MASLD

In the Era of Liver-Directed Treatment

How to Maximize Benefits from Liver-Directed Treatment?

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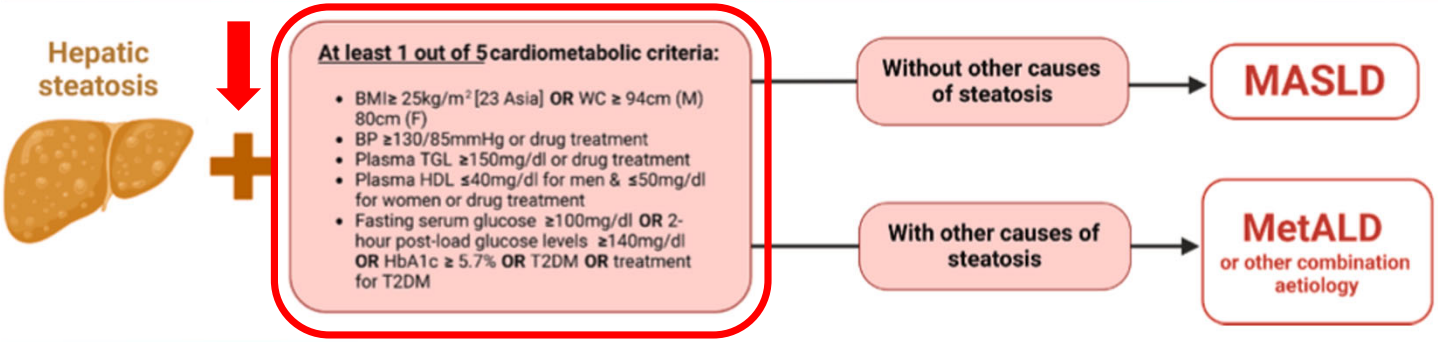
metabolic dysfunction-associated steatotic liver disease (MASLD)





BMI > 23



>130/85 mmHg

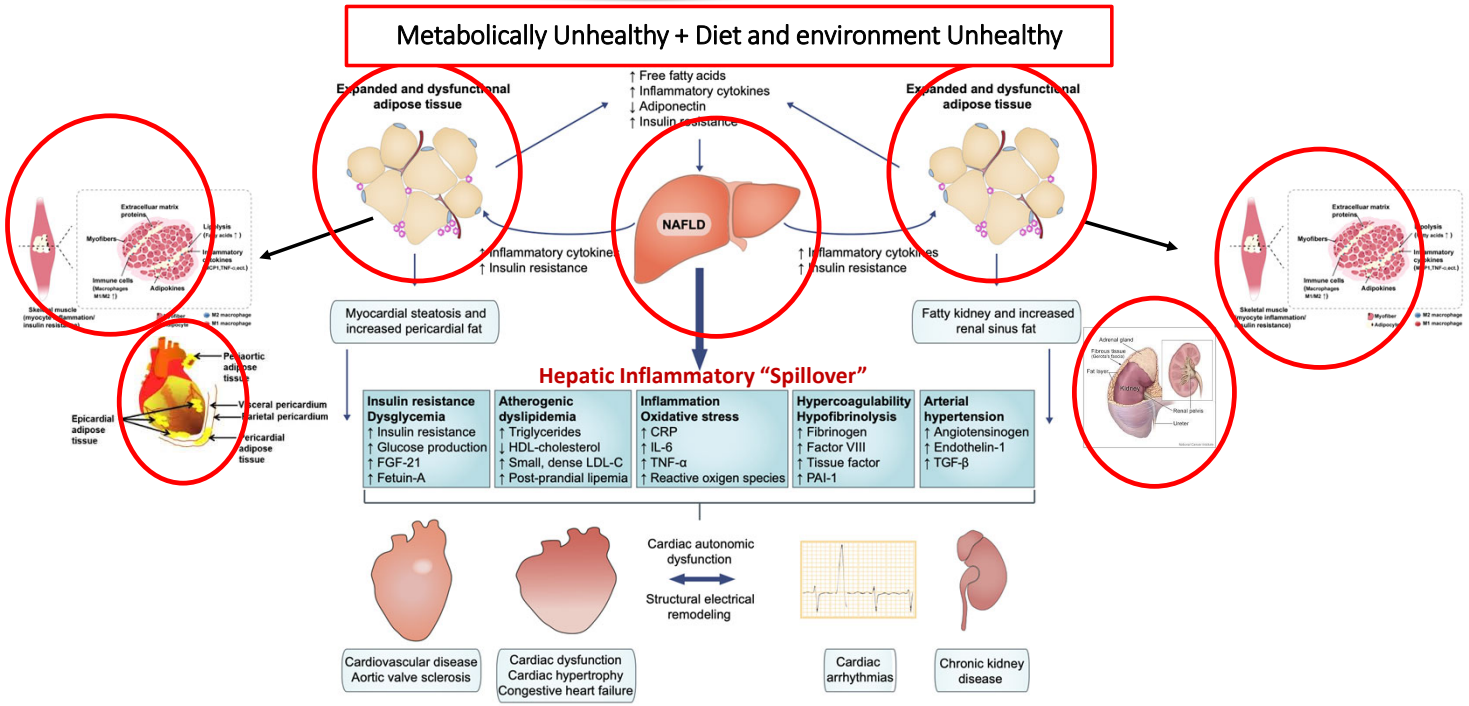


FBS > 100-125 mg/dl

TG > 150 mg/dl

HDL-Cholesterol < 39 mg/dl

Excess Fat is The Main Driver of Metabolic Dysfunction-Associated Steatotic Liver Disease



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Standard Basic Treatment Strategy for MASLD

- Comprehensive lifestyle modification (nutrition, exercise, and behaviour modification)
- Optimal control of comorbid metabolic conditions
- Pharmacologic treatment with Pioglitazone and Vitamin E could be considered in appropriate patients.
- Glucagon-like peptide 1 (GLP-1) and GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists for the treatment of type 2 diabetes and overweight/obesity.

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What Does " *Liver-directed* Treatment for MASLD " Mean?

