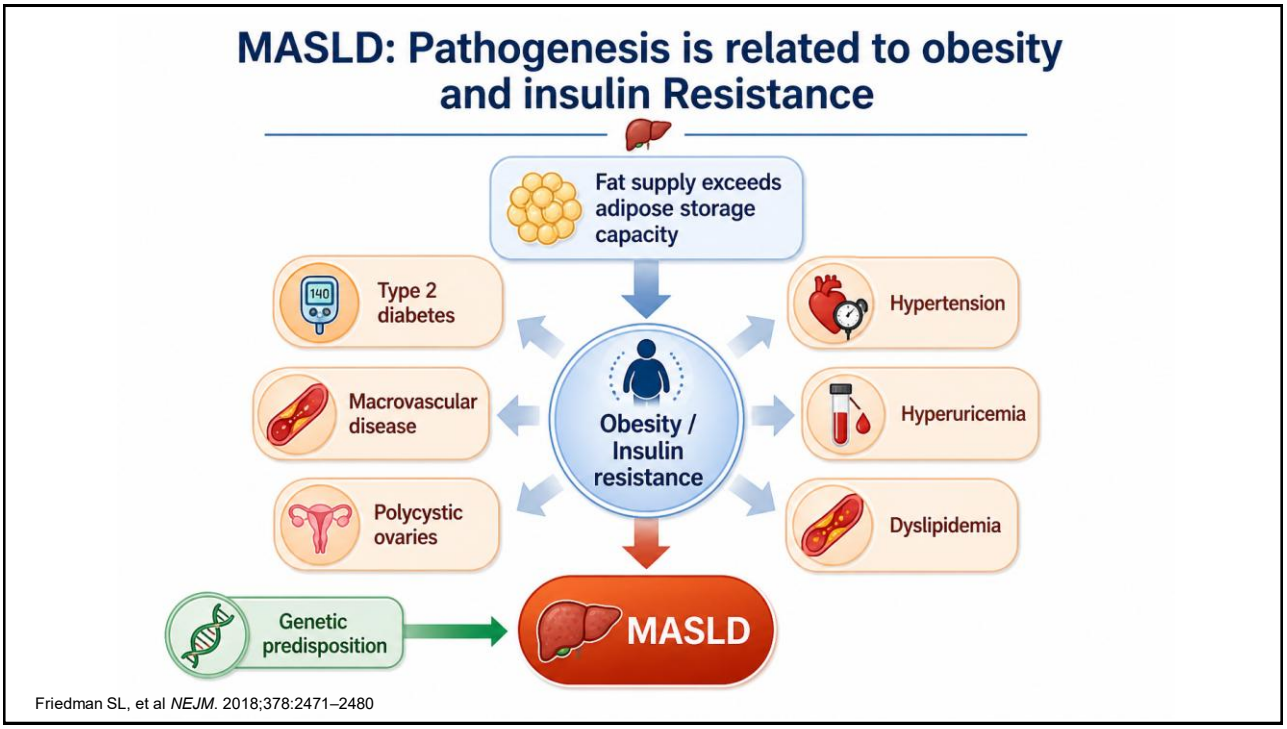
MASLD: Pathogenesis is related to obesity and insulin Resistance
Fat supply exceeds adipose storage capacity
Type 2 diabetes
Hypertension
Macrovascular disease
Obesity / Insulin resistance
Hyperuricemia
Polycystic ovaries
Dyslipidemia
Genetic predisposition
MASLD
Friedman SL, et al NEJM. 2018;378:2471–2480

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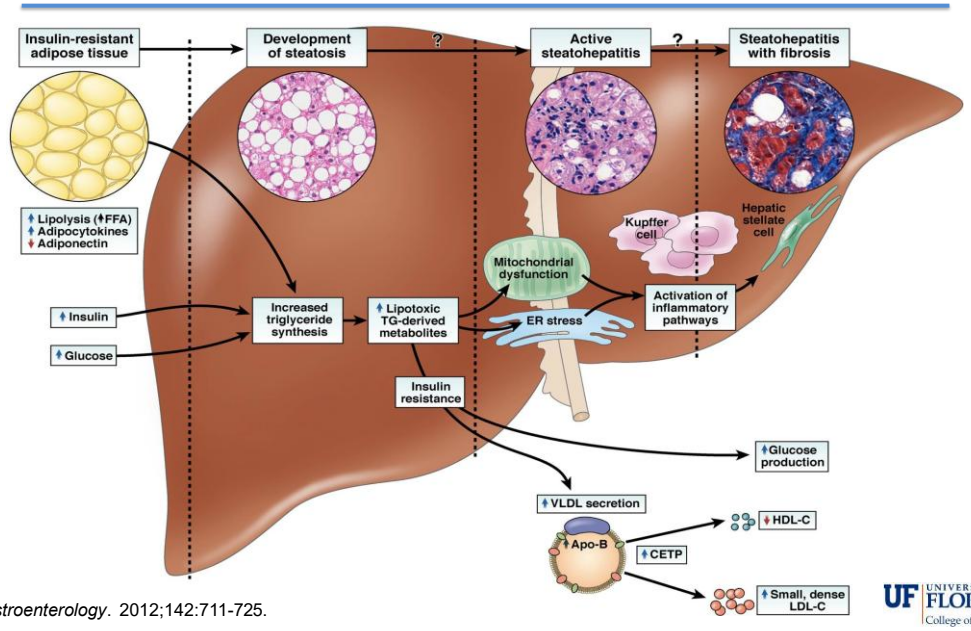
## From Obesity and T2D to MASH with Cirrhosis




Cusi K. *Gastroenterology*. 2012;142:711-725.

UF UNIVERSITY of FLORIDA College of Medicine

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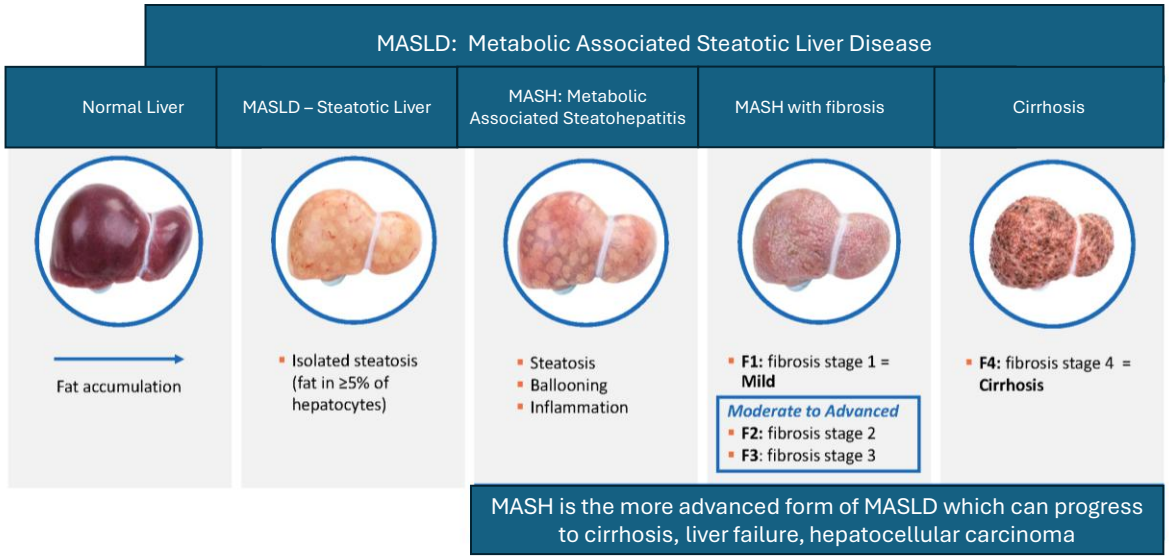
## MASLD Is a Chronic and Progressive Liver Disease




**Hepatocytes,** liver cells. **Steatosis,** excess fat in liver cells. **Steatohepatitis,** build up of excess fat in liver cells causing inflammation and damage.

1. Sheka AC, et al. JAMA. 2020;323(12):1175-83. 2. Alkhouri N, McCullough AJ. Gastroenterol Hepatol (N Y). 2012;8(10):661-8. 3. EASL–EASD–EASO. J Hepatol. 2016;64:1388-402. 4. Diehl AM, Day C. NEJM. 2017;377:3063-72. 5. Honda et al. Int J Mol Sci. 2020;21:4039.

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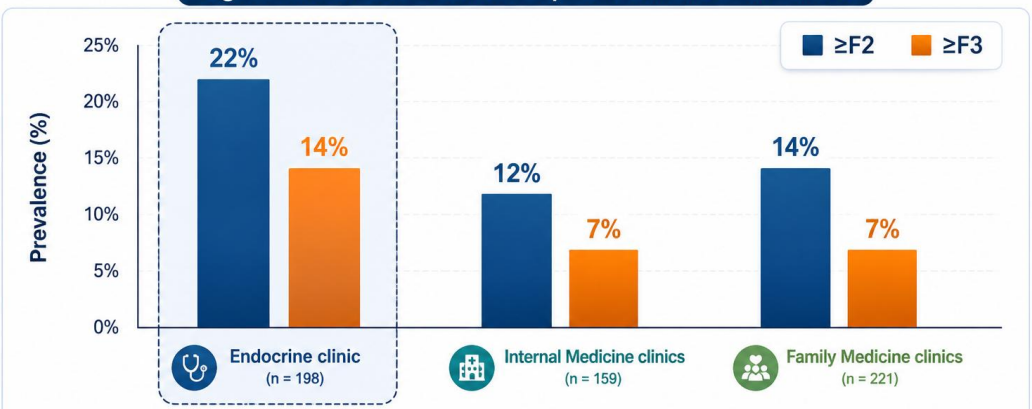
## Prevalence of Significant Liver Fibrosis in People with Obesity + Type 2 Diabetes and MASLD in the Outpatient Setting

**Significant liver fibrosis was most prevalent in endocrine clinics.**




Total number = 578 participants with obesity and type 2 diabetes mellitus (65% of all people with T2D).

From Endocrine clinics (Endo) n = 198; Internal Medicine clinics (IM) n = 159; Family Medicine clinics (FM) n = 221.

Zobair M et al. *Endocrine Practice* (2023)

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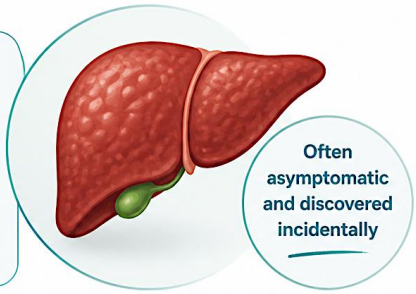
## How does MASLD Present?

### Symptoms

- Usually asymptomatic; majority discovered by chance
- Fatigue frequently present
- Right upper quadrant discomfort




### Often an "Incidental Finding"

- Incidental abnormal LFTs
- Incidental "bright liver" on imaging
- Incidental hepatomegaly

Early detection through screening and routine evaluation is key to preventing progression.

De Alwis. *Dig Dis.* 2016;34:19.

