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Dr. Mohammad Taher

Gastroenterologist

TEHRAN UNIVERSITY OF MEDICAL SCIENCES

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Overview of Clinical Practice in MASH and Fibrosis

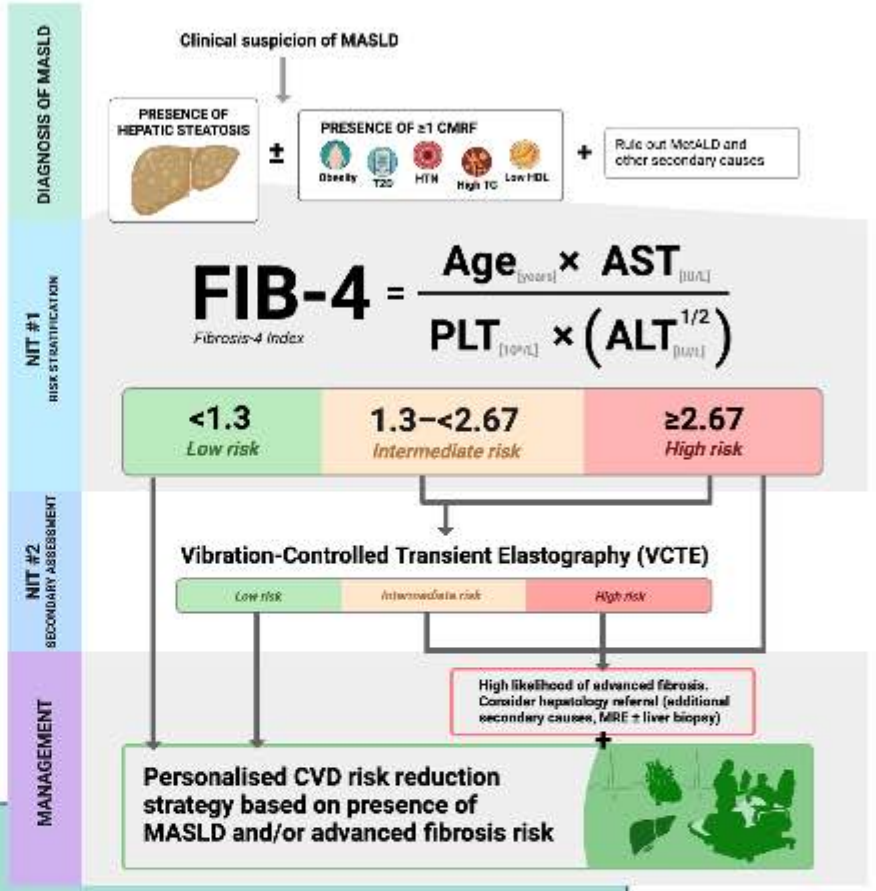


Selecting the best therapy for each patient requires stepwise approach.

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Screening High-Risk Patients for Advanced MASLD Fibrosis

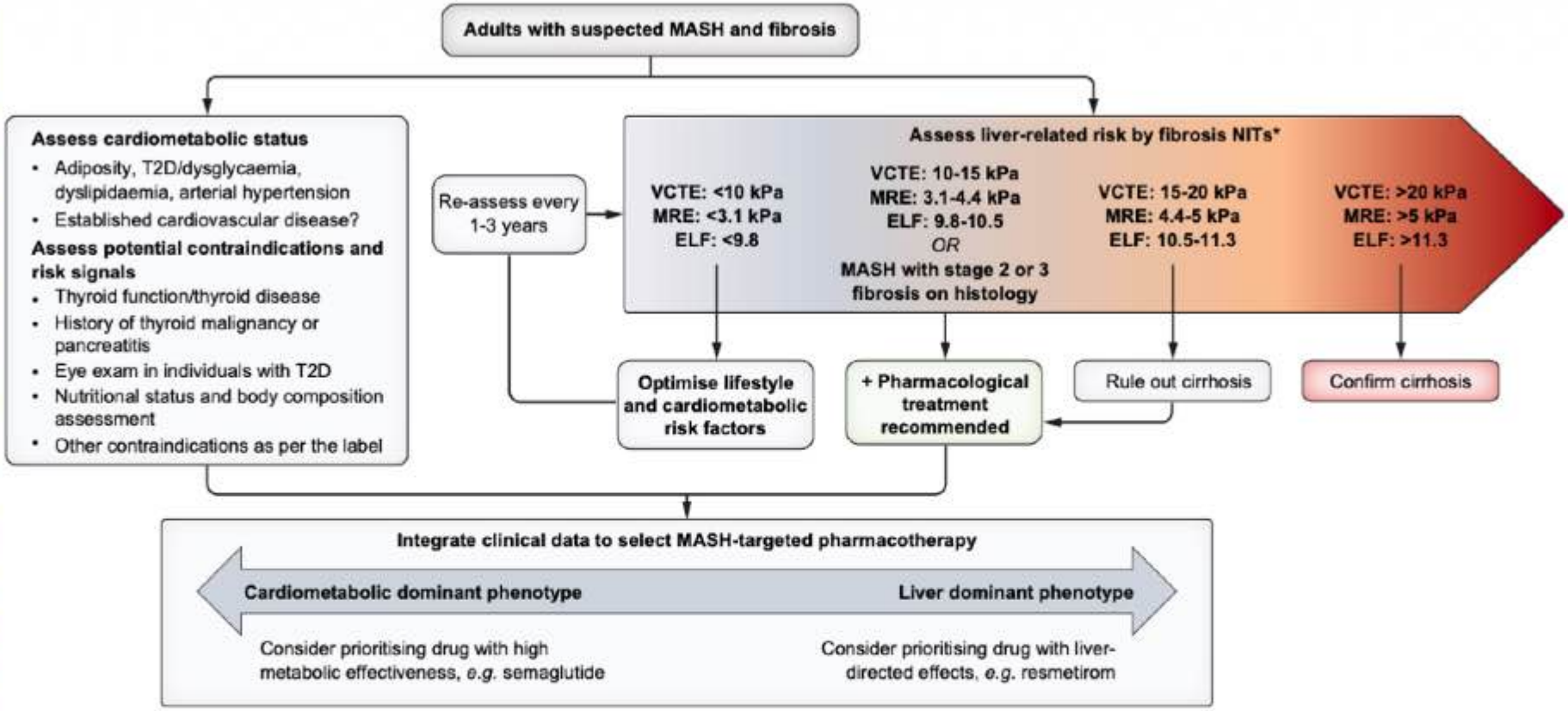
- Patients with hepatic steatosis and cardiometabolic risk factors—particularly obesity, type 2 diabetes, hypertension, hypertriglyceridemia, or low HDL—should undergo stepwise fibrosis risk assessment.
- FIB-4 is recommended as a first-line non-invasive test, followed by VCTE in patients with intermediate or high risk, to identify those who may require evaluation for liver-directed therapy.