- **MASLD, STEP 1**

  Body Fat Excess,

  Simple Liver Steatosis,

  No Liver Inflammation,

  No Liver Fibrosis

- **MASLD, STEP 2**

  Body Fat Excess,

  Steatohepatitis

  +

  Starting Liver Fibrosis

- **MASLD, STEP 3**

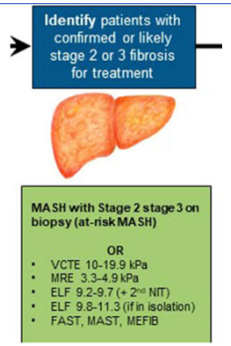
  ± Body Fat Excess,

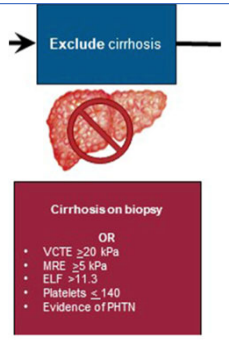
  Established Advanced Liver Fibrosis with

  Clinically Significant Portal

  Hypertension







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The Treatment for Step 2 of MASLD has 2 primary endpoints

- **MASLD, STEP 1**

  Body Fat Excess,

  Simple Liver Steatosis,

  No Liver Inflammation,

  No Liver Fibrosis

- **MASLD, STEP 2**

  Body Fat Excess, Steatohepatitis

  +

  Starting Liver Fibrosis

- **MASLD, STEP 3**

  ± Body Fat Excess,

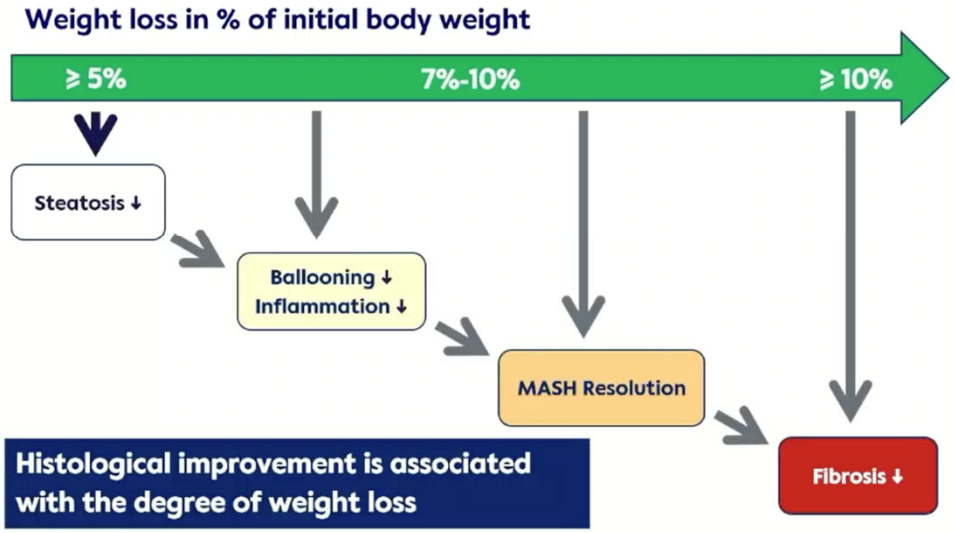
  Established Advanced Liver Fibrosis with

  Clinically Significant Portal Hypertension

- **Resolution of** steatohepatitis (**inflammation**) without worsening of fibrosis
- **Improvement of fibrosis,** at least one stage without worsening of steatohepatitis

Weight Loss, the Main and Standard Non-pharmacological MASLD Liver-directed Treatment

Treatment of MASLD: Non-pharmacological therapy



1. **Weight loss**: dietary & behavioural measures, overweight individuals should reduce weight by ≥5 % for steatotis, 7-10% for inflammation and ≥10 % for fibrosis improvement
2. **Dietary recommendation**: prefer Mediterranean diet; limit ultra-processed food, avoid sugar-sweetened beverages, discourage alcohol
3. **Physical activity**: tailored to individual's preferences and ability (preferably >150 min/week moderate)

EASL-EASD-EASO MASLD clinical practice guideline. *J Hepatol*. 2024 (*in press*)

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FIRST PHARMACOLOGICAL LIVER-DIRECTED TREATMENT

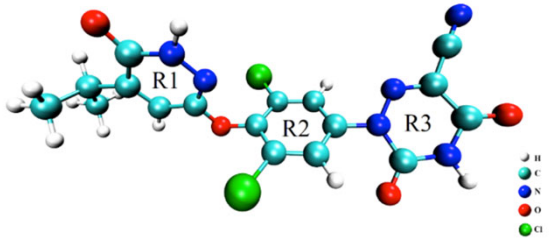


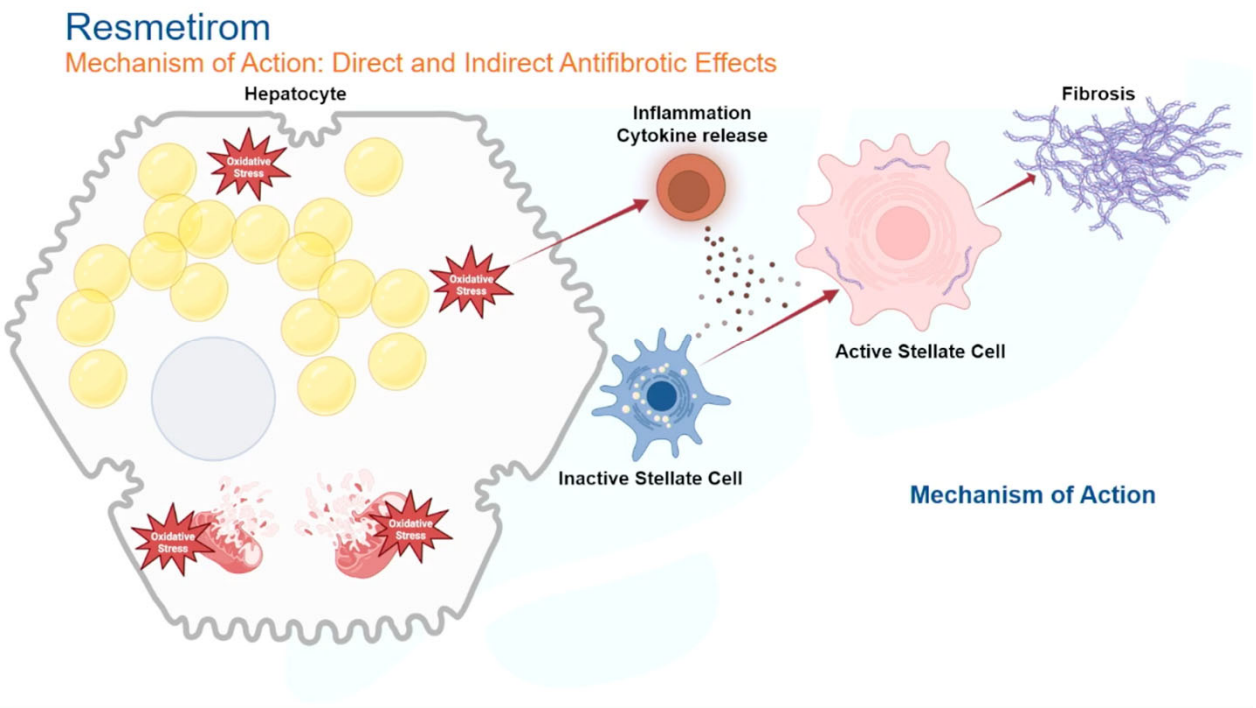
Fig. 1 Molecular structure of resmetirom.

