Current Hypertension Reports (2026) 28:33
https://doi.org/10.1007/s11906-026-01380-9

REVIEW

MASLD and Cardiovascular Risk: Mechanisms and Implications for Clinical Practice

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Received: 12 June 2026 / Accepted: 13 July 2026

Abstract

Purpose of Review Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized as a systemic cardiometabolic disease. This review summarizes recent advances in epidemiology, pathophysiology, biomarkers, and treatment relevant to cardiovascular risk assessment and management.

Recent Findings Fibrosis stage is the strongest independent predictor of cardiovascular outcomes in MASLD, conferring up to a 2.5-fold increase in events beyond traditional risk factors. Noninvasive tools, including Fibrosis-4 (FIB-4) and liver stiffness measurement, also predict cardiovascular mortality. Semaglutide and resmetirom offer dual hepatic and cardiometabolic benefits.

Summary MASLD affects 38% of adults globally, and cardiovascular disease (CVD) is the leading cause of death across disease stages. Fibrosis-based risk stratification remains absent from standard cardiovascular risk models despite its prognostic value. Therapies with combined liver and cardiovascular benefits are promising, but whether improving liver disease reduces cardiovascular events remains uncertain.

Keywords Metabolic-Dysfunction Associated Steatohepatitis · Hepatic Fibrosis · Cardiovascular Risk · Cardiometabolic Syndrome, Cardiovascular–Kidney–Metabolic Syndrome · MASH

Abbreviations

MASLD	Metabolic dysfunction-associated steatotic liver disease
FFA	Free fatty acid
PNPLA3	Patatin-like phospholipase domain-containing protein 3
TM6SF2	Transmembrane 6 superfamily member 2
TMAO	Trimethylamine N-oxide
LPS	Lipopolysaccharide
SREBP-1c	Sterol regulatory element-binding protein 1c
ChREBP	Carbohydrate-responsive element-binding protein
VLDL	Very-low-density lipoprotein
LDL	Low-density lipoprotein
IL	Interleukin
TNF-α	Tumor necrosis factor alpha
NLRP3	Nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3
ECM	Extracellular matrix
CV	Cardiovascular
ApoB	Apolipoprotein B
VCAM-1	Vascular cell adhesion molecule 1
ICAM-1	Intercellular adhesion molecule 1
CRP	C-reactive protein
PAI-1	Plasminogen activator inhibitor 1
LV	Left ventricular

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Published online: 01 August 2026

Introduction

Metabolic-dysfunction associated steatotic liver disease (MASLD), formerly termed nonalcoholic fatty liver disease (NAFLD), has evolved from a liver-centric diagnosis to a systemic cardiometabolic disease defined by hepatic steatosis in the presence of metabolic dysfunction [1, 2]. The nomenclature change was accompanied by a shift from exclusion-based to inclusion-based diagnostic criteria, now requiring hepatic steatosis plus at least one cardiometabolic risk factor [1]. This shift emphasizes its integration within the broader cardiovascular–kidney–metabolic (CKM) spectrum [3]. Despite these changes, 99% of individuals who meet NAFLD criteria also meet MASLD criteria, indicating that the renaming does not invalidate the existing evidence base [4]. For the remainder of this manuscript, we will use the terms MASLD and MASH (metabolic dysfunction associated steatohepatitis) to refer to this disease.

Cardiovascular disease (CVD) is the leading cause of death in patients with MASLD, with a 10-year cumulative incidence of 8.1% [5]. Even in MASLD-related cirrhosis, cardiovascular mortality substantially exceeds liver-related mortality (17.3% vs. 9.2% at 10 years, respectively) [5]. This risk persists beyond traditional risk factors and is strongly modified by fibrosis stage, which confers up to a 2.5-fold increase in cardiovascular events [5–7].

Despite this, MASLD remains underrecognized in cardiovascular risk assessment. This review synthesizes emerging evidence linking MASLD to CVD and outlines a clinically actionable framework for cardiologists, general practitioners, and other clinicians involved in cardiometabolic risk assessment and prevention.

Epidemiology & Clinical Risk

MASLD affects 38% of adults globally and is projected to exceed 55% by 2040, driven by obesity and metabolic syndrome [2, 5, 8]. Burden is highest in Latin America (44.4%) and lowest in Western Europe (25.1%), with rapid growth across Northern Africa, the Middle East, and Asia [2, 5]. In the United States, prevalence is highest among Hispanic individuals, particularly Mexican Americans, and lowest among Black individuals [8]. Disparities in MASLD mirror those seen in CVD, influenced by genetics, metabolic risk, and social determinants [8].

Prevalence is highest among individuals with type 2 diabetes (65–70%), obesity (70–80%), and prediabetes (37–50%)—populations already at elevated cardiovascular risk [2, 5, 8]. Sex also modifies risk. Premenopausal women have approximately 50% lower MASLD prevalence than men, attributable to estrogen's protective effects on hepatic lipid metabolism and insulin sensitivity, though this advantage is lost after menopause [8].

MASLD confers ~ 1.5-fold higher risk of cardiovascular events, increasing to ~ 2.5-fold in advanced fibrosis (fibrosis stage 3 or higher), with a clear dose–response relationship across cardiometabolic burden [2, 5]. This relationship is also bidirectional, reflecting shared upstream drivers of insulin resistance and metabolic dysfunction [8]. These patterns reinforce MASLD as a systemic risk enhancer rather than an isolated liver condition.

Pathophysiology Linking MASLD to Cardiovascular Disease

MASLD promotes CVD through interconnected pathways involving insulin resistance, atherogenic dyslipidemia, inflammation, endothelial dysfunction, and thrombosis. In MASLD, insulin resistance arises from upstream metabolic drivers such as excess adiposity, altered adipokine signaling, and increased free fatty acid flux, leading to hepatic steatosis, dysregulated lipogenesis, and abnormal hepatokine release. These hepatic changes drive systemic effects including atherogenic dyslipidemia, endothelial dysfunction, inflammation, and thrombosis, while cardiovascular and neurohormonal feedback further worsens liver injury, reflecting a bidirectional liver and heart axis (Fig. 1).

Insulin Resistance

Insulin resistance represents the central mechanism linking MASLD to CVD, functioning as a metabolic driver that promotes both hepatic steatosis and vascular injury. Increased adipose tissue lipolysis leads to elevated circulating free fatty acids (FFAs), which are taken up by the liver and promote triglyceride accumulation while also exerting direct lipotoxic effects on the vascular endothelium. These processes contribute to oxidative stress and early endothelial dysfunction, establishing a direct interface between hepatic metabolic disturbance and atherosclerosis [4, 5, 9].

Within the liver, insulin signaling becomes selectively impaired, resulting in reduced suppression of gluconeogenesis while de novo lipogenesis remains active. This imbalance promotes hyperglycemia, hepatic lipid accumulation, and increased production of very low-density lipoprotein (VLDL), linking hepatic metabolism directly to circulating atherogenic lipoproteins through sterol regulatory element-binding protein 1c and carbohydrate-responsive element-binding protein pathways [4, 9, 10]. Concurrently, altered hepatokine signaling, including increased fetuin-A and selenoprotein P, and increased release of pro-inflammatory adipokines such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), amplify systemic inflammation and endothelial dysfunction [4, 9, 10].