"Cardiovascular-Liver-Metabolic Health: Recommendations in Screening, Diagnosis, and Management of Metabolic Dysfunction-Associated Steatotic Liver Disease in Cardiovascular Disease via Modified Delphi Approach." *Circulation* vol. 151,1 (2025):

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Stepwise Treatment Selection of Liver Fibrosis in MASLD



* VCTE needs confirmation by repeated testing or an additional non-invasive test; ELF should ideally be confirmed by an additional non-invasive test.

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How to Interpret FibroScan in MASLD

EASL–EASD–EASO 2026 | Fibrosis assessment & eligibility for MASH-targeted therapy

1 Liver Stiffness Measurement (LSM)

kPa | Clinical risk stratification & treatment evaluation

<10 kPa	**BELOW THE SUGGESTED NIT RANGE**	Does not rule out F2–F3; assess clinical context.
10–<15 kPa	**POTENTIAL TREATMENT CANDIDATE**	Confirm by repeat VCTE or another fibrosis NIT.
15–20 kPa	**HIGHER LIVER-RELATED RISK**	Confirm measurement and carefully exclude cirrhosis.
>20 kPa	**EVALUATE FOR CIRRHOSIS**	Further workup is needed before selecting therapy.

EASL 2026: confirmed VCTE 10–20 kPa may support treatment evaluation.

2 Controlled Attenuation Parameter

CAP | Estimated steatosis (dB/m)

S ≥ 1	**≥248** dB/m	Mild-or-greater steatosis
S ≥ 2	**≥268** dB/m	Moderate-or-greater steatosis
S3	**≥280** dB/m	Severe steatosis

CAP cutoffs are approximate, not EASL 2026 treatment criteria.

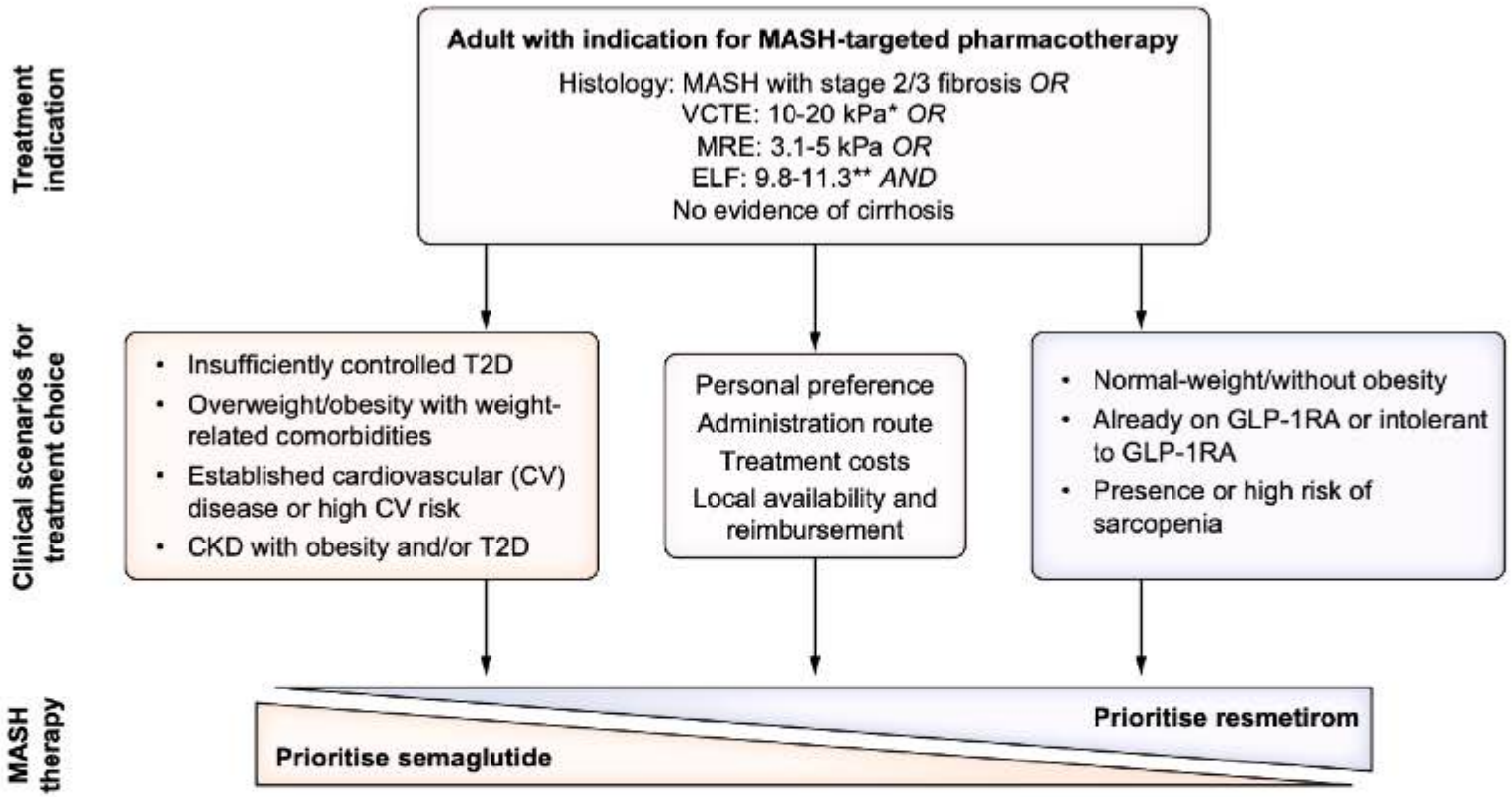
CAP does not diagnose MASH or determine fibrosis stage.