After more than 2 decades of research,

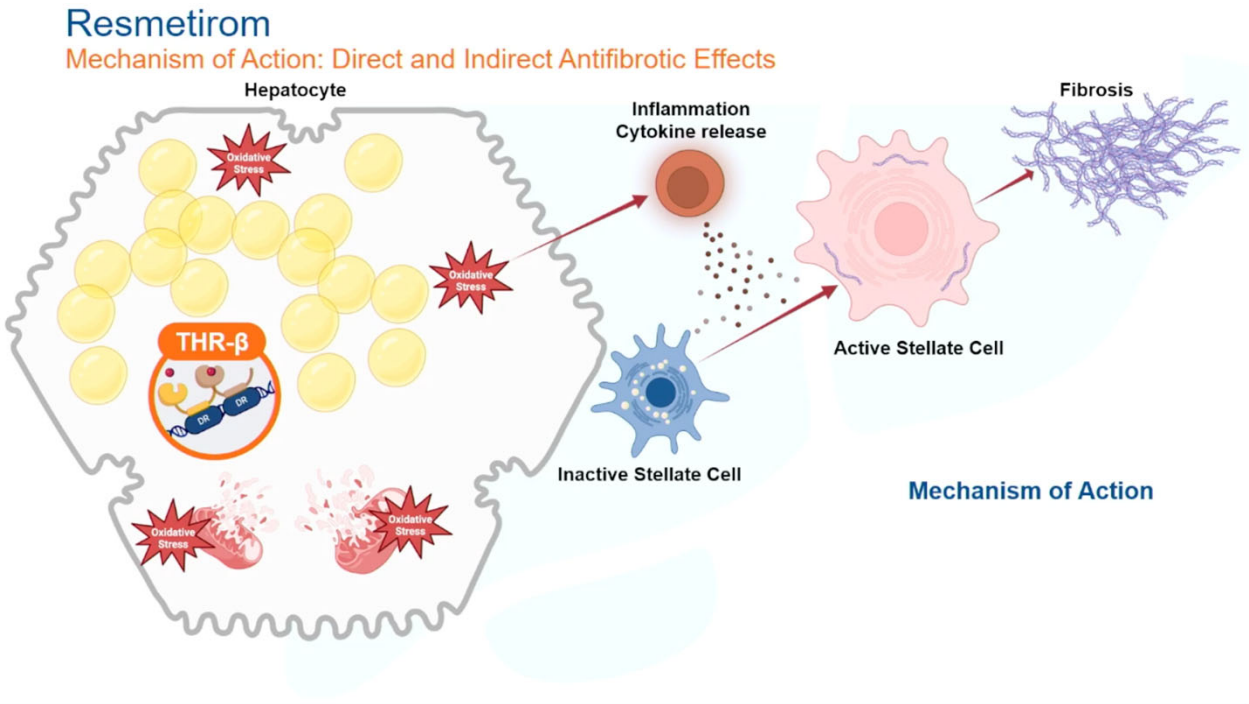
Resmetirom, The First Pharmacological Liver-directed Treatment for MASLD

Received accelerated approval from the United States Food and Drug Administration (FDA) in March 2024 for the treatment of at-risk MASH/NASH with moderate to advanced liver fibrosis.

What happens in MASLD Step 2?



How does Resmetirom act in MASLD Step 2?



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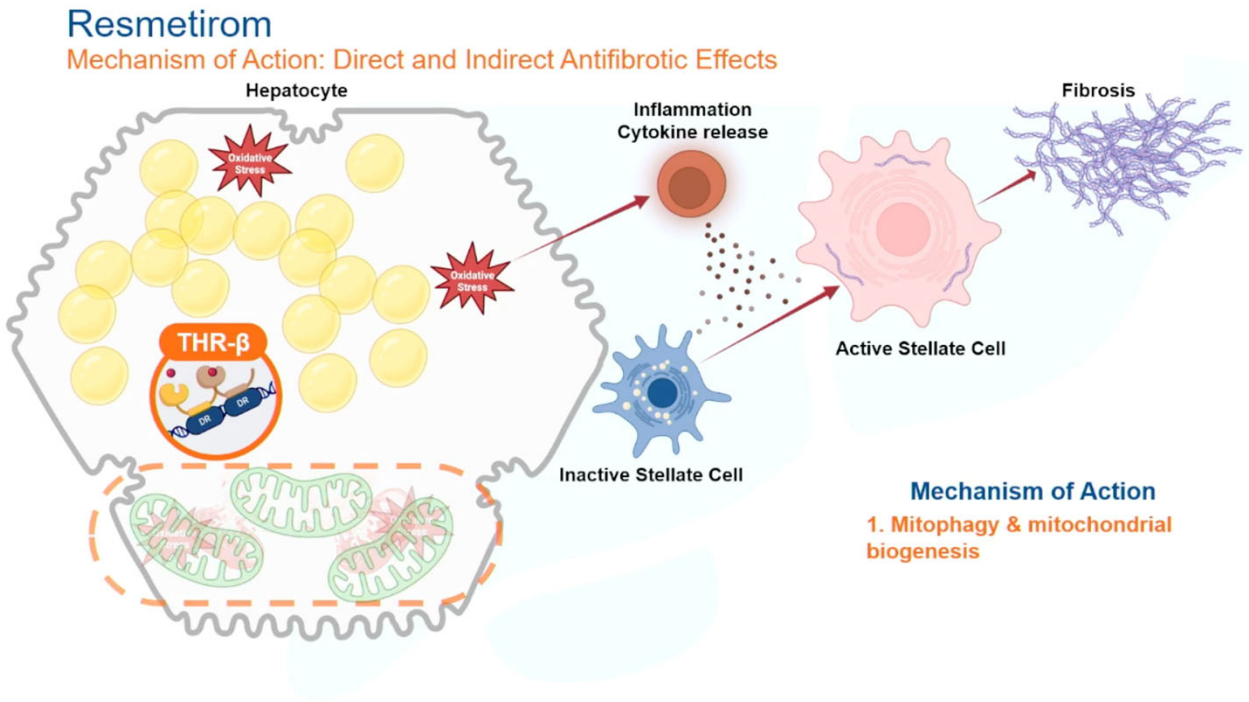