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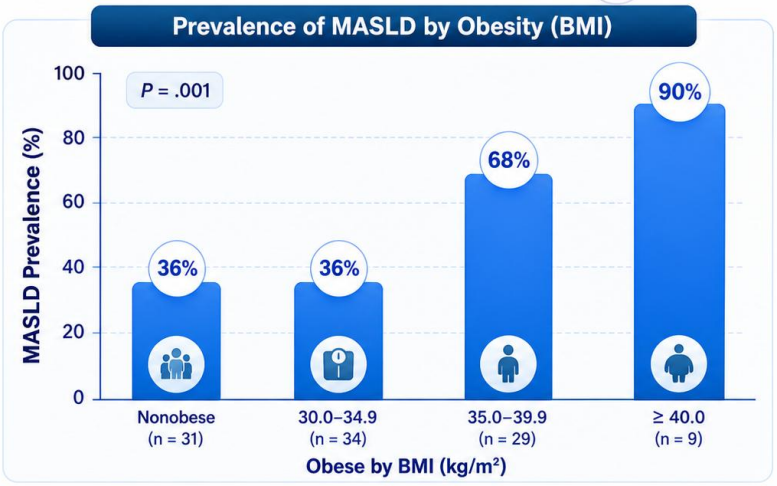
# Prevalence of MASLD in Patients with T2DM and Normal AST/ALT




Patients with T2DM and normal AST or ALT evaluated for liver triglyceride content by H-MRS, insulin sensitivity, and adipose tissue insulin resistance (N = 103)

**Prevalence of MASLD in overall cohort:** **50%**

Among these patients, prevalence of MASH: **56%**

Paola Portillo-Sanchez et al. *J Clin Endocrinol & Metab* (2015)

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# Why is it imperative to diagnose MASLD?

**High prevalence:** ~25–38% of U.S. adults (≈100M people)

**Silent disease:** majority asymptomatic, normal AST/ALT common

**All stages of MASLD** are associated with increased risk for other comorbidities (T2D, CVD, CKD, cancers)

**Fibrosis drives outcomes:** ≥F2 linked to ↑ liver-related & all-cause mortality

**Actionable:** noninvasive screening (FIB-4 → elastography) identifies high-risk patients

**Treatment era:** lifestyle, GLP-1 RAs, and resmetirom for MASH with fibrosis

**Early identification and intervention can prevent progression and improve liver and cardiometabolic outcomes.**

Alqahtani SA et al. Hepatol Commun. 2021; Rinella ME et al. Hepatology. 2023; Kanwal F et al. Gastroenterology. 2026

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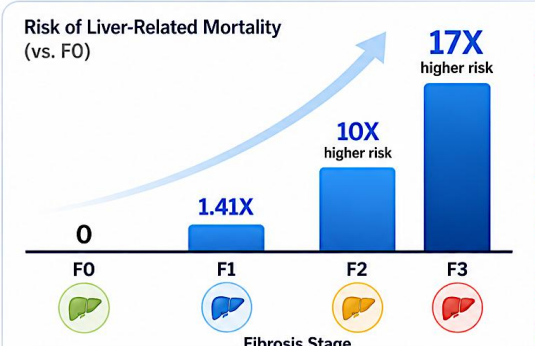
# Goal: Treat Before Major Adverse Liver Outcomes Occur

**Up to 17X Higher Risk of Liver-Related Mortality in Patients with MASH with Moderate to Advanced Fibrosis[1]**




**~22%** of patients with F3 fibrosis progress to cirrhosis within 2 years[2]

**Goal:** Treat MASH with moderate to advanced fibrosis **before negative patient outcomes occur**

1. Angulo P, et al. Gastroenterology. 2015;149:389-397. | 2. Loomba R, Adams L. Hepatology. 2019;70(6):1885-1888.

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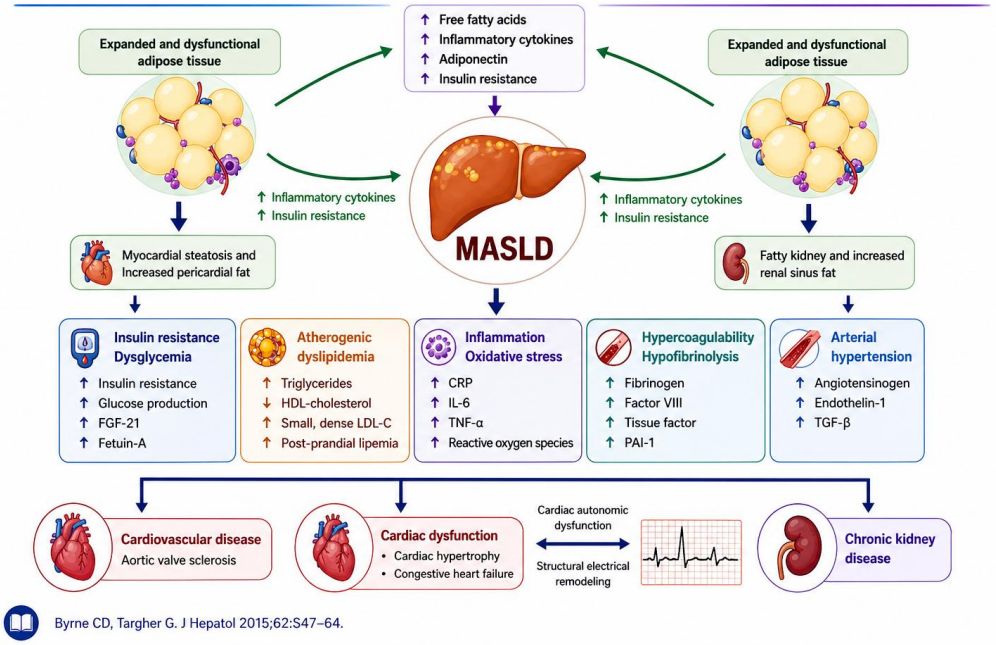
# Putative connection between MASLD, CVD and CKD




Byrne CD, Targher G. J Hepatol 2015;62:S47–64.

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# MASH Screening

## WHO TO SCREEN

- **T2DM/insulin resistance**
- **Obesity** with 1 or more metabolic risk factor
- **Hepatic steatosis** or abnormal LFTs

## HOW TO SCREEN (NON-INVASIVE)

- **FIB-4**
- **Enhanced Liver Fibrosis Score (ELF)**
- **Fibroscan (VCTE)**

**Early identification of patients at risk for advanced fibrosis allows timely intervention to prevent progression and improve outcomes.**

FIB-4 = Fibrosis-4 Index; ELF = enhanced liver fibrosis test; VCTE = vibration-controlled transient elastography

Kanwal F, et al. *Gastroenterology* 2026 (online ahead of print) DOI: 10.1053/j.gastro.2026.01.047

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# Limitations of FIB-4 for Screening in MASLD

*Important constraints that limit FIB-4 as a stand-alone screening test*

### 1. Large Indeterminate Range

Large numbers report in the indeterminate range → requires second-line testing

### 2. Age-Related Misclassification

False positives in older adults; reduced sensitivity in < 35

### 3. Does Not Screen for Early Fibrosis

Limited ability to detect early (stages F0–F1) disease

### 4. Susceptible to Confounders

AST/ALT (alcohol, muscle), platelets (inflammation) can skew results

### 5. Not Disease-Specific

Cannot distinguish MASLD from other chronic liver diseases

### 6. Unreliable in Acute Illness

Reduced reliability due to laboratory variability and acute inflammatory states

**CLINICAL IMPLICATION:** AASLD recommends FIB-4 as a first-line triage tool, not stand-alone screening; **requires confirmatory testing** (e.g., elastography, ELF, or other validated assessments)

AASLD Practice Guidance (2023–2024) | EASL Guidelines (2021–2024) | Sterling et al. Hepatology 2006
McPherson et al. Gut 2017 | Castera et al. J Hepatol 2019

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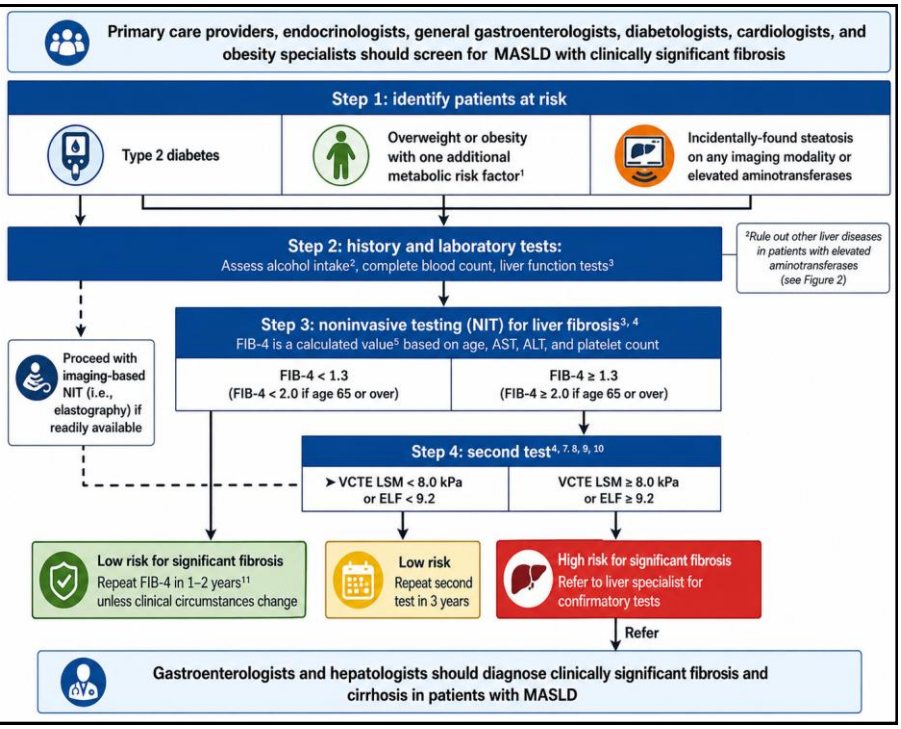
# AGA MASLD Clinical Care Pathway




Adapted from Kanwal F, et al. *Gastroenterology* 2026 (online ahead of print) DOI: 10.1053/j.gastro.2026.01.047