SCAN QUALITY **≥10 valid readings • IQR/median ≤30% • Correct probe** Confounders: meals, inflammation, cholestasis, congestion

CLINICAL TAKEAWAY **Confirm VCTE 10–20 kPa and exclude cirrhosis; LSM does not determine exact F2/F3 stage.**

Source: EASL–EASD–EASO. J Hepatol. 2026; Fig. 1. doi:10.1016/j.jhep.2026.08.028 | CAP: indicative published thresholds.

Decision Pathway for MASH-Targeted Pharmacotherapy



* confirmed by repeated testing or an additional non-invasive test
** ideally confirmed by an additional non-invasive test

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Factors to consider in the MASH-targeted treatment selection

Table 3. Factors to consider in the choice of MASH-targeted pharmacotherapy.

Factor	Resmetirom	Semaglutide
Administration route	Oral, once daily	SC injection, once weekly
Weight effect	Neutral	~10% reduction (72 weeks)
Glycaemic effect	None	Significant HbA1c reduction
Lipid effect	LDL ↓16%, TG ↓19%, Lp(a) ↓35%	Modest lipid improvement (TG ↓, HDL↑)
Gastrointestinal tolerability	Diarrhoea (mild to moderate), nausea; often transient (first 12 weeks)	Nausea, vomiting, constipation, diarrhoea; dose-dependent
Key drug interactions	CYP2C8 inhibitors (gemfibrozil contraindicated, clopidogrel requires dose reduction); statin dose caps (rosuvastatin/simvastatin ≤20 mg; atorvastatin/pravastatin ≤40 mg)	Minimal hepatic drug interactions; may delay gastric emptying affecting oral drug absorption
Thyroid considerations	Lowers free T4 ~20%; baseline TSH required; avoid if uncontrolled thyroid disease	No thyroid concerns; boxed warning for thyroid C-cell tumours (rodent data)
Gallbladder risk	Increased cholelithiasis/cholecystitis	Increased gallbladder events (class effect)
Contraindications	Decompensated liver disease, active autoimmune hepatitis/PBC, uncontrolled thyroid disease, significant alcohol use, gemfibrozil/cyclosporine use	Personal/family history of MTC, MEN2; potential for temporary worsening of diabetic retinopathy

CYP2C8, cytochrome P450 2C8; HbA1c, glycated haemoglobin; Lp(a), lipoprotein(a); MASH, metabolic dysfunction-associated steatohepatitis; MEN2, multiple endocrine neoplasia type 2; MTC, medullary thyroid carcinoma; PBC, primary biliary cholangitis; SC, subcutaneous; T4, thyroxine; TG, triglycerides; TSH, thyroid-stimulating hormone.

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Clinical Interpretation of the Two MASLD Endotypes

Cardiometabolic MASLD

- Marked dysglycemia, hypertriglyceridemia & hypertension
- Systemic metabolic phenotype
- High chronic liver disease risk
- Much higher cardiovascular disease and type 2 diabetes risk

Molecular pattern: cholesterol metabolism, glycolysis, systemic metabolic pathways

Liver-Specific MASLD

- Younger patients with marked ALT/AST elevation
- Greater genetic predisposition to hepatic fat (especially PNPLA3)
- Liver-centered lipid handling and inflammation
- High chronic liver disease risk, but lower cardiometabolic risk

Molecular pattern: hepatic lipid handling, inflammation, bile-acid/lipid metabolism

Similar liver severity at baseline, but distinct biology and different clinical trajectories.

These endotypes may ultimately require different therapeutic strategies.

Potential Therapeutic Implications of MASLD Endotypes

Liver-Specific MASLD

- Liver-centered pathophysiology
- Abnormal hepatic lipid-droplet handling
- Greater genetic susceptibility to hepatic fat
- Potentially more suitable for liver-targeted therapy



Resmetirom
Targets hepatic lipid content and inflammation

Cardiometabolic MASLD

- Systemic metabolic dysfunction
- Higher risk of type 2 diabetes and cardiovascular disease
- Priority on weight loss and glucose/lipid control
- Cardiovascular risk reduction