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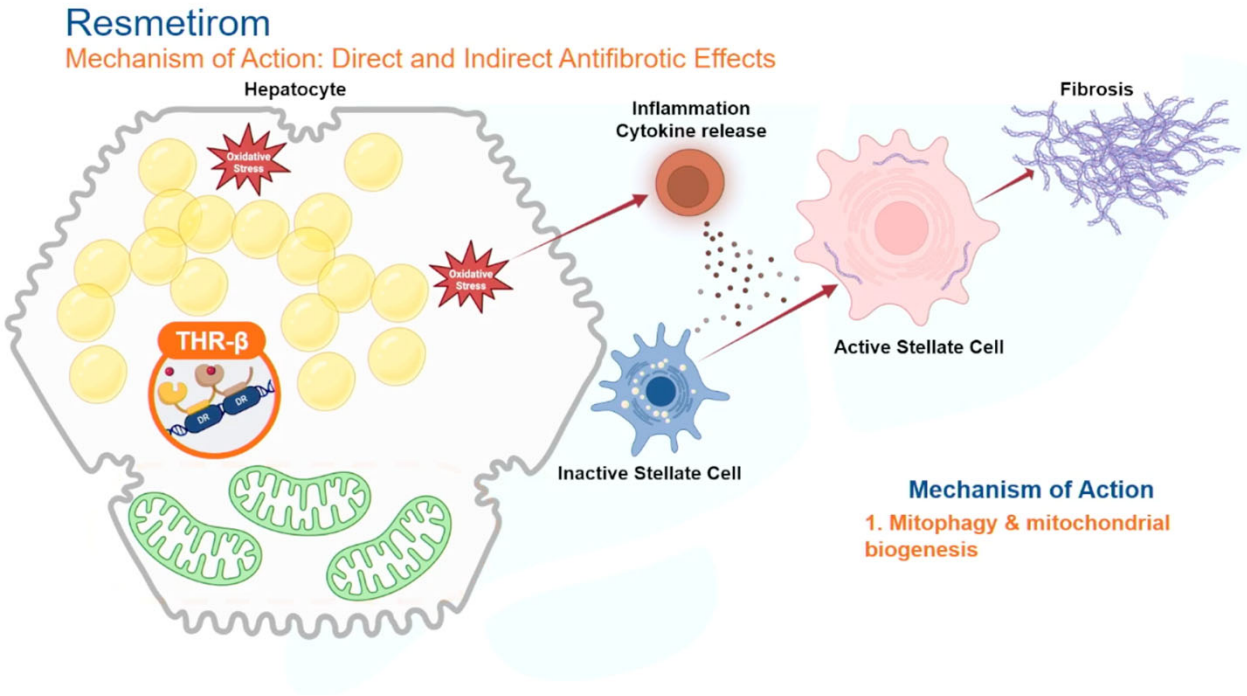

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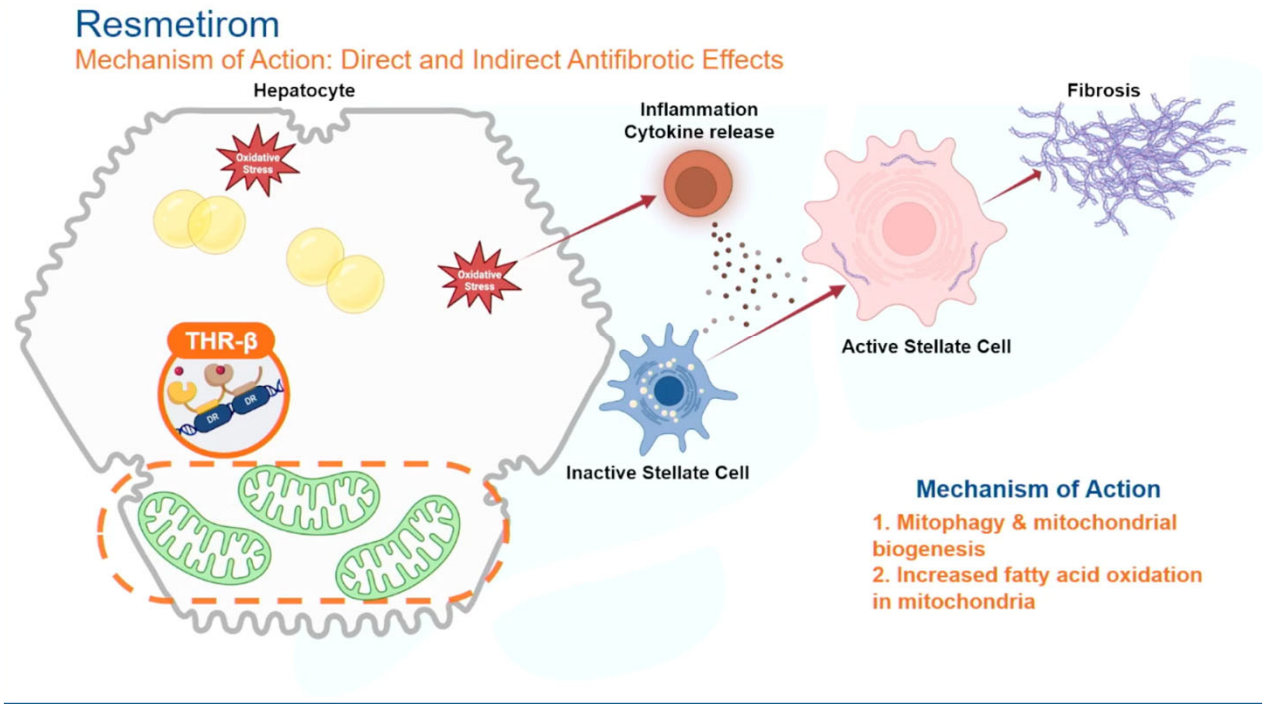
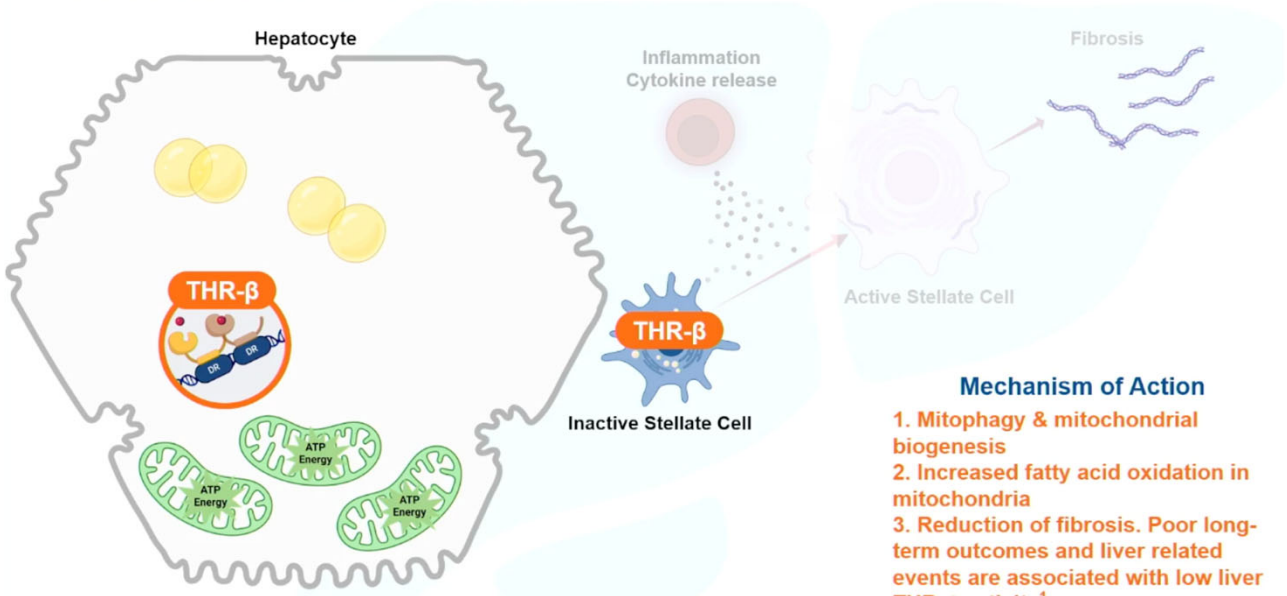