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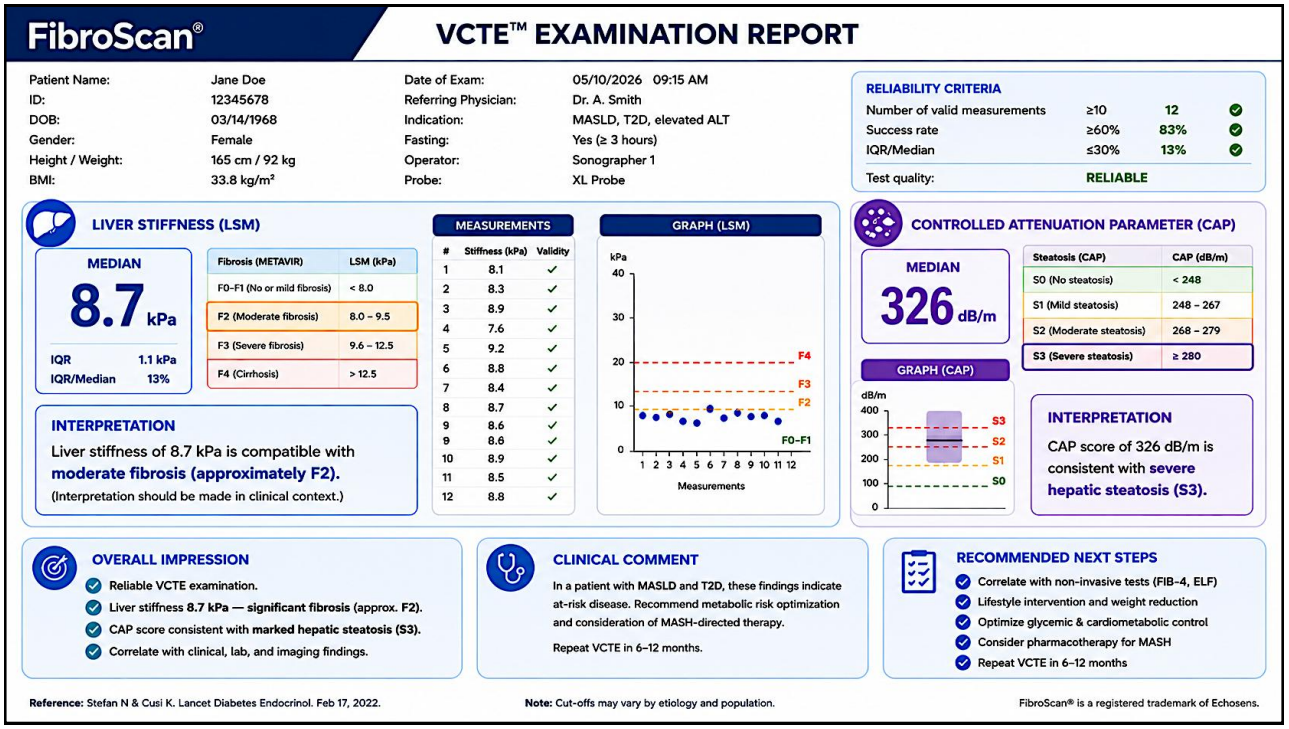
FibroScan®
VCTE™ EXAMINATION REPORT
Patient Name: Jane Doe
ID: 12345678
DOB: 03/14/1968
Gender: Female
Height / Weight: 165 cm / 92 kg
BMI: 33.8 kg/m²
Date of Exam: 05/10/2026 09:15 AM
Referring Physician: Dr. A. Smith
Indication: MASLD, T2D, elevated ALT
Fasting: Yes (≥ 3 hours)
Operator: Sonographer 1
Probe: XL Probe
RELIABILITY CRITERIA
Number of valid measurements ≥10 12
Success rate ≥60% 83%
IQR/Median ≤30% 13%
Test quality: RELIABLE
LIVER STIFFNESS (LSM)
MEDIAN
8.7 kPa
IQR 1.1 kPa
IQR/Median 13%
Fibrosis (METAVIR) LSM (kPa)
F0–F1 (No or mild fibrosis) < 8.0
F2 (Moderate fibrosis) 8.0 – 9.5
F3 (Severe fibrosis) 9.6 – 12.5
F4 (Cirrhosis) > 12.5
INTERPRETATION
Liver stiffness of 8.7 kPa is compatible with moderate fibrosis (approximately F2).
(Interpretation should be made in clinical context.)
MEASUREMENTS
# Stiffness (kPa) Validity
1 8.1
2 8.3
3 8.9
4 7.6
5 9.2
6 8.8
7 8.4
8 8.7
9 8.6
9 8.6
10 8.9
11 8.5
12 8.8
GRAPH (LSM)
kPa
F4
F3
F2
F0–F1
Measurements
CONTROLLED ATTENUATION PARAMETER (CAP)
MEDIAN
326 dB/m
Steatosis (CAP) CAP (dB/m)
S0 (No steatosis) < 248
S1 (Mild steatosis) 248 – 267
S2 (Moderate steatosis) 268 – 279
S3 (Severe steatosis) ≥ 280
GRAPH (CAP)
dB/m
S3
S2
S1
S0
INTERPRETATION
CAP score of 326 dB/m is consistent with severe hepatic steatosis (S3).
OVERALL IMPRESSION
Reliable VCTE examination.
Liver stiffness 8.7 kPa — significant fibrosis (approx. F2).
CAP score consistent with marked hepatic steatosis (S3).
Correlate with clinical, lab, and imaging findings.
CLINICAL COMMENT
In a patient with MASLD and T2D, these findings indicate at-risk disease. Recommend metabolic risk optimization and consideration of MASH-directed therapy.
Repeat VCTE in 6–12 months.
RECOMMENDED NEXT STEPS
Correlate with non-invasive tests (FIB-4, ELF)
Lifestyle intervention and weight reduction
Optimize glycemic & cardiometabolic control
Consider pharmacotherapy for MASH
Repeat VCTE in 6–12 months
Reference: Stefan N & Cusi K. Lancet Diabetes Endocrinol. Feb 17, 2022.
Note: Cut-offs may vary by etiology and population.
FibroScan® is a registered trademark of Echosens.

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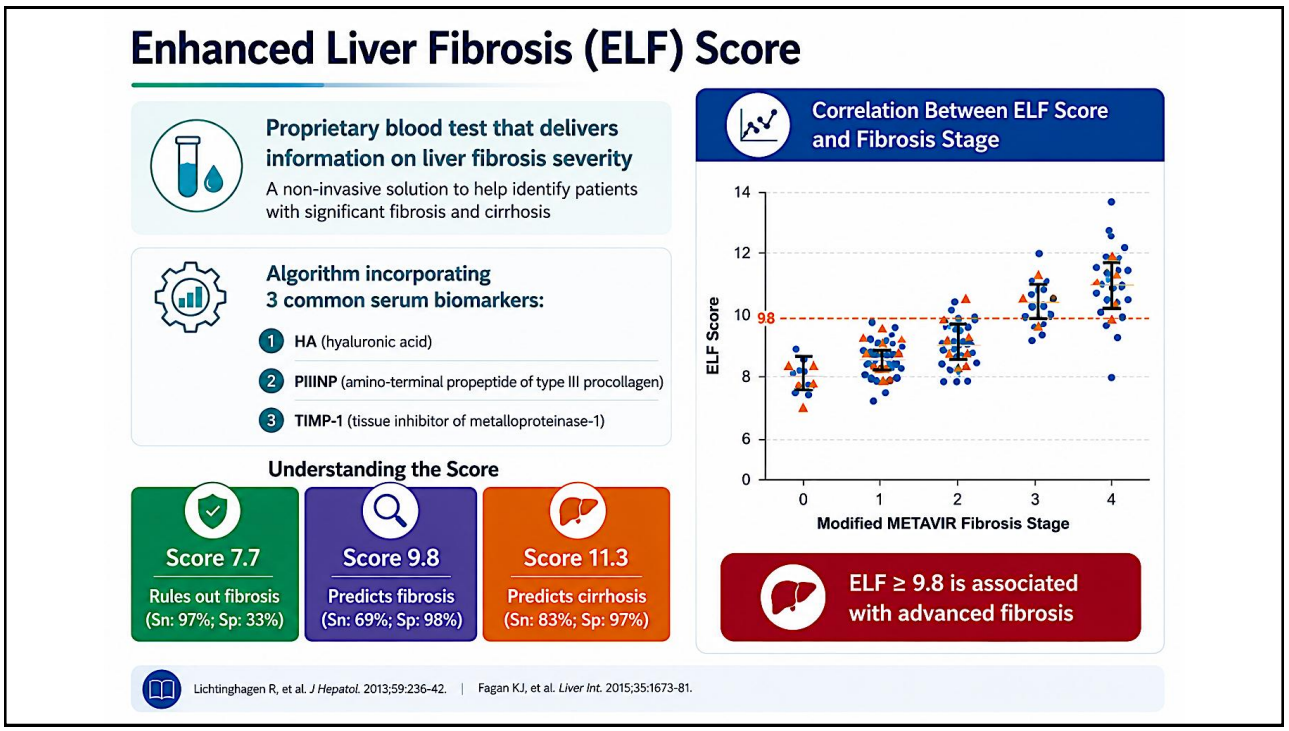
Enhanced Liver Fibrosis (ELF) Score
Proprietary blood test that delivers information on liver fibrosis severity
A non-invasive solution to help identify patients with significant fibrosis and cirrhosis
Algorithm incorporating 3 common serum biomarkers:
1 HA (hyaluronic acid)
2 PIIINP (amino-terminal propeptide of type III procollagen)
3 TIMP-1 (tissue inhibitor of metalloproteinase-1)
Understanding the Score
Score 7.7
Rules out fibrosis
(Sn: 97%; Sp: 33%)
Score 9.8
Predicts fibrosis
(Sn: 69%; Sp: 98%)
Score 11.3
Predicts cirrhosis
(Sn: 83%; Sp: 97%)
Correlation Between ELF Score and Fibrosis Stage
ELF Score
9.8
Modified METAVIR Fibrosis Stage
ELF ≥ 9.8 is associated with advanced fibrosis
Lichtinghagen R, et al. J Hepatol. 2013;59:236-42. | Fagan KJ, et al. Liver Int. 2015;35:1673-81.

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# Role of ELF in Clinical Algorithms

## GUIDELINE-BASED APPROACH (AASLD/EASL)

**STEP 1**

**FIB-4 (rule-out)**

Use FIB-4 to identify patients at low risk for advanced fibrosis

**STEP 2**

**ELF or VCTE (risk stratification)**

Use ELF or VCTE to further stratify risk of advanced fibrosis

## BEST USE CASES FOR ELF

**1. INDETERMINATE FIB-4**

Clarify risk in patients with indeterminate FIB-4 results

**2. FAILED OR UNRELIABLE VCTE**

Useful when VCTE is not feasible, failed, or results are unreliable

**3. LONGITUDINAL MONITORING**

Track changes in fibrosis over time to monitor disease progression or treatment response

AASLD 2023–2024 | EASL 2021–2024 | Newsome PN J Hepatol 2020 | Vali Y BMJ 2020 | Day JW Hepatology 2021

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# Testing to rule out other causes of liver disease

**VIRAL HEPATITIS PANELS:** Hepatitis B surface antigen (HBsAg) and Hepatitis C antibody (anti-HCV)

**ALCOHOL HISTORY & TESTING: IRON STUDIES:** Serum iron, total iron-binding capacity (TIBC), and ferritin are used to rule out hereditary hemochromatosis.

**AUTOIMMUNE MARKERS:** Antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and sometimes anti-liver kidney microsome (LKM) antibodies for autoimmune hepatitis.

**METABOLIC & GENETIC SCREEN:** Ceruloplasmin (for Wilson's disease, especially in younger patients)

**THYROID FUNCTION TESTS:** Thyroid-stimulating hormone (TSH) to rule out hypothyroidism

Newsome PN, et al. *Gut* (2018) DOI: 10.1136/gutjnl-2017-314924

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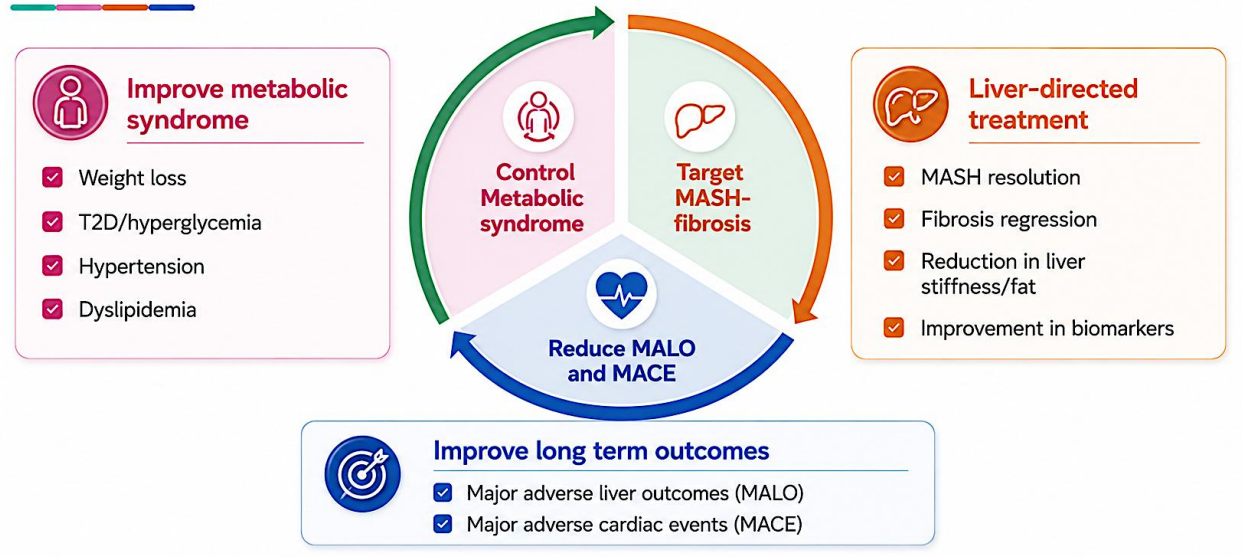
# The Goals for MASH Management




Ref: Finney AC et al. Front Cardiovasc Med. 2023 May 2;10:1116861. | Younossi ZM et al. Hepatol Commun. 2023 Dec 22;8(1):e0352. | Targher G et al. Gut. 2024 Mar 7;73(4):691-702.