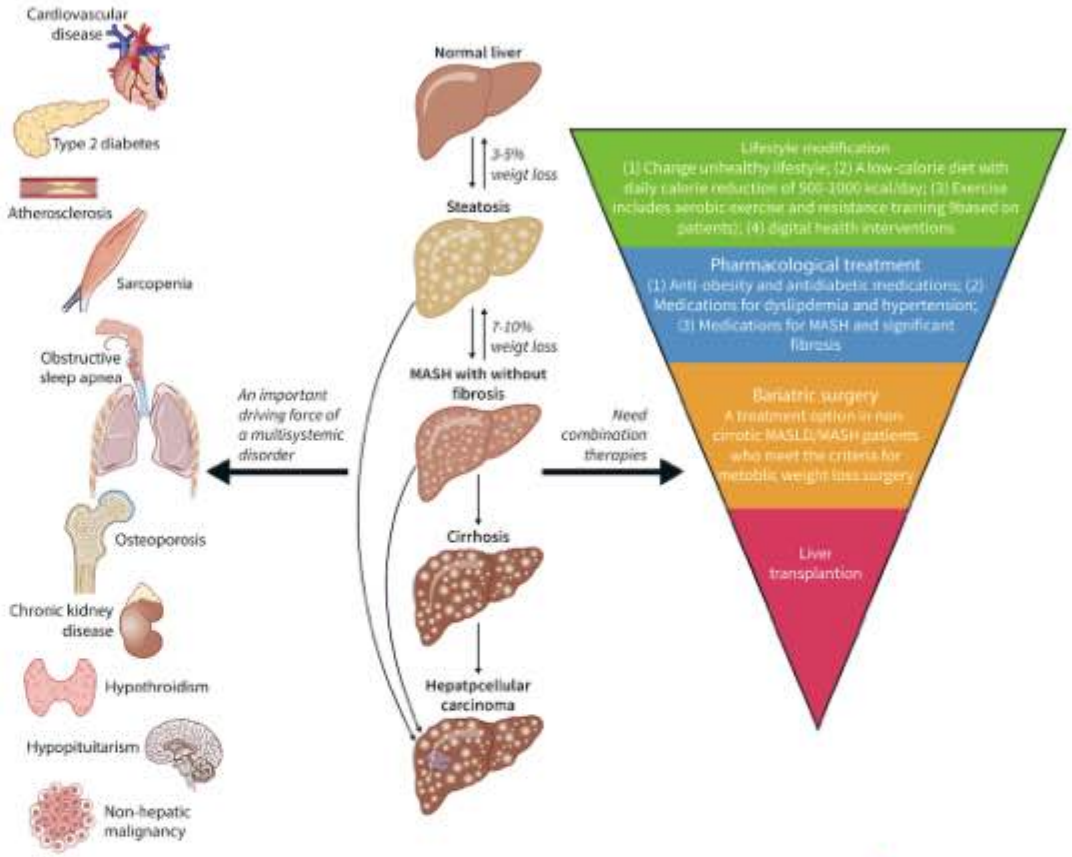
GLP-1–based therapies
Semaglutide • Tirzepatide

Distinct MASLD endotypes may ultimately require different therapeutic strategies.
Hypothesis-generating; prospective studies are required before cluster-guided treatment can be recommended.

Therapeutic Management of MASLD

The management of the underlying metabolic drivers of the disease by lifestyle modification and weight loss is the cornerstone of the treatment of MASLD/MASH.

For MASLD patients with overweight/obesity, a weight loss of 3-5% can reduce steatosis, while 7% weight loss can lead to MASH regression, and 10% weight loss may result in fibrosis regression.



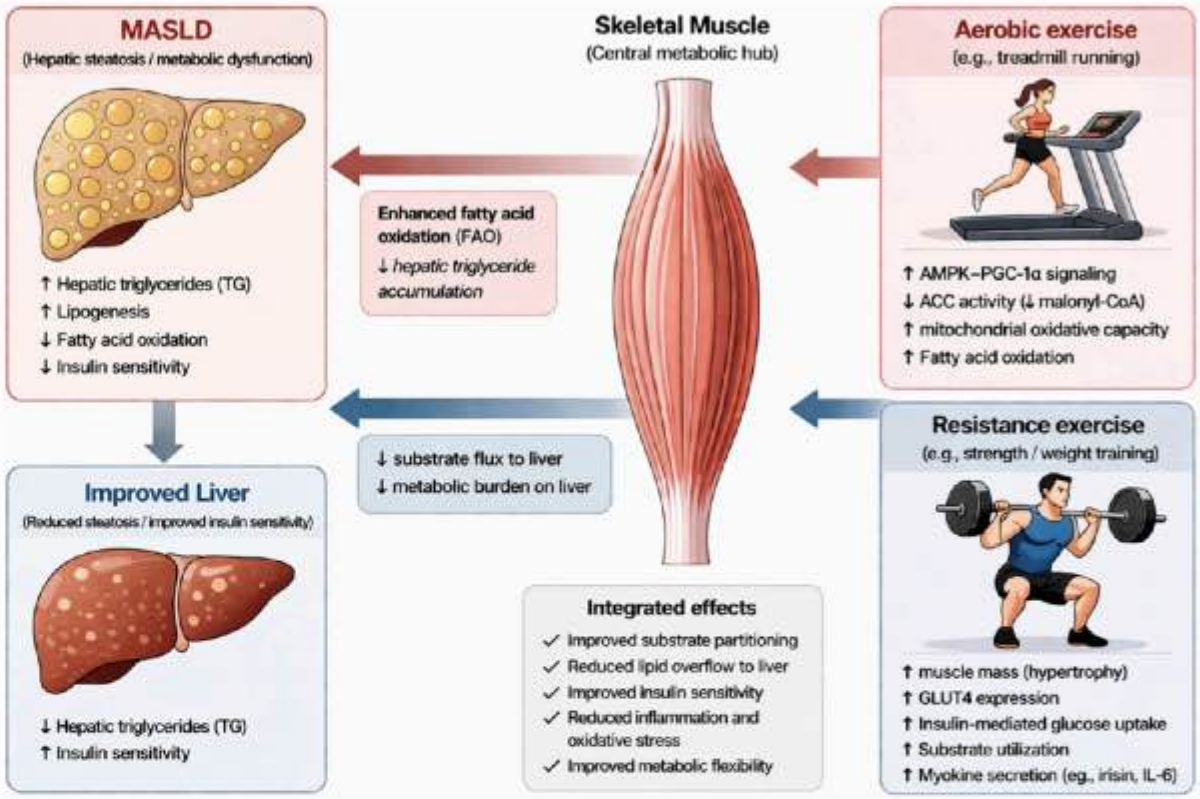
"Cardiovascular-Liver-Metabolic Health: Recommendations in Screening, Diagnosis, and Management of Metabolic Dysfunction-Associated Steatotic Liver Disease in Cardiovascular Disease via Modified Delphi Approach." *Circulation* vol. 151,1 (2025):

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Lifestyle Recommendations in MASLD Management

Patients should be encouraged to follow a Mediterranean-style diet rich in vegetables, whole grains, nuts, olive oil, fish, and lean protein, while limiting sweets, refined carbohydrates, processed foods, fast food, sugary drinks, red and processed meat, and excess salt.

