Residual Risk Reduction initiative

Metabolic Dysfunction-Associated Steatohepatitis (MASH)

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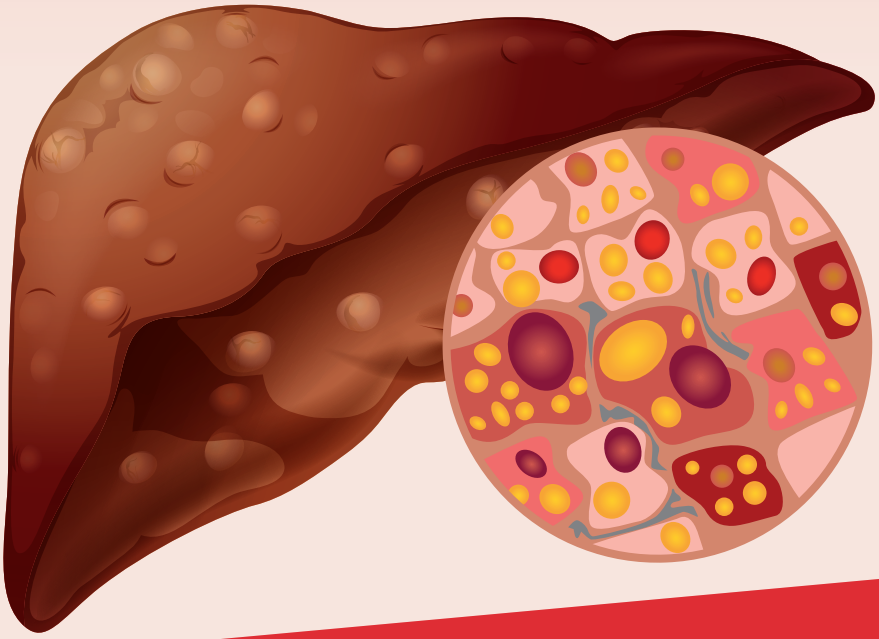


DEFINING TOMORROW'S VASCULAR STRATEGIES

This book is a poignant tribute to

Professor Jean-Charles Fruchart,

who co-authored this work
before his passing in September 2024.

Published posthumously, it stands as a tribute
to his enduring legacy and contributions to the
scientific community.

Preface

Metabolic dysfunction-associated fatty liver disease (MAFLD)[1], formerly known as non-alcoholic fatty liver disease (NAFLD), is an umbrella term covering the spectrum of fatty liver diseases, ranging from isolated steatosis to the most severe form, metabolic dysfunction-associated steatohepatitis (MASH)[1], formerly known as non-alcoholic steatohepatitis (NASH). Over the last three decades, the prevalence of MAFLD has surged by over 50%, paralleling the rising pandemics of obesity, pre-diabetes, and type 2 diabetes, affecting more than 30% of the global general population[2]. The increasing prevalence of MASH has resulted in it becoming the leading cause of liver transplantation in the USA and Europe[3].

Diagnosis and management of MASH present multiple challenges. Symptoms are often silent or non-specific, leading to delayed diagnosis. There is, therefore, an urgent need for approved and clinically applicable biomarkers for MASH to facilitate early detection. Another significant gap is the lack of specific treatments for MAFLD and MASH, despite their high incidence and growing global health impact.

In this context, the advent of novel therapeutic avenues is particularly promising. The introduction of thyroid receptor beta agonists, such as Resmetirom, marks a significant advance in the management of MASH. Resmetirom has recently become the first drug in its class approved by the FDA[4], representing a meaningful step towards addressing the underlying metabolic dysfunction associated with MASH. By targeting thyroid hormone signaling pathways, resmetirom has shown potential in reducing hepatic fat, fibrosis, and improving related metabolic parameters[5].

Alongside thyroid receptor beta agonists, the PPAR (peroxisome proliferator-activated receptor) class is under investigation as a potential therapeutic avenue for treating MAFLD and MASH. PPARα and PPARγ agonists are particularly being explored for their roles in modulating lipid metabolism and insulin sensitivity, which are key factors in the management of fatty liver diseases.

This latest booklet and slide deck from the Residual Risk Reduction Initiative provides an accessible resource on MASH epidemiology, diagnosis, and management. .

References:

1. Younossi ZM, *et al. Hepatol* 2023;**77**:1335-47.
2. Shirazi F, *et al. J Clin Exp Hepatol* 2020;**10**:30-6.
1. Rinella ME, *et al. J Clin Gastroenterol* 2022;**56**:685-96.
2. Younossi ZM, *et al. Hepatology* 2023;**77**:1335-47.
3. Shirazi F, *et al. J Clin Exp Hepatol* 2020;10:30-6.
4. Guirguis E, *et al. Ann Pharmacother* 2025;59:162-73.
5. Stephen A. Harrison *et al. N Engl J Med* 2024;**390**:497-509.

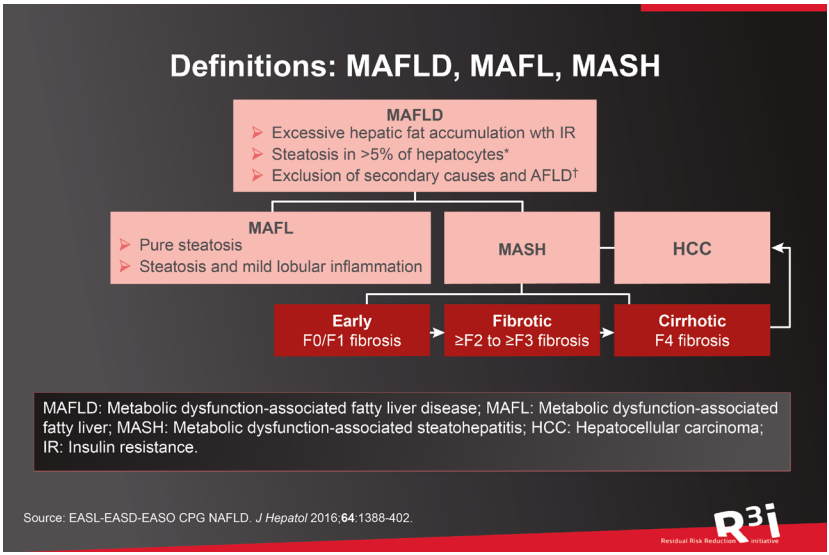
Contents

Background to MAFLD/MASH

SECTION

1

Residual Risk Reduction initiative

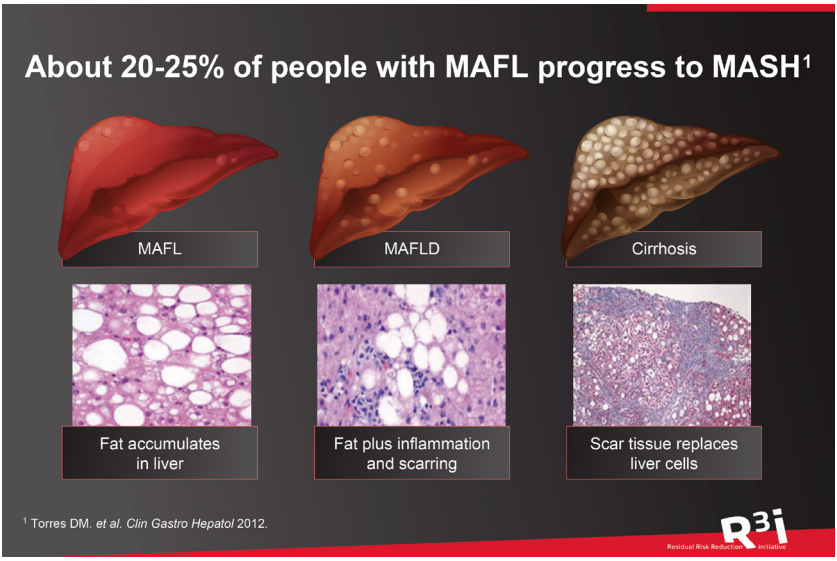


Definitions: MAFLD, MAFL, MASH

Metabolic dysfunction-associated fatty liver disease (MAFLD) comprises a spectrum of related liver disorders, ranging from Metabolic Dysfunction-Associated fatty liver (MAFL; simple steatosis) to Metabolic Dysfunction-Associated Steatohepatitis (MASH). MASH, the most severe form of MAFLD, is defined by the presence of liver damage in the form of steatosis, hepatocyte ballooning, and lobular inflammation, with or without fibrosis. MASH is a serious liver disease that can lead to liver scarring (cirrhosis), hepatocellular carcinoma (HCC), liver transplantation and early death.

Reference:

EASL-EASD-EASO CPG MAFLD. *J Hepatol* 2016;**64**:1388-402.



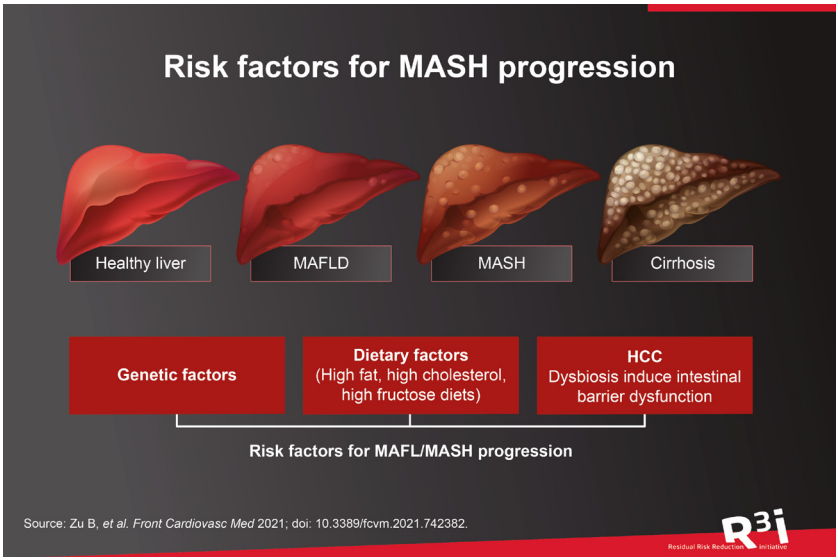
Progression of MAFLD

Progression of MAFLD follows four stages:

- Liver fat accumulation (MAFL)
- Early MASH (no or negligible fibrosis), with fatty infiltration and liver inflammation
- Advanced or bridging fibrosis with excessive accumulation of extracellular matrix proteins, including collagen, in the liver
- Liver cirrhosis

Reference:

EASL-EASD-EASO CPG MAFLD. *J Hepatol* 2016;**64**:1388-402.

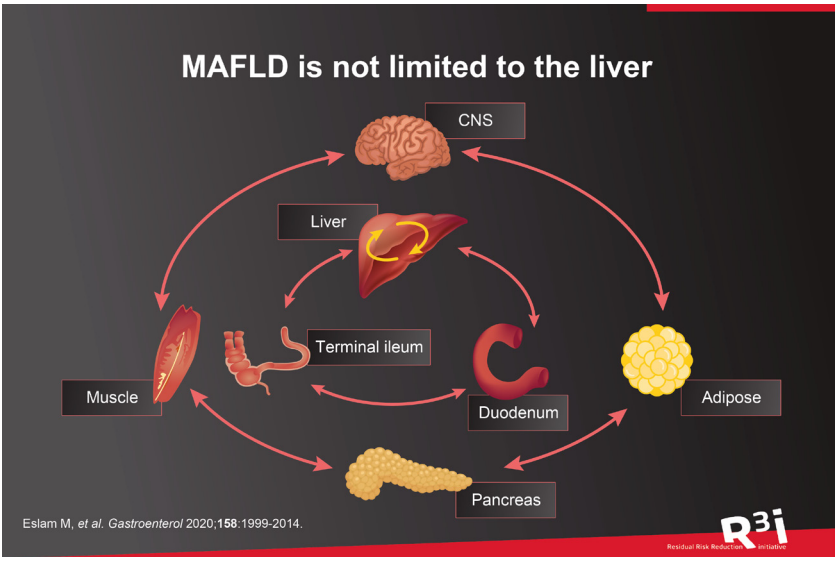


Risk factors for MASH progression

Inherited and environmental factors contribute to the progression to MASH. Dietary factors are one of the most important environmental factors that lead to MASH.

Reference:

Zu B, *et al. Front Cardiovasc Med* 2021; doi: 10.3389/fcvm.2021.742382

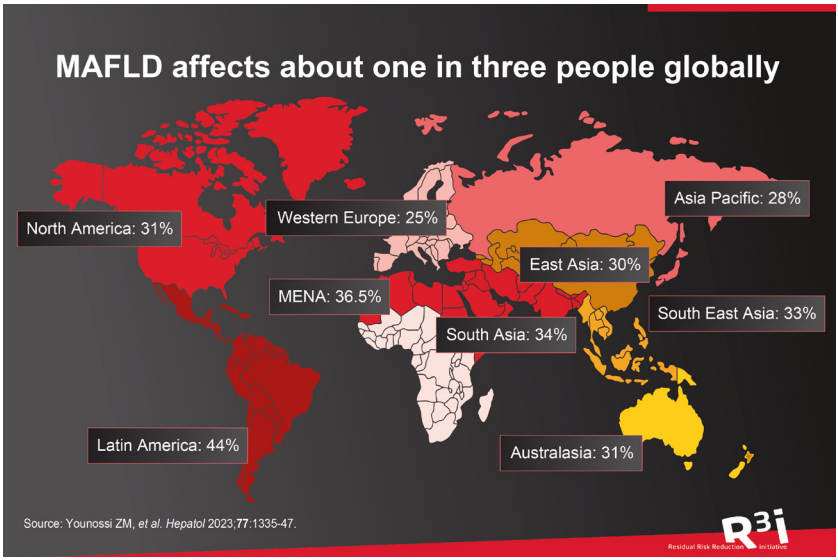


MAFLD is not limited to the liver

Recent studies suggest that MAFLD should be defined as a disease of global metabolic dysfunction, as this more accurately reflects the inter-organ crosstalk implicated in the heterogeneous pathogenesis of disease.[1] On this basis, it was recommended that MAFLD be renamed as "metabolic associated fatty liver disease" or MAFLD.[2]

References:

1. Fouad Y, *et al. Liver Int* 2020;**40**:1254-61.
2. Eslam M, *et al. Gastroenterol* 2020;**158**:1999-2014.

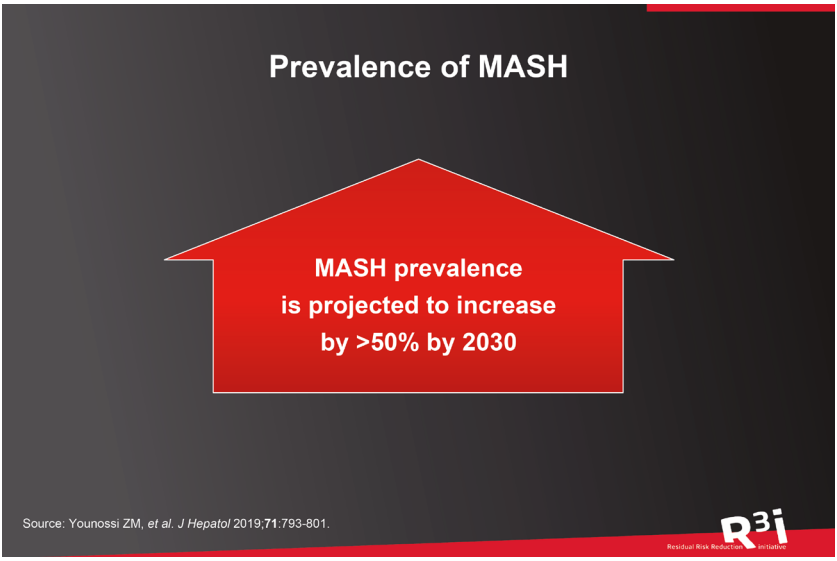


Prevalence of MAFLD

In a meta-analysis including 9,361,716 people in 92 studies, MAFLD was estimated to affect about 30% of the global population (pooled prevalence 30.05%, 95% confidence interval [CI] 27.88% to 32.22%).[1]

Reference:

1. Younossi ZM, *et al. Hepatol* 2023;**77**:1335-47.



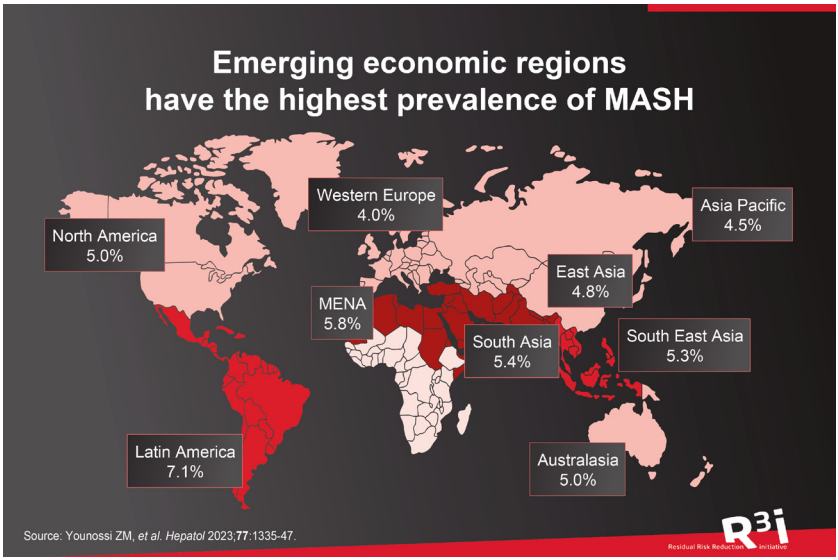
Prevalence of MASH

The reported prevalence of MASH varies substantially, largely due to the lack of a cost-effective and widely available minimally invasive diagnostic test, and the absence of specific symptoms before end-stages of the disease. In the previous meta-analysis by Younossi *et al.* (2023), the reported global prevalence for MASH was 5.27%, higher in individuals with type 2 diabetes mellitus (T2DM).[1] Another meta-analysis of eight studies reported that the frequency of biopsy confirmed MASH among MAFLD patients ranged from 15.9% to 68.3%.[2]

References:

1. Younossi ZM, *et al. Hepatol* 2023;**77**:1335-47.

2. Dufour J-F, *et al. Endocrine & Metab Sci* 2021;3: doi.org/10.1016/j.endmts.2021.100089

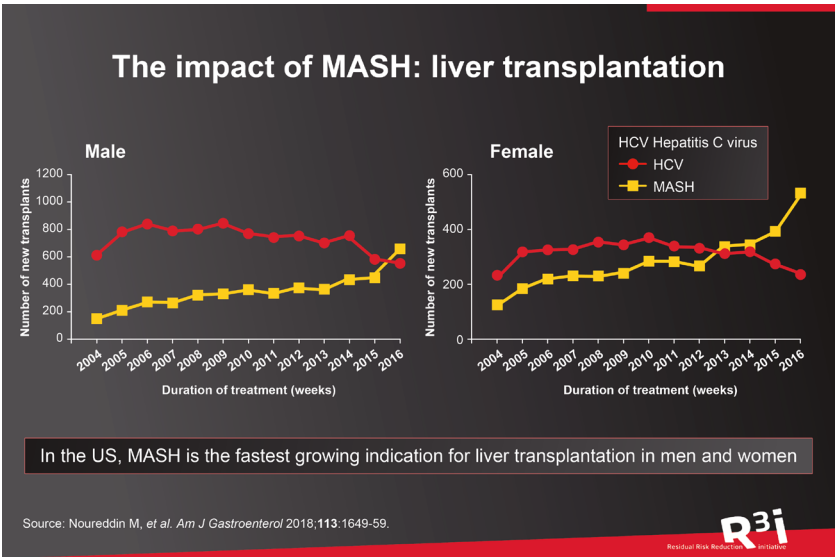


Emerging economic regions have the highest prevalence of MASH

Overall, emerging economic regions, notably the Middle East and North Africa (MENA), Latin America, and South and South-East Asia, have the highest prevalence of MASH.