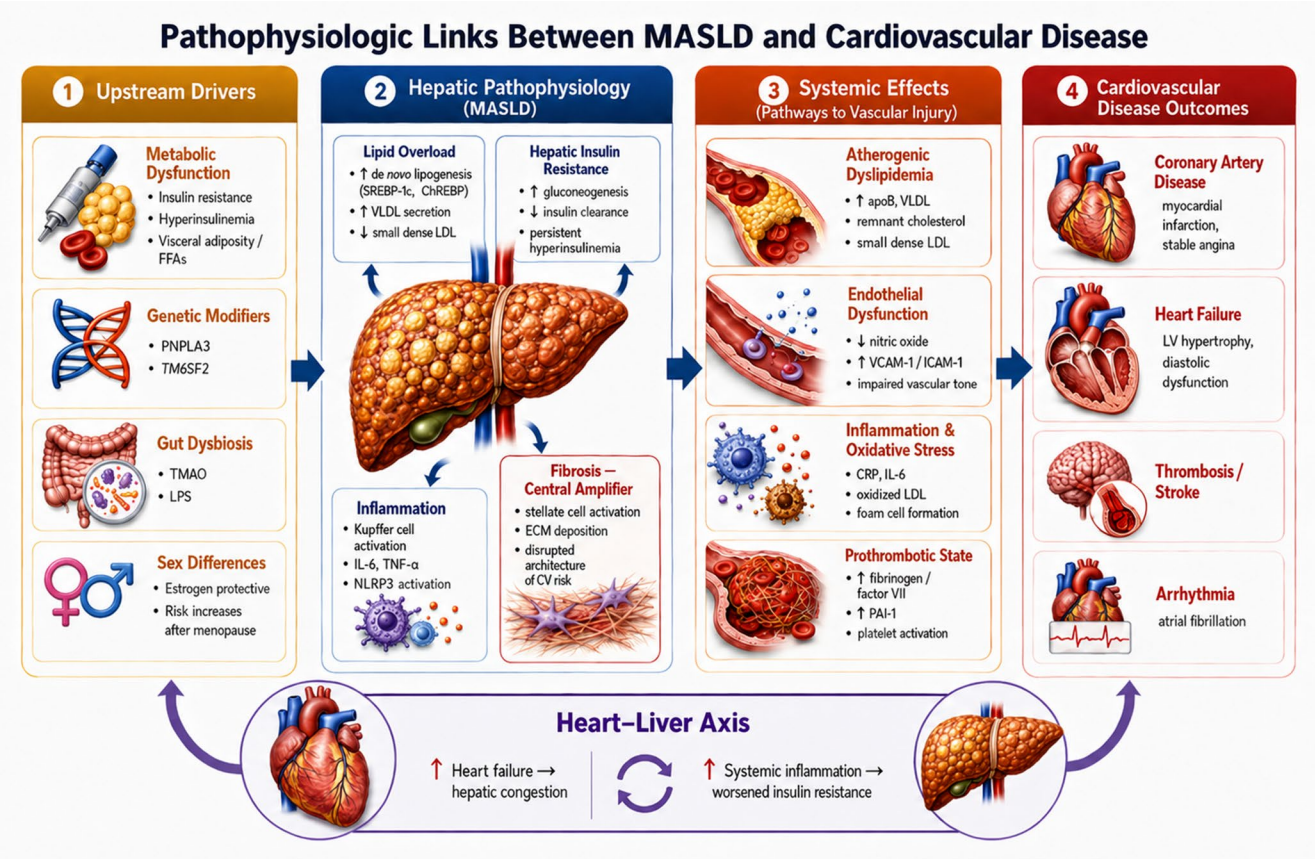

Fig. 1 Pathophysiologic links between metabolic dysfunction-associated steatotic liver disease and cardiovascular disease. The figure illustrates how upstream drivers, including metabolic dysfunction, genetic modifiers, gut dysbiosis, and sex-related differences, promote hepatic lipid accumulation, insulin resistance, inflammation, and fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD). These hepatic changes contribute to systemic vascular injury through atherogenic dyslipidemia, endothelial dysfunction, inflammation, oxidative stress, and a prothrombotic state, increasing the risk of coronary artery disease, heart failure, thromboembolism, stroke, and arrhythmia. Cardiovascular risk is increased approximately 1.5-fold in MASLD and up to approximately 2.5-fold in advanced fibrosis. The heart–liver axis highlights bidirectional interactions between heart failure, hepatic congestion, systemic inflammation, and insulin resistance. Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; FFA, free fatty acid; PNPLA3, patatin-like phospholipase domain-containing protein 3; TM6SF2, transmembrane 6 superfamily member 2; TMAO, trimethylamine N-oxide; LPS, lipopolysaccharide; SREBP-1c, sterol regulatory element-binding protein 1c; ChREBP, carbohydrate-responsive element-binding protein; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; IL, interleukin; TNF-α, tumor necrosis factor alpha; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; ECM, extracellular matrix; CV, cardiovascular; ApoB, apolipoprotein B; VCAM-1, vascular cell adhesion molecule 1; ICAM-1, intercellular adhesion molecule 1; CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor 1; LV, left ventricular. Figure created with author direction and assistance from ChatGPT/DALL-E image-generation software, followed by author review and editing

At the cellular level, accumulation of lipid intermediates such as diacylglycerols impairs insulin receptor signaling through protein kinase C activation, while reduced hepatic insulin clearance sustains hyperinsulinemia. These processes contribute to activation of the sympathetic nervous system and renin–angiotensin–aldosterone system, promoting hypertension, vascular stiffness, and further endothelial injury [4, 9, 10]. In this context, hepatic insulin resistance is not simply a metabolic abnormality but a signal of systemic vascular risk that may precede and outpace conventional clinical markers [4, 5, 9].

Atherogenic Lipid Profile

The dyslipidemia associated with MASLD reflects profound alterations in hepatic lipid handling and extends beyond conventional lipid measurements. Elevated triglycerides, VLDL, apolipoprotein B-containing lipoproteins, and remnant cholesterol occur alongside reduced high-density lipoprotein (HDL) levels, a pattern observed in approximately 60–70% of patients [9–11]. This profile arises from increased substrate delivery to the liver, enhanced lipogenesis, impaired mitochondrial beta-oxidation, and reduced

lipid export, resulting in sustained overproduction of triglyceride-rich lipoproteins [4, 9–11].

A defining feature of this dyslipidemia is the enrichment of small dense low-density lipoprotein (sLDL) particles, which exhibit increased arterial wall penetration, prolonged circulation time, and greater susceptibility to oxidative modification. These properties enhance their atherogenic potential and promote plaque formation and progression within the arterial wall [9, 10]. Coronary computed tomography angiography studies demonstrate a higher prevalence of high-risk plaque features in MASLD, including positive remodeling and spotty calcification [12].

In addition to fasting abnormalities, postprandial lipid metabolism is significantly altered in MASLD, leading to prolonged exposure to triglyceride-rich lipoproteins and remnant particles. This extended exposure promotes oxidative stress, endothelial dysfunction, and foam cell formation, contributing to both subclinical and overt atherosclerosis [9, 11]. Importantly, remnant cholesterol retains prognostic significance even when low-density lipoprotein (LDL) cholesterol is controlled, suggesting that reliance on traditional lipid metrics may underestimate residual cardiovascular risk [11].