Regular physical activity should be individualized based on the patient's ability and lifestyle, with a general target of at least **150 minutes of moderate-intensity aerobic exercise per week** to support weight loss and metabolic improvement.



Roh H-T, Bae J-Y. Exercise as a Metabolic Therapy for MASLD: Beyond Weight Loss Toward Sustainable Exercise Strategies. *Medicina*. 2026

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The Evolving MASH Therapeutic Landscape

Drug class	Representative agents	Key evidence/development status	Major limitations/safety concerns
PPAR agonists	Pioglitazone, elafibranor, lanifibranor, saroglitazar	Pioglitazone: histological benefit; elafibranor: phase 3 failure; lanifibranor: positive phase 2; saroglitazar: approved in India	Weight gain, edema, class heterogeneity
FXR agonists	Obeticholic acid	Phase 3 fibrosis benefit but not fully approved	Pruritus, dyslipidemia
THR-β agonists	Resmetirom	FDA approved (2024)	Generally well-tolerated
GLP-1 receptor agonists	Liraglutide, semaglutide	Semaglutide: FDA approved (2025)	Gastrointestinal effects
FGF21 analogs	Pegozafermin, efruxifermin	Early trials: improved fibrosis/metabolic markers	Confirmatory trials needed
Antioxidants	Vitamin E	Efficacy in non-diabetic patients	Long-term cardiovascular/oncologic safety concerns
Failed targeted therapies	Selonsertib, cenicriviroc	Phase 3 failure or no MASH resolution	Single-pathway limitations

Tirzepatide	GIP/GLP-1 dual agonist	Phase 3	Reduced liver fat by 8.1% over 52 weeks in T2DM patients; improved ALT, AST, GGT
Retatrutide	GCGR/GIPR/GLP-1R triple agonist	Phase 3	Significant body weight loss in obese patients; improved liver health markers in preclinical models

Yu, Jiang, and Yong Peng. "The immunometabolic mechanisms and therapeutic targets of metabolic dysfunction-associated steatohepatitis." *Frontiers in medicine*. 20 May. 2026,

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AASLD and EASL Guideline recommendations

Resmetirom is the first FDA-approved medication for the treatment of MASH with moderate to advanced liver fibrosis.

- **Resmetirom** can be considered for treatment of adults with MASH and moderate to advanced liver fibrosis (consistent with F2-F3) based on latest AASLD guidelines.
- Based on EASL guidelines, adults with non-cirrhotic MASH and significant liver fibrosis should be considered for targeted treatment with **Resmetirom**, demonstrating resolution of MASH and fibrosis with acceptable safety and tolerability.

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

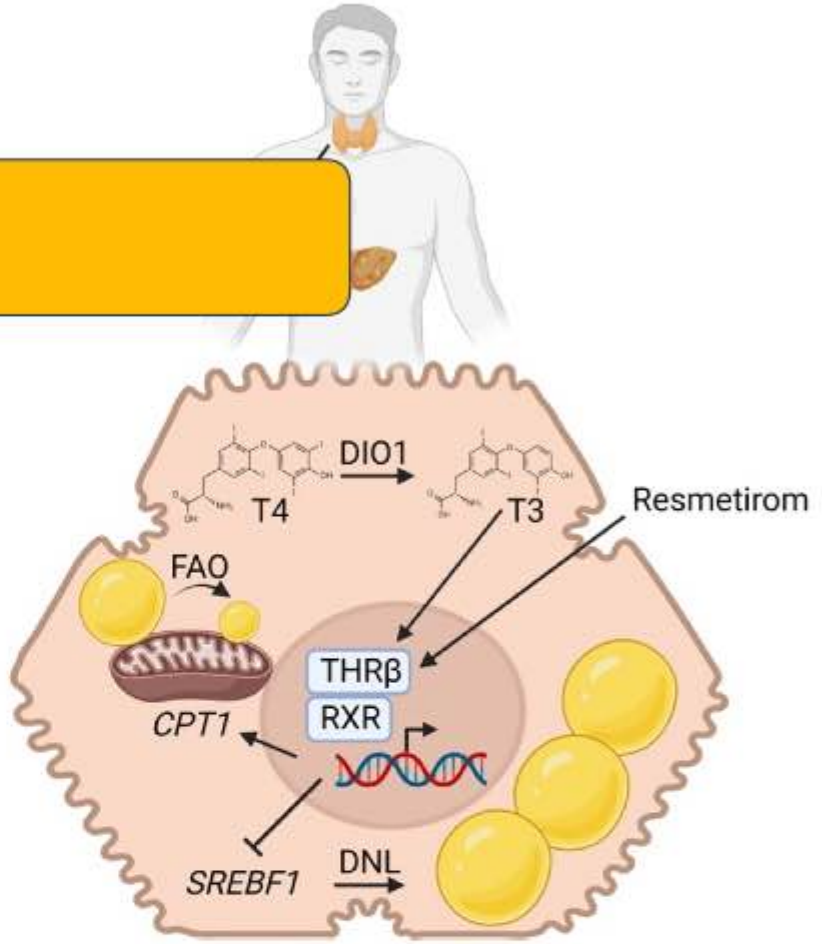
EASL™
The Home of Hepatology

Nature reviews Gastroenterology & hepatology vol. 15,1 (2018): 11-20.
Hepatology 81(1):p 312-320, January 2025.