Reference:

Younossi ZM, *et al. Hepatol* 2023;**77**:1335-47.

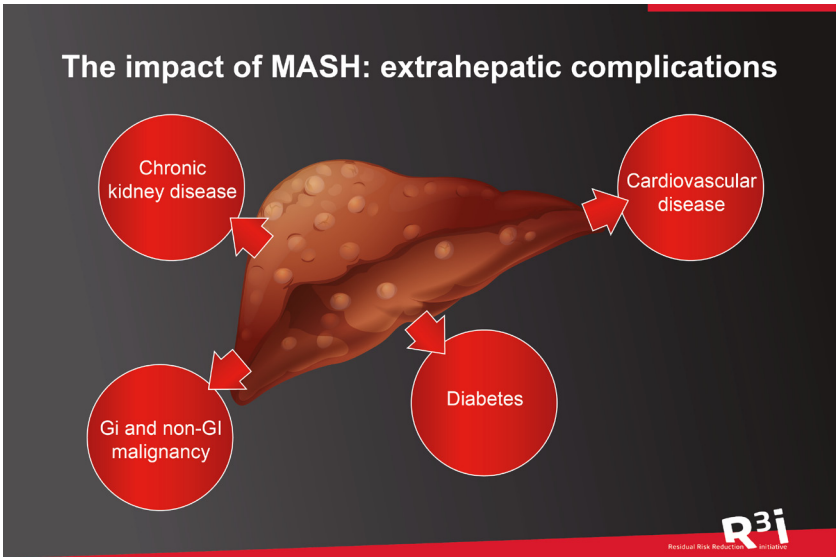


The impact of MASH: liver transplantation

MASH is associated with an increased risk of hepatocellular carcinoma (HCC), requirement for liver transplantation (LT), and liver-related mortality. Data from Europe and the USA show that MASH is the fastest growing indication for LT over the last 20 years.[1,2] In the US, among women without HCC, MASH is already the leading reason for LT,[3] and is predicted to be the leading cause of LT in both men and women by 2025.[1]

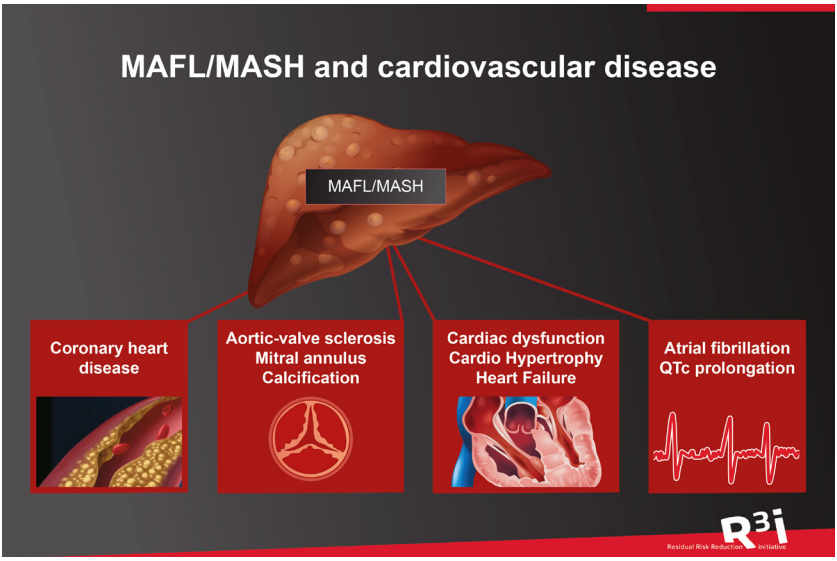
References:

1. Adam R, *et al. Transpl Int* 2018;**31**:1293-317.
2. Younossi ZM, *et al. Clin Gastroenterol Hepatol* 2021;**19**:580-9.
3. Noureddin M, *et al. Am J Gastroenterol* 2018;**113**:1649-59.



The impact of MASH: extrahepatic complications

Beyond the liver, MAFL/MASH is associated with an increased risk of extra-hepatic complications including chronic kidney disease (CKD), malignancy and cardiovascular disease (CVD).

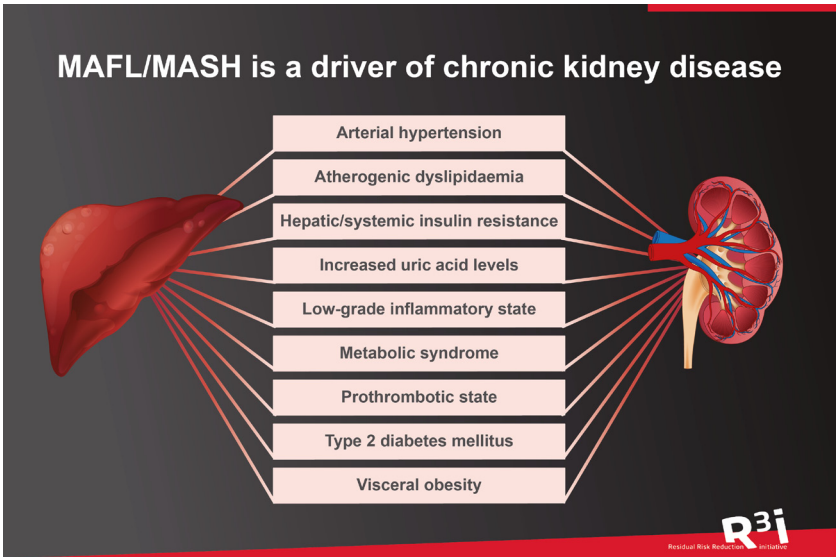


MAFL/MASH and cardiovascular disease

MAFLD increases atherosclerotic risk, adding to cardiovascular risk factors such as dyslipidaemia, obesity, arterial hypertension, and T2DM. In a meta-analysis of 16 studies including 34,043 patients (median 7-year follow-up), patients with MAFLD had a 64% higher risk of developing fatal or non-fatal cardiovascular events versus those without MAFLD, and the incidence of CVD was proportional to the severity of MAFL/MASH.[1] An updated meta-analysis in over 5 million patients reported that MAFLD was associated with an increased long-term risk (by 45%) of fatal or non-fatal CVD events.[2] The underlying pathophysiology behind this association is still incompletely understood.

References:

1. Targher G, *et al. Hepatol* 2016;**65**:589–600.
2. Mantovani A, *et al. Lancet Gastroenterol Hepatol* 2021;**6**:903-913.

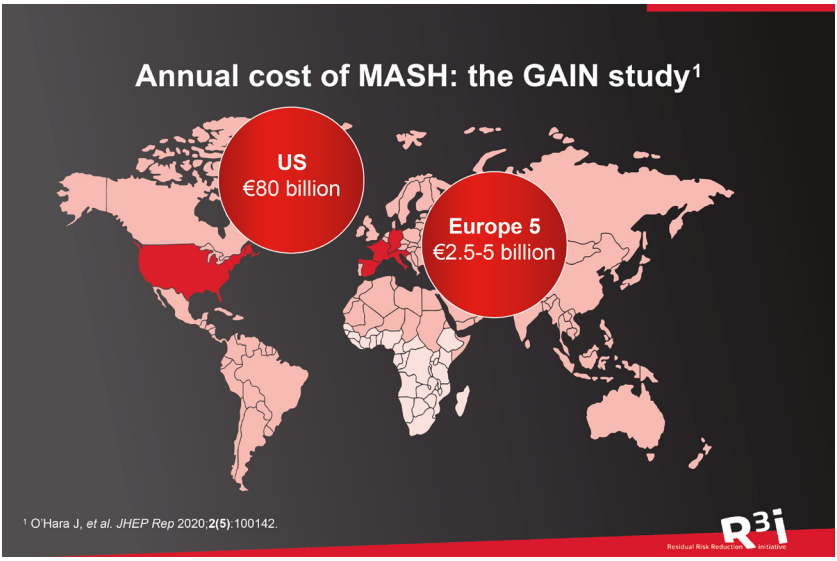


MAFL/MASH and chronic kidney disease

MAFL and CKD share common features. Both are associated with obesity, T2DM, metabolic syndrome, and insulin resistance. Studies show that CKD may co-exist with MAFL/MASH and these conditions may exacerbate one another. In a meta-analysis including 13 studies with 1,222 032 individuals (28.1% with MAFLD), MAFLD was associated with a ~1.45-fold increase in long-term risk of incident CKD≥ stage 3. This increased risk was independent of age, sex, obesity, hypertension, diabetes, and other conventional CKD risk factors.

Reference:

Mantovani A, *et al. Gut* 2022;**71**:156-62.



Economic burden of MAFLD/MASH

Globally, MAFLD/MASH poses a major economic challenge. Costs and healthcare utilisation are particularly high in patients with more severe MASH, or those who have other diseases or complications in addition to MASH.[1]

The Global Assessment of the Impact of MASH (GAIN) study provided insights into the cost landscape for the real-world MASH population across five European countries (France, Germany, Italy, Spain, and the UK) and the US.[2] MASH-related annual costs were €2,763, €4,917, and €5,509 per patient for the direct medical, non-medical and indirect cost categories, respectively. Direct medical costs for non-MASH related events were almost as high as medical costs for MASH-related events.

References:

1. Witkowski M, *et al. PharmacoEconomics* 2022;**40**:751-76.
2. O'Hara J, *et al. JHEP Rep* 2020;**2**(5):100142.

Key Points

- MASH is a serious liver disease that can lead to cirrhosis, liver transplantation (LT) and early death.
- Prevalence is projected to increase by >50% by 2030.
- By 2025, MASH will be the leading cause of LT in men and women in the USA.
- MASH increases the risk of cardiovascular disease, chronic kidney disease, and malignancy.
- Management of MASH is a major global challenge.

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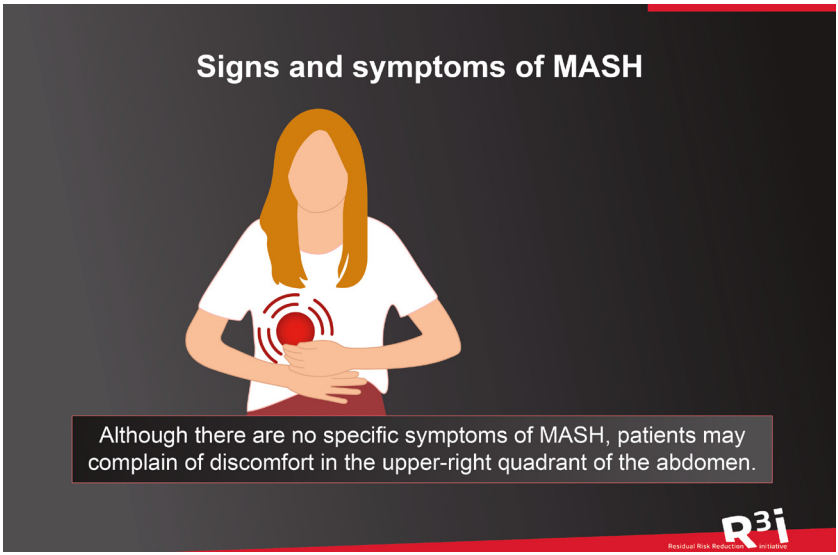
Diagnosis of MASH

SECTION

2

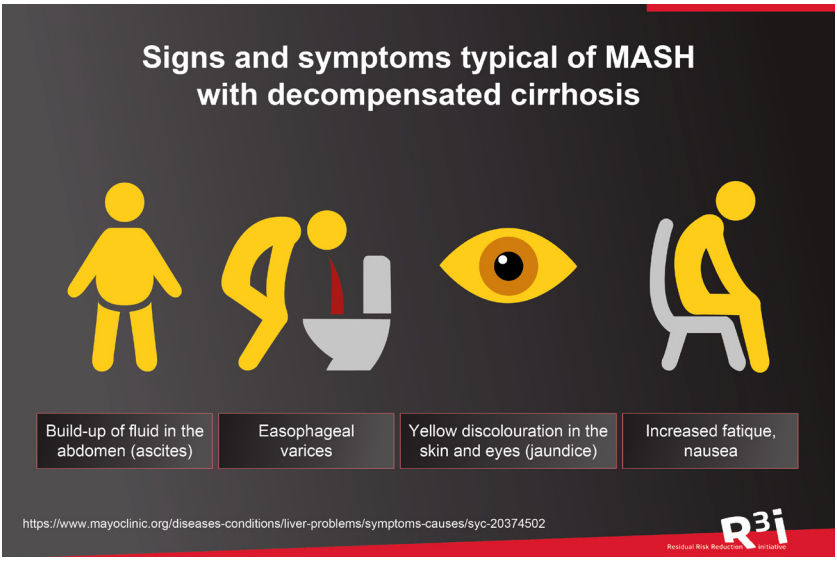
Residual Risk Reduction initiative



Signs and symptoms of MASH

Patients with MASH do not have specific symptoms before the stage of decompensated cirrhosis. Some patients experience non-specific symptoms such as fatigue, general body pain, and/or discomfort in the upper-right quadrant of the abdomen.

MASH is usually discovered incidentally through imaging, surgery or liver enzyme tests performed for unrelated reasons.

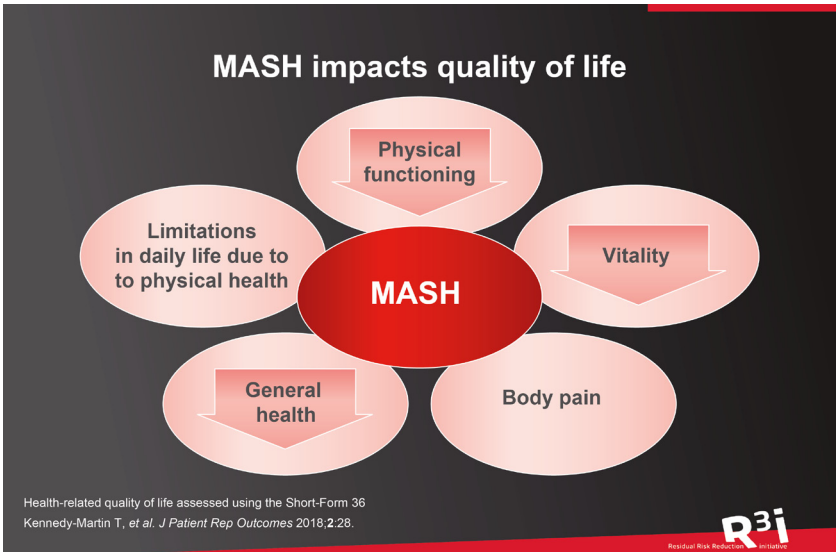


Signs and symptoms of MASH

Patients with MASH and decompensated cirrhosis, when the liver cannot regenerate anymore, may exhibit a range of symptoms and signs including abdominal discomfort, irregular sleep patterns, gastrointestinal pain, hepatic encephalopathy, and yellowing of the skin and eyes. Signs of portal hypertension include ascites, oesophageal varices, enlarged spleen, enlarged blood vessels beneath the skin's surface, and pruritus.

Reference:

https://www.mayoclinic.org/diseases-conditions/liver-problems/symptoms-causes/syc-20374502

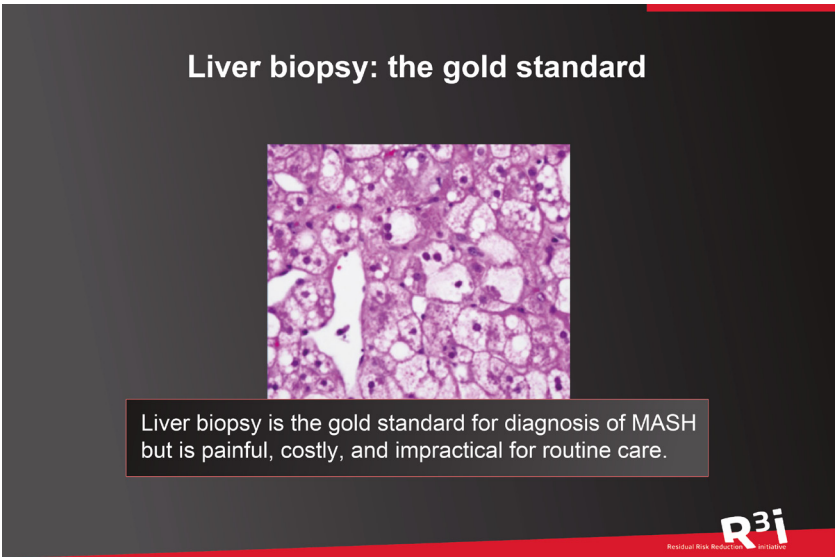


MASH impacts quality of life

MASH has a negative impact on patients' quality of life. In a systematic review of studies that assessed health-related quality of life in patients with MASH, there was a substantial negative impact when compared with the general population, or patients with MAFLD.