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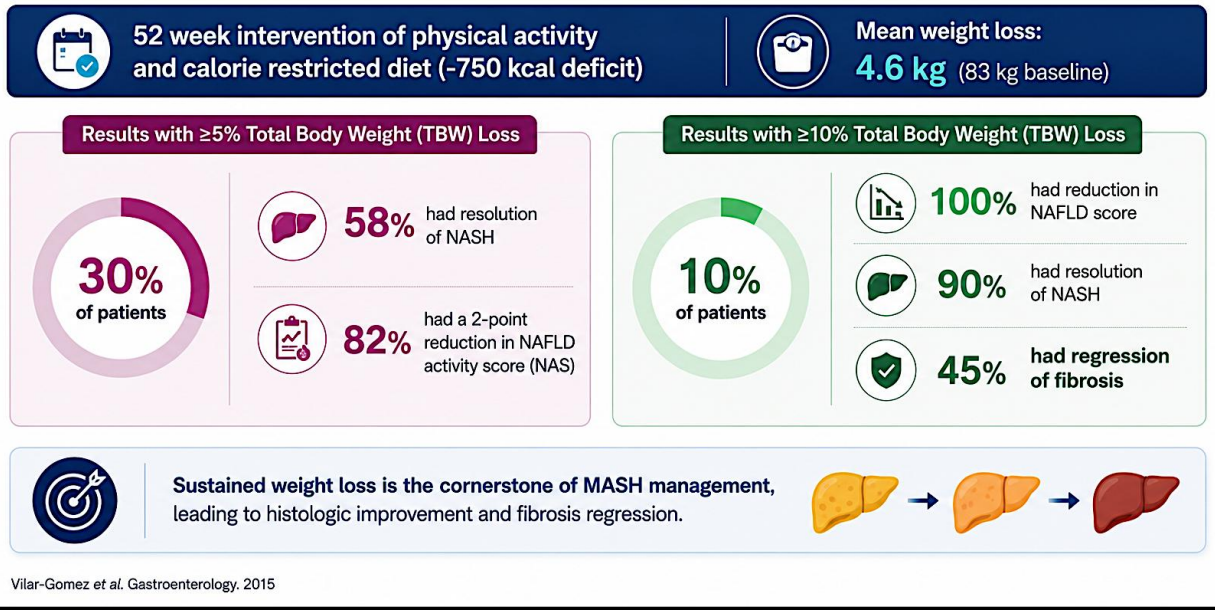
# Management of NAFLD/NASH: Weight Loss




Vilar-Gomez *et al.* Gastroenterology. 2015

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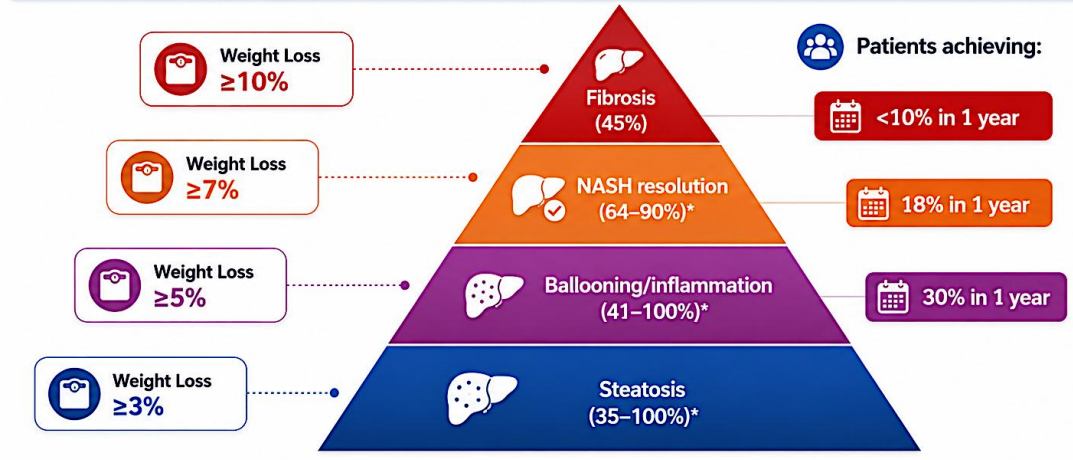
# Lifestyle Therapy for MASLD

**Sustained weight loss** is the foundation of MASLD management and is associated with resolution of steatosis, inflammation, and fibrosis.




Vilar-Gomez E, et al. *Gastroenterology*. 2015;149:367–378. | Promrat K, et al. *Hepatology*. 2010;51:121–129. | Harrison SA, et al. *Hepatology*. 2009;49:80–86. | Wong VWS, et al. *J Hepatol*. 2013;59:536–54.

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# Mediterranean Diet in NAFLD: Observational Study

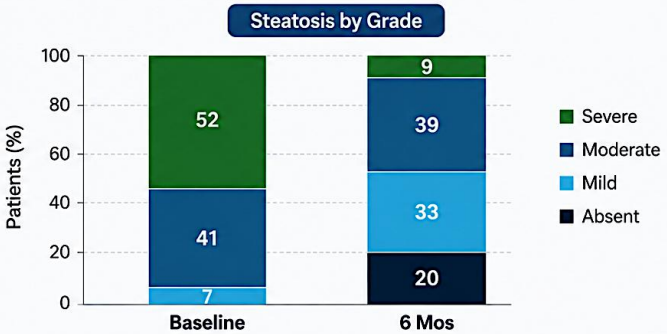
## DESIGN

6-month observational study of **Mediterranean diet** intervention with monthly nutrition counseling in patients with NAFLD

N = 46

## RESULTS

Frequency of grade ≥ 2 steatosis decreased in **> 80%**, with resolution in **20%**




*Gelli. World J Gastroenterol.* 2017;23:3150.

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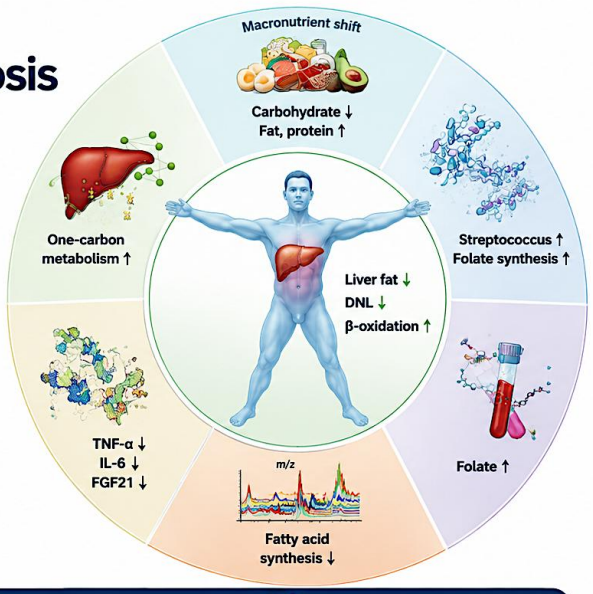
# Carbohydrate Restriction has Rapid Benefits in Hepatic Steatosis

**14 day study of low carbohydrate diet on liver fat content (by MRS)**

- **10 obese subjects** with high liver fat
- **Diet:** <30 gm CHO, isocaloric to minimize impact of weight loss
- **Weight loss:** 1.8%
- **Mean reduction of liver fat:** 43.8%
- **Returned to baseline** 1 – 3 mos

**43.8%** Reduction in liver fat




Short-term carbohydrate restriction rapidly reduces liver fat and favorably modulates metabolic, inflammatory and microbial pathways.

Rapid metabolic benefits beyond weight loss.

*Mardinoglu, A et al. 2018, Cell Metabolism 27, 559–571*

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# Is there an optimal diet for MASLD?

**Mediterranean diet**

good choice for a balanced diet with **strong evidence for benefit**

**Low carbohydrate diets**

are effective in the short term, but **adherence** is difficult and **long-term data are lacking**

Avoidance of **added sugars** (especially fructose in beverages) is **recommended**. None of the diets have evidence of consistent superiority.

Key is likely to be **patient preference and adherence.**

Rinella M et al. *Hepatology* 2023

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# Exercise in MASLD:
## *Effect on Liver Fat and ALT*

**28 randomized trials**
of exercise-based interventions in patients with NAFLD and underlying metabolic disorders (N = 1644)

**Reduction in intrahepatic lipid content**

Standardized mean difference:
**-0.69**
(95% CI: -0.90 to -0.48)

**Reduction in ALT**

ALT → ALT

Weighted mean difference:
**-3.30 IU/L**
(95% CI: -5.57 to -1.04)

Regular exercise is associated with significant reductions in liver fat and ALT in patients with MASLD.

*Orci. Clin Gastroenterol Hepatol. 2016;14:1398.*

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# Lifestyle Modification in Fatty Liver Disease: EASL Multidisciplinary Clinical Practice Guideline

**Energy restriction**
- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

**Fructose intake**
- Avoid fructose-containing food and drink

**Coffee consumption**
- No liver-related limitations

**Comprehensive lifestyle approach**

**Daily alcohol intake**
- Strictly below 30 g men and 20 g women

**Macronutrient composition**
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein
- Mediterranean diet is suggested

**Physical activity**
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

EASL–EASD–EASO CPG NAFLD. *J Hepatol* 2016; 64:1388–402

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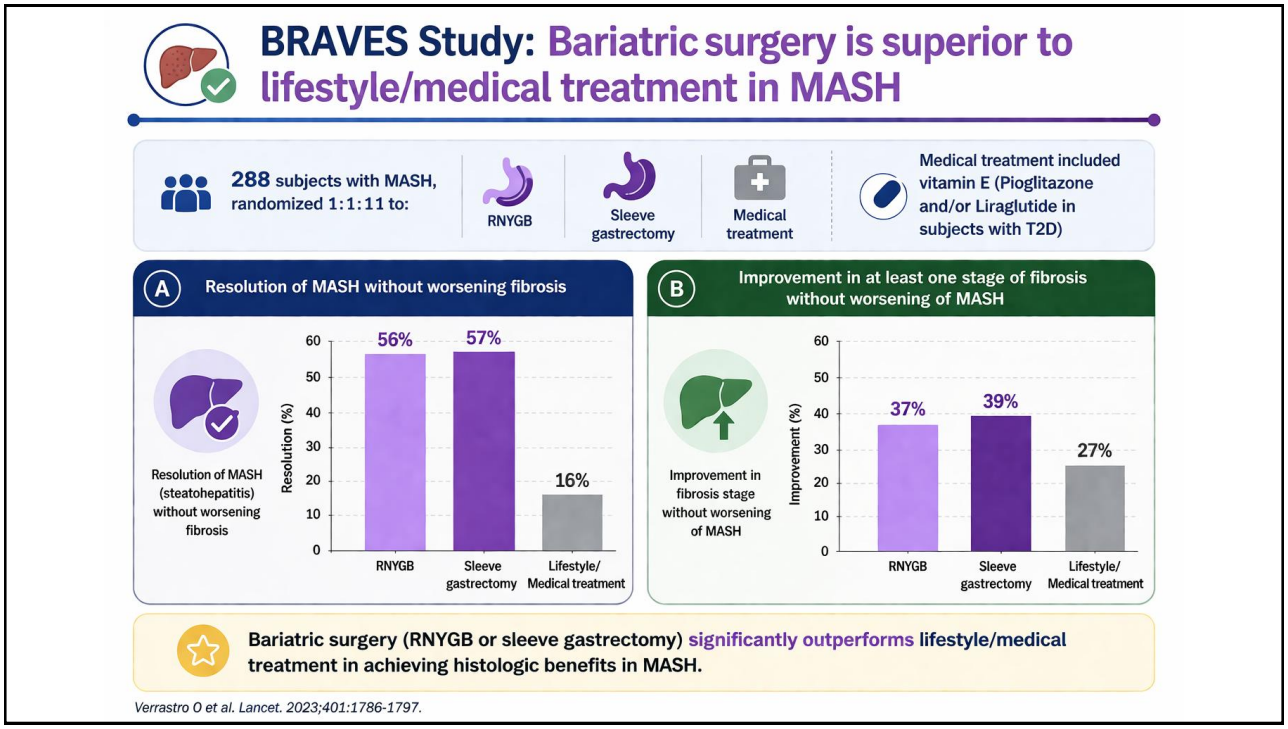