How does Resmetirom act in MASLD Step 2?

Resmetirom

Mechanism of Action: Direct and Indirect Antifibrotic Effects



Mechanism of Action

1. Mitophagy & mitochondrial biogenesis
2. Increased fatty acid oxidation in mitochondria
3. Reduction of fibrosis. Poor long-term outcomes and liver related events are associated with low liver THR-β activity[1]

1. Kendall, T.J., Jimenez-Ramos, M., Turner, F. *et al.* An integrated gene-to-outcome multimodal database for metabolic dysfunction-associated steatotic liver disease. *Nat Med* **29**, 2939–2953 (2023). https://doi.org/10.1038/s41591-023-02602-2

How does Resmetirom act in MASLD Step 2?

The role of THR β agonists in MASLD

Metabolic dysregulation

↓

Downregulation of deiodinase (DIO) activity

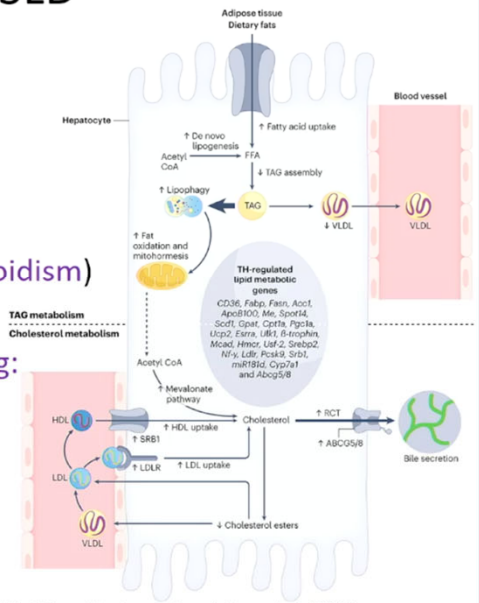
↓

Reduced conversion of T4 to T3 (intrahepatic hypothyroidism)

THR β agonists maintain lipid homeostasis by increasing:

- lipophagy, fatty acid β-oxidation
- mitochondrial turnover
- cholesterol clearance

The result is decreased steatosis and inflammation



Sinha RA et al. Actions of thyroid hormones and thyromimetics on the liver. Nat Rev Gastroenterol Hepatol. 2025

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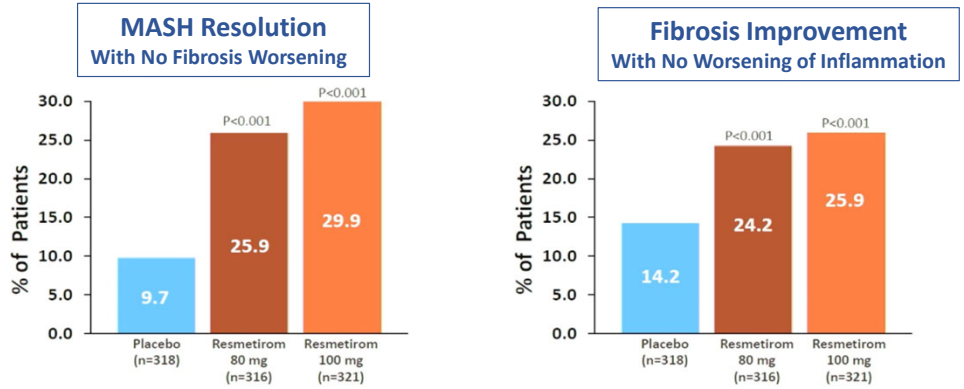
Based on findings from the one-year trial data of the MAESTRO-NASH clinical trial, combined with safety data from the MAESTRO-NAFLD-1 trial, Resmetirom ACHIVED both 2 primary endpoints for MASH treatment:

Resmetirom (52 weeks, phase 3 study)

primary endpoints: resolution of NASH and fibrosis improvement



Harrison SA, et al. N Engl J Med. 2024

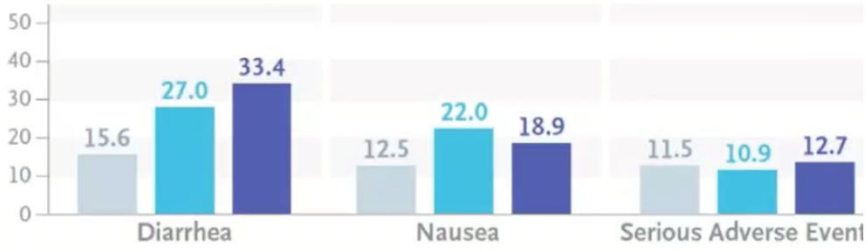
Resolution of steatohepatitis (**inflammation**) without worsening of fibrosis (It was 26-30% compared with 10% for Resmetirom and Placebo, respectively)

Improvement of fibrosis, at least one stage without worsening of steatohepatitis at 52 weeks (It was 24-26% compared with 14% for Resmetirom and Placebo, respectively)

Treatment of MASLD: Thyroid hormone receptor β agonist Resmetirom

N=966, 52 weeks, ~66% Type 2 DM, ~60% F3, BMI ~35 kg/m²; RES 100 vs. 80 mg/d vs. PLACEBO

- Improvements in cardiometabolic biomarkers (LDL cholesterol) and fibrosis NITs (ELF, VCTE)
- Acceptable safety, gastrointestinal side effects (nausea, diarrhea)
- No data on liver-related outcomes or long-term safety



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Resmetirom "is indicated in CONJUNCTION with DIET and EXERCISE and Optimal control of comorbid metabolic conditions as standard basic treatment of at-risk non-cirrhotic MASH with moderate to advanced liver fibrosis in ADULTS."

- **Standard Basic Non-pharmacological MASLD Treatment**

  DIET

  EXERCISE

  Optimal control of comorbid metabolic conditions

+

- **Pharmacological**

Liver-directed Treatment

WHOM TO TREAT (at-risk MASH Population)

Four Evidences are Needed for Liver-directed Treatment (to be at-risk MASH case);

- **1. ≥3 of 5 cardiometabolic risk factors (BMI>30, BP>130/85, Glu>100, TG>150, and HDL<40-50), and**
- **2. Steatosis (CAP of 280 dB/m or more within the past 3 months), and**
- **3. MASH (AST/ALT>17-20 U/L, without other causes like HBV, HCV, AIH, PBC, PSC, alcohol, or biopsy-confirmed MASH with NAS score 4 and more), and**
- **4. Liver fibrosis (HAI stage 2-4 of on liver biopsy up to 3 years, or LSM>8.5-15 kPa within the past 3 months)**

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Not all efficacy and safety data on Resmetirom in patients with cirrhosis have been published yet, so Resmetirom is not recommended for persons with;

- **Concomitant uncontrolled active liver diseases** (such as AIIH and PBC)
- **Cirrhosis**, including LSM via Fibroscan >20 kPa or on liver biopsy
- **Signs of portal hypertension**, ascites, varices, portosystemic venous collaterals, or hepatic encephalopathy, irrespective of liver biopsy
- **Elevated bilirubin, Platelets <140,000/mL, Hepatic nodularity** on imaging not otherwise explained

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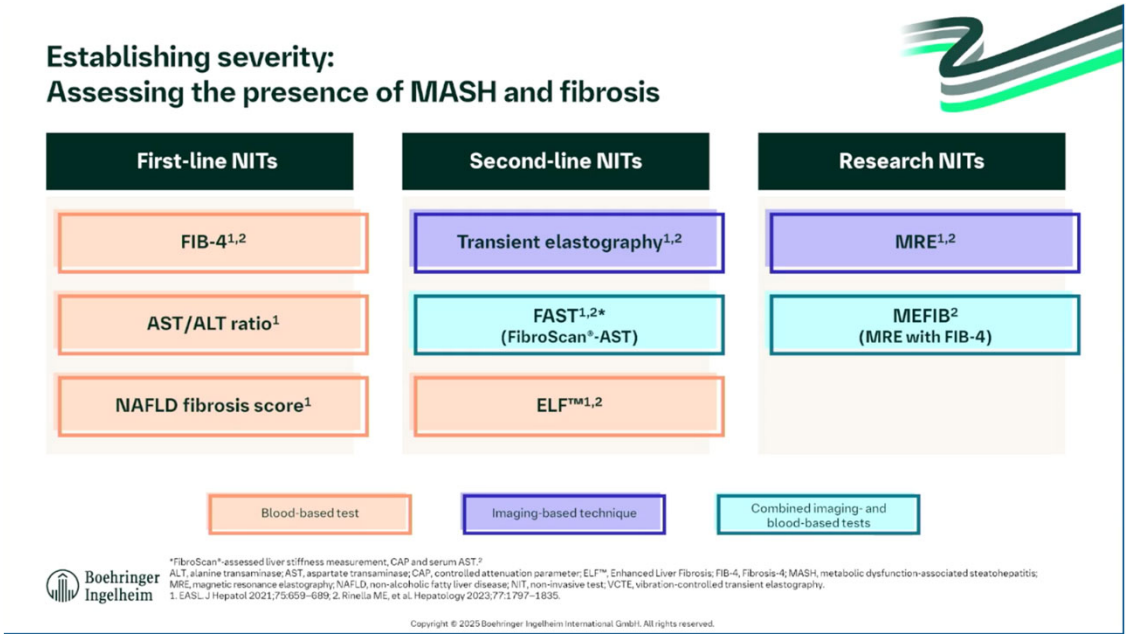
There are no FDA-approved non-invasive tests to diagnose MASH with significant fibrosis or to monitor response to pharmacotherapy.