Systemic Inflammation

Inflammation represents a central pathway linking hepatic disease to vascular injury in MASLD, extending beyond the liver to influence systemic atherogenesis. The liver serves as a major source of circulating inflammatory mediators, including C-reactive protein, IL-6, and TNF-α, which promote endothelial activation, impair vascular homeostasis, and contribute to plaque instability [4, 9, 13].

In MASH, activation of Kupffer cells and recruitment of inflammatory macrophages amplify these pathways, creating a sustained pro-inflammatory environment that affects both hepatic and vascular tissues [4, 9, 13]. Oxidative stress acts in parallel with inflammation to accelerate vascular injury, driven by mitochondrial dysfunction and impaired beta-oxidation [14]. These processes promote lipid peroxidation and formation of oxidized low-density lipoprotein, which plays a central role in foam cell formation and plaque development [14].

Activation of the nod-like receptor family, pyrin domain containing protein 3 (NLRP3) inflammasome further integrates metabolic and inflammatory pathways through release of interleukin-1 beta and interleukin-18, contributing to endothelial dysfunction and plaque destabilization [15]. Together, these mechanisms suggest that inflammatory activity in MASLD may sustain vascular risk even when traditional lipid targets are achieved [4, 9].

Endothelial Dysfunction

Endothelial dysfunction emerges early in MASLD and reflects a convergence of metabolic, inflammatory, and oxidative pathways. Elevated asymmetric dimethylarginine (ADMA) and hyperhomocysteinemia impair nitric oxide bioavailability, leading to reduced vasodilation, increased vascular tone, platelet activation, and upregulation of adhesion molecules that promote vascular inflammation [9, 11, 13]. Clinically, this is evident as impaired flow-mediated dilation and contributes to early atherosclerotic alterations, including increased coronary artery calcium and carotid intima-media thickness [9, 11].

Prothrombotic State

MASLD is also associated with a prothrombotic state characterized by increased production of coagulation factors, impaired fibrinolysis, and enhanced platelet activation [4, 13, 16]. Elevated fibrinogen, factor VIII, and plasminogen activator inhibitor-1 levels promote clot persistence, while platelet–leukocyte interactions further amplify vascular inflammation [4, 13, 16]. These abnormalities create a vascular environment that favors both plaque formation and acute thrombotic events [4].

Hepatic Fibrosis as Central Amplifier

Liver fibrosis stage represents the most consistent marker of cardiovascular risk in MASLD and reflects the cumulative burden of metabolic, inflammatory, and vascular injury. A meta-analysis including 5.8 million individuals demonstrated a 1.45-fold increased risk of cardiovascular events in MASLD, rising to 2.50-fold in patients with advanced fibrosis [2, 5]. Cohort studies further show that fibrosis indices independently predict cardiovascular mortality beyond traditional cardiometabolic risk factors [2].

This relationship reflects sustained exposure to insulin resistance, inflammation, oxidative stress, endothelial dysfunction, and atherogenic dyslipidemia [2, 17]. These processes contribute to structural cardiac changes, including left ventricular hypertrophy and diastolic dysfunction [17]. Coronary imaging studies demonstrate increased prevalence of coronary plaque and obstructive disease in MASLD [12]. These findings support fibrosis as an integrative marker of systemic cardiovascular risk.

Genetic Risk Modifiers

Genetic variation highlights the heterogeneity of MASLD and underscores that hepatic fat accumulation does not

uniformly translate into cardiovascular risk. The patatin-like phospholipase domain-containing protein 3 (PNPLA3) I148M variant strongly predisposes to hepatic steatosis and fibrosis but is not consistently associated with increased cardiovascular risk [18, 19].

Similarly, the transmembrane 6 superfamily member 2 (TM6SF2) E167K variant impairs VLDL secretion, leading to hepatic lipid accumulation while lowering circulating atherogenic lipoproteins [18, 19]. Other variants, including membrane bound acylglycerrophosphatidylinositol O-acyltransferase 7 (MBOAT7), glucokinase regulator (GCKR), and hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13), further influence hepatic lipid metabolism and fibrosis progression [18, 19]. These findings suggest that cardiovascular risk in MASLD is influenced by underlying metabolic pathways rather than hepatic fat alone.

Gut Dysbiosis

Alterations in gut microbiota composition contribute to MASLD and cardiovascular risk through increased intestinal permeability and systemic inflammation [20]. Translocation of bacterial products such as lipopolysaccharide activates inflammatory pathways that affect both the liver and vascular system [20].

Trimethylamine N-oxide (TMAO), a microbiota-derived metabolite, has been associated with endothelial dysfunction, platelet activation, and atherosclerosis [21]. Experimental data support its role in foam cell formation and altered cholesterol metabolism, while clinical studies demonstrate associations with subclinical coronary atherosclerosis [21]. These findings suggest that gut-derived metabolites may contribute to cardiovascular risk beyond traditional metabolic pathways.

Sex Hormones

Sex hormones influence MASLD through effects on adipose distribution, insulin resistance, hepatic lipid metabolism, and vascular biology. Estrogen is broadly protective, and its loss after menopause promotes visceral adiposity, hepatic steatosis, and endothelial dysfunction, paralleling increases in MASLD prevalence and fibrosis risk in women [22, 23]. Androgen-related effects are sex-specific: androgen excess in women (e.g., polycystic ovarian syndrome) and testosterone deficiency in men are each associated with higher MASLD risk and adverse cardiometabolic profiles [24]. These hormone-driven differences likely contribute to cardiovascular risk through dyslipidemia, inflammation, and vascular dysfunction, supporting the need for sex-specific risk assessment in MASLD. However, evidence supporting hormone therapy as a treatment strategy remains limited [25].

From Mechanisms to MASLD Diagnosis and Risk Stratification

These pathways converge in liver fibrosis, which serves as both a marker of hepatic injury and an integrative measure of systemic cardiometabolic risk. Fibrosis stage is the strongest predictor of hepatic and cardiovascular outcomes in MASLD and underpins current clinical algorithms [2]. Noninvasive biomarkers have therefore largely replaced liver biopsy for fibrosis risk stratification in most settings. Clinically, they are used to exclude cirrhosis, identify at-risk MASH (fibrosis stage 2 or higher), and monitor disease trajectory [2]. These indications are distinct and require appropriate tool selection (Tables 1).

The Fibrosis-4 (FIB-4) index, which incorporates age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count, is the recommended first-line test because it is inexpensive and reliably excludes at-risk MASH and advanced fibrosis when low (< 1.3 in adults aged 35–64, or < 2.0 in adults aged ≥ 65 years) [2]. It also independently predicts all-cause and cardiovascular mortality, suggesting prognostic value beyond the liver [26]. Because its positive predictive value is limited, patients with FIB-4 ≥ 1.3 require second-line testing [2].

In patients with FIB-4 ≥ 1.3, second-line assessment relies on liver stiffness measurement, most commonly with vibration-controlled transient elastography (VCTE), which predicts cirrhosis, hepatocellular carcinoma (HCC), and mortality and correlates with subclinical atherosclerosis and cardiovascular events. The enhanced liver fibrosis (ELF) score is a validated blood-based alternative that reflects extracellular matrix remodeling and vascular stiffness [27]. Magnetic resonance elastography (MRE) offers greater accuracy but is limited by cost and availability.