Reference:

Kennedy-Martin T, *et al. J Patient Rep Outcomes* 2018;**2**:28.

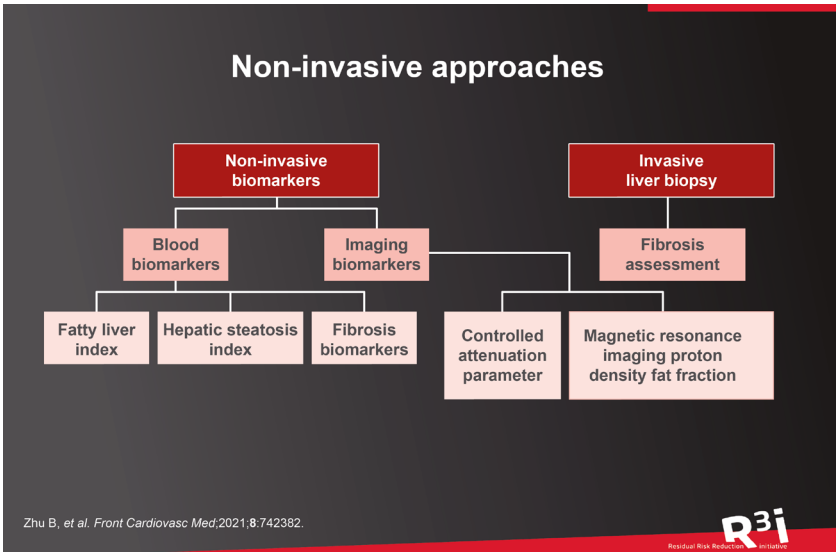


Liver biopsy: the gold standard

Liver biopsy is considered the gold standard to diagnose MASH and to quantify disease activity and fibrosis stage. MASH diagnosis requires the presence of steatosis, lobular or portal inflammation, and ballooning.[1] Liver biopsy is also recommended by drug regulatory authorities as the inclusion criteria and the primary therapeutic endpoint in MASH clinical trials.[2] However, this invasive procedure is painful for patients and costly. There are also challenges in the use of liver biopsy in clinical trials, such as evaluation reliability and sampling error.[2]

References:

1. EASL–EASD–EASO CPG MAFLD *J Hepatol* 2016;**64**:1388-402.
2. Tong XR, *et al. Acta Pharmacologica Sinica* 2022;**43**:1200-9.



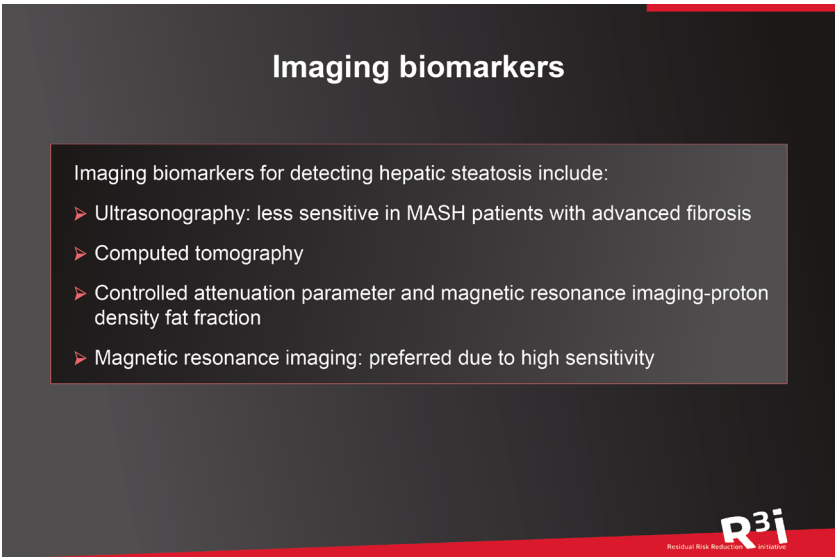
Non-invasive approaches

Non-invasive biomarkers mainly focus on the detection of hepatic steatosis. These have potential roles in identifying patients with a worse prognosis in secondary and tertiary care, monitoring disease progression, and predicting response to therapeutic interventions, thereby reducing the need for liver biopsy.[1]

Clinical guidelines recommend the use of non-invasive techniques such as imaging and blood biomarkers to detect the presence of MASH and advanced fibrosis in MAFLD patients.[2]

References:

1. Zhu B, *et al. Front Cardiovasc Med;*2021;**8**:742382.
2. EASL–EASD–EASO CPG MAFLD *J Hepatol* 2016;**64**:1388-402.

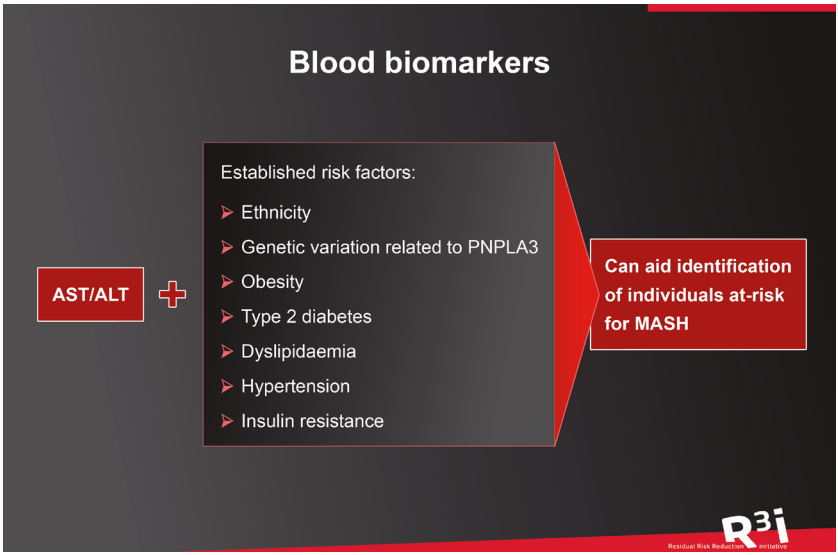


Imaging biomarkers

Imaging biomarkers for evaluation of MASH include ultrasonography, computed tomography, and magnetic resonance imaging (MRI). Of these, MRI is preferred for detection of hepatic steatosis accurately and efficiently due to its high sensitivity (approaching 100% even at low steatosis levels).[1,2]

References:

1. Zhu B, *et al. Front Cardiovasc Med;*2021;**8**:742382.
2. Bannas P, *et al. Hepatol* 2015;**62**:1444-55.

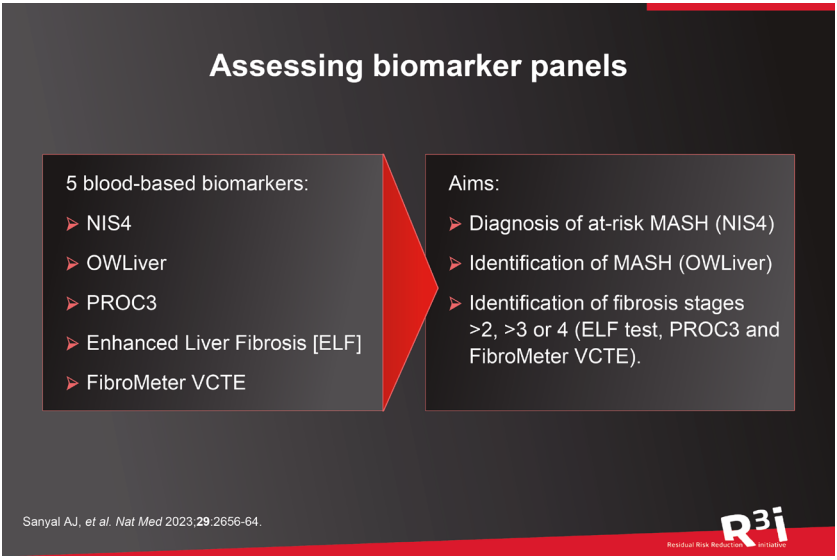


Blood biomarkers

Liver function tests, in conjunction with other risk factors such as type 2 diabetes, hypertension and abdominal obesity, can aid the identification of patients at risk for MASH but are not sufficient to diagnose MASH. This is because liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can be normal in a proportion of patients with MASH or advanced fibrosis.

Reference:

Zhu B, *et al. Front Cardiovasc Med;*2021;**8**:742382.



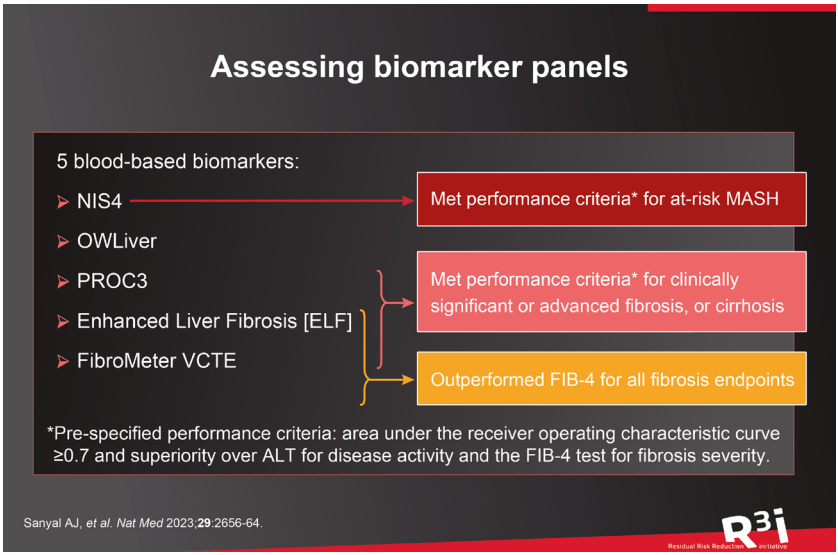
Assessing biomarker panels

Non-invasive tests for diagnosing MASH and fibrosis, particularly blood-based tests, are an area of intensive research, with potential applicability for clinical trials and wider clinical use, thereby reducing the need for liver biopsy.

The Non-Invasive Biomarkers for Metabolic Liver Disease (NIMBLE) project aims to address this issue by qualifying non-invasive tests for MAFLD, and evaluating biomarkers for diagnostic enrichment of 'at-risk' MASH and its subcomponents. A recent study evaluated the diagnostic performance of 5 blood-based panels in an observational cohort of over 1,000 patients with MAFLD. The panels were intended to diagnose at-risk MASH (NIS4), the presence of MASH (OWLiver), or fibrosis stages >2, >3 or 4 (enhanced liver fibrosis [ELF] test, PROC3 and FibroMeter VCTE). Performance was assessed by the area under the receiver operating characteristic curve (AUROC ≥0.7) and superiority over ALT for disease activity and the FIB-4 test for fibrosis severity.

Reference:

Sanyal AJ, *et al. Nat Med* 2023;**29**:2656-64.

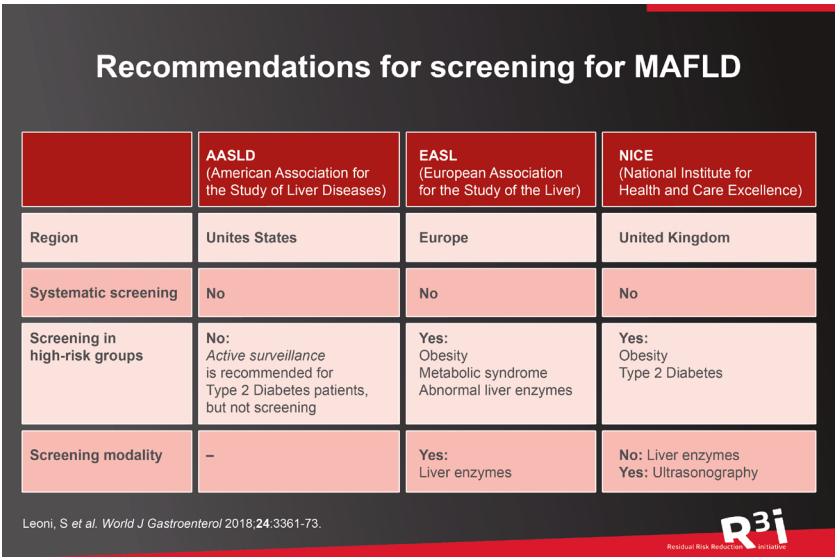


Assessing biomarker panels

In this study, multiple biomarkers met the prespecified criteria for the diagnosis of MASH, at-risk MASH, and varying severity of fibrosis in individuals with MAFLD. These findings are critical to the development of qualified non-invasive tests that can be used to identify individuals with at-risk MASH and its subcomponents for both routine practice and application in clinical trials.

Reference:

Sanyal AJ, *et al. Nat Med* 2023;**29**:2656-64.



Recommendations for screening for MAFLD

European guidelines recommend that MAFLD should be looked for in patients with obesity (associated with a 10-fold increase in the risk of MAFLD[1]), T2DM or metabolic syndrome,[2] although other guidelines are more cautious in advocating the need for data for the cost-effectiveness of such screening/case-finding programmes.[3] Clinical guidelines do, however, recommend the use of non-invasive tests such as imaging and blood tests, to assess for the presence of MASH in MAFLD patients.[2,4]

References:

1. Younossi ZM, *et al. Gut* 2020;**69**(3):564-8.

2. EASL-EASD-EASO Clinical Practice Guidelines *J Hepatol* 2016;**64**:1388-402.

3. Newsome PN, *et al. Gut* 2018;**67**:6-19.

4. Leoni, S *et al. World J Gastroenterol* 2018;**24**:3361-73.

Key Points

- Liver biopsy is the gold standard for diagnosis of MASH; however, the procedure is painful and costly.
- Non-invasive tests for diagnosing MASH and fibrosis, particularly blood-based tests, are an area of intensive research.
- Guidelines recommend the use of non-invasive tests such as imaging and blood tests, to assess for the presence of MASH in MAFLD patients.

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Treatment of MASH – current options

SECTION

3

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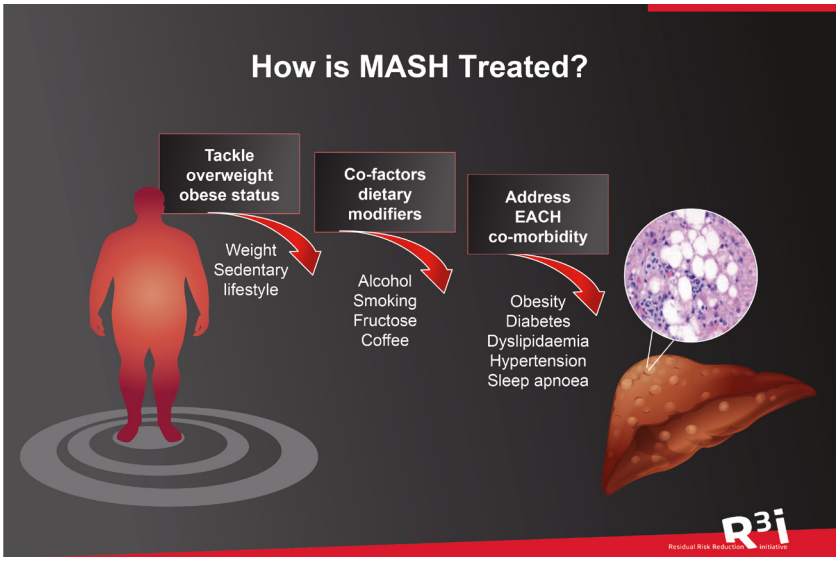
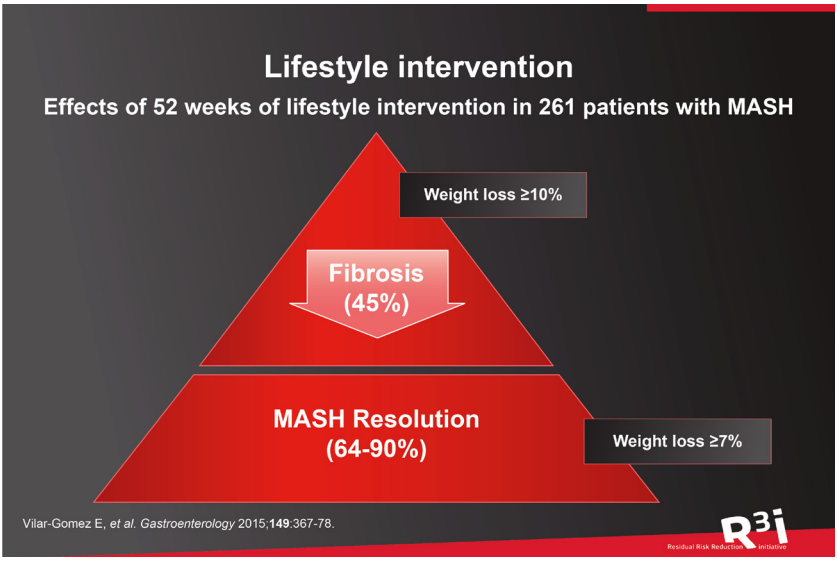


How is MASH treated?

The aim of MASH treatment is to delay, halt, or reverse progression of liver disease. Despite increasing global prevalence of MAFLD, however, there are currently no approved medications specifically for MASH. As most patients with MASH are obese, treatment focuses on diet, lifestyle modification and exercise.

Reference:

Zhu B, *et al. Front Cardiovasc Med;*2021;**8**:742382.