*Verrastro O et al. Lancet. 2023;401:1786-1797.*

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# Medications to treat diabetes and their efficacy in MASLD

| Medication | Liver fat | Disease activity (steatohepatitis/NAS) |
|---|---|---|
| Metformin | Unchanged | Neutral |
| Pioglitazone | Decreased | Improved[a] |
| Insulin | Decreased | Effect unknown |
| GLP-1 RAs (semaglutide and liraglutide) | Decreased | Improved[a] |
| SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin) | Decreased | Effect unknown |
| DPP-IV inhibitors (sitagliptin and vildagliptin) | Unchanged (in RCTs) | Effect unknown |

[a] *Improvement in some histological features, but not consistently in all studies.*

Chan W et al. *J Obes Metab Syndr* 2023; 32: 197-213

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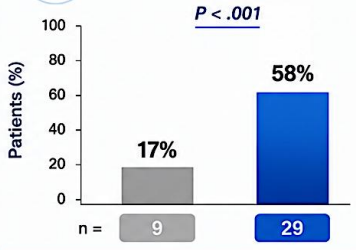
# Pioglitazone in NASH With Prediabetes/T2D: 18-Mo Outcomes *(not approved for MASH)*

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

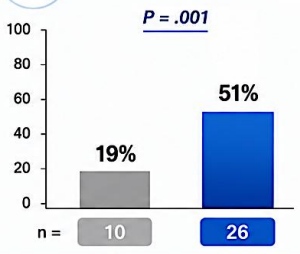
Placebo (N = 51)
Pioglitazone 45 mg QD (N = 50)

**PRIMARY ENDPOINTS AT 18 MONTHS**

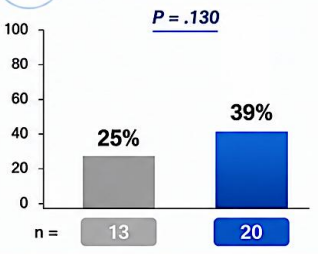
**≥ 2-Point Reduction in NAS (No Worsening of Fibrosis)**




**Resolution of NASH**




**≥ 1-Point Improvement in Fibrosis**




Pioglitazone 45 mg daily significantly improved liver histology in patients with NASH and prediabetes/T2D, including greater **reduction in NAS** and higher rates of **NASH resolution**.

[1] *Cusi. Ann Intern Med. 2016;165:305.*

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# SGLT-2 Inhibitors: Effects on Liver Fat and Measures of Fibrosis *(not approved for MASH)*

## LIVER FAT

SGLT-2 inhibitors consistently **reduce liver fat independent** of weight loss.

- Significant reductions in liver fat (MRI-PDFF) demonstrated in multiple randomized controlled trials.
- Effects on liver fat occur even with **minimal or no weight loss.**
- Consistent improvements observed across different SGLT-2 inhibitors.

## FIBROSIS (NONINVASIVE MEASURES)

SGLT-2 inhibitors show **favorable effects** on measures of fibrosis.

- Significant **reductions in liver stiffness** measured by transient elastography (VCTE).
- Decreases in serum **fibrosis biomarkers** (e.g., Pro-C3, PIIINP).
- Suggested **antifibrotic potential**, though histologic data are limited.

**KEY TAKEAWAY:** SGLT-2 inhibitors reduce liver fat independent of weight loss and improve noninvasive measures of fibrosis, supporting their role as a **promising therapy in MASLD.**

*Sources: Armstrong MJ, et al. J Hepatol. 2023;79:1351–1366.*
*Zelber-Sagi S, et al. Liver Int. 2024;44:1179–1196.*

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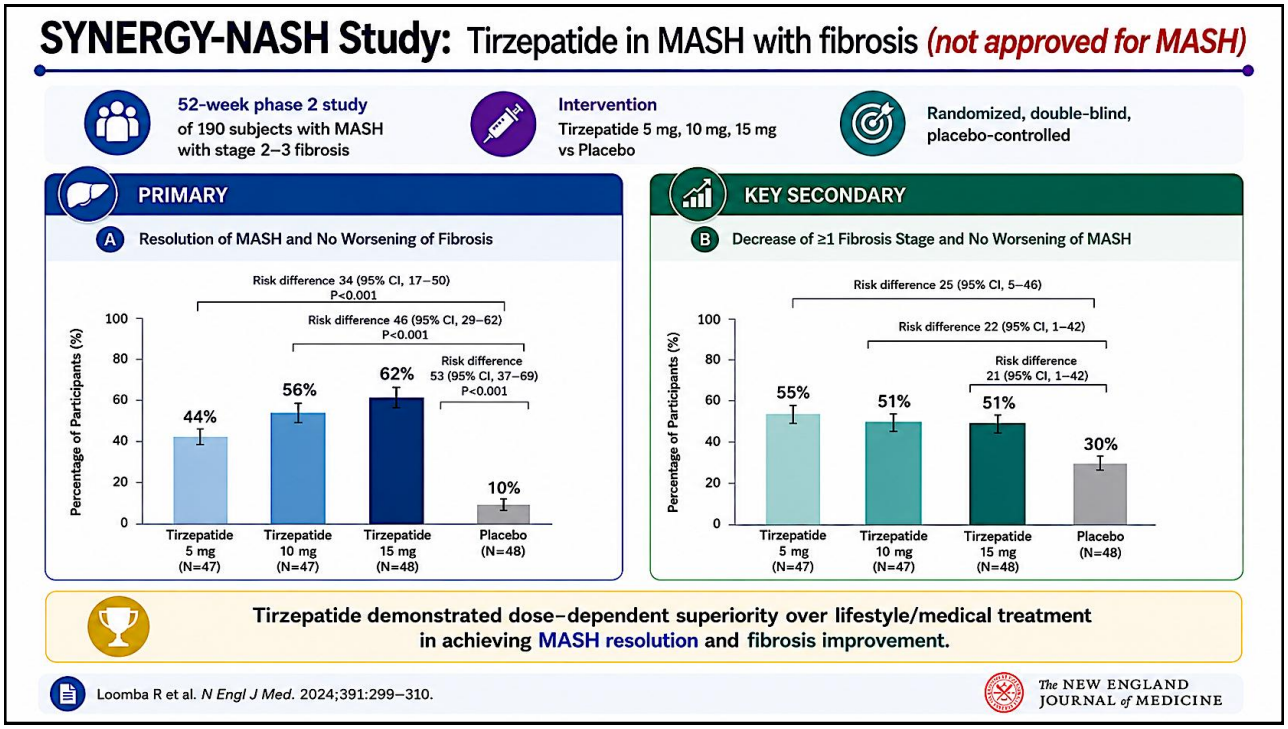
SYNERGY-NASH Study: Tirzepatide in MASH with fibrosis (not approved for MASH)
52-week phase 2 study
of 190 subjects with MASH
with stage 2–3 fibrosis
Intervention
Tirzepatide 5 mg, 10 mg, 15 mg
vs Placebo
Randomized, double-blind,
placebo-controlled
PRIMARY
A Resolution of MASH and No Worsening of Fibrosis
Risk difference 34 (95% CI, 17–50)
P<0.001
Risk difference 46 (95% CI, 29–62)
P<0.001
Risk difference
53 (95% CI, 37–69)
P<0.001
Percentage of Participants (%)
44%
56%
62%
10%
Tirzepatide 5 mg (N=47)
Tirzepatide 10 mg (N=47)
Tirzepatide 15 mg (N=48)
Placebo (N=48)
KEY SECONDARY
B Decrease of ≥1 Fibrosis Stage and No Worsening of MASH
Risk difference 25 (95% CI, 5–46)
Risk difference 22 (95% CI, 1–42)
Risk difference
21 (95% CI, 1–42)
55%
51%
51%
30%
Tirzepatide demonstrated dose–dependent superiority over lifestyle/medical treatment
in achieving MASH resolution and fibrosis improvement.
Loomba R et al. N Engl J Med. 2024;391:299–310.
The NEW ENGLAND JOURNAL of MEDICINE

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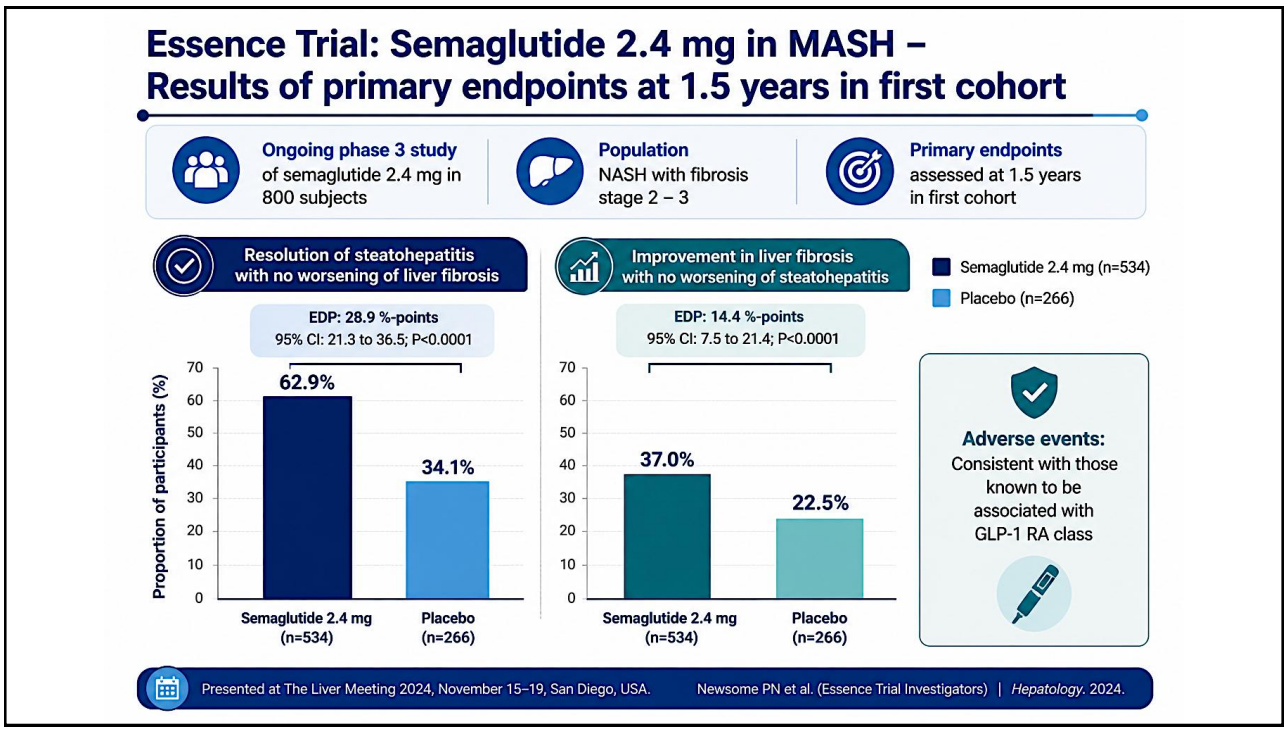
Essence Trial: Semaglutide 2.4 mg in MASH –
Results of primary endpoints at 1.5 years in first cohort
Ongoing phase 3 study
of semaglutide 2.4 mg in
800 subjects
Population
NASH with fibrosis
stage 2 – 3
Primary endpoints
assessed at 1.5 years
in first cohort
Resolution of steatohepatitis
with no worsening of liver fibrosis
EDP: 28.9 %-points
95% CI: 21.3 to 36.5; P<0.0001
Proportion of participants (%)
62.9%
34.1%
Semaglutide 2.4 mg (n=534)
Placebo (n=266)
Improvement in liver fibrosis
with no worsening of steatohepatitis
EDP: 14.4 %-points
95% CI: 7.5 to 21.4; P<0.0001
37.0%
22.5%
Semaglutide 2.4 mg (n=534)
Placebo (n=266)
Semaglutide 2.4 mg (n=534)
Placebo (n=266)
Adverse events:
Consistent with those
known to be
associated with
GLP-1 RA class
Presented at The Liver Meeting 2024, November 15–19, San Diego, USA.
Newsome PN et al. (Essence Trial Investigators) | Hepatology. 2024.