Several emerging tools may further refine risk discrimination. The metabolic dysfunction-associated fibrosis 5 (MAF-5) score incorporates metabolic variables to improve fibrosis detection [28], whereas Agile 3 + and Agile 4 combine liver stiffness with clinical variables to improve detection of advanced fibrosis and cirrhosis [27]. Pro-C3-based scores such as ADAPT (Age, DiAbetes, Pro-C3, plaTelet count) and ALPACA (ALcoholic liver disease Pro-C3, AST/ALT, plAtelets, and Clinical variable Assessment) reflect active fibrogenesis and are also associated with cardiovascular events, underscoring shared hepatic and vascular remodeling pathways [29]. Metabolic indices such as the triglyceride-glucose (TyG) index also predict MASLD and cardiovascular outcomes, reinforcing their shared pathophysiology [30]. Emerging proteomic models may further improve atherosclerotic cardiovascular disease (ASCVD) prediction by capturing MASLD-related molecular signals not reflected in conventional clinical variables [31].

Table 1 Risk stratification tools in MASLD: A Cardiovascular (CV) perspective

Biomarker	*Components*	*Clinical Role*	*Strengths*	*Limitations*	*CV Relevance*
RISK SCORES					
FIB-4	Age, AST, ALT, Platelets	First line fibrosis risk stratification, recommended in all at risk populations, rules out advanced fibrosis when low	NPV (85–90%) for advanced fibrosis, widely available, no cost, independently validated across multiple settings with age adjusted versions available	Poor PPV (58–62%) thus requires confirmation testing, high indeterminate rate, accuracy varies in some age groups	Predicts all-cause mortality (HR 1.49) and CV mortality (HR 1.48) independently. Serial FIB-4 predicts CV events. Higher scores associated with coronary artery calcification (CAC) progression in MASLD
MAF-5	Waist circumference, BMI, Diabetes status, AST, Platelets	Fibrosis detection, first-line screening alternative to FIB-4	Superior AUC vs. FIB-4 (0.81), metabolic inputs better reflect MASLD pathophysiology, age-independent, more metabolic risk factor inclusion than FIB-4	Less validated, not integrated into standard algorithms, requires waist measurement	Metabolic inputs are core CV risk drivers. May help track ASCVD risk along with fibrosis.
Agile 3+ / Agile 4	Liver stiffness (VCTE), AST, ALT, Platelets, Diabetes Status, Sex	Advanced fibrosis (Agile 3 + AUC 0.87) and cirrhosis (Agile 4 AUC 0.90) confirmation, can be useful for longitudinal monitoring, combines VCTE with clinical variables	Fewer indeterminate results vs. FIB-4 or VCTE alone and validated for serial use and long-term liver outcomes	Requires VCTE input	Incorporates diabetes, a shared driver of both hepatic and CV outcomes. May be helpful in tracking CV-relevant disease trajectory over time
TyG Index and Sub-Indices (TyG-WC, TyG-BMI, TyG-WHtR)	Triglycerides, Fasting glucose, +/- waist circumference, +/- BMI, +/- waist-to-height ratio	Surrogate for measuring insulin resistance and can help in MASLD and MASH risk prediction	Inexpensive, captures visceral adiposity and dyslipidemia, not liver specific and strong in elderly MASLD	Not validated for fibrosis staging, sensitivity and specificity varies across sub-indices	Inherently a metabolic-CV tool that predicts hepatic and adverse CV outcomes simultaneously. Strong CV mortality risk prediction in elderly MASLD. Underutilized despite dual relevance
IMAGING BIOMARKERS					
VCTE	Liver stiffness (kPa), controlled attenuation parameter (steatosis)	Second-line confirmatory fibrosis staging. If LSM ≥ 8.0 kPa, refer to hepatology	Non-invasive, predicts cirrhosis, HCC and all-cause mortality, best validated and most widely available imaging tool, serial measurements can track disease progression	Operator dependent, unreliable in high BMI, hepatic congestion, acute hepatitis or ascites, and requires specialized equipment, limited availability in primary care	Higher liver stiffness independently correlates with subclinical atherosclerosis and CV events. Stiffness is not liver-specific, structural changes captured by VCTE reflect systemic vascular pathology.
MRE	Hepatic stiffness (kPa)	Gold-standard noninvasive fibrosis staging accuracy compared to liver biopsy	Superior diagnostic accuracy across all fibrosis stages, not impacted by BMI	High cost, limited availability, not feasible in routine or non-specialist practice	No direct CV outcome data and is currently a research tool but mechanistic CV relevance mirrors VCTE
BLOOD BIOMARKERS					
ELF Panel	Hyaluronic acid, TIMP-1, PIINP	Second-line fibrosis confirmation when VCTE is unavailable. If ELF ≥ 9.8, refer to hepatology	Blood based, captures extra-cellular matrix (ECM) turnover, validated across the MASLD spectrum with approximately 98% sensitivity for advanced fibrosis	Less available than FIB-4, higher cost and required specialist ordering in most centers	Measures systemic ECM remodeling, not just hepatic. Elevated components correlate with arterial stiffness and systemic vascular remodeling. Bridges liver and vascular pathology
NIS2+ / NIS4	mIR-34a-5p, a2-macroglobulin, YKL-40, adiponectin, +/- AST, +/- HbA1c	Identifies "at-risk" MASH, the population most likely to benefit from pharmacotherapy	Built for determining treatment eligibility, correlated with active inflammation and fibrosis	Needs wider validation, not integrated into standard care pathways, proprietary formula	At-risk MASH is the highest risk group for both hepatic progression and CV events. Identifying these patients can prompt proper management.

Table 1 (continued)

Biomarker	*Components*	*Clinical Role*	*Strengths*	*Limitations*	*CV Relevance*
Pro-C3	N-terminal propeptide of Type III collagen	Fibrosis activity assessment, component of ADAPT and ALPACA composite scores	Reflects active fibrogenesis and increases in a stepwise manner with fibrosis stage, validates composites	Not integrated in routine algorithms, wider validation needed, limited availability	Independently associated with CV events
Pro-SCORE2	MASLD associated proteins (FABP4, IL7R, EDA2R) and SCORE2	Integrated ASCVD and MASLD risk prediction, enhances standard CV risk models	C-index improvement of 7.5–9.6% over SCORE-2, key MASLD mediators identified	Not validated at scale, not clinical available, requires proteomics platform	Moves from organ-specific biomarkers to integrated CV-hepatic markers

Abbreviations: ADAPT Age, diabetes, *PRO-C3*, and platelet count, *ALPACA* Advanced liver fibrosis prediction algorithm, *ALT* Alanine aminotransferase, *ASCVD* Atherosclerotic cardiovascular disease, *AST* Aspartate aminotransferase, *AUC* Area under the receiver operating characteristic curve, *BMI* Body mass index, *CAC* Coronary artery calcification, *CV* Cardiovascular, *ECM* Extracellular matrix, *EDA2R* Ectodysplasin *A2* receptor, *ELF* Enhanced Liver Fibrosis, *FABP4* Fatty acid-binding protein 4, *FIB-4* Fibrosis-4 index, *HbA1c* Hemoglobin A1c, *HCC* Hepatocellular carcinoma, *HR* Hazard ratio, *IL7R* Interleukin-7 receptor, *kPa* Kilopascal, *LSM* Liver stiffness measurement, *MAF-5* Metabolic dysfunction-associated fibrosis-5, *MASLD* Metabolic dysfunction-associated steatotic liver disease, *MASH* Metabolic dysfunction-associated steatohepatitis, *MRE* Magnetic resonance elastography, *NIS* Noninvasive test for steatohepatitis, *NPV* Negative predictive value, *PIINP* N-terminal propeptide of type III procollagen, *PPV* Positive predictive value, PRO-C3 N-terminal propeptide of type III collagen, SCORE2 Systematic Coronary Risk Evaluation 2, TIMP-1 Tissue inhibitor of metalloproteinase 1, TyG Triglyceride-glucose, VCTE Vibration-controlled transient elastography, WC Waist circumference, *WHtR* Waist-to-height ratio, *YKL-40* Chitinase-3-like protein 1