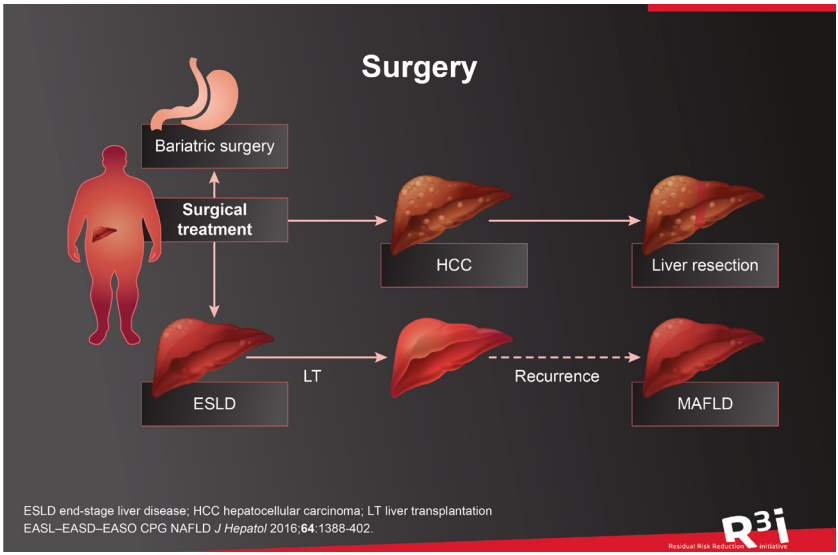


Lifestyle intervention

A pragmatic, individually-tailored approach is required, with dietary restriction and a progressive increase in aerobic exercise/resistance training.[1] The ultimate goal is to achieve and sustain weight loss of up to 10% of bodyweight, as this has been shown to improve most of the histopathological features of MASH.[2] However, most patients struggle to attain this goal and may require additional support.[3]

References:

1. EASL–EASD–EASO CPG MAFLD *J Hepatol* 2016;**64**:1388-402.
2. Vilar-Gomez E, *et al. Gastroenterology* 2015;**149**:367-78.
3. Mazzotti A, *et al. J Hepatol* 2018;**69**:1155-63.



Surgery

Bariatric surgery is an option in patients unresponsive to lifestyle changes and pharmacotherapy. Prospective data have shown an improvement in all histological lesions of MASH, including fibrosis.

Liver transplantation is an accepted procedure in patients with MASH and end-stage liver disease.

Reference:

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


Pharmacotherapy
R3i
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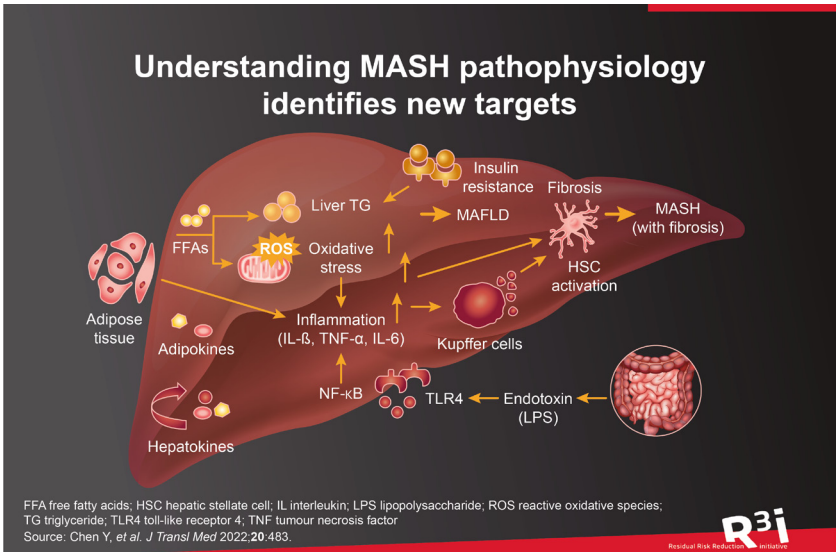
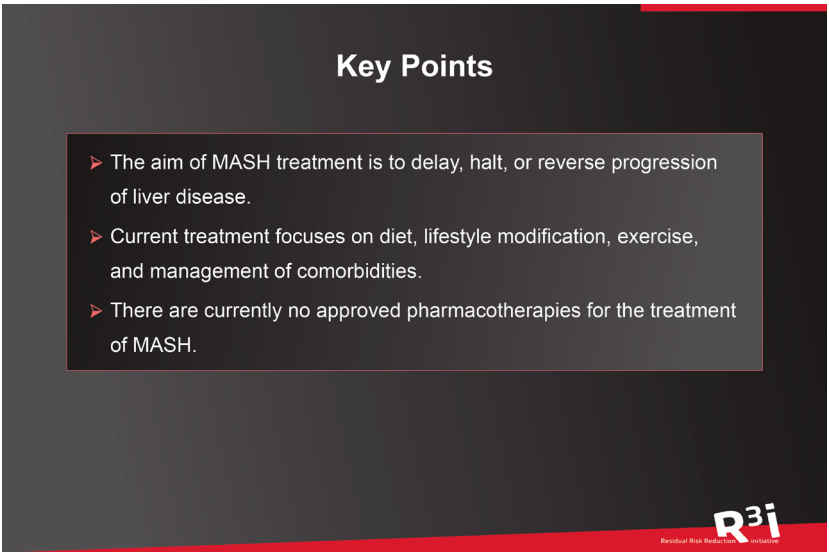


Understanding MASH pathophysiology identifies new targets

Although the pathogenesis of MASH is not completely understood, the current 'multiple-hits' hypothesis implicates parallel pathogenic influences that act synergistically to drive the development of MASH. The main drivers of liver cell injury are lipotoxicity caused by free fatty acids (FFAs) and their derivatives combined with mitochondrial dysfunction. Elevated oxidative and endoplasmic reticulum stress may be key drivers of liver inflammation and fibrosis. Despite steady progress in understanding MAFL/MASH pathophysiology and identification of novel targets, however, translating this to novel therapies for MASH has been difficult.

Reference:

Noureddin M, *et al. Curr Hepatol Rep* 2018;**17**: 350-60.


Key Points
The aim of MASH treatment is to delay, halt, or reverse progression of liver disease.
Current treatment focuses on diet, lifestyle modification, exercise, and management of comorbidities.
There are currently no approved pharmacotherapies for the treatment of MASH.
R3i
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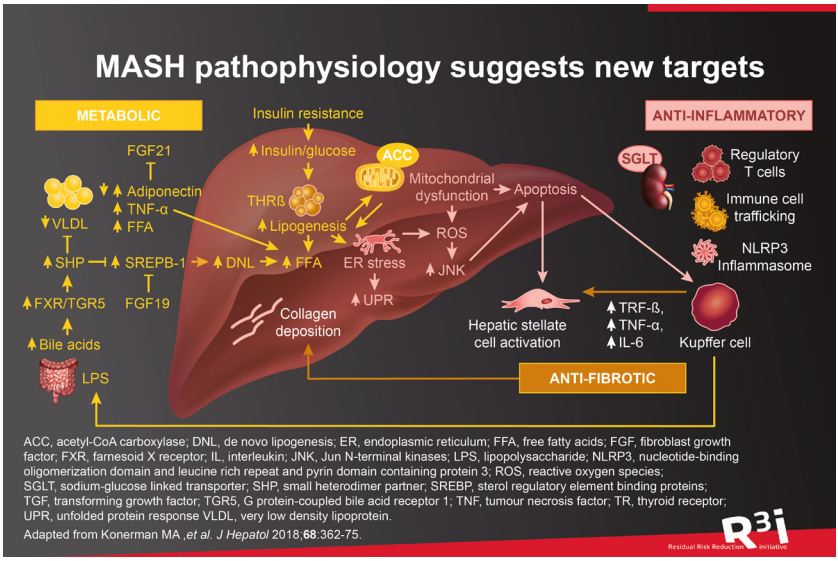
Treatment of MASH – novel therapies

SECTION

4

Residual Risk Reduction initiative



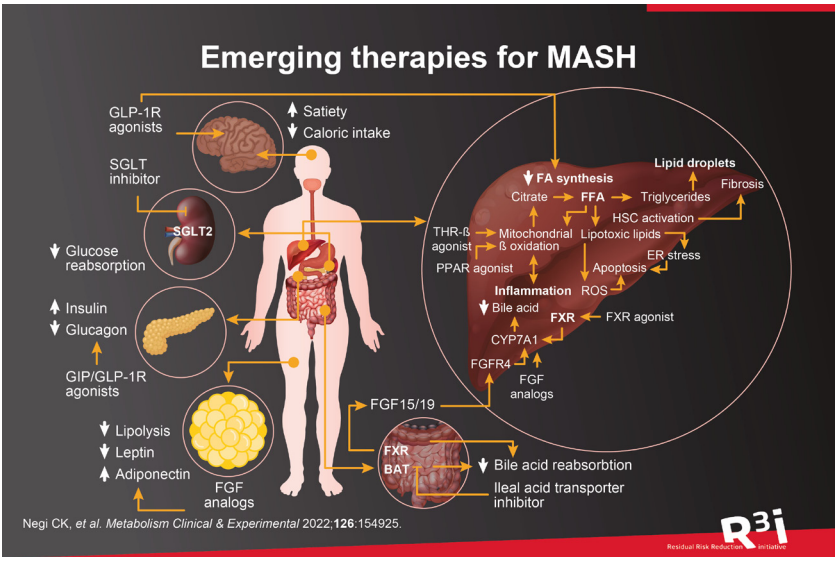
MASH pathophysiology suggests new targets

Many factors are implicated in the development of MASH. Accumulation of hepatic free cholesterol and FFAs results in hepatocellular injury characterized by oxidative stress, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, apoptosis, and subsequent expression of proinflammatory cytokines and inflammatory factors. Hepatocellular injury further leads to the activation of immune and apoptotic cell death pathways. Activation of proinflammatory (M1) Kupffer cells is the critical step that contributes to the pathogenesis of fibrogenesis during MASH progression.

Understanding the pathogenesis of MASH suggests new targets. As metabolic disorders are involved in the development and progression of MAFLD, maintaining and improving metabolic homeostasis is a key focus for therapeutic strategies for MASH.

Reference:

Zhu B, *et al Front Cardiovasc Med* 2021;**8**:742382.

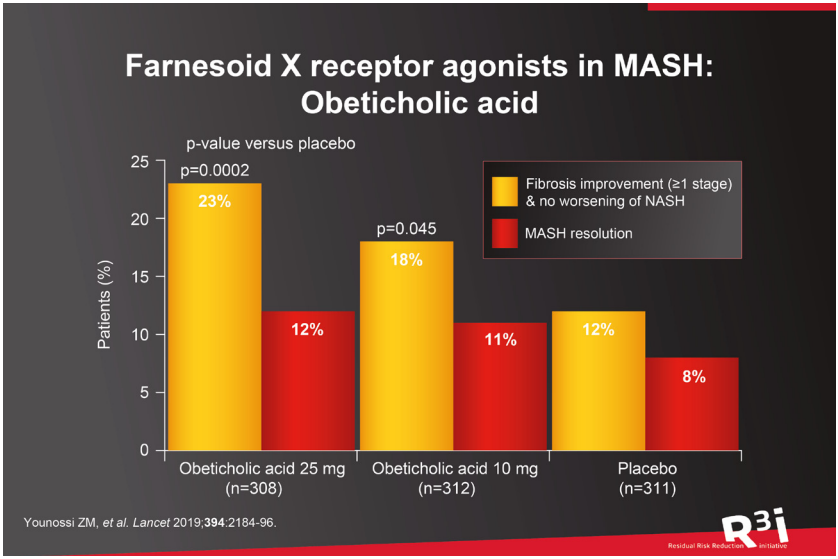


Emerging therapies for MASH

The remainder of this section focuses on some of the metabolic targeted therapies, including farnesoid X receptor (FXR) agonists, thyroid hormone receptor (THR)β agonists, fibroblast growth factor (FGF) analogs, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium–glucose cotransporter-2 (SGLT-2) inhibitors. Peroxisome proliferator-activated receptor (PPAR) agonists will be the focus of Section 5.

Reference:

Negi CK, *et al. Metabolism Clinical & Experimental* 2022;**126**:154925.

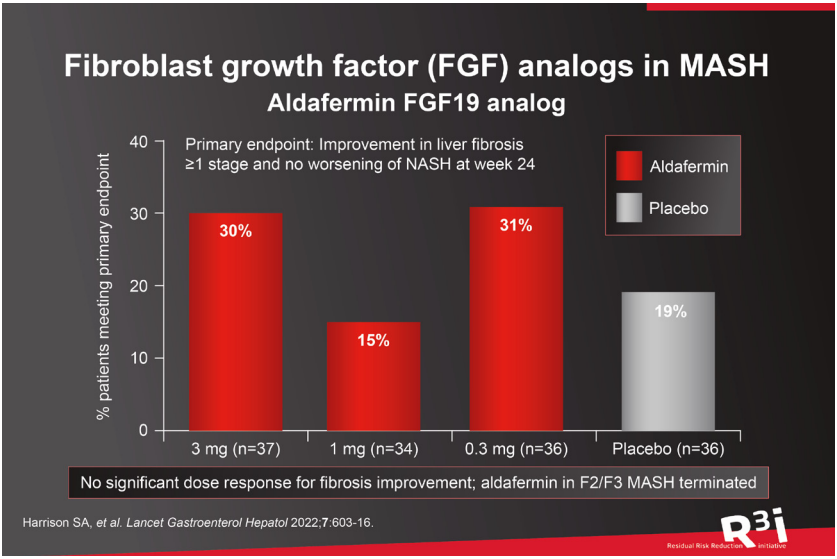


Farnesoid X receptor agonists in MASH: Obeticholic acid

FXR is a key regulator of bile acid synthesis, and hepatic triglyceride and glucose homeostasis. Activation of FXR improves hepatic steatosis and inflammation. The FXR agonist obeticholic acid is already approved for primary biliary cholangitis in the USA. In early clinical trials, obeticholic acid improved histology and fibrosis scores in patients with MAFLD.[1] In the phase III trial REGENERATE, treatment with obeticholic acid 25 mg showed significant improvement in fibrosis with no worsening of MASH in patients with stage F2/F3 fibrosis in a prespecified 18 month interim analysis, although the MASH resolution endpoint was not met.[2] However, obeticholic acid has not gained approval as adverse effects (including pruritus, elevated low-density lipoprotein cholesterol [LDL-C], and liver failure) outweigh potential benefit.[3] Several other FXR agonists have been investigated, with pruritus and elevated LDL-C reported with some.[4,5]

References:

1. Rinella M, *et al. J Hepatol* 2022;**76**:536-48.
2. Younossi ZM, *et al. Lancet* 2019;**394**:2184-96.
3. Mullard A, *Nat Rev Drug Discov* 2020;**19**: 501.
4. Harrison SA, *et al. J Hepatol* 2021;**75**:25-33.
5. Ratziu V, *et al. J Hepatol* 2022;**76**:506-17.



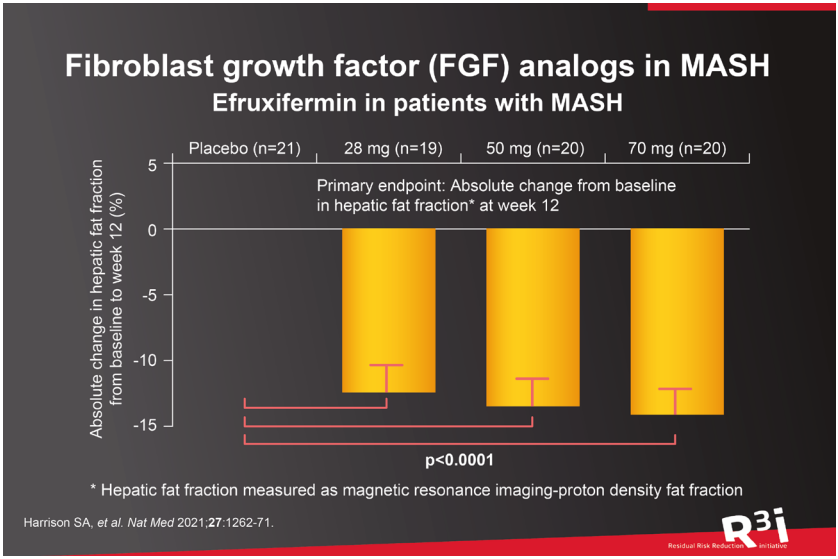
FGF analogs in MASH

The FGF peptide family includes 22 members which bind to five receptors (FGFR1-4 and FGFRL1). Among these, FGF19 (a peptide directly targeting the liver) and FGF21 (a peptide mainly secreted by the liver) have immunoregulatory, hepatoprotective, and regulatory metabolic effects, suggesting therapeutic potential in MAFLD.[1]

In a phase II trial, aldafermin (NGM282) an analog of FGF19 that binds to FGFR4/KLB, decreased liver fat content and levels of serum transaminases (ALT and AST) in patients with MASH.[2] In the ALPINE 2/3 trial in MASH patients with stage 2/3 fibrosis (F2/F3), treatment with aldafermin failed to meet the primary endpoint (fibrosis improvement by >1 stage with no worsening of MASH) but did alleviate hepatic fibrosis without worsening MASH.[3] Phase III clinical development of aldafermin in F2/F3 MASH has been terminated.

References:

1. Ocker M. *World J Gastroenterol* 2020;**26**:279-90.
2. Harrison SA, *et al. Gastroenterol* 2021;**160**:219-231.e1
3. Harrison SA, *et al. Lancet Gastroenterol Hepatol* 2022;**7**:603-16.



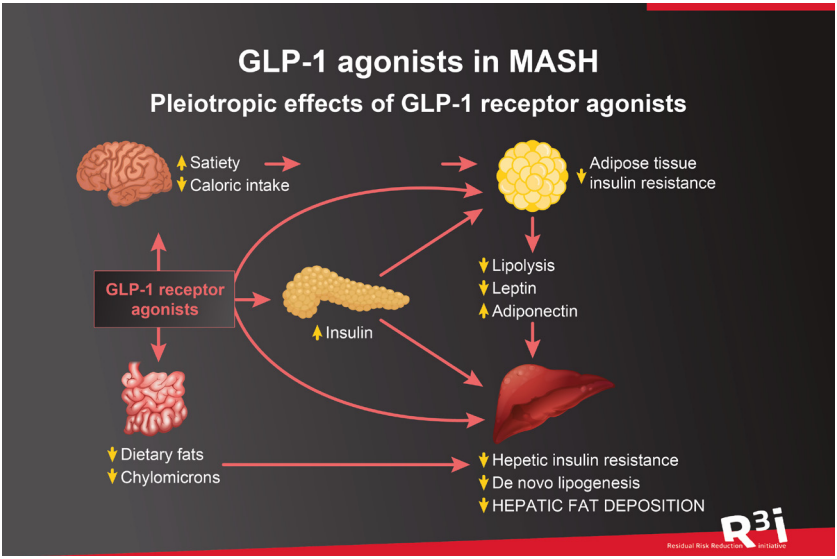
Fibroblast growth factor (FGF) analogs in MASH

Another of the FGF peptide family, FGF21, was shown to reduce hepatic steatosis and peroxidation damage in MASH by regulating the activation and oxidation of fatty acids in the liver.[1]

Two FGF21 analogs, pegbelfermin (BMS-986036) and efruxifermin (AKR001), showed therapeutic potential in patients with MASH.[2,3] In the BALANCED trial, a randomized, placebo-controlled study, treatment with efruxifermin significantly reduced hepatic fat fraction in patients with MASH (fibrosis stages 1-3), with an acceptable safety profile.[3] Pegbelfermin is in phase II trials in patients with MASH and stage 3 liver fibrosis (NCT03486899) or compensated cirrhosis (NCT03486912).