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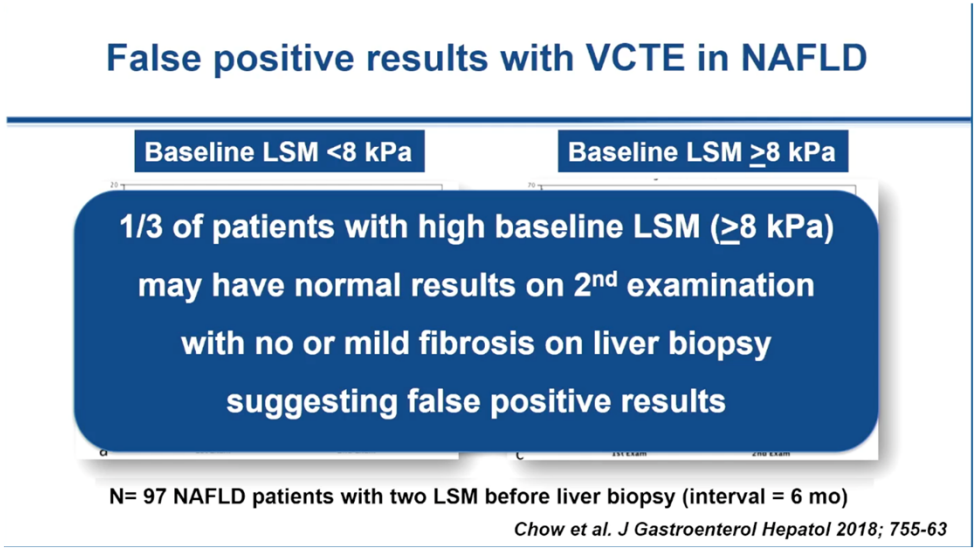

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▶ **Table 2** Overview of eligible patients for resmetirom treatment with statin use, weight distribution and presence of ≥3 cardiometabolic risk factors. The latter comprise type 2 diabetes, arterial hypertension, elevated triglycerides ≥150 mg/dL, low high-density lipoprotein cholesterol and/or body mass index ≥30 kg/m^2. FAST, FibroScan-AST; NAS, non-alcoholic fatty liver disease activity score; VCTE, vibration-controlled transient elastography.

	Full histology available (n=180)	**FAST available (without full histology) (n=638)**			**VCTE available (without full histology) (n=755)**	
Eligibility criteria for resmetirom therapy	F2/3 fibrosis and NAS ≥4	FAST score ≥0.67 & VCTE <15 kPa	FAST score ≥0.67 with platelets ≥140×10^9/L	VCTE 10–15 kPa or FAST score ≥0.67 with platelets ≥140×10^9/L	VCTE 10–15 kPa with platelets ≥140×10^9/L	VCTE 8–15 kPa
Eligible patients	61/180 (33.9)	41/638 (6.4)	95/638 (14.9)	191/638 (30.0)	130/755 (17.2)	206/755 (27.3)
Statin use	16/61 (26.2)	6/41 (14.6)	28/94 (29.8)	51/189 (27.0)	33/129 (25.6)	53/203 (26.1)
Weight ≥100 kg	29/61 (47.5)	17/41 (41.5)	53/95 (55.8)	95/191 (49.7)	55/130 (42.3)	95/206 (46.1)
Cardiometabolic risk factors (≥3)	33/53 (62.3)	23/34 (67.6)	61/82 (74.4)	107/155 (69.0)	60/95 (63.2)	97/159 (61.0)

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▶ **Table 3** Comparison between non-invasive and invasive assessment of fibrotic MASH. FAST, FibroScan-AST Score; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatotic hepatitis.

		Histologic assessment	
		No Resmetirom	**Resmetirom**
LSM < 15 kPa & FAST ≥ 0.67	No Resmetirom	103	47 **(30% under prescription)**
	Resmetirom	9 **(45% over prescription)**	11

Messer EK et al. Evaluating Resmetirom Eligibility... Z Gastroenterol | © 2025

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While liver biopsy is not typically recommended for fibrosis staging in the current clinical practice of patient selection, however, histologic examination remains the gold standard for:

- quantifying fibrosis in doubtful equivocal extremes of liver fibrosis

- for cases with suspicion of concomitant liver disease (e.g., AIH)

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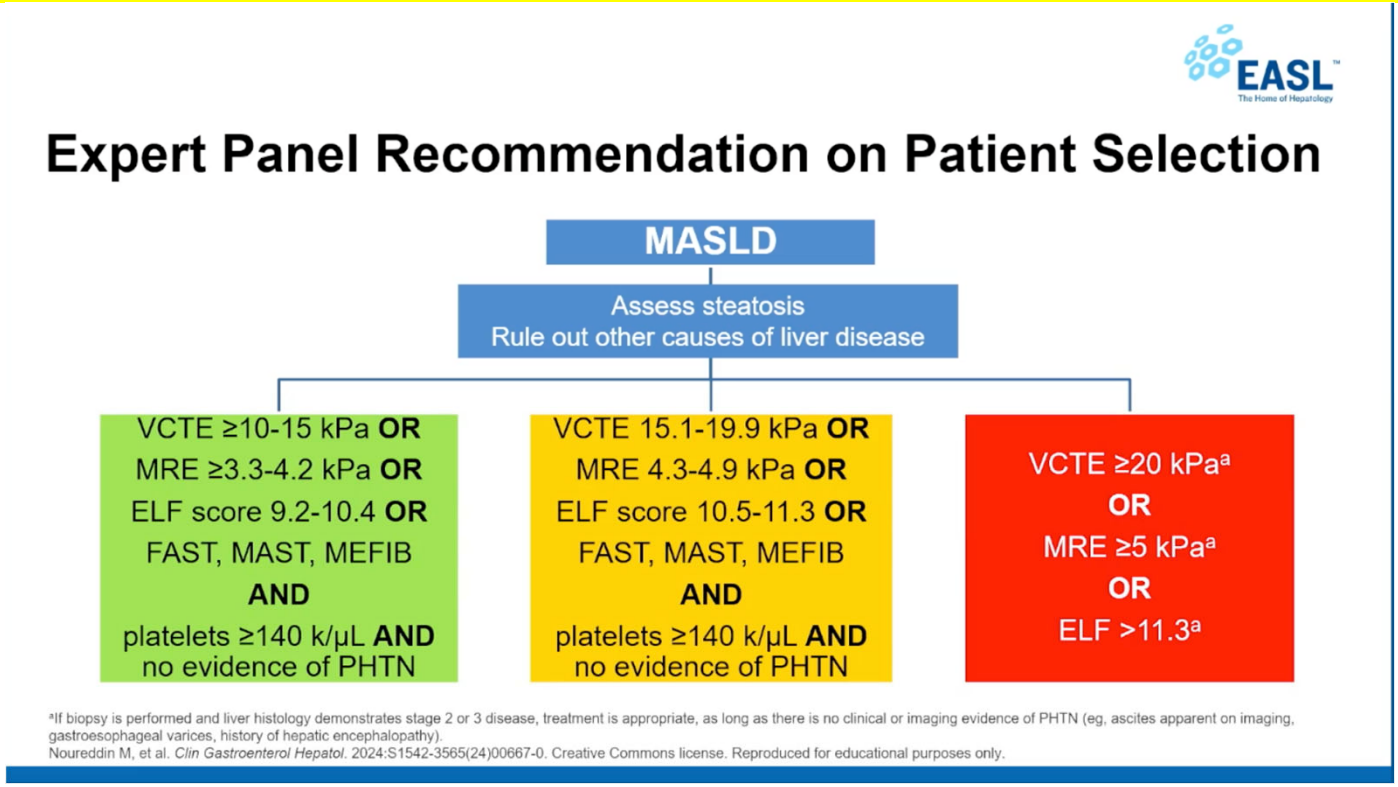