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# Real-World Discontinuation of Subcutaneous Semaglutide in MASLD Patients

*A retrospective cohort study using Optum Market Clarity data (2017–2024)*

**BACKGROUND**

MASLD and its progressive subtype, MASH, are chronic liver conditions with progression to the latter underdiagnosed in clinical practice. SC semaglutide is being investigated for MASH in the ESSENCE clinical trial (NCT0482218), where >89% of participants remained persistent at 72 weeks.

**STUDY AIM**

To assess alignment between real-world medication compliance and that observed in the ESSENCE trial among MASLD patients starting SC semaglutide for an approved indication.

**METHODS**

- Retrospective cohort of MASLD patients initiating SC semaglutide (Ozempic® or Wegovy®) from 2017–2024 in Optum Market Clarity data
- 12-month baseline period prior to index date (first prescription claim) used for sample selection and covariate measurement
- Excluded patients with other liver diseases (e.g., viral hepatitis) or severe MASH complications (e.g., cirrhosis)
- Discontinuation: gap in medication coverage ≥45 days
- Follow-up: index date to death, dropout, or end of data availability
- Outcomes: Kaplan-Meier (KM) persistence and time-to-discontinuation

**KEY RESULTS**

**36,531** adults included

- 69.5% (n=25,371) had type 2 diabetes
- Mean (SD) age: 52.6 (12.0) years
- 63.0% (n=23,021) female

Patients who discontinued SC semaglutide: **64.3%** (n=23,473)

**DISCONTINUATION TIMING**

- 56.3% (n=20,566) discontinued within 1 year
- 60.1% (n=21,966) discontinued within 72 weeks
- Mean time-to-discontinuation: 24.7 weeks (SD 28.6)
- Mean follow-up time: 77.9 weeks (SD 57.6)

**KM ESTIMATES** (accounting for censoring)

- 64% (95% CI: 63%–64%) discontinued by 1 year
- 72% (95% CI: 71%–72%) discontinued by 72 weeks

**CONCLUSION**

The majority of MASLD patients discontinued SC semaglutide, with 72% doing so within 72 weeks of initiation. Results are consistent with findings from similar observational studies and highlight the importance of monitoring SC semaglutide use patterns in a real-world setting, especially with respect to the resultant impact on liver outcomes as well as BMI and glycemic goals.

*Abbreviations:* MASLD, metabolic dysfunction–associated steatotic liver disease; MASH, metabolic dysfunction–associated steatohepatitis; SC, subcutaneous; KM, Kaplan-Meier; CI, confidence interval; SD, standard deviation; BMI, body mass index.

Clark S et al. Presented at AASLD 2026

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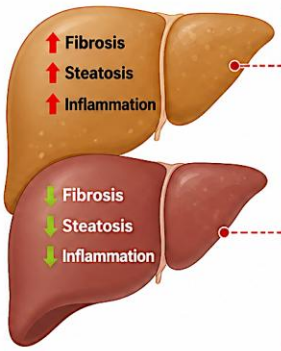
# GLP-1 MEDICINES

**Dual Pathways for Improving Metabolic Liver Disease**

**INDIRECT METABOLIC EFFECTS**

- ↓ Weight
- ↓ Glucose
- ↓ Lipids
- ↓ Inflammation




**DIRECT HEPATIC ACTIONS**

**GLP-1R+ PERICENTRAL LSECs**

Liver sinusoidal endothelial cell (LSEC)
GLP-1 receptors mediate direct hepatic action

**PARACRINE SIGNALING TO KEY LIVER CELLS**

Immune cells | Hepatic stellate cells | Hepatocytes

LSEC GLP-1Rs communicate metabolic signals to a wide range of intrahepatic cells

**KEY HIGHLIGHTS**

- Semaglutide improves metabolic liver disease partly via intrahepatic GLP-1 receptors.
- The hepatic GLP-1R is expressed within T cells and endothelial cells.
- Liver sinusoidal endothelial cell GLP-1 receptors transduce hepatic GLP-1 action.
- LSEC GLP-1Rs communicate metabolic signals to a wide range of intrahepatic cell types.

GLP-1 medicines act through both systemic metabolic improvements and direct intrahepatic mechanisms to reduce fibrosis, steatosis, and inflammation.

Gonzalez-Rellan, M et al. Cell Metabolism. 2026;38:1–20

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# Follow-Up of At-Risk MASH on Semaglutide

**Monitoring :**

- Clinical (q3–6 mo): weight, BP, adherence | Target ≥10% weight loss
- Laboratory (q3–6 mo): AST/ALT, platelets, HbA1c, lipids

⚠ ALT normalization ≠ fibrosis regression[1–3]

**Fibrosis Surveillance:**

- FIB-4 (q6–12 mo): rising value should trigger escalation[4]
- Elastography (q1–2 yr): track liver stiffness trend[5]

→ Fibrosis trend > single measurement[5]

**Escalation:**

- Rising fibrosis markers, weight loss <5–7%, persistent metabolic risk[2,4]
- Intensify therapy, consider combination[6]

**Advanced Disease (≥F3):**

- Referral to gastroenterology for HCC surveillance q6 mo (US ± AFP)[7]

**Management success = fibrosis stability**[5,8]


**References**

1. Chalasani N, et al. *Hepatology.* 2018;67(1):328-357.
2. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction–associated steatotic liver disease (MASLD). *J Hepatol.* 2024;81(3):492-542.
3. Rinella ME, et al. *Hepatology.* 2023;77(5):1797-1835.
4. Sterling RK, et al. *Hepatology.* 2006;43(6):1317-1325.
5. European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol.* 2015;63(1):237-264.
6. Younossi ZM, et al. *Hepatology.* 2023;78(6):1878-1911.
7. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology.* 2018;67(1):358-380.
8. Singh S, et al. *Lancet Gastroenterol Hepatol.* 2015;1(3):196-208.


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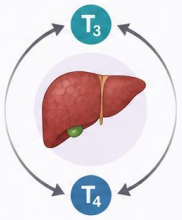
# Resmetirom: Rationale of Using Selective Thyroid Hormone β as Treatment of MASH

**1 Thyroid hormone affects metabolism of fatty acids[1]**

- Fatty acid uptake
- Lipogenesis
- Lipolysis
- Beta-oxidation
- Bile acid metabolism




Thyroid hormone signaling in the liver

**2 Key biological and clinical rationale[2]**

- Hypothyroidism is associated with higher risk of NAFLD/NASH
- Thyroid hormone receptor β predominates in liver parenchymal cells
- Free T4 levels are lower in NAFLD patients
- Low Free T3 is independent risk factor for advance fibrosis


**Resmetirom is a selective thyroid hormone receptor β agonist designed to target liver-specific pathways to improve steatohepatitis and fibrosis in MASH.**


1. Wirth E et al. Exp Rev Endocrine & Metab 2022;17:425-434;
2. Li et al. JCEM 2023;108:1602-1613.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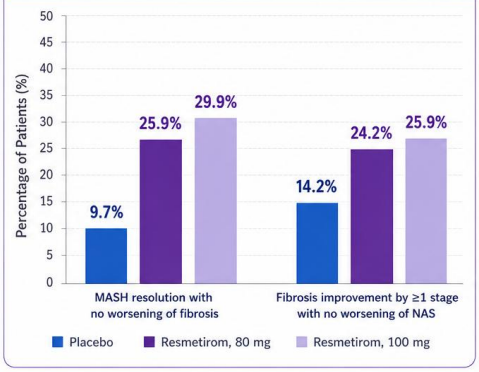
# Maestro Study: Resmetirom for Treatment of MASH with Fibrosis

52-week, phase 3, randomized double-blind study of 955 subjects with MASH with fibrosis 1B – 3

Randomized 1:1:1
Resmetirom 80 mg, Resmetirom 100 mg, or Placebo

Well-powered study evaluating key histologic and metabolic endpoints over 52 weeks

## PRIMARY ENDPOINTS (52 weeks)




## KEY EFFICACY FINDINGS

**MASH resolution with no worsening of fibrosis** *[Primary endpoint]*
→ *Resmetirom 80 mg, 100 mg > placebo*
*(25.9% & 29.9% vs 9.7% resp., P<0.001)*

**Fibrosis score improvement ≥ 1 with no worsening of NAS**
*[Primary endpoint]*
→ *Resmetirom 80 & 100 mg > placebo*
*(24.2% & 25.9% vs 14.2%, resp., P<0.001)*

**Percent change in LDL at week 24**
→ *Resmetirom 80 & 100 mg > placebo*
*(-13.6% & -16.3% vs 0.1%)*

## SAFETY SUMMARY

Adverse events were mild/moderate and more frequent in resmetirom groups 80 mg & 100 mg vs placebo:
- Diarrhea (27% & 33.4% vs 15.6%), self-limited with time
- Nausea (22% & 18.9% vs 12.5%)

**Resmetirom 80 mg and 100 mg significantly improved MASH resolution and fibrosis without worsening of NAS, with a favorable safety profile over 52 weeks.**

Harrison S et al. *N Engl J Med* 2024; 390: 497-509; Leff P, Rich N. *Evidence-Based GI* April 2024: 6-13.