References:

1. Fisher FM, *et al. Gastroenterol* 2014;**147**:1073-83.e6
2. Sanyal AJ, *et al. Nat Rev Gastroenterol Hepatol* 2019;**16**:377-86.
3. Harrison SA, *et al. Nat Med* 2021;**27**:1262-71.



GLP-1 receptor agonists in MASH

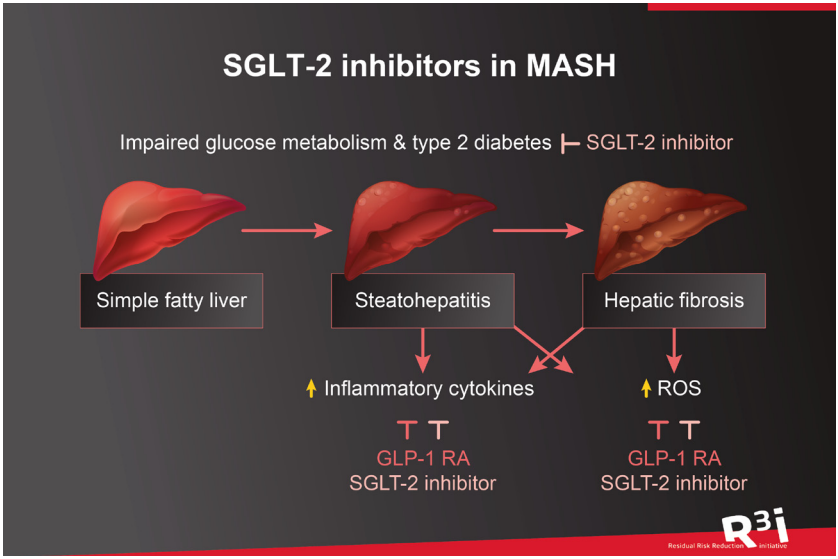
GLP-1 receptor agonists are antidiabetic agents that have been shown to improve liver histology in animal models of MASH. Several have been investigated in patients with MASH.

Semaglutide showed a significantly higher percentage of patients with MASH resolution without worsening of fibrosis, compared with placebo (59% versus 17%). However, the confirmatory secondary endpoint of fibrosis improvement with no worsening of MASH was not met.[1] Liraglutide treatment was also associated with reduction in liver fat content and liver enzymes in patients with MASH.[2] Given the beneficial effects of GLP-1 receptor agonists in maintaining glycaemic control and weight loss, these represent an attractive potential therapeutic option in MASH.

In a post hoc analysis, the dual glucose-dependent insulinotropic polypeptide (GIP) receptor agonist tirzepatide significantly improved liver function and MASH-related biomarkers, including reduction in ALT and AST, in T2DM patients.[3] The SYNERGY-MASH trial (NCT04166773) is evaluating tirzepatide in MASH. The primary endpoint is the percentage of patients with absence of MASH with no worsening of fibrosis on liver histology.

References:

1. Newsome PN, *et al. N Engl J Med* 2021;**384**:1113-24.
2. Armstrong MJ, *et al. Lancet* 2016;**387**:679-90.
3. Hartman ML, *et al. Diabetes Care* 2020;**43**:1352-5.



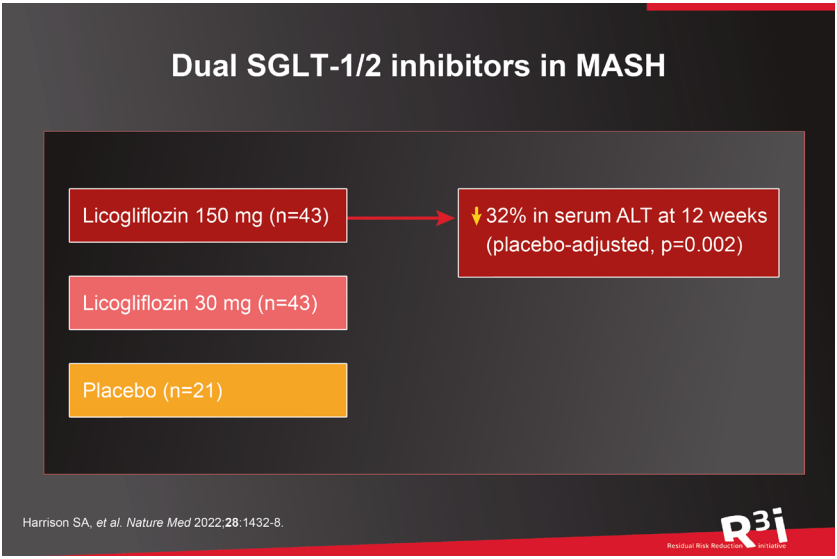
SGLT-2 inhibitors in MASH

SGLT-2 inhibitors may have therapeutic potential in MAFLD/MASH by reducing insulin resistance and improving glucose control, thereby lowering hepatic fat accumulation and inflammation, although their exact mechanism in this context is not fully elucidated. Treatment with dapagliflozin improved liver steatosis in patients with T2DM and MAFLD,[1] and reduced liver fat fraction and visceral adipose tissue volume in obese patients with T2DM.[2] A phase III trial is evaluating efficacy and safety in MASH (NCT03723252).

Empagliflozin improved hepatic steatosis and fibrosis in patients with MAFLD and T2DM and reduced body weight and abdominal fat.[3] Treatment also improved steatosis and fibrosis and reduced liver enzyme levels in MAFLD patients without T2DM.[4] Another SGLT-2 inhibitor, canagliflozin, reduced hepatic fat content, and improved liver enzymes and glycaemic control in T2DM patients with MAFLD.[5]

References:

1. Shimizu M, *et al. Diabetes Obes Metab* 2019;**21**:285-92.
2. Latva-Rasku A, *et al. Diabetes Care* 2019;**42**:931-7.
3. Chehrehgosha H, *et al. Diabetes Ther* 2021;**123**:843-61.
4. Taheri H, *et al. Adv Ther* 2020;**37**:4697-708.
5. Inoue M, *et al. J Diabetes Invest* 2019;**10**:1004-11.

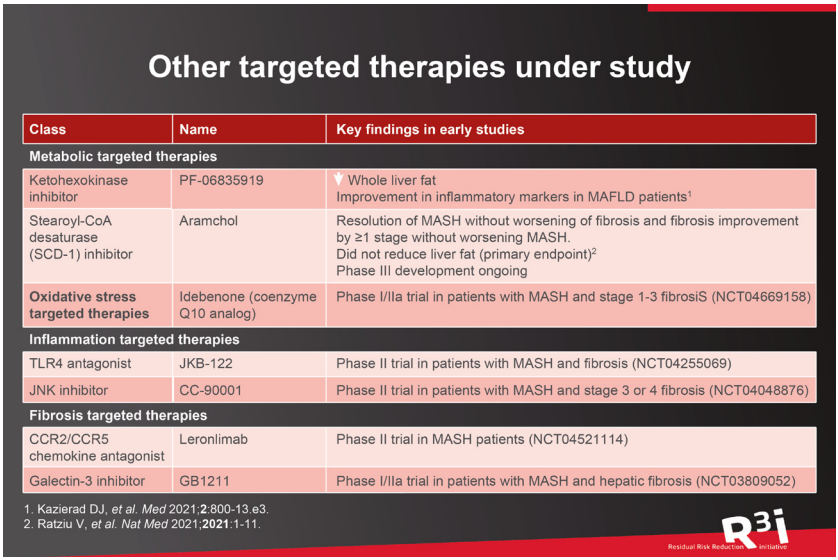


Dual SGLT-1/2 inhibitors in MASH

Dual SGLT-1/2 inhibitors have been investigated for efficacy in MASH. In a phase IIa trial, treatment with the SGLT-1/2 inhibitor licogliflozin 150 mg led to a significant reduction in serum ALT levels after 12 weeks (by 32%, placebo-adjusted, p=0.002), the primary endpoint of the study. The lower dose (30 mg) did not meet this endpoint. Further studies of longer duration are needed.

Reference:

Harrison SA, *et al. Nature Med* 2022;**28**:1432-8.



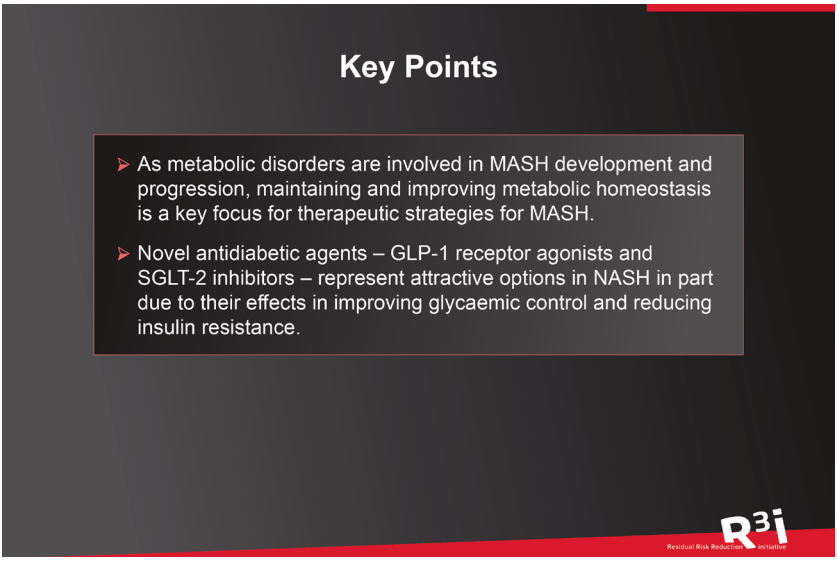
Other targeted therapies under study

Most of the focus for novel therapies relates to improving metabolic deregulation associated with MASH. There is also interest in potential therapies targeting inflammation and fibrosis, as well as precision medicine approaches such as antisense drugs designed to inhibit the production of patatin-like phospholipase domain-containing 3 (PNPLA3) protein, found on the surface of intracellular lipid droplets.[1]

The following section focuses on PPAR modulation as a potential therapeutic approach for MASH.

Reference:

1. Lindén D, *et al. Mol Metab* 2019;**22**:49-61.

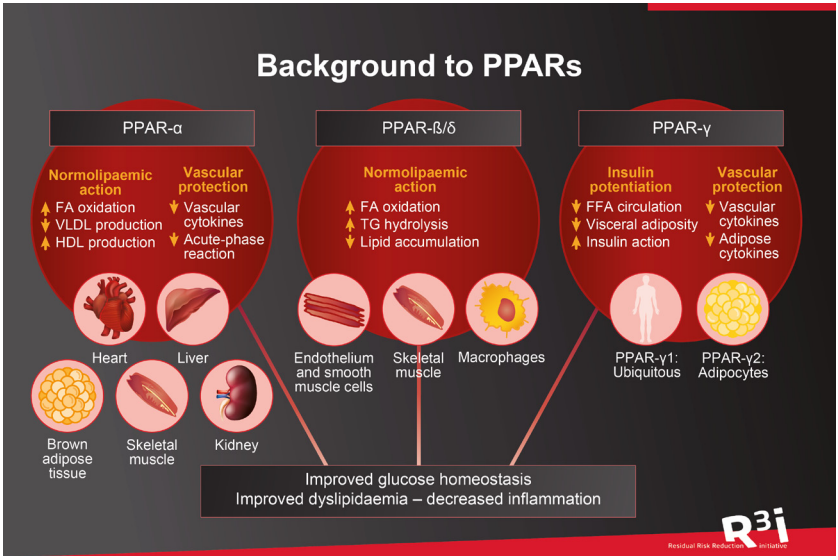

Key Points
As metabolic disorders are involved in MASH development and progression, maintaining and improving metabolic homeostasis is a key focus for therapeutic strategies for MASH.
Novel antidiabetic agents – GLP-1 receptor agonists and SGLT-2 inhibitors – represent attractive options in NASH in part due to their effects in improving glycaemic control and reducing insulin resistance.
R3i
Residual Risk Reduction Initiative

PPAR agonists in MASH

SECTION

5

Residual Risk Reduction initiative



Background to PPARs

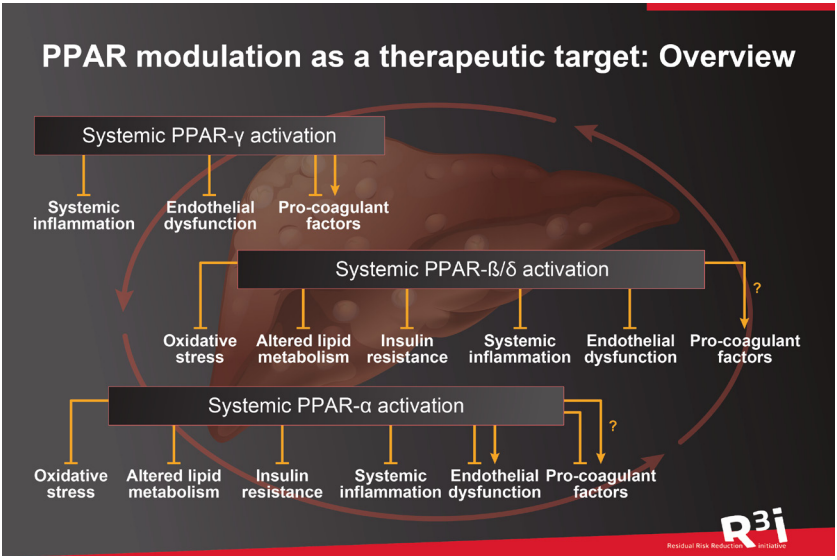
PPARs are ligand-activated nuclear receptor proteins which function as transcription factors that regulate several processes involved in lipid metabolism, glucose homeostasis, and insulin signalling and therefore represent attractive potential targets in MAFLD/MASH.

There are three isotypes of PPARs (PPARα, PPARβ/δ and PPARγ), each encoded by separate genes and expressed in different cell types and tissues. These isotypes have different functions.[1,2]

For further information refer to **https://www.r3i.org/slidekits-7**: SSPARMα at the Crossroads of Obesity, Diabetes and Cardiovascular Diseases - SECOND EDITION

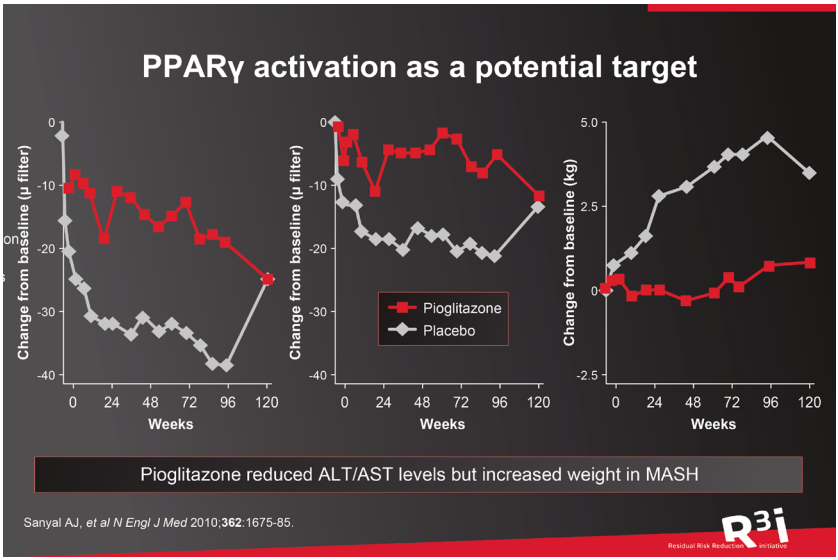
Reference:

1. Fruchart JC. *Cardiovasc Diabetol* 2013;**12**:82.
2. Braissant O, *et al. Endocrinol* 1996;**137**:354-66.



PPAR modulation as a therapeutic target: Overview

Increasing evidence supports PPAR modulation as a potential therapeutic target for MAFLD/MASH. To date, PPAR agonists represent one of the most advanced classes of anti-MASH molecules currently in the pipeline of drug development.



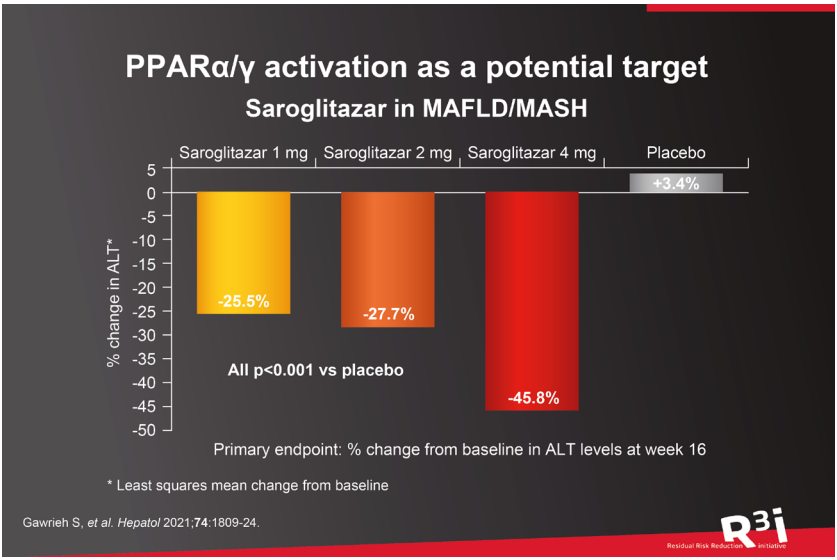
PPARγ activation as a potential target

PPARγ agonists including thiazolidinediones, such as pioglitazone (a synthetic ligand of PPARγ), are clinically used to treat T2DM. Pioglitazone has been investigated in non-diabetic patients with MASH. The PIVENS trial showed that treatment with pioglitazone reduced hepatic steatosis, lobular inflammation, and hepatocellular ballooning, as well as liver enzyme levels in MASH patients. However, pioglitazone did not meet the prespecified criteria for the primary outcome (improvement in the histologic features of MASH) and increased weight.[1] Long-term treatment was well-tolerated, and effective in improving metabolic and histological parameters of MASH.[2] Pioglitazone is contraindicated in patients with established heart failure or at increased risk of heart failure.