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Xelivex® Mechanism of Action

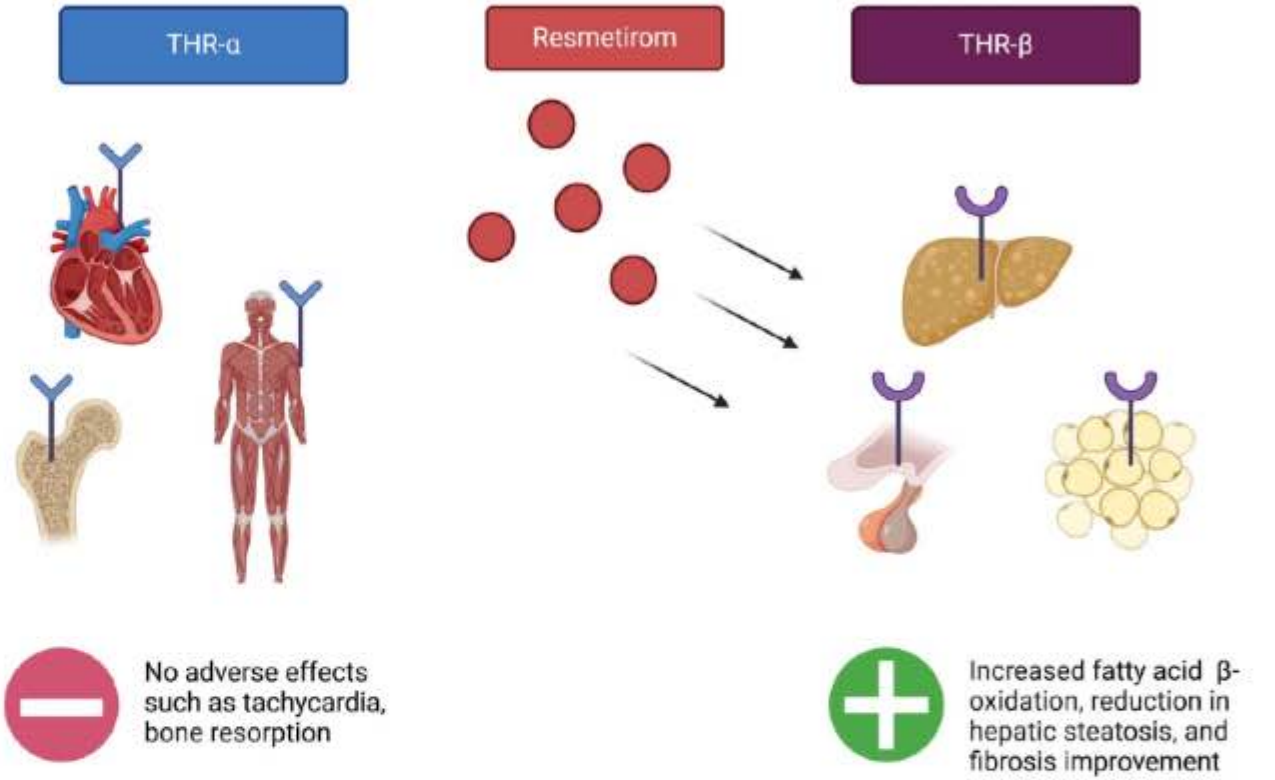
Xelivex® is a liver-directed, orally active agonist of thyroid hormone receptor (THR), improving lipid metabolism, and hepatic inflammation.



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J Med Chem 2014; 57: 3912–23

Selectivity of Xelivex® and Its Effects on Different Organs

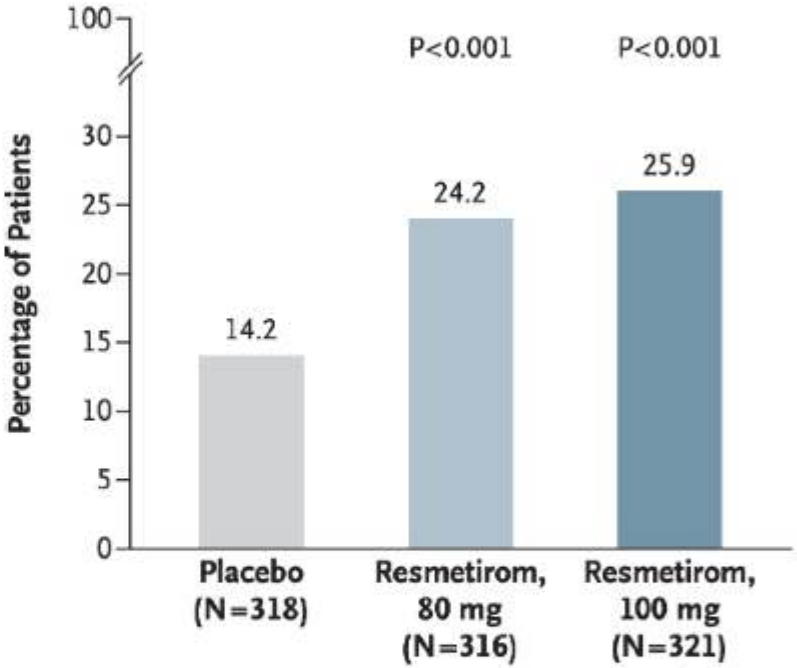


J Med Chem 2014; 57: 3912–23

Maximum Liver Fibrosis Improvement by Resmetirom

Resmetirom significantly improves liver fibrosis by at least one stage.

Resmetirom showed effective fibrosis regression, with ≥1-stage improvement observed in 24-26% of patients.