Taken together, these data support fibrosis markers as cardiovascular risk enhancers in MASLD. Because liver fibrosis is not captured in traditional CV risk models, cardiovascular risk may be underestimated in persons with MASLD. Elevated FIB-4, liver stiffness, or other markers consistent with liver fibrosis stage 2 or higher should therefore prompt hepatology referral and consideration of intensified cardiovascular risk management.

Clinical Implications and Management

In clinical practice, identification of clinically significant fibrosis should prompt hepatology referral, treatment of underlying metabolic drivers, and intensified cardiovascular risk reduction coupled with use of hepatic fibrosis-directed therapy [32]. Sustained weight loss remains the most established intervention associated with fibrosis regression, and to date bariatric surgery provides the strongest real-world evidence for combined liver and cardiovascular outcome benefit in appropriately selected patients [33]. Liver-directed pharmacologic options are evolving: resmetirom and semaglutide are conditionally approved for noncirrhotic MASH with F2–F3 fibrosis, and SGLT2 inhibitors and GLP-1 receptor agonists provide established cardiovascular and renal benefits in patients with cardiometabolic disease (Table 2). However, whether improvement in hepatic fibrosis independently reverses cardiovascular disease or reduces cardiovascular events has not been definitively established; therefore, fibrosis should currently be viewed as both a treatment target and a marker that should trigger intensified cardiovascular prevention.

MASLD Screening Strategies

Because fibrosis predicts both liver-related and cardiovascular outcomes, current practice emphasizes targeted case finding rather than population screening in individuals with metabolic risk factors. Liver ultrasound is not recommended for MASLD screening because of its limited sensitivity for mild steatosis [8]. In patients with a high pretest probability of MASLD—such as those with type 2 diabetes, overweight or obesity plus an additional metabolic risk factor, or elevated aminotransferases—it is reasonable to proceed directly to fibrosis risk stratification without liver imaging [8, 23, 34]. Incidental hepatic steatosis identified on imaging should likewise prompt fibrosis risk stratification.

Risk escalates with metabolic burden—for example, each unit increase in body mass index (BMI) confers a 1.3-fold higher risk of advanced fibrosis in diabetes [35]—supporting more frequent monitoring in the highest-risk groups [32]. In specialty or primary care settings with access to imaging-based noninvasive tests, consideration may be given to skipping the FIB-4 index, especially in individuals with diabetes who are at the highest risk (MASLD prevalence 37–70%; up to 38% with advanced fibrosis) [32].

MASLD as a Cardiovascular Risk Enhancer

This fibrosis-based diagnostic approach has direct cardiovascular implications. The American Heart Association (AHA) recognizes MASLD as both a contributor to and marker of increased ASCVD risk, although it is not yet included in standard risk calculations [7, 36]. Because fibrosis markers

Table 2 Established and emerging pharmacologic therapies in persons with MASLD across the hepatic–cardiorenal axis

Drug	Drug Class	Indication	Liver yield Trial/Study	*N* of Participants	Duration of Trial	MASH resolution	Fibrosis Reduction	CV Outcomes	Kidney Outcomes	Other metabolic benefits	Recommendation
Resmiterom	THR-β agonist	MASH F2-F3	MAESTRO-NASH (Phase 3)	966	52 wk	MASH resolution 25.9% (80 mg), 29.9% (100 mg) vs. 9.7% (placebo); ↓ Liver fat ~ 30% by MRI-PDFF	Fibrosis reduction 24.2% (80 mg), 25.9% (100 mg) vs. 14.2% (placebo)	CV outcomes under evaluation	Not studied	↓ LDL 13–16%, ↓ Lp(a) 30–36%, neutral on body weight	First line for non-cirrhotic MASH with F2-F3 fibrosis
Semaglutide (weekly SC)	GLP-1	MASH F2-F3/Diabetes/Obesity	ESSENCE (Phase 3)	800	72 wk	MASH resolution 62.9% vs. 34.3% in placebo	Fibrosis reduction 36.8% vs. 22.4% in placebo	SELECT trial: HR of 0.80 MACE; real-world data: HR of 0.59 for cardiovascular events	FLOW trial: HR 0.76 in CKD progression	STEP trials: mean weight loss of 14.9%–17.4% over 68 weeks	First line for diabetes and/or obesity in MASLD
Lisinopril	ACEi	Hypertension/CKD	Observational studies	Large cohorts	Long-term	MASH resolution not assessed; Possible ALT improvement and HCC prevention	Fibrosis reduction not assessed. Potential fibrosis benefit, HR 0.70 MALO vs. CCB	Proven CV benefit in HTN/HF, reduced CV risk in MASLD cohorts	Renal protective	↓ Insulin resistance	First line for HTN with CKD in MASLD
Losartan	ARB	Hypertension/CKD	Observational studies	Large cohorts	Long-term	MASH resolution not assessed; Non-significant ALT reduction	Fibrosis reduction not assessed. Non-significant fibrosis changes	Proven CV benefit in HTN/HF, reduced CV risk in MASLD cohorts	Renal protective	↓ Insulin resistance	Recommended for HTN/CKD
Amlodipine	CCB	Hypertension	Observational studies	Large cohorts	Long-term	MASH resolution not assessed; Neutral	Fibrosis reduction not assessed. Neutral	BP control reduces CV risk	Neutral	Metabolically neutral (no significant effects on weight, glucose, or lipids)	Recommended for HTN

Table 2 (continued)