Another PPARγ agonist, rosiglitazone, did not improve MASH but did show improvement in hepatic steatosis and transaminase levels.[3]

References:

1. Sanyal AJ, *et al N Engl J Med* 2010;**362**:1675-85.
2. Cusi K, *et al. Ann Intern Med* 2016;**165**:305-15.
3. Ratziu V, *et al. Hepatol* 2010;**51**:445-53.

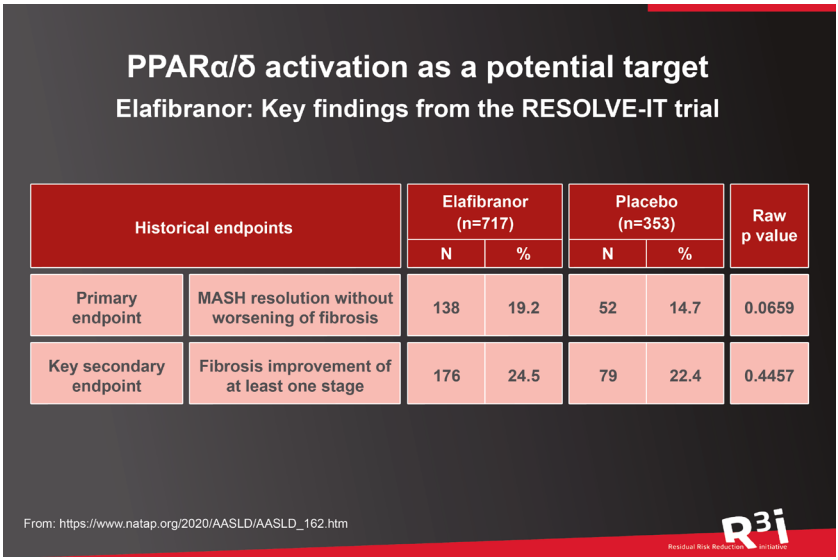


Saroglitazar in MAFLD/MASH

Saroglitazar, a dual PPARα/γ agonist, reduced serum ALT levels and liver fat content, markers of hepatocellular injury, and insulin resistance, and atherogenic dyslipidaemia in patients with MAFLD/MASH in a phase II trial. There was a mean weight gain of 1.5 kg with the highest dose (saroglitazar 4 mg) versus 0.3 kg with placebo.[1] There is an ongoing trial in patients with MASH and fibrosis patients (2 and 4 mg doses), with a primary endpoint of resolution of MASH with no worsening of fibrosis (NCT05011305).

Reference:

Gawrieh S, *et al. Hepatol* 2021;**74**:1809-24.

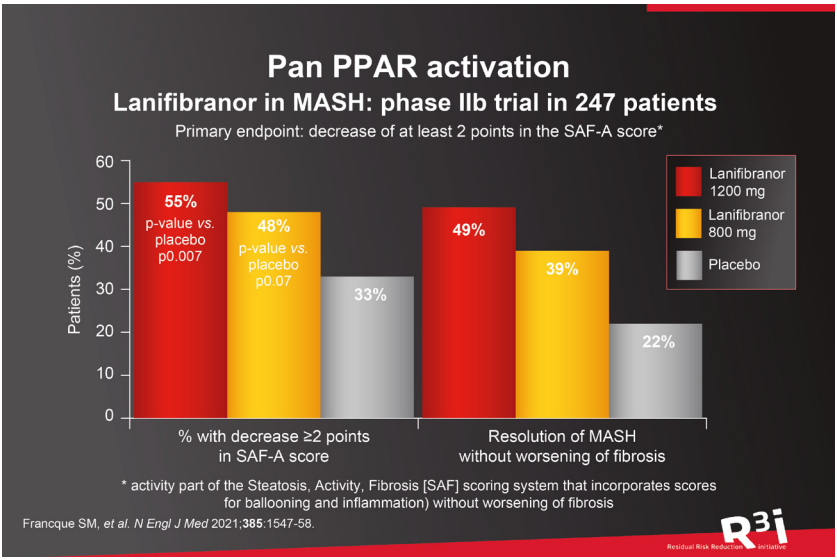


PPARα/δ activation as a potential target

Dual PPARα/δ agonists have been a focus of interest in MAFLD/MASH. The first of these agonists, elafibranor, was terminated after failing to achieve the primary histological endpoint of MASH resolution without worsening of fibrosis in the RESOLVE-IT phase III trial.[1]

Reference

1. **https://inthought.com/analysis/genfit-terminates-resolve-it-trial-elafibranor-MASH/**

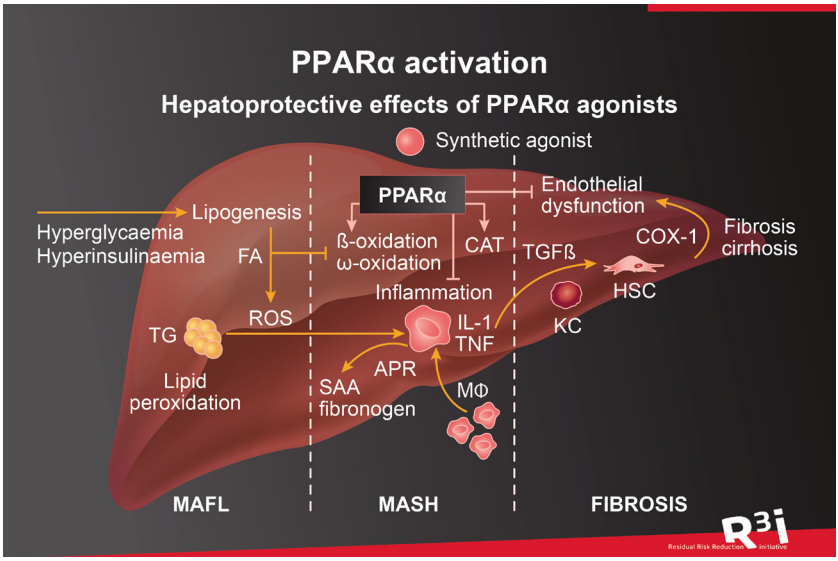


Pan PPAR activation

Lanifibranor (IVA337), a pan-PPAR agonist for all three isotypes of PPAR, met both the primary and key secondary efficacy endpoints, showing significant effects on MASH resolution without worsening of fibrosis and improvement of fibrosis without worsening of MASH, in patients with non-cirrhotic MASH. Liver enzyme levels decreased and levels of most lipid, inflammatory, and fibrosis biomarkers improved in the lanifibranor groups.[1] There is an ongoing phase III trial (NCT04849728).

Reference:

Francque SM, *et al. N Engl J Med* 2021;**385**:1547-58.



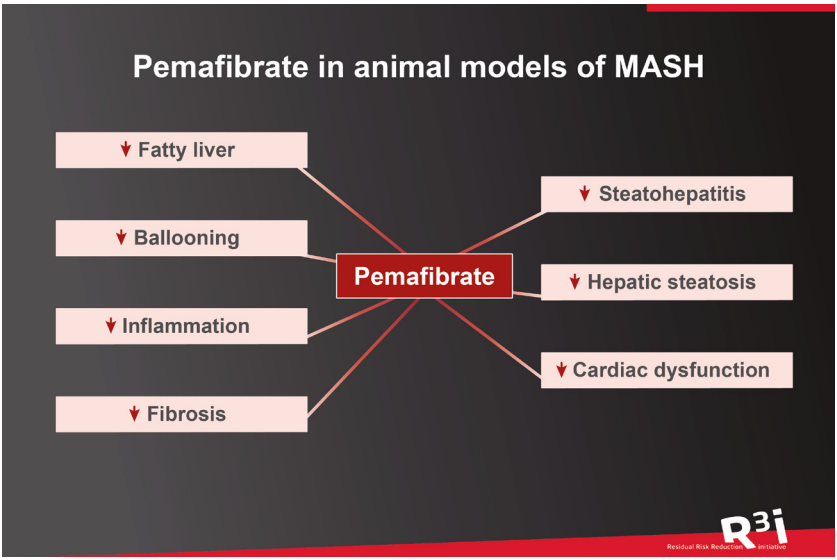
PPARα activation

Interest in PPARα as a potential therapeutic target dates from over 20 years ago, when gemfibrozil was first tested in patients with MASH, showing reduction in ALT/AST levels.[1]

The development of pemafibrate, a selective peroxisome proliferator-activated alpha modulator (SPPARMα) with increased potency and selectivity for the PPARα subtype,[2] provided the opportunity to test the therapeutic potential of PPARα modulation in MAFLD/MASH.

References:

1. Basaranoglu M, *et al. J. Hepatol* 1999;**31**:384.
2. Fruchart JC, *et al. Cardiovasc Diabetol* 2019;**18**:71.

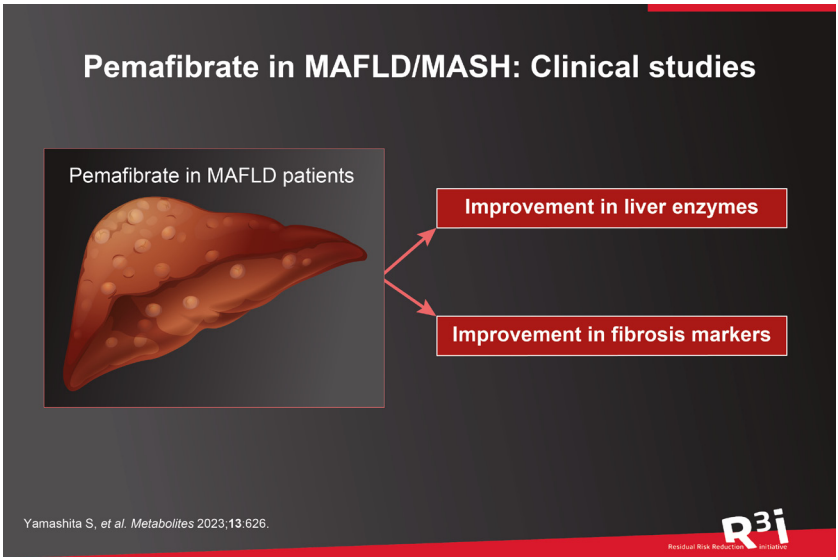


Pemafibrate in animal models of MASH

Pemafibrate has shown favourable effects in preclinical studies using different animal models of MAFLD/MASH.[1] In a rodent model of MASH, pemafibrate reduced liver function test values and improved fatty liver, ballooning, inflammation, and fibrosis.[2,3] Additionally, in a novel mouse model of diet-induced steatohepatitis-related cardiomyopathy, pemafibrate attenuated hepatic steatosis, steatohepatitis, and cardiac dysfunction.[4]

References:

1. Yamashita S, *et al. Metabolites* 2023;**13**: 626.
2. Honda Y, *et al. Sci Rep* 2017;**7**:42477.
3. Sasaki Y, *et al. Sci Rep* 2020;**10**:7818.
4. Kanno K, *et al. Sci Rep* 2022;**12**:2996.

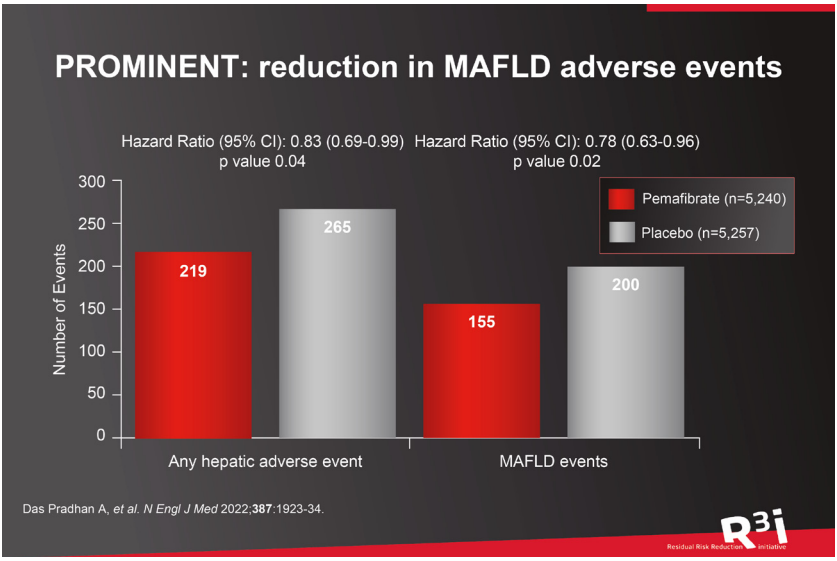


Pemafibrate in MAFLD/MASH: Clinical studies

Several retrospective studies in Japan consistently showed that pemafibrate ameliorated MAFLD, with reduction in serum levels of liver enzymes (ALT, alkaline phosphatase, and γ-glutamyl transferase), as well as improvement in fibrosis markers such as AST/platelet ratio index and FIB-4 index.[1-3] Pemafibrate (0.1 mg twice daily) for 12 weeks also led to significant reduction in serum ALT levels in patients with MAFLD and dyslipidaemia.[4]

References:

1. Hatanaka T, *et al. Intern Med* 2021;**60**:2167-74.
2. Shinozaki S, *et al. Clin Exp Hepatol* 2020;**6**:270-4.
3. Shinozaki S, *et al. Clin Exp Hepatol* 2021;**7**:172-7.
4. Seko Y, *et al. Hepatol Res* 2020;**50**:1328-36.

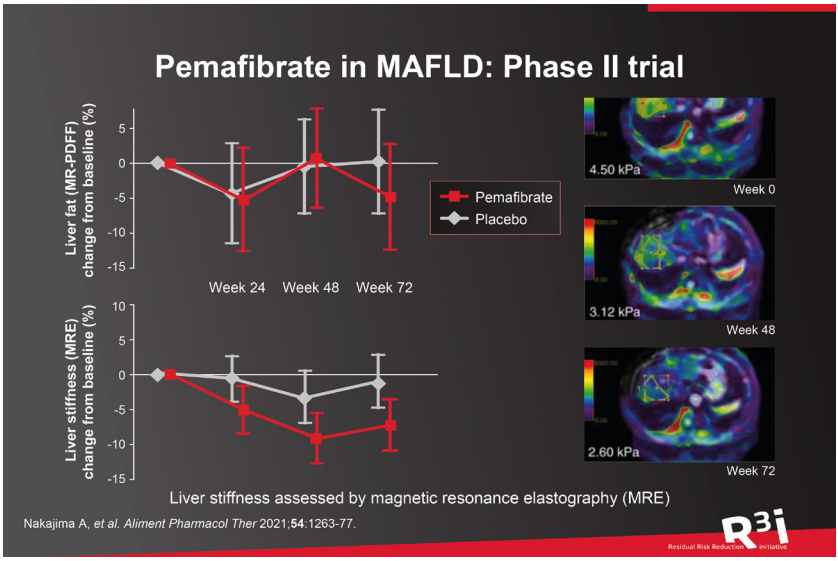


PROMINENT: reduction in MAFLD events

There is also evidence from the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial to indicate that treatment with pemafibrate was associated with significant reduction in investigator-reported MAFLD adverse events and any hepatic adverse events.

Reference:

Das Pradhan A, *et al. N Engl J Med* 2022;**387**:1923-34.

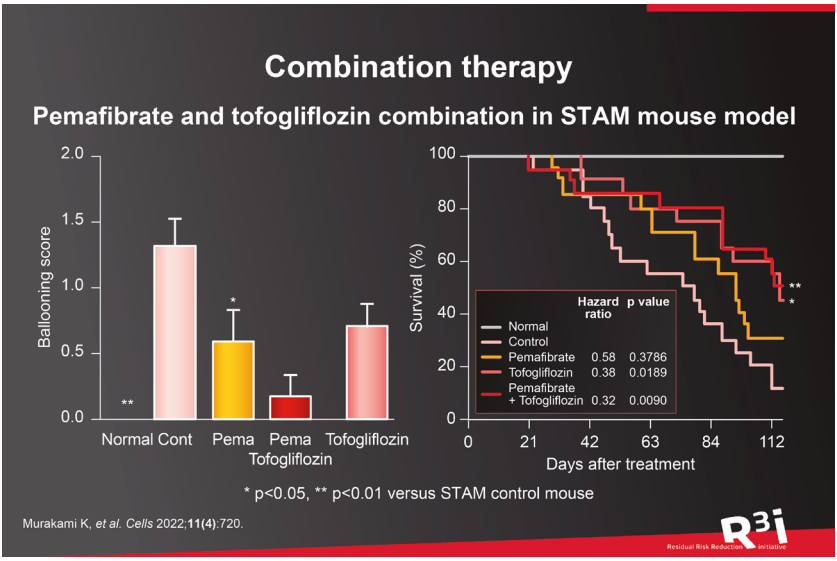


Pemafibrate in MAFLD: Phase II trial

In a phase II trial in 118 patients with MAFLD, pemafibrate 0.2 mg twice daily for 72 weeks reduced liver stiffness (from week 48), as well as levels of liver enzymes (ALT) and LDL-C. There was, however, no significant change in hepatic fat content, the primary endpoint. These findings suggest a role for pemafibrate in combination with an agent that may reduce liver fat content.

Reference:

Nakajima A, *et al. Aliment Pharmacol Ther* 2021;**54**:1263-77.