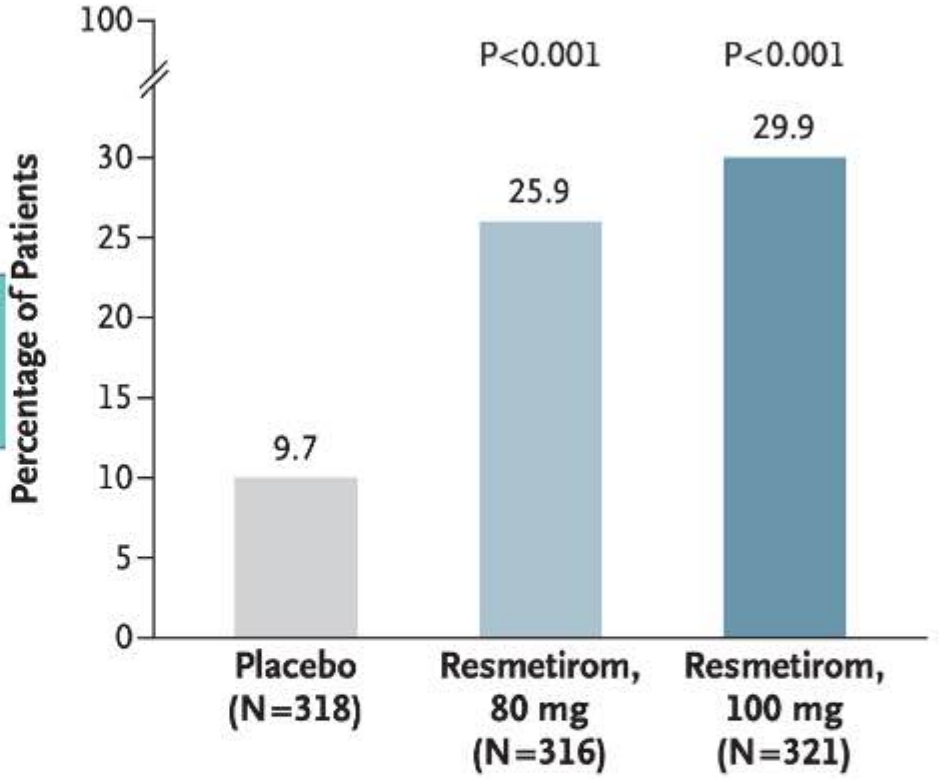


The New England journal of medicine vol. 390,6 (2024): 497-509.

xeliver® Resmetirom

Resmetirom demonstrated significant resolution of MASH after a period of 52 weeks.

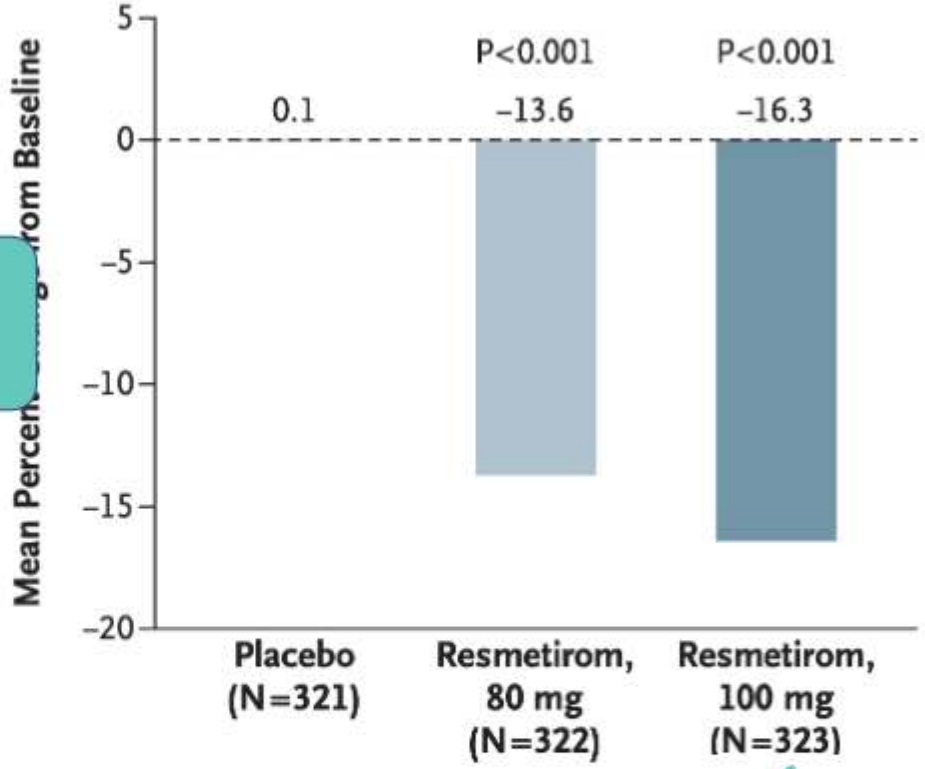
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omparison to



The New England journal of medicine vol. 390,6 (2024): 497-509.

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Resmetirom expressed outstanding LDL level reduction after 24 weeks of treatment.



The New England journal of medicine vol. 390,6 (2024): 497-509.

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Early real-world effectiveness of resmetirom in adults with metabolic dysfunction-associated steatohepatitis and moderate-to-advanced fibrosis

Abstract No. 174 | Clinical Science | MASLD: Therapy

BACKGROUND

Resmetirom is a THR-beta agonist approved in the US in 2024 for adults with noncirrhotic MASH and moderate-to-advanced fibrosis.

Aim: assess early real-world effectiveness in US practice.