Drug	Drug Class	Indication	Liver yield Trial/Study	*N* of Participants	Duration of Trial	MASH resolution	Fibrosis Reduction	CV Outcomes	Kidney Outcomes	Other metabolic benefits	Recommendation
Semaglutide (daily, PO)	GLP-1	Diabetes/Obesity	Observational study	169	6 mo	MASH resolution not assessed; Improvement of ALT, hepatic steatosis index and FIB-4 index	Fibrosis reduction not assessed	SOUL trial: HR 0.86 of MACE	SOUL trial: HR 0.91 (0.80–1.05; $P=0.19$), not statistically significant for major kidney disease events	OASIS trial: weight loss of ~13.6% with 25 mg, ~15% at 68 weeks at 50 mg	Recommended for diabetes (Rybelsus), obesity (Wegovy)
Liraglutide	GLP-1	Diabetes	LEAN (Phase 2)	52	48 wk	MASH resolution 39% vs. 9% in placebo	Fibrosis reduction not assessed. Slow fibrosis progression 9% vs. 36% in placebo	LEADER trial: HR 0.87 MACE	Not studied	SCALE trials: 8.0% mean weight loss (vs. 2.6% placebo) at 56 weeks	Recommended for diabetes and/or obesity in MASLD
Dulaglutide	GLP-1	Diabetes	D-LIFT (Phase 2)	64	24 wk	MASH resolution not assessed; Relative liver fat reduction: -26.4%	Fibrosis reduction not assessed. Non-significant reductions in liver stiffness	REWIND: HR 0.88 MACE; HR 0.76 stroke	REWIND: HR 0.85 composite renal outcome; AWARD-7: less decline in eGFR vs. insulin glargine (CKD G3–4)	AWARD-11: Modest weight loss (3.0–4.7 kg); modest reduction in visceral adiposity	Recommended for diabetes
Tirzepatide	GIP/GLP-1	Diabetes/Obesity	SYNERGY-NASH (Phase 2b, 3)	190	52 wk	MASH resolution 44% (5 mg), 56% (10 mg), 62% (15 mg) vs. 10% (placebo)	Fibrosis reduction 55% (5 mg), 51% (10 mg), 51% (15 mg) vs. 30% (placebo)	SURPASS-CVOT: HR 0.92 MACE; HR 0.84 mortality	SURPASS and meta-analyses: albuminuria reduction in T2DM	SURMOUNT trials: up to 20.9% mean weight loss at 72 weeks (vs. 3.1% placebo)	First line for obesity with MASLD

Table 2 (continued)

Drug	Drug Class	Indication	Liver yield Trial/Study	*N* of Participants	Duration of Trial	MASH resolution	Fibrosis Reduction	CV Outcomes	Kidney Outcomes	Other metabolic benefits	Recommendation
Dapagliflozin	SGLT-2i	Diabetes/CKD	DEAN (Phase 2b)	154	48 wk	MASH resolution 23% vs. 8% in placebo	Fibrosis reduction 45% vs. 20% in placebo	DECLARE: HR 0.93 MACE; HR 0.73 HF	DAPA-CKD: HR 0.61 in kidney-specific composite	Weight loss (~2–3 kg); ↓ blood pressure (~3–5 mmHg); ↓ uric acid	First line for diabetes with CKD or CKD without diabetes
Empagliflozin	SGLT-2i	Diabetes/CKD	EMPA-REG OUTCOME (Phase 3)	2477	28 wk	MASH resolution not assessed; ↓ Liver fat 22%; ↓ ALT	Fibrosis reduction not assessed	EMPA-REG: HR 0.86 MACE; HR 0.65 HF	EMPA-KIDNEY: HR 0.72 in kidney-specific composite	Weight loss (~2–3 kg); ↓ blood pressure (~3–5 mmHg); ↓ uric acid	First line for diabetes with CKD
Canagliflozin	SGLT-2i	Diabetes/CKD	CANVAS post hoc	10,131	Mean of 188.2 weeks	MASH resolution not assessed; 35% ALT improvement	Fibrosis reduction not assessed	CANVAS: HR 0.86 MACE	CREDENCE: HR 0.70 in kidney-specific composite	Weight loss (~2–3 kg); ↓ blood pressure (~3–5 mmHg); ↓ uric acid	First line for diabetes with CKD
Metformin	Biguanide	Diabetes	Observational and cohort studies	Large cohorts	Long-term	MASH resolution not assessed; Minimal direct steatosis benefit	No histologic improvement	↓ CV risk in diabetes	Neutral	Weight-neutral or modest weight loss	Recommended for diabetes
Linagliptin	DPP-4i	Diabetes	Cohort studies	Large cohorts	Long-term	MASH resolution not assessed; Modest ALT reduction	No histologic improvement	Neutral (except saxagliptin , ↑ HF)	Neutral	Weight neutral	Recommended for diabetes
Pioglitazone	PPAR-γ	Diabetes	PIVENS (Phase 3)	247	96 wk	MASH resolution not assessed; ALT and AST improvement, reductions in hepatic steatosis	No histologic improvement	↓ MACE; ↑ HF	Neutral	Weight gain	Not recommended as first-line therapy for diabetes

Table 2 (continued)

Drug	Drug Class	Indication	Liver yield Trial/Study	*N* of Participants	Duration of Trial	MASH resolution	Fibrosis Reduction	CV Outcomes	Kidney Outcomes	Other metabolic benefits	Recommendation
Atorvastatin	Statin	Lipid-Lowering Agents	GREACE (post-hoc), IDEAL (post-hoc)	Large cohorts	Long-term	MASH resolution not assessed; ALT and AST improvement	Fibrosis reduction not assessed	↓68% CV events in pt with abnormal liver function, 39% relative risk reduction in normal liver function; ↓44% CV events (80 mg vs. simvastatin 20–40 mg)	Neutral	↓ LDL; ↓ triglycerides; ↑ HDL	First line for dyslipidemia in MASLD
Rosuvastatin	Statin	Lipid-Lowering Agents	Small prospective study	20	12 mo	MASH resolution (histologic) was observed in 19 of 20 patients	Fibrosis reduction not assessed	JUPITER trial: ↓44% MACE	JUPITER trial: median eGFR improvement	↓ LDL; ↓ triglycerides; ↑ HDL	First line for dyslipidemia in MASLD
Simvastatin	Statin	Lipid-Lowering Agents	Small RCT	16	12 mo	MASH resolution not assessed; No statistically significant improvement in serum aminotransferases, hepatic steatosis	No statistically significant improvement in fibrosis	HPS study: ↓18% CHD death; ↓24% major vascular events	Neutral	↓ LDL; ↓ triglycerides; ↑ HDL	First line for dyslipidemia in MASLD
Evolocumab	PCSK9i	Lipid-Lowering Agents	Small retrospective study	29	Mean of 23.69 ± 11.18 mo	MASH resolution not assessed; Possible steatosis reduction	Fibrosis reduction not assessed	FOURIER: HR 0.85 MACE; HR 0.73 MI; HR 0.79 stroke	Neutral	↓ LDL; ↓ Lp(a); ↓ triglycerides	Recommended for dyslipidemia

Table 2 (continued)

Drug	Drug Class	Indication	Liver yield Trial/Study	*N* of Participants	Duration of Trial	MASH resolution	Fibrosis Reduction	CV Outcomes	Kidney Outcomes	Other metabolic benefits	Recommendation
Alirocumab	PCSK9i	Lipid-Lowering Agents	Small retrospective study	29	Mean of 23.69 ± 11.18 mo	MASH resolution not assessed; Possible steatosis reduction	Fibrosis reduction not assessed	ODYSSEY OUTCOMES: HR 0.85 MACE; HR 0.83 mortality	Neutral	↓ LDL; ↓ Lp(a); ↓ triglycerides	Recommended for dyslipidemia
Pipeline MASH-Targeted Therapies											
Survodutide	GLP-1/glucagon	Pipeline	ESSENCE (Phase 2b)	293	48 wk	MASH resolution 47% (2.4 mg), 62% (4.8 mg), 43% (6.0 mg) vs. 14% (placebo); ↓ Liver fat 64–73%	Fibrosis reduction 34% (2.4 mg), 36% (4.8 mg), 32% (6.0 mg) vs. 18% (placebo)	CV outcomes under evaluation	Not studied	Up to 18.7% weight loss at 46 weeks	Under development for MASLD
Cotadutide	GLP-1/glucagon	Pipeline	PROXYMO (Phase 2b/3, terminated by manufacture)	74	19 wk	MASH resolution not assessed; Improvement in hepatic fat fraction, AST, ALT	Fibrosis reduction not assessed	Not studied	Not studied	Weight loss, glycemic and lipid benefits	Development for MASLD ended by manufacture
Pemvidutide	GLP-1/glucagon	Pipeline	Phase 1, IMPACT (Phase 2, ongoing)	212	48 wk	MASH resolution pending; Steatosis reduction and ALT improvement at phase 1 clinical trial	Fibrosis pending	Not studied	Not studied	Weight loss benefits	Under development for MASLD
Retatrutide	GIP/GLP-1/glucagon	Pipeline	Phase 2a	98	48 wk	MASH resolution not assessed; ↓ Liver fat 42.9%–82.4%	Fibrosis reduction not assessed	CV outcomes under evaluation	Not studied	Weight loss 8.7–24.2% over 48 weeks	Under development for MASLD, obesity