Combination therapy

Rational combination therapy represents a future approach for the effective management of MAFLD/MASH. One approach under evaluation is the combination of pemafibrate extended-release and SGLT-2 inhibitor tofogliflozin, in patients with MASH and liver fibrosis (NCT05327127). This strategy is supported by preclinical findings using a mouse model which showed that the combination of pemafibrate and tofogliflozin prevented ballooning degeneration of hepatocytes and HCC progression.[1]

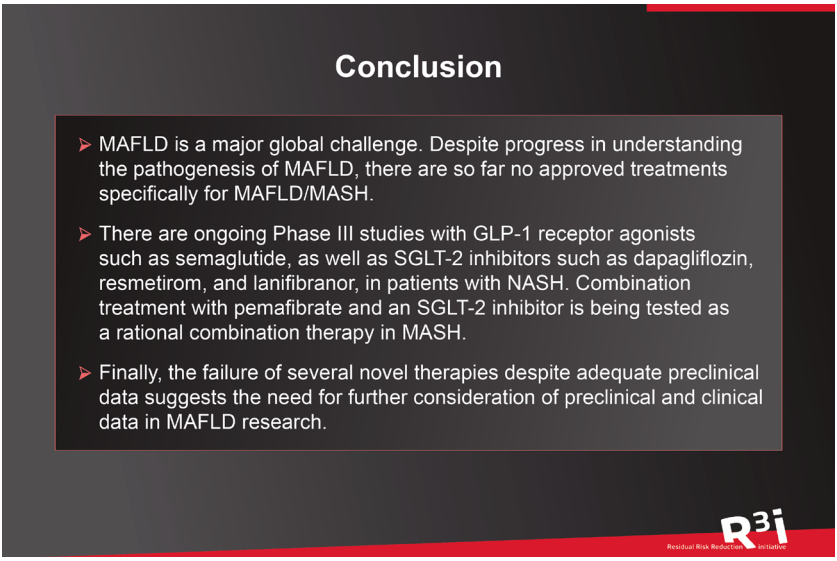
Reference:

1. Murakami K, *et al. Cells* 2022;**11(4)**:720.

Key Points

- Given the role of PPAR subtypes in lipid metabolism, glucose metabolism, and inflammation, PPAR modulation is a focus of interest for novel treatments for MAFLD/MASH.
- Saroglitazar has been approved in India by the Drug Controller General of India for the treatment of MASH.
- Lanifibranor, a pan-PPAR agonist, is the first drug candidate to have shown significant effects on MASH resolution with no worsening of fibrosis and improvement of fibrosis with no worsening of MASH. Phase III development is ongoing.
- Evidence from experimental and preliminary clinical studies suggests a potential therapeutic role for the SPPARMα pemafibrate in MAFLD/MASH.
- Rational combination therapy represents a future approach for effective management for MAFLD/MASH. One combination strategy being tested is pemafibrate with the SGLT-2 inhibitor, tofogliflozin.
- Finally, the failure of several novel therapies despite adequate preclinical data suggests the need for further consideration of preclinical and clinical data in MAFLD research.

R3i Residual Risk Reduction initiative


Conclusion
MAFLD is a major global challenge. Despite progress in understanding the pathogenesis of MAFLD, there are so far no approved treatments specifically for MAFLD/MASH.
There are ongoing Phase III studies with GLP-1 receptor agonists such as semaglutide, as well as SGLT-2 inhibitors such as dapagliflozin, resmetirom, and lanifibranor, in patients with NASH. Combination treatment with pemafibrate and an SGLT-2 inhibitor is being tested as a rational combination therapy in MASH.
Finally, the failure of several novel therapies despite adequate preclinical data suggests the need for further consideration of preclinical and clinical data in MAFLD research.
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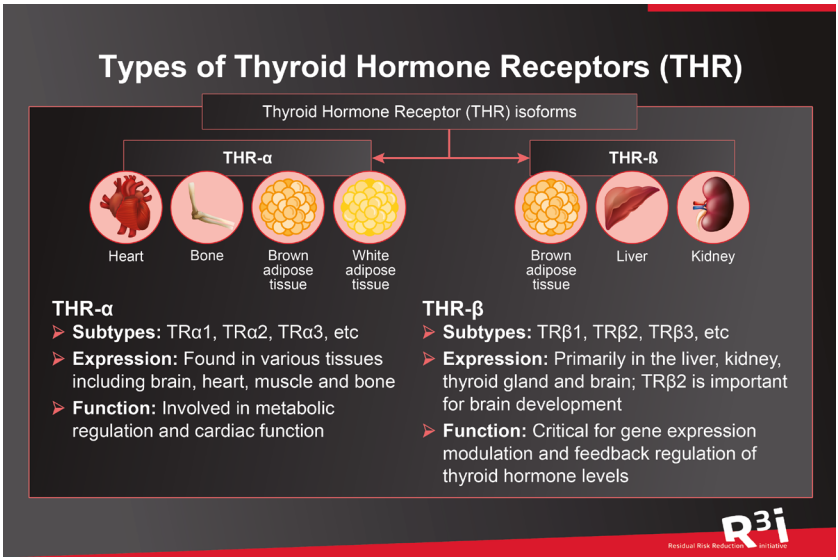
PPAR agonists in MASH

THR-ß agonists in MASH

SECTION

6

Residual Risk Reduction initiative



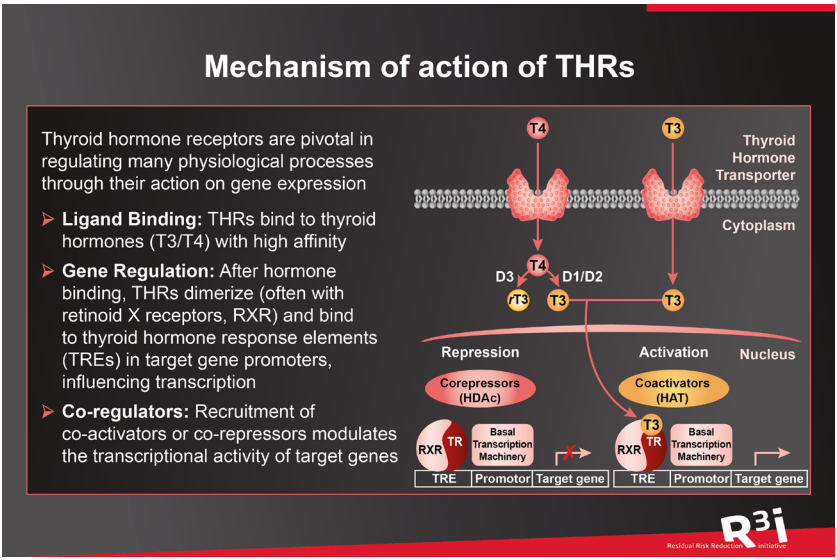
The types of Thyroid Hormone Receptors (THR) are divided into two main isoforms: THR-α and THR-ß

THR-α:
There are subtypes: TRα1, TRα2, TRα3, etc., which are expressed in various tissues, including the brain, heart, muscle, and bone, and play a role in metabolic regulation and cardiac function.

THR-ß:
There are subtypes: TRß1, TRß2, TRß3, etc., which are found primarily in the liver, kidney, thyroid gland, and brain, with TRß2 being important for brain development.

They are essential for modulating gene expression and feedback regulation of thyroid hormone levels.

Each isoform has distinct tissues where they are predominantly expressed, highlighting their specific roles in the body's regulatory mechanisms.



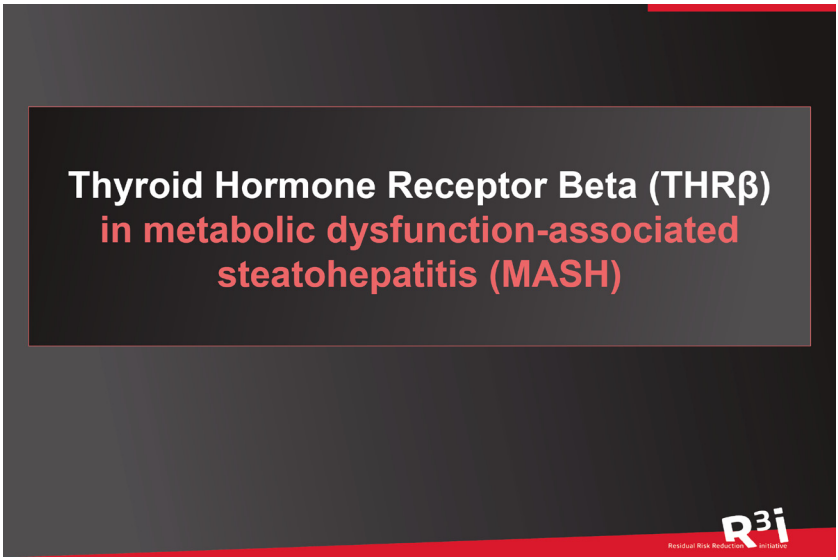
The mechanism of action of Thyroid Hormone Receptors (THRs) and their role in gene expression

T4 and T3 enter the cell via thyroid hormone transporters. T4 is converted to T3 or rT3 through D1/D2 or D3 enzymes.

THRs exhibit high affinity for thyroid hormones T3 and T4. Upon binding with hormones, THRs often dimerize with retinoid X receptors (RXR) and then attach to thyroid hormone response elements (TREs) on target gene promoters. This binding significantly influences transcription processes.

The Co-regulators play a crucial role in modulating gene transcription:

- Repression: Involves the recruitment of corepressors like HDAC, reducing gene transcription.
- Activation: Involves coactivators like HAT, enhancing transcription.


Thyroid Hormone Receptor Beta (THRβ)
in metabolic dysfunction-associated
steatohepatitis (MASH)
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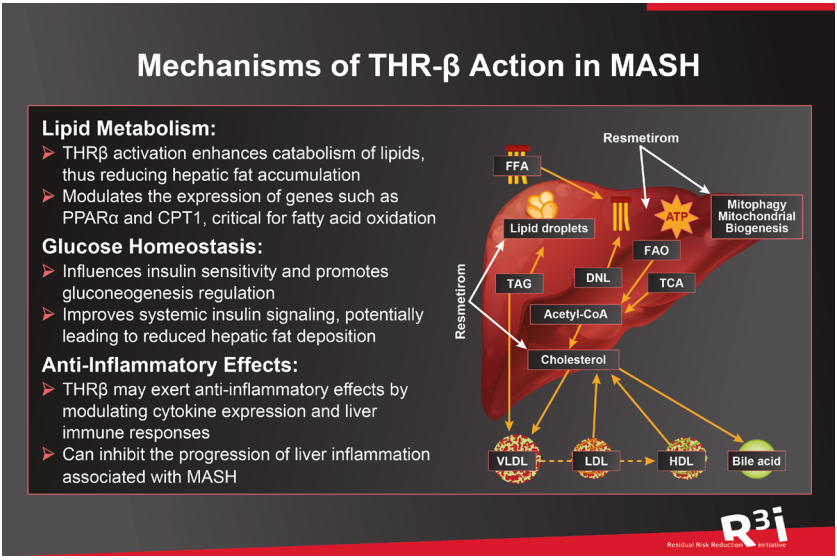


THRβ's comprehensive role in managing lipid metabolism, glucose homeostasis, and inflammation in the context of liver diseases like MASH.

Lipid Metabolism:

- THRβ Activation enhances lipid catabolism, thereby reducing fat accumulation in the liver by modulating the genes expression like PPARα and CPT1, essential for fatty acid oxidation.

Glucose Homeostasis:

- THRβ Activation influences insulin sensitivity and regulates gluconeogenesis.
- Improves systemic insulin signaling, potentially decreasing hepatic fat deposition.

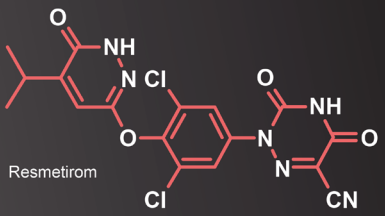
Anti-Inflammatory Effects:

- THRβ may reduce inflammation by affecting cytokine expression.
- It can inhibit progression of liver inflammation seen in NASH.

Resmetirom affects various metabolic pathways.

- Involvement in lipogenesis (TAG, FFA), oxidation (FAO), and energy production (ATP).
- Effects on cholesterol, VLDL, LDL, HDL, and bile acid production.

Resmetirom: The first Thyroid Hormone Receptor Beta agonist approved by the FDA for MASH treatment



Resmetirom

- Resmetirom is a selective thyroid hormone receptor beta (THRβ) agonist
- Approved by the FDA as the first THRβ agonist for the treatment in metabolic dysfunction-associated steatohepatitis (MASH)

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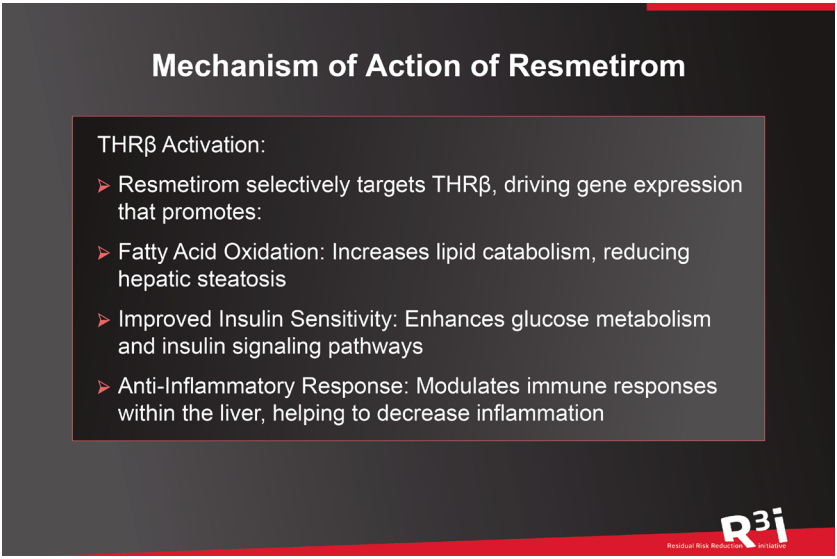
Mechanism of Action of Resmetirom
THRβ Activation:
Resmetirom selectively targets THRβ, driving gene expression that promotes:
Fatty Acid Oxidation: Increases lipid catabolism, reducing hepatic steatosis
Improved Insulin Sensitivity: Enhances glucose metabolism and insulin signaling pathways
Anti-Inflammatory Response: Modulates immune responses within the liver, helping to decrease inflammation
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Clinical Efficacy of Resmetirom

Phase II and Phase III trials demonstrated significant improvements in liver histology, including:

- Reduction in liver fat content
- Decreased inflammation and fibrosis
- Improved metabolic parameters in patients with MASH

Endpoints Achieved:

- Significant improvement in the MAS (MAFLD Activity Score) as measured by liver biopsy
- Improved metabolic markers, including liver enzymes and lipid profiles

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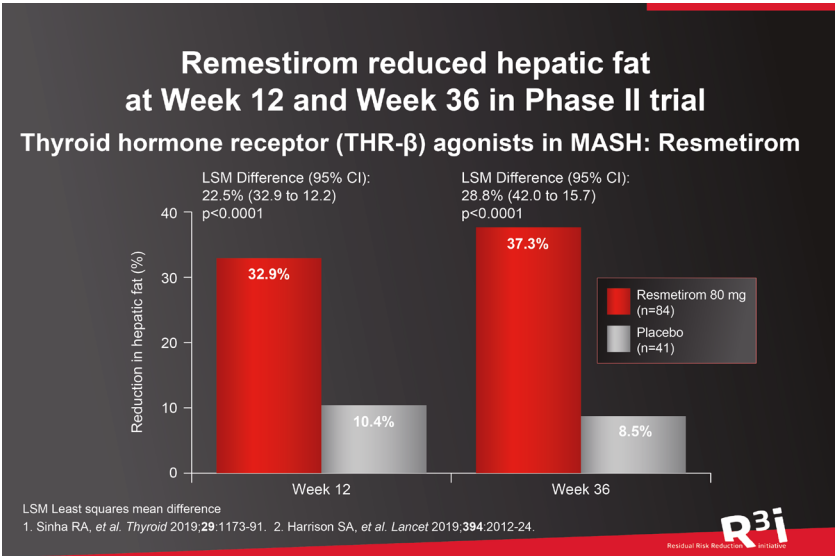
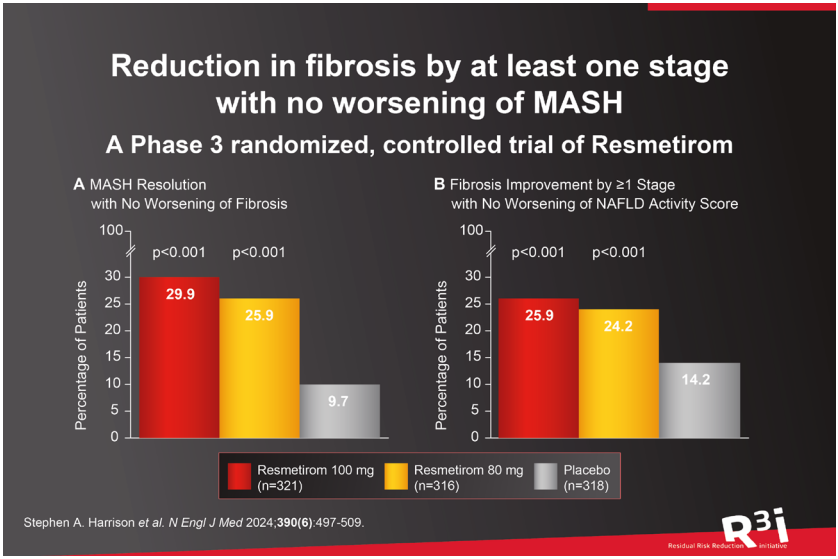


A phase II trial evaluated resmetirom (MGL-3136), a liver-directed selective THRβ agonist, in 84 patients with biopsy confirmed MASH (fibrosis stages 1-3) and hepatic fat fraction of at least 10% at baseline. Resmetirom reduced hepatic fat (as assessed by MRI-proton density fat fraction, MRI-PDFF) at week 12 and week 36 ($p<0.0001$ for both endpoints) and improved hepatic inflammation. Transient diarrhoea and nausea were most commonly reported.