METHODS

1) Single-arm retrospective cohort
2) Latica real-world database
3) Adults with >=1 resmetirom prescription
4) 712 patients included | mean treatment duration: 5.7 months

Common risk factors: hypertension 77%, obesity 71%

RESULTS

Clinically meaningful improvements over ~6 months

FAST score	ALT	LSM by VCTE
↓ 0.18 (n=28)	↓ 13.6 U/L (n=330)	↓ 2.2 kPa (n=70)

Response thresholds met

FAST	ALT	VCTE
42.9% (≥0.22 reduction)	46.7% (≥17 U/L or ≥20% reduction)	41.4% (≥30% reduction)

Subgroup observations

- Statin and non-statin users showed similar overall trends.
- Lipid markers improved in both groups.
- GLP-1 concomitant users and non-users showed similar ALT/AST declines and slight BMI reduction.
- LSM decline was greater with GLP-1 concomitant use: −3.2 vs −1.9 kPa.
- CAP declined in both groups: −39.5 vs −43.9 dB/m.

Treatment-related AE discontinuation: ~2%
Most common reason: diarrhea

CONCLUSION

In this real-world analysis, resmetirom was associated with **clinically meaningful improvements** in blood and imaging biomarkers over approximately 6 months, suggesting early effectiveness consistent with the 52-week MAESTRO-NASH trial.

Larger cohorts with longer follow-up are needed to assess long-term outcomes.

Discontinuation due to treatment-related adverse events was uncommon.

***Source**: study abstract provided by user*

Real-world effectiveness of one year of Resmetirom treatment in at-risk metabolic dysfunction–associated steatohepatitis

Abstract No. 3697 | Clinical Science | MASLD: Therapy

BACKGROUND

Resmetirom, a selective thyroid hormone receptor-β agonist, has shown histologic efficacy in MASH. Real-world treatment response data remain limited.



Aim: To assess hepatic and metabolic responses to at least 1 year of resmetirom using noninvasive tests (NITs).

METHODS

- Retrospective real-world study
- Adults with presumptive F2/F3 at-risk MASH
- Outpatient hepatology practice
- 599 patients prescribed resmetirom (Mar 2024–Jul 2025)
- 331 completed ≥52 weeks
- Excluded: GLP-1/GIP analog users (n=268)
- **Final analysis: n=204**

Assessments: aminotransferases, fibrosis scores (e.g., FIB-4, FAST), VCTE/CAP, lipid parameters, tolerability

Baseline characteristics (n=204)

Mean age	55 years
Male	42%
Mean BMI	37.7 kg/m²
T2DM	49.5%
Dyslipidemia	33.8%
Hypertension	54.9%

RESULTS (After 52 Weeks of Resmetirom)

62.7% achieved ≥1-stage reduction in liver fibrosis by VCTE

Mean VCTE kPa reduction	↓ 32.2%
Mean CAP reduction	↓ 21.1%
AST	↓ −12.5 IU/L
ALT	↓ −22.44 IU/L

Lipid Parameters

Total cholesterol	↓ −24.36 mg/dL
LDL-C	↓ −26.19 mg/dL
Triglycerides	↓ −68.6 mg/dL
HDL-C	↑ +5.5 mg/dL

8% discontinued due to adverse events

CONCLUSION

In real-world clinical practice, 52 weeks of resmetirom was associated with **significant improvements in liver fibrosis, steatosis, liver enzymes, and cardiometabolic parameters** in patients with at-risk MASH.

Therapy was generally **safe and well tolerated,** supporting the effectiveness of resmetirom in routine care.

Source: study abstract provided by user

Twelve-month changes in liver function enzymes and lipids in patients receiving resmetirom

Abstract No. 840 | Clinical Science | MASLD: Therapy

BACKGROUND

Resmetirom is a THR-beta selective agonist.

Approved in the US in March 2024 for adults with noncirrhotic MASH and moderate-to-advanced fibrosis.

Aim: assess 12-month changes in ALT, AST, and LDL-C in routine practice.



METHODS

Retrospective cohort study

Truveta deidentified EHR + medication dispensing data

Adults ≥18 years initiating resmetirom on/after Mar 14, 2024

Follow-up through Oct 17, 2025

Outcomes: ALT, AST, LDL-C at baseline and 12 months

Analyses stratified by T2D and GLP-1 use

N=728 with 12-month follow-up

- Mean age 58 years
- 36% male
- 52% T2D
- 30% GLP-1 use

RESULTS

Key 12-month changes

ALT	AST	LDL-C
64.5 → 43.1 U/L	50.1 → 35.4 U/L	93.9 → 85.4 mg/dL
↓ -21.5 U/L	↓ -14.7 U/L	↓ -8.5 mg/dL
$p < 0.01$	$p < 0.01$	$p < 0.05$
$n=222$	$n=222$	$n=85$

Subgroup observations

ALT and AST declines were similar regardless of T2D status or GLP-1 use.

LDL-C reductions were similar in T2D and non-T2D patients.

LDL-C reduction was smaller in baseline GLP-1 users: -1.0 vs -11.9 mg/dL (small subgroup).

CONCLUSION

Mean liver function tests decreased over 12 months in patients receiving resmetirom.

Improvements in ALT and AST were observed irrespective of T2D or GLP-1 use.

LDL-C decreased overall; reductions were smaller in baseline GLP-1 users.

Further research should evaluate additional non-invasive measures and longer-term outcomes.

Source: *study abstract provided by user*

Key Takeaways

FROM FIBROSIS ASSESSMENT TO TARGETED MASH TREATMENT

01

Fibrosis assessment guides eligibility

Confirmed VCTE 10–20 kPa can support treatment evaluation after cirrhosis is excluded.

02

MASH-targeted therapy should be individualized

Integrate liver-related risk, cardiometabolic comorbidities and patient preferences.

03

Xelivex® improves key histological outcomes

Studies showed higher MASH resolution and fibrosis improvement vs placebo at Week 52.

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The silent savior of *liver*

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Thank you!