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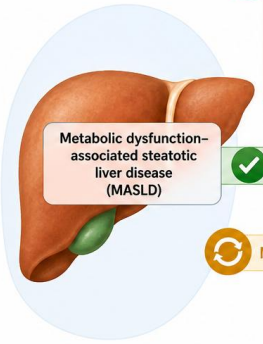
# Selection of Patients for Therapy with Resmetirom

**NOT RECOMMENDED**
- Cirrhosis, including LSM via VCTE >20 kPa or MRE >5 kPa
- Concomitant active liver disease
- Excess alcohol use (>20/30 g/d in women/men)
- Active thyroid disease




**RECOMMENDED**

| | |
|---|---|
| Imaging-based NILDA | VCTE: LSM 8–15 kPa[a]<br>MRE: LSM 3.1–4.4 kPa[a] |
| Liver histology | MASH with F2–F3[b] |

**MAY BE USED**

**Individualized decisions by a specialist experienced in liver fibrosis for:**
- LSM values outside the recommended ranges
- Other NILDA data consistent with F2–F3[c]

**OTHER CONSIDERATIONS**

Not recommended for alcohol intake > 20 g/d in women or >30 g/d in men

Not recommended for autoimmune hepatitis, primary biliary cirrhosis or those with active gallbladder disease

**Lower dose if on clopidogrel**
- TSH within 6 months of initiation
- Address abnormal thyroid function
- Consider TSH at 3 to 6 mo intervals

If on statin, reduce dose at initiation as long as LDL goals are met

[a] Modified from the AASLD NILDA guidelines.[5]
[b] MASH = metabolic dysfunction–associated steatohepatitis.
[c] F2–F3 = moderate to advanced fibrosis.

**Careful patient selection and monitoring help maximize benefits and minimize risks with resmetirom.**

Chen, V. Hepatology 81(1):312-320, January 2025. doi: 10.1097/HEP.0000000000001112 81

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# How to choose between semaglutide and resmetirom
## in a patient with comorbid T2D and high risk MASH?

**1 INITIAL CHOICE**

**Start Semaglutide**
If obese and not already on incretin therapy, start semaglutide **0.25 mg QW** and titrate up to **2 mg**.

OR

**Consider Resmetirom**
If intolerant to semaglutide or if lean MASLD, consider **resmetirom**.

**2 CONSIDER REFERRAL TO GASTROENTEROLOGY**

- To rule out **secondary causes** of liver disease (if you are not comfortable doing so)
- To **monitor** efficacy of treatment
- To institute **non-GLP-1RA** therapies (ie: resmetirom)
- To use established **clinical pathways** to follow for progression/ hepatocellular carcinoma

**GOAL**

Reduce liver inflammation and fibrosis progression, prevent cirrhosis and liver-related complications, and improve cardiometabolic outcomes.

**Note:** Treatment decisions should be individualized based on patient characteristics, preferences, tolerability, and access.

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# GLP-1RA + Resmetirom — Current Evidence

*What we know from available data*

**LIMITED PRIMARY DATA**

Primary data remain insufficient to guide decisions about concomitant treatment with a GLP-1RA and resmetirom in patients with MASH.

**POST-HOC ANALYSIS: MAESTRO-NASH TRIAL**

- ✓ Efficacy and safety of resmetirom were comparable in the subset of patients receiving stable doses of GLP-1RAs (~14%).

**HISTOLOGICAL BENEFITS OF ≥5% WEIGHT LOSS**

- ✓ Equally observed in all treatment arms (placebo, resmetirom 80 mg, and 100 mg).
- ✓ Indicates that the effects of weight loss and resmetirom therapy are independent, and potentially complementary to each other.

**TAKEAWAY**

These preliminary findings suggest that combining weight loss with resmetirom may offer **additional benefits** and that the combination of GLP-1RA and resmetirom has the potential to confer **further benefits**.

Kanwal F, et al. *Gastroenterology* 2026 (online ahead of print) DOI: 10.1053/j.gastro.2026.01.047

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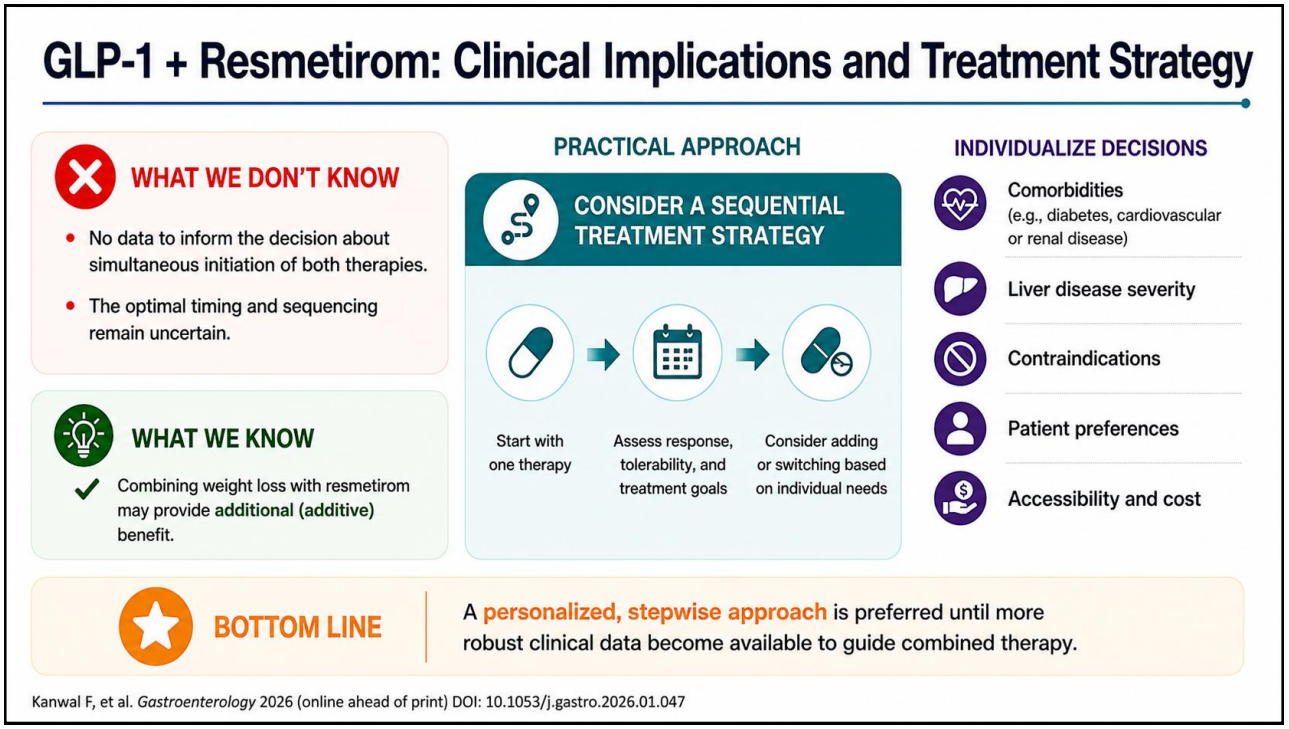
GLP-1 + Resmetirom: Clinical Implications and Treatment Strategy
WHAT WE DON'T KNOW
No data to inform the decision about simultaneous initiation of both therapies.
The optimal timing and sequencing remain uncertain.
WHAT WE KNOW
Combining weight loss with resmetirom may provide additional (additive) benefit.
PRACTICAL APPROACH
CONSIDER A SEQUENTIAL TREATMENT STRATEGY
Start with one therapy
Assess response, tolerability, and treatment goals
Consider adding or switching based on individual needs
INDIVIDUALIZE DECISIONS
Comorbidities (e.g., diabetes, cardiovascular or renal disease)
Liver disease severity
Contraindications
Patient preferences
Accessibility and cost
BOTTOM LINE
A personalized, stepwise approach is preferred until more robust clinical data become available to guide combined therapy.
Kanwal F, et al. Gastroenterology 2026 (online ahead of print) DOI: 10.1053/j.gastro.2026.01.047

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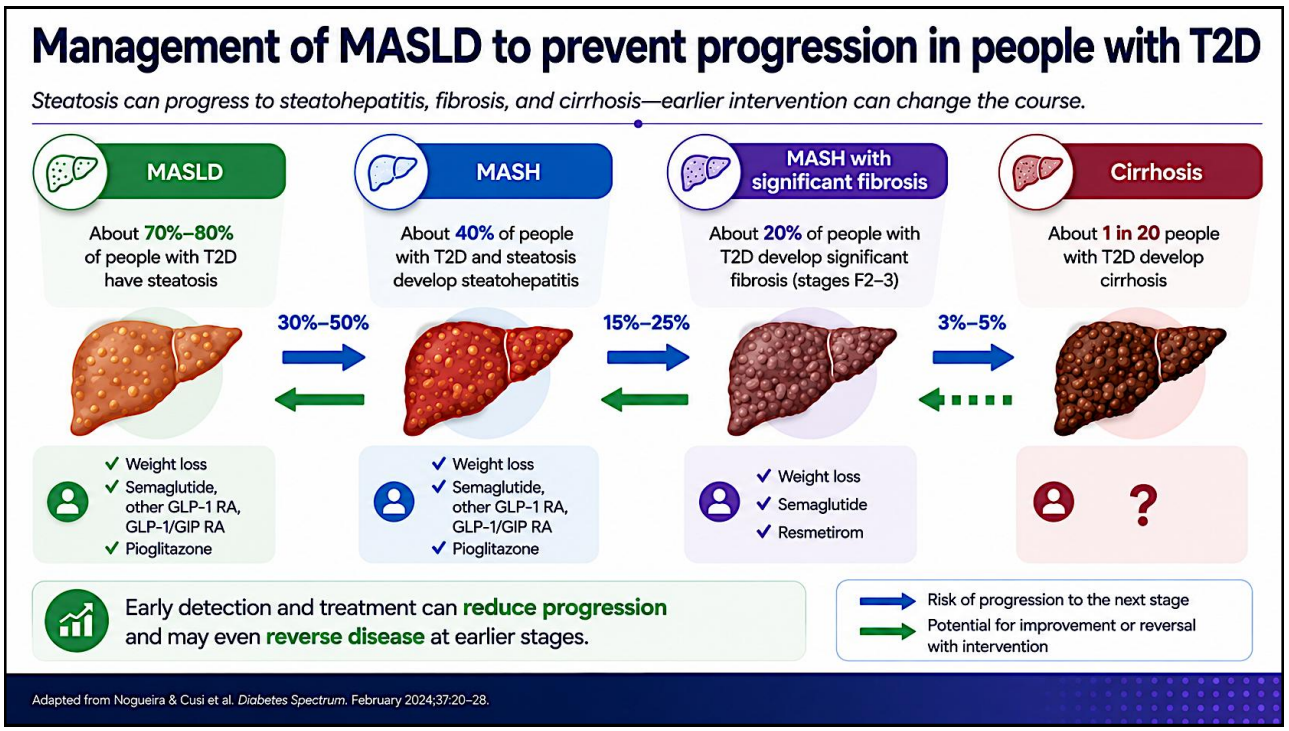
Management of MASLD to prevent progression in people with T2D
Steatosis can progress to steatohepatitis, fibrosis, and cirrhosis—earlier intervention can change the course.
MASLD
About 70%–80% of people with T2D have steatosis
MASH
About 40% of people with T2D and steatosis develop steatohepatitis
MASH with significant fibrosis
About 20% of people with T2D develop significant fibrosis (stages F2–3)
Cirrhosis
About 1 in 20 people with T2D develop cirrhosis
30%–50%
15%–25%
3%–5%
Weight loss
Semaglutide, other GLP-1 RA, GLP-1/GIP RA
Pioglitazone
Weight loss
Semaglutide, other GLP-1 RA, GLP-1/GIP RA
Pioglitazone
Weight loss
Semaglutide
Resmetirom
?
Early detection and treatment can reduce progression and may even reverse disease at earlier stages.
Risk of progression to the next stage
Potential for improvement or reversal with intervention
Adapted from Nogueira & Cusi et al. Diabetes Spectrum. February 2024;37:20–28.