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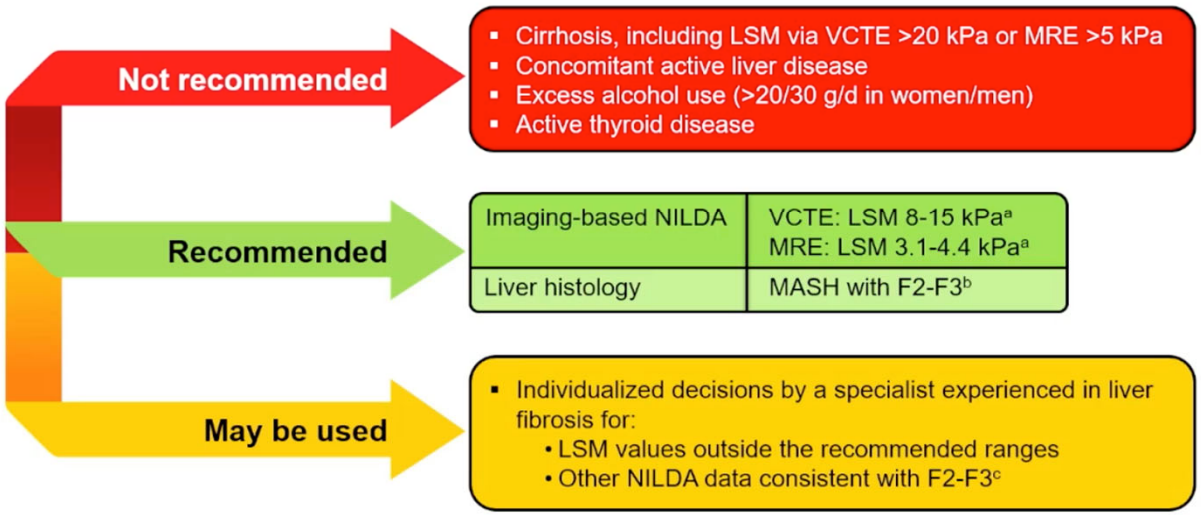
AASLD Guidance for Patient Selection



[a]Modified from the AASLD NILDA guidelines. [b]Liver biopsy is not routinely recommended for staging of MASH. [c]Imaging-based NILDA is preferred (eg, shear wave elastography [applying local standards for F2-F3]) vs ELF score (9.2-10.4). The latter range is based on the IQR from the MAESTRO trial data; no recommendations are available from the AASLD NILDA guidelines.
NILDA: noninvasive liver disease assessment.

Liver-directed Treatment Safety Check

- Symptomatic gallstone-related conditions such as acute cholecystitis
- Active, untreated thyroid disease (hyperthyroidism or hypothyroidism)

Liver-directed Treatment Safety Check

- **Resmetirom is a cytochrome P450 inhibitor**
  - **Clopidogrel (Plavix)**

    Resmetirom dose reduction is recommended (80 mg/d for persons who weigh 100 kg or more; 60 mg/d for persons who weigh less than 100 kg)
  - **Statins**

    When taken concurrently with Resmetirom, the recommended maximum dosages for rosuvastatin and simvastatin are 20 mg/day, and for atorvastatin and pravastatin are 40 mg/day.

On-treatment monitoring - After starting

1. Initial assessment during the first 3 months (safety and tolerability)

- to exclude the presence of a **hepatotoxicity** signal and to confirm the absence of concomitant liver disease with the initiation of any new drug.

- Hepatic function panel testing should be obtained at baseline and at periodic intervals to determine response and adverse events.

- **Side effects management**
  - The most common adverse reactions induced by Resmetirom were mild to moderate GI disorders, mainly nausea and diarrhea, followed by constipation, abdominal pain, and vomiting.

On-treatment monitoring - After starting

2. Assessment at the sixth month (early response monitoring)

- a 17 U/L or greater decrease in ALT
- reduction of ALT to 40 U/L or less
- at least 30% reduction from baseline
- normalization or significant improvement in ALT

- **Persons whose ALT remains consistently elevated may be judged as non-responders.**
- **Fibroscan may be considered, as it can suggest an early response.**
- **Importantly, the absence of response at 6 months may be inadequate to assess treatment response fully.**

On-treatment monitoring - After starting

3. Assessment at the month 12, not before, and then annually (efficacy monitoring)

Continue treatment if:

Aminotransferases **improved** (compared with baseline or normalization)

Aminotransferases are **stable**, **but other** indications of disease improvement are present (eg, improvement in MRI-PDFF or Fibroscan).

Changes in CAP score in isolation are insufficient to determine treatment response; however, an improved CAP score would support improvement in MASH.

Fibroscan, although not an ideal marker for monitoring the response to Resmetirom, should be part of regular patient monitoring **every 12 months.**

A **20-30% or greater change** in kPa on MRE or a decrease in LSM to less than 10 kPa may be useful to define a meaningful change for improvement and, by extension, for worsening.

In those who had MRI-PDFF at baseline, a reduction in MRI-PDFF of >30% suggests a likely histologic response.

Stabilization of fibrosis after one year of treatment may portend important long-term benefits.

On-treatment monitoring - After starting

Stopping Rules:

- Drug not tolerated
- Significantly worsening ALT (>20-30%), especially for persons with advanced fibrosis
- >5 Kpa or >20-30% increase in liver stiffness or worsening in at least >2 NITs
- No response in MRI-PDFF (<30% relative to baseline improvement) if obtained at baseline

Challenges in Liver-targeted MASLD Treatment

- MASLD population with DM or HTN, but Less than three cardiometabolic risk factors ?
- MASLD population with fibrosis, but normal liver enzymes ?
- MASLD population with significant fibrosis (cirrhosis) ?
- GLP-1 or Resmetirom as starting treatment, which one ?
- MASLD with other concomitant liver diseases ?