Table 2 (continued)

Drug	Drug Class	Indication	Liver yield Trial/Study	*N* of Participants	Duration of Trial	MASH resolution	Fibrosis Reduction	CV Outcomes	Kidney Outcomes	Other metabolic benefits	Recommendation
Lanifibranor	Pan-PPAR	Pipeline	NATIVE (Phase 2b); NATiV3 (Phase 3, ongoing)	247	24 wk	MASH resolution 39% (800 mg), 49% (1200 mg) vs. 22% (placebo); ↓ Liver fat	Fibrosis reduction 34% (800 mg), 48% (1200 mg) vs. 29% (placebo)	Not studied	Not studied	↓ Lipids, ↓ insulin resistance, weight gain	Under development for MASLD
Pegozafermin	FGF21 analogues	Pipeline	ENLIVEN (phase 2b), ENLIGHTEN-Fibrosis (phase 3, ongoing) and ENLIGHTEN-Cirrhosis (phase 3, ongoing)	219	24 wk	MASH resolution 37% (15 mg), 23% (30 mg), 26% (45 mg) vs. 2% (placebo)	Fibrosis reduction 22% (15 mg), 26% (30 mg), 27% (45 mg) vs. 7% (placebo)	Not studied	Not studied	↓ TG, ↓ LDL, ↑ HDL	Under development for MASLD
Efruxifermin	FGF21 analogues	Pipeline	HARMONY (Phase 2b, F2, F3), SYMMETRY (Phase 2b, F4), SYNCHRONY (phase 3, ongoing)	126	96 wks	MASH resolution 62% (28 mg), 57% (50 mg) vs. 24% (placebo)	Fibrosis reduction 46% (28 mg), 75% (50 mg) vs. 24% (placebo)	Not studied	Not studied	↓ TG, ↓ LDL	Under development for MASLD
Efimosfermin alfa	FGF21 analogues	Pipeline	Phase 2a/b trial; ZENITH-2 (phase 3 ongoing)	67	24 wk	MASH resolution 68% vs. 29% in placebo	Fibrosis reduction 45% vs. 21% in placebo	Not studied	Not studied	Not studied	Under development for MASLD

Abbreviations: *ACEi* Angiotensin-converting enzyme inhibitor, *ALT* Alanine aminotransferase, *ARB* Angiotensin receptor blocker, *AST* Aspartate aminotransferase, *BP* Blood pressure, *CCB* Calcium channel blocker, *CHD* Coronary heart disease, *CKD* Chronic kidney disease, *CV* Cardiovascular, *DPP-4i* Dipeptidyl peptidase-4 inhibitor, *eGFR* Estimated glomerular filtration rate, *FGF21* Fibroblast growth factor 21, *FIB-4* Fibrosis-4 index, *GIP* Glucose-dependent insulinotropic polypeptide, *GLP-1* Glucagon-like peptide-1, *HDL* High-density lipoprotein, *HF* Heart failure, *HCC* Hepatocellular carcinoma, *HR* Hazard ratio, *HTN* Hypertension, *LDL* Low-density lipoprotein, *Lp(a)* Lipoprotein(a), *MACE* Major adverse cardiovascular events, *MALO* Major adverse liver outcomes, *MASH* Metabolic dysfunction-associated steatohepatitis, *MASLD* Metabolic dysfunction-associated steatotic liver disease, *MI* Myocardial infarction, *MRI-PDFF* Magnetic resonance imaging–proton density fat fraction, PCSK9i Proprotein convertase subtilisin/kexin type 9 inhibitor, *PO* Oral, *PPAR* Peroxisome proliferator-activated receptor, *RCT* Randomized controlled trial, *SC* Subcutaneous, *SGLT-2i* Sodium–glucose cotransporter-2 inhibitor, *T2DM* Type 2 diabetes mellitus, *TG* Triglycerides, *THR-β*Thyroid hormone receptor beta, *wk* Week

capture risk not reflected in traditional models, elevated FIB-4, liver stiffness, or other tests consistent with liver fibrosis stage 2 or higher could be considered cardiovascular risk enhancers that may justify lower thresholds for additional cardiac testing (e.g., coronary artery calcium scoring) and more aggressive prevention strategies [36]. Emerging frameworks such as the CKM syndrome further support integrated, multidisciplinary care [3]. Cardiologists, general practitioners, nephrologists, endocrinologists and hepatologists are therefore well positioned to incorporate fibrosis markers into cardiovascular risk assessment and guide multidisciplinary management.

Lifestyle Interventions with Dual Hepatic and Cardiovascular Benefits

Weight Management

Weight reduction remains the cornerstone of lifestyle therapy in MASLD. Clinically, a weight loss of ≥ 5% is associated with reductions in hepatic steatosis, while ≥ 7–10% weight loss improves necroinflammation, and ≥ 10% may lead to regression of liver fibrosis [37]. Among those with normal BMI (lean MASLD), even modest weight loss (3–5%) improves MASH [38].

Among weight-loss strategies, bariatric surgery achieves the greatest sustained weight loss. Patients undergoing bariatric surgery experience significantly greater total body weight loss compared with those managed with medications and/or lifestyle interventions alone (20.6% vs. 2.5%, $P < 0.001$), along with lower average MASLD fibrosis scores [39]. Bariatric surgery provides the strongest evidence for cardiovascular risk reduction in MASLD. In the SPLENDOR study (n = 1,158; median follow-up 7 years), bariatric surgery was associated with a 70% lower risk of major adverse cardiovascular events (MACE), and an 88% reduction in major adverse liver outcomes (MALO) [5, 33]. Pharmacologic therapies are discussed below.

Dietary Strategies and Micronutrients

The Mediterranean diet is the most evidence-supported dietary pattern for MASLD and has been shown to reduce hepatic steatosis even in the absence of weight loss, likely through anti-inflammatory and antioxidant mechanisms. Adherence to the Mediterranean diet has been associated with reduced overall mortality and lower risk of CVD and diabetes [40, 41].

Limiting fructose intake, especially from high-fructose corn syrup and sugary drinks, is strongly advised for MASLD. Excessive consumption increases MASLD and hepatic fibrosis risk in a dose-dependent way and causes cardiometabolic issues, regardless of total calories [41]. Restricting added sugars to under 20 g/day can improve MASH even without weight loss [36]. Conversely, fructose from whole fruits is not linked to MASLD and should not be limited [42].