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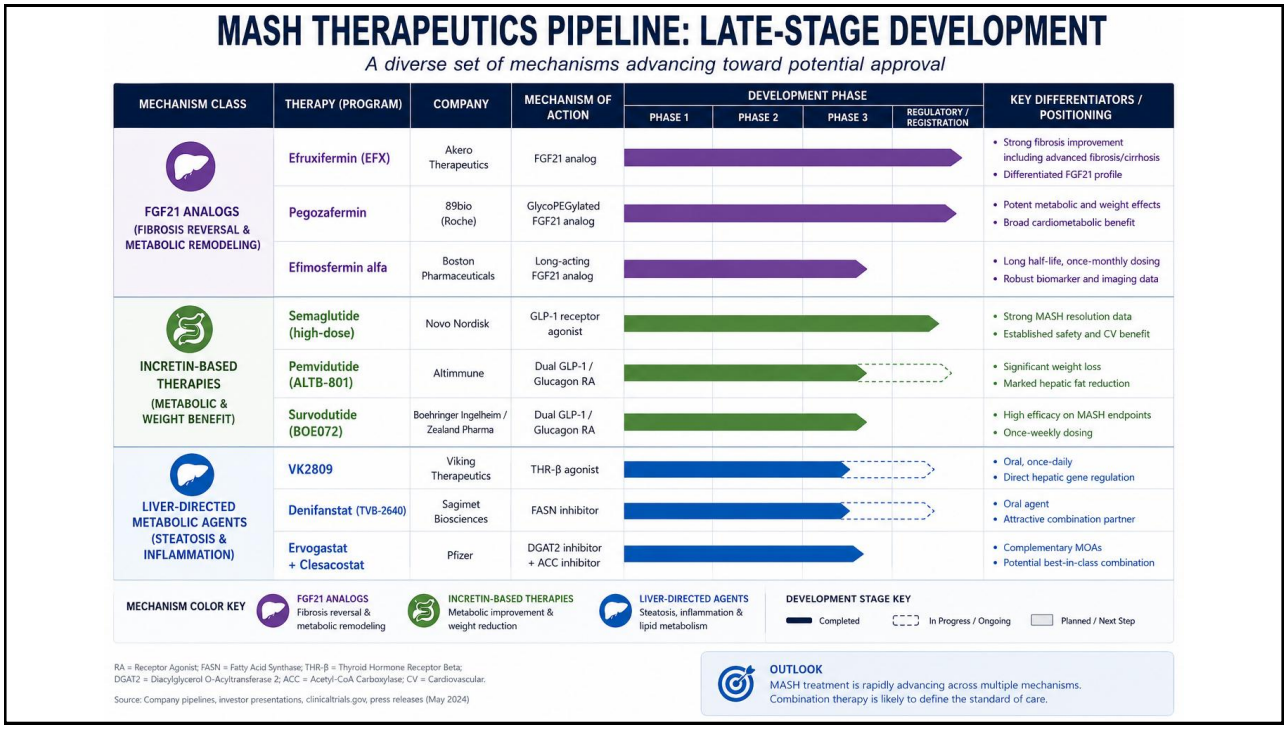
MASH THERAPEUTICS PIPELINE: LATE-STAGE DEVELOPMENT
A diverse set of mechanisms advancing toward potential approval
MECHANISM CLASS
THERAPY (PROGRAM)
COMPANY
MECHANISM OF ACTION
DEVELOPMENT PHASE
PHASE 1
PHASE 2
PHASE 3
REGULATORY / REGISTRATION
KEY DIFFERENTIATORS / POSITIONING
FGF21 ANALOGS (FIBROSIS REVERSAL & METABOLIC REMODELING)
Efruxifermin (EFX)
Akero Therapeutics
FGF21 analog
• Strong fibrosis improvement including advanced fibrosis/cirrhosis
• Differentiated FGF21 profile
Pegozafermin
89bio (Roche)
GlycoPEGylated FGF21 analog
• Potent metabolic and weight effects
• Broad cardiometabolic benefit
Efimosfermin alfa
Boston Pharmaceuticals
Long-acting FGF21 analog
• Long half-life, once-monthly dosing
• Robust biomarker and imaging data
INCRETIN-BASED THERAPIES (METABOLIC & WEIGHT BENEFIT)
Semaglutide (high-dose)
Novo Nordisk
GLP-1 receptor agonist
• Strong MASH resolution data
• Established safety and CV benefit
Pemvidutide (ALTB-801)
Altimmune
Dual GLP-1 / Glucagon RA
• Significant weight loss
• Marked hepatic fat reduction
Survodutide (BOE072)
Boehringer Ingelheim / Zealand Pharma
Dual GLP-1 / Glucagon RA
• High efficacy on MASH endpoints
• Once-weekly dosing
LIVER-DIRECTED METABOLIC AGENTS (STEATOSIS & INFLAMMATION)
VK2809
Viking Therapeutics
THR-β agonist
• Oral, once-daily
• Direct hepatic gene regulation
Denifanstat (TVB-2640)
Sagimet Biosciences
FASN inhibitor
• Oral agent
• Attractive combination partner
Ervogastat + Clesacostat
Pfizer
DGAT2 inhibitor + ACC inhibitor
• Complementary MOAs
• Potential best-in-class combination
MECHANISM COLOR KEY
FGF21 ANALOGS
Fibrosis reversal & metabolic remodeling
INCRETIN-BASED THERAPIES
Metabolic improvement & weight reduction
LIVER-DIRECTED AGENTS
Steatosis, inflammation & lipid metabolism
DEVELOPMENT STAGE KEY
Completed
In Progress / Ongoing
Planned / Next Step
RA = Receptor Agonist; FASN = Fatty Acid Synthase; THR-β = Thyroid Hormone Receptor Beta; DGAT2 = Diacylglycerol O-Acyltransferase 2; ACC = Acetyl-CoA Carboxylase; CV = Cardiovascular.
Source: Company pipelines, investor presentations, clinicaltrials.gov, press releases (May 2024)
OUTLOOK
MASH treatment is rapidly advancing across multiple mechanisms. Combination therapy is likely to define the standard of care.

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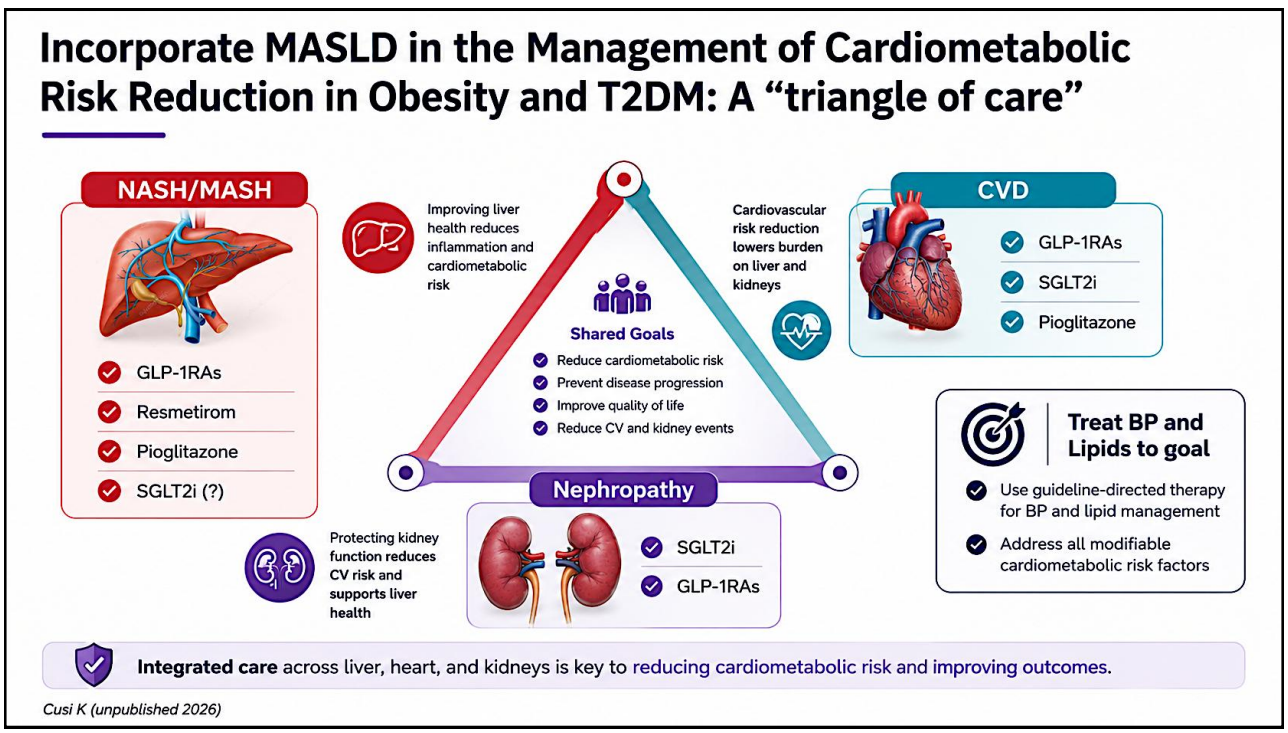
Incorporate MASLD in the Management of Cardiometabolic Risk Reduction in Obesity and T2DM: A "triangle of care"
NASH/MASH
GLP-1RAs
Resmetirom
Pioglitazone
SGLT2i (?)
Improving liver health reduces inflammation and cardiometabolic risk
Cardiovascular risk reduction lowers burden on liver and kidneys
Shared Goals
Reduce cardiometabolic risk
Prevent disease progression
Improve quality of life
Reduce CV and kidney events
CVD
GLP-1RAs
SGLT2i
Pioglitazone
Nephropathy
SGLT2i
GLP-1RAs
Protecting kidney function reduces CV risk and supports liver health
Treat BP and Lipids to goal
Use guideline-directed therapy for BP and lipid management
Address all modifiable cardiometabolic risk factors
Integrated care across liver, heart, and kidneys is key to reducing cardiometabolic risk and improving outcomes.
Cusi K (unpublished 2026)

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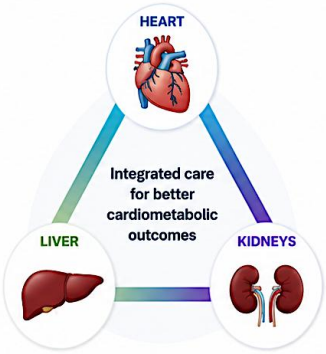
# MASLD Clinical Implications

*Addressing MASLD is essential to reduce cardiometabolic risk and improve outcomes.*

1. **MASLD and diabetes (i.e., T2D or T1D w/cardiometabolic risk factors [CMRFs])** interact as "disease enhancers" of each other.
2. **In endocrine clinics** about **≥40%** of people with **T2D** have MASH and **≥20%** are at risk of cirrhosis (have "at-risk" MASH).
3. **People with T2D (or T1D with obesity/CMRFs) should be risk-stratified** for "at risk" MASH (i.e., having significant liver fibrosis).
4. **Multiple mechanisms at play.** From a treatment perspective, obesity, insulin resistance, hyperglycemia and other CMRFs benefit from lifestyle changes, pharmacotherapy for obesity (i.e., GLP-1RA) or T2DM (i.e., pioglitazone and/or GLP-1RA) and metabolic surgery.
5. **When diagnosed with MASLD,** lifestyle management and newer generation antihyperglycemic agents (incretin therapies and SGLT-2 inhibitors) can prevent progression and increase likelihood of regression.
6. **In patients with at-risk MASH,** treatment with semaglutide and/or resmetirom has the potential to induce regression.
7. **Develop a multidisciplinary team** and refer to GI/liver specialists if additional risk stratification and treatment (i.e., resmetirom) needed.




Early identification and comprehensive management of MASLD can reduce liver disease progression, cardiovascular events, and kidney complications.

Treat the whole patient. Improve outcomes.