References:

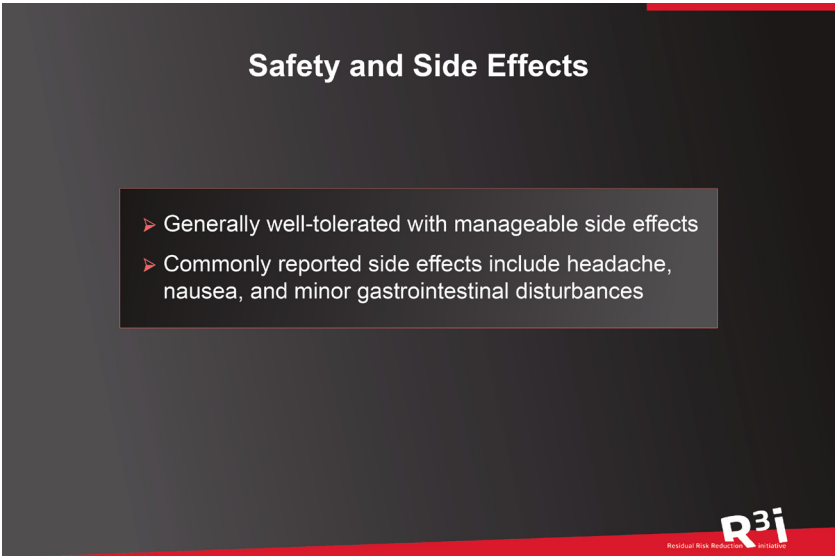
1. Sinha RA, *et al. Thyroid* 2019;**29**:1173-91.
2. Harrison SA, *et al. Lancet* 2019;**394**:2012-24.



In a Phase 3 trial involving 966 patients with biopsy-confirmed Metabolic dysfunction-Associated Steatohepatitis (MASH) and fibrosis stages of F1B, F2, or F3 (ranging from F0 [no fibrosis] to F4 [cirrhosis]), at week 52, a 24.2% improvement in fibrosis by at least one stage without worsening of the Metabolic-dysfunction associated Fatty Liver Disease (MAFLD) activity score was observed in the 80 mg resmetirom group and a 25.9% improvement in the 100 mg resmetirom group. This is in comparison to a 14.2% improvement in the placebo group. These differences were statistically significant with $p < 0.001$ for both comparisons with the placebo group.

Reference:

Stephen A. Harrison *et al. N Engl J Med* 2024;**390**(6):497-509.


Safety and Side Effects
Generally well-tolerated with manageable side effects
Commonly reported side effects include headache, nausea, and minor gastrointestinal disturbances
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Conclusion

- Resmetirom represents a significant advancement in the treatment of MASH, specifically targeting THRβ to improve liver health and metabolic function
- Ongoing research and post-marketing data will further elucidate its long-term efficacy and safety profile in diverse populations

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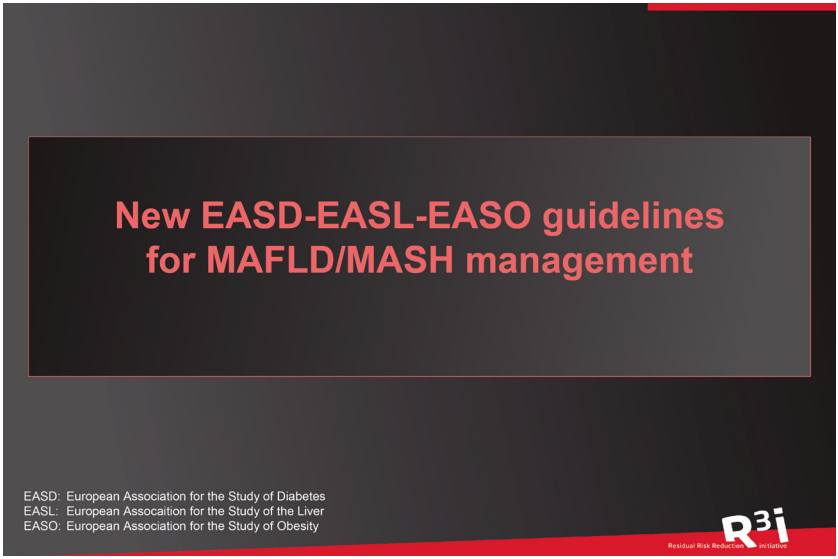
Guideline recommendations for management of MAFLD/MASH

SECTION

7

Residual Risk Reduction initiative


New EASD-EASL-EASO guidelines
for MAFLD/MASH management
EASD: European Association for the Study of Diabetes
EASL: European Assocaition for the Study of the Liver
EASO: European Association for the Study of Obesity
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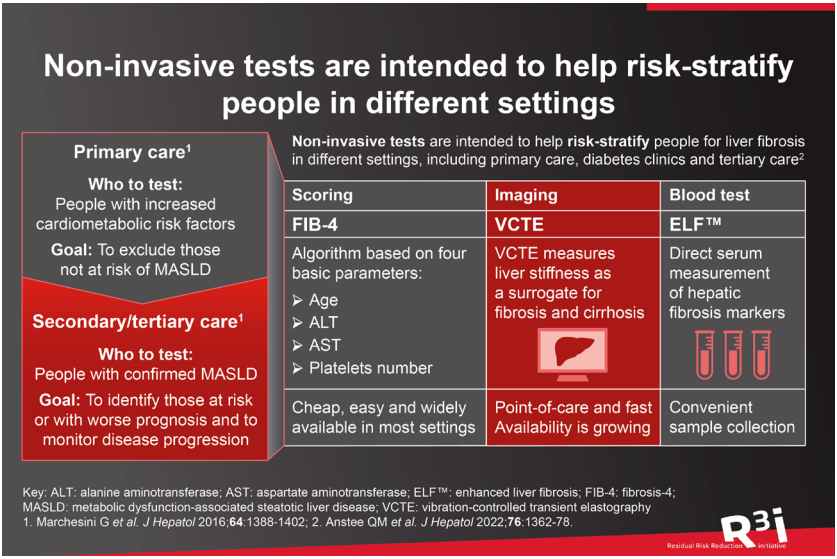

Information on non-invasive tests used for risk stratification of liver fibrosis in different healthcare settings, such as primary care, diabetes clinics, and tertiary care. It emphasizes the importance of stratifying patients based on risk factors.

In primary care, the focus is on people with increased cardiometabolic risk factors, with the goal of excluding those not at risk of metabolic dysfunction-associated steatotic liver disease (MASLD).

In secondary/tertiary care, the focus shifts to people with confirmed MASLD, aiming to identify those at risk of worse prognosis and to monitor disease progression.

The tests mentioned include:

- FIB-4: A scoring method calculated from the following variables: age, ALT, AST, and platelets number. It is cheap, easy to calculate, and widely available.
- VCTE (Vibration-Controlled Transient Elastography): measures liver stiffness, as a surrogate for fibrosis and cirrhosis. It's a point-of-care non-invasive test with growing availability.
- ELF™ (Enhanced Liver Fibrosis): a non-invasive blood test for direct serum measurement of hepatic fibrosis markers.

References:

1. Marchesini G *et al. J Hepatol* 2016;**64**:1388-402.
2. Anstee QM *et al. J Hepatol* 2022;**76**:1362-78.

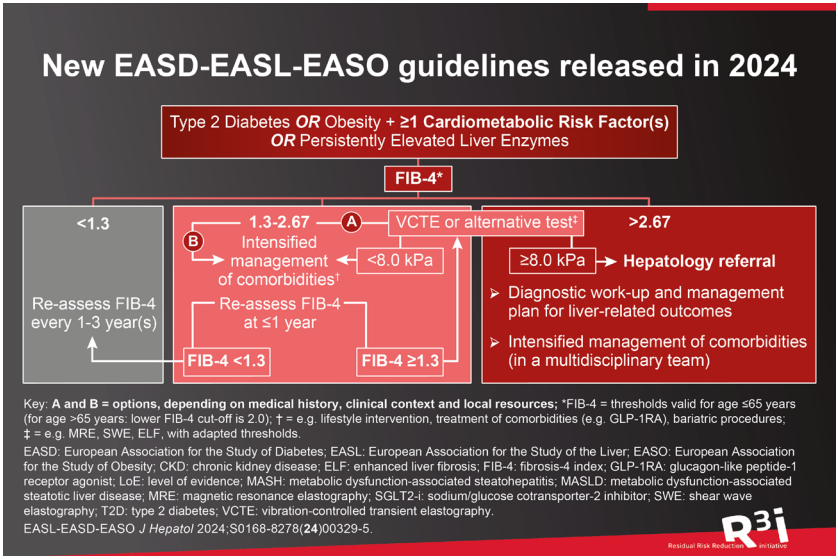

Illustration of the new EASD-EASL-EASO guidelines (2024) for patients with type 2 diabetes, obesity plus at least one cardiometabolic risk factor, or elevated liver enzymes. It outlines a process for evaluating liver fibrosis risk using the FIB-4 test, with results guiding further actions:

- FIB-4 score < 1.3: reassess FIB-4 every 1-3 year(s).
- FIB-4 score between 1.3 and 2.67: choose between two options:
- Option A: Use VCTE (Vibration-Controlled Transient Elastography) or an alternative test.
  - If VCTE is <8.0 kPa, reassess FIB-4 within 1 year.
  - If VCTE is ≥8.0 kPa, refer to a hepatologist.
- Option B: Intensify management of comorbidities and reassess FIB-4 within 1 year.
  - If FIB-4 <1.3, continue monitoring.
  - If FIB-4 ≥1.3, go for further assessment.
- FIB-4 score ≥ 2.67: referral to a hepatologist for diagnostic workup and management plan, focusing on liver-related outcomes and intensified management of comorbidities in a multidisciplinary team.

Reference:

EASL-EASD-EASO *J Hepatol* 2024;**S0168-8278**(24)00329-5.

New EASD-EASL-EASO guidelines released in 2024

GLP-1RAs are safe to use in MASH (including compensated cirrhosis) and should be used for their respective indications, namely T2D and obesity, as their use improves cardiometabolic outcomes

(LoE 2, strong recommendation, strong consensus)

SGLT2 inhibitors are safe to use in MASLD and should be used for their respective indications, namely T2D, heart failure and CKD

(LoE 3, strong recommendation, strong consensus

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AASLD recommendations for safety and efficacy monitoring of patients receiving resmetirom
AASLD: American Association for the Study of Liver Diseases
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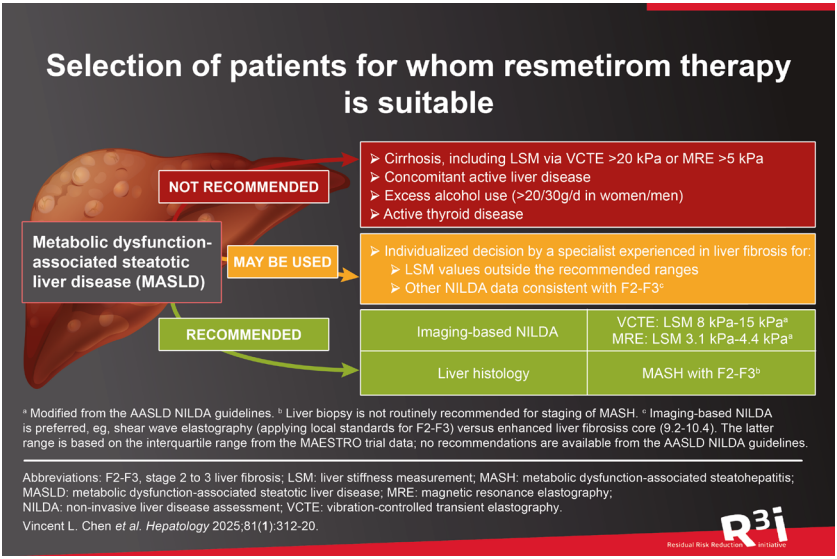
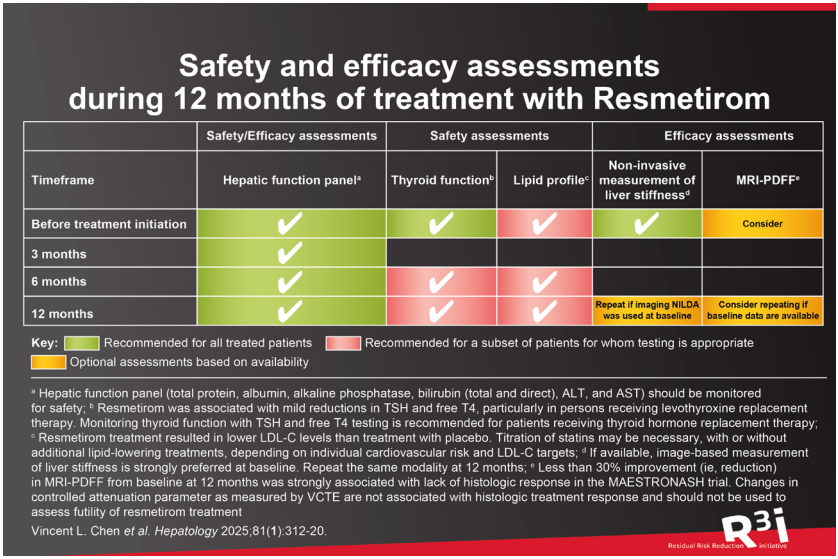


The criteria for selecting patients eligible for resmetirom therapy aimed at treating metabolic dysfunction-associated steatotic liver disease (MASLD):

1. Not Recommended: For patients with cirrhosis, commitment active liver disease, high alcohol consumption, or active thyroid disease.
2. Recommended: For patients with MASLD, imaging-based non-invasive liver disease assessment (NILDA) or liver histology, it is advised when liver stiffness measurement (LSM) falls within specific ranges between 8 kPa to 15 kPa by vibration-controlled transient elastography (VCTE) and between 3,1 kPa to 4,4 kPa by magnetic resonance elastography (MRE) and patients within stages 2 to 3 liver fibrosis (F2-F3) by liver histology.
3. May Be Used: A specialist should make individualized decisions for cases where LSM values fall outside the recommended ranges, considering other consistent NILDA data.

Reference:

Vincent L. Chen *et al. Hepatology* 2025;**81**(1):312-20.



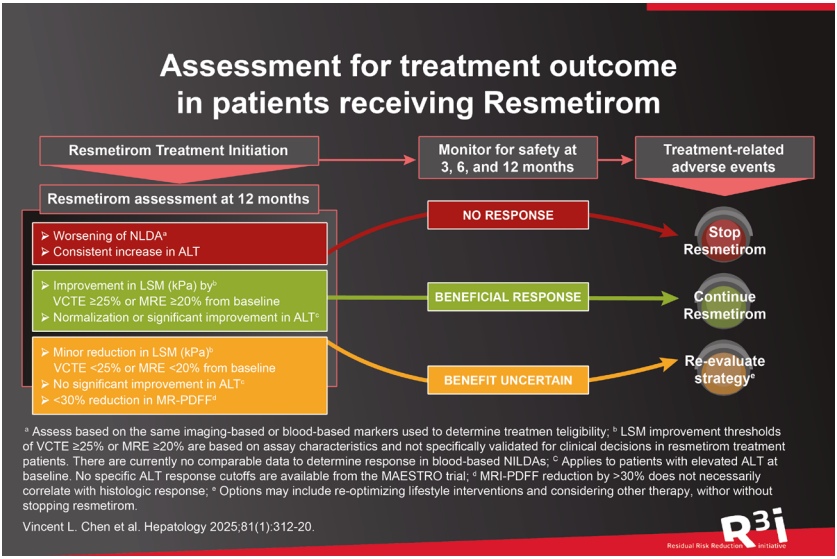
The safety and efficacy assessments conducted over 12 months of treatment with Resmetirom

Assessments are conducted at baseline, 3 months, 6 months, and 12 months.

- **Safety Assessments:**
  - Hepatic Function Panel: Recommended at all time points for all patients. This includes monitoring of total protein, albumin, alkaline phosphatase, bilirubin, ALT, and AST.
  - Thyroid Function: Reductions in TSH and free T4 were noted; therefore, thyroid function monitoring is suggested, especially for patients on levothyroxine replacement therapy.
  - Lipid Profile: Recommended at all assessment points, with potential adjustments in statin therapy.
- **Efficacy Assessments:**
  - Non-Invasive Measurement of Liver Stiffness: Conducted before treatment and at 12 months, recommended if baseline or imaging technology (e.g., NI-LDA) is used.
  - MRI-PDFF: Optional at baseline and 12 months to assess liver fat reduction, considered significant if over 30%.

Reference:

Vincent L. Chen *et al.* *Hepatology* 2025;**81**(1):312-20.



An assessment strategy for patients receiving Resmetirom treatment

The process evaluates patients' responses after 12 months to determine the course of action:

1. **No Response (Red Zone):**
   - Indicators: Worsening of noninvasive liver disease assessment (NILDA) or consistent increase in ALT levels.
   - Action: Stop Resmetirom.

2. **Beneficial Response (Green Zone):**
   - Indicators: Significant improvement in liver stiffness measure (LSM) or normalization/significant improvement in ALT.
   - Action: Continue Resmetirom.

3. **Uncertain Benefit (Yellow Zone):**
   - Indicators: Minor reduction in LSM, minimal improvement in ALT, or <30% reduction in MRI-proton density fat fraction (MRI-PDFF).
   - Action: Re-evaluate treatment strategy, considering lifestyle changes or alternative therapies.

Reference:

Vincent L. Chen *et al. Hepatology* 2025;**81**(1):312-20.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CKD	Chronic kidney disease
CI	Confidence interval
CVD	Cardiovascular disease
ELF test	Enhanced liver fibrosis test
ER	Endoplasmic reticulum
FFA	Free fatty acid
FGF	Fibroblast growth factor
FXR	farnesoid X receptor
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
HCC	Hepatocellular carcinoma
LDL-C	Low-density lipoprotein cholesterol
LT	Liver transplantation
MAFLD	Metabolic dysfunction-associated fatty liver disease
MASH	Metabolic dysfunction-associated steatohepatitis
MENA	Middle East and North Africa

MRI	Magnetic resonance imaging
MRI-PDFF	MRI proton density fat fraction
MAFL	Metabolic dysfunction-associated fatty liver
PNPLA3	Patatin-like phospholipase domain-containing 3
PPARα	Peroxisome proliferator-activated receptor alpha
SGLT-2	Sodium–glucose cotransporter-2
SPPARMα	Selective peroxisome proliferator-activated alpha modulator
T2DM	Type 2 diabetes mellitus
THR	Thyroid hormone receptor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