Micronutrient deficiencies are also common in MASLD and may exacerbate disease progression [41]. Screening and correcting deficiencies in vitamin E, vitamin D, zinc, selenium, thiamine, and vitamin A, should be considered, especially in advanced liver disease [43]. Observational data show that multivitamin users with MASLD had lower all-cause mortality (Hazard Ratio (HR) 0.94; 95% Confidence Interval (CI), 0.88–1.00), reduced CVD risk (HR 0.72), and lower chronic kidney disease (CKD) risk (HR 0.73), but no significant reduction in liver-related mortality or cirrhosis, suggesting broader cardiometabolic benefits [44].

Among micronutrient interventions, vitamin E has the strongest evidence for potential benefit in MASLD [6]. In the PIVENS trial, vitamin E 800 international units (IU) daily improved histologic features of MASH in non-diabetic adults compared with placebo over 96 weeks [45]. Similarly, the TONIC trial demonstrated increased MASH resolution in children and adolescents (58% vs. 28%) [46]. However, vitamin E has not been shown to meaningfully reduce fibrosis and, with the emergence of new Food and Drug Administration (FDA) approved liver-targeted therapies, its role in MASH treatment is now limited. Additionally, the U.S. Preventive Services Task Force does not recommend vitamin E supplementation for CVD prevention; dietary sources such as nuts and seeds are preferred [47].

Physical Activity

Physical activity in patients with MASLD is associated with significant reductions in both all-cause and cardiovascular mortality, with evidence of a dose-dependent relationship between exercise volume or intensity and survival outcomes [48]. Importantly, exercise improves cardiovascular risk profiles and reduces hepatic steatosis even in the absence of significant weight loss. Exercise frequency, whether performed daily or in a "weekend warrior" pattern, provides comparable cardiovascular and mortality benefits [49]. In addition, the type of exercise (aerobic or resistance training) does not appear to significantly influence outcomes; however, multicomponent physical activity (combining aerobic and resistance training) is associated with the greatest reduction in predicted ASCVD risk in the MASLD population [50].

Therefore, at least 150 min per week of moderate-intensity aerobic exercise (or ≥ 75 min of vigorous-intensity

exercise), along with resistance training two to three times per week is recommended. Even in patients with advanced fibrosis or cirrhosis, regular physical activity has been shown to reduce portal pressure, improve frailty and sarcopenia, and enhance overall quality of life [23].

Reducing sedentary behavior, which is distinct from structured exercise, is also associated with lower cardiovascular risk in patients with MASLD. Sedentary behavior independently increases cardiovascular risk in MASLD, with > 6.5 h/day associated with a 16–21% higher risk of major cardiovascular outcomes compared with ≤ 3.5 h per day of sedentary time [51]. Thus, both increasing physical activity and interrupting prolonged sitting with brief activity (e.g., ~ 10 min of light walking) throughout the day is recommended [8].

Other Lifestyle Modifications

Complete alcohol avoidance is recommended as a first-line behavioral modification for MASLD by multiple clinical guidelines. MetALD (MASLD with moderate alcohol intake) is associated with worse outcomes, including a 56% higher risk of adverse liver events and an 8% increase in all-cause mortality compared with MASLD alone [52], suggesting there is no safe threshold of alcohol intake in MASLD. Although moderate alcohol consumption (1–2 drinks per day) has been associated with reduced CVD risk in the general population, this potential benefit does not appear to apply to individuals with MASLD [53].

Coffee intake (≥ 3 cups per day), independent of caffeine content, is associated with a lower risk of MASLD and liver fibrosis [23], as well as a lower risk of CVD without an increased risk of hypertension [54]. Proposed mechanisms include antioxidant and anti-inflammatory effects of coffee polyphenols (such as chlorogenic acid), adenosine receptor antagonism that may limit hepatic fibrosis, and improved lipid and metabolic homeostasis.

Smoking cessation is strongly recommended in patients with MASLD because of its adverse effects on both hepatic and cardiovascular outcomes [55]. Compared with current smokers, individuals who have never smoked demonstrate significantly lower incidences of liver cirrhosis, hepatic decompensation, HCC, and CVD [56].

Obstructive sleep apnea (OSA) affects 40–80% of persons with MASLD and links to worse liver disease [57]. While adherence to continuous positive airway pressure (CPAP) therapy might modestly lower liver enzymes and cardiometabolic factors, it hasn't shown significant effects on steatosis or fibrosis [58]. Therefore, treating OSA is important for overall health, but its impact on liver and cardiovascular outcomes in MASLD seems limited.

Although the gut–liver axis is central to MASLD pathogenesis, microbiome-targeted therapies have shown mixed results. Probiotics and synbiotics improve surrogate markers such as liver enzymes and steatosis on imaging but have not consistently demonstrated benefits in histologic endpoints or clinical outcomes [59]. Likewise, fecal microbiota transplantation has not produced meaningful improvements in clinical outcomes in pre cirrhotic MASLD [60].

Pharmacotherapies with Cardiovascular Benefit in the CKM Spectrum

Given the frequent overlap between MASLD and cardiometabolic comorbidities, pharmacologic therapy should be selected to address shared CKM risk pathways and, when possible, prioritize agents with established cardiovascular, renal, metabolic, and/or hepatic benefit (Table 2).

Hypertension Management

Optimal management of cardiometabolic comorbidities, including hypertension, is part of comprehensive MASLD care [37]. Given the elevated cardiovascular risk in patients with MASLD, more intensive blood pressure control (e.g., < 130/80 mmHg) may be appropriate, particularly in individuals with diabetes or established CVD. Although no specific antihypertensive class has been prospectively studied in persons with MASLD, renin–angiotensin–aldosterone system (RAAS) inhibitors are generally preferred [37].

A target trial demonstrated that treatment with angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs) was associated with lower all-cause mortality, reduced risk of MALO, and fewer MACE compared to calcium channel blockers in MASLD [61]. One study found that ACE inhibitors, but not ARBs, were associated with reduced liver-related events, suggesting that ACE inhibitors may be superior to ARBs for liver outcomes; however, this finding requires further confirmation [62]. Other first-line options include thiazide diuretics and calcium channel blockers, consistent with general hypertension guidelines.

Beta-blockers are generally not preferred as first-line antihypertensive treatment in patients with MASLD due to potential adverse metabolic effects, although they remain appropriate when there is a strong cardiovascular indication (e.g., post-myocardial infarction (MI), heart failure, atrial fibrillation) [63]. Non-selective beta-blockers (especially carvedilol) are indicated for variceal bleeding prophylaxis and preventing decompensation in patients with compensated cirrhosis.

Diabetes Management

Incretin-Based Therapies

Incretin-based therapies are cornerstone treatments within the CKM framework. Among these, semaglutide has the strongest evidence. Subcutaneous semaglutide 2.4 mg weekly received conditional FDA approval for MASH in 2025 based on the phase 3 ESSENCE trial in persons with MASH and F2–F3 fibrosis. Over 72 weeks, semaglutide significantly increased MASH resolution (62.9% vs. 34.3%) and fibrosis improvement (36.8% vs. 22.4%; both $P < 0.001$), alongside meaningful weight loss (~ 10.5%) and reductions in liver stiffness [64]. While weight loss was somewhat lower than in obesity trials (STEP: 14.9–17.4%) [65], semaglutide's cardiovascular and renal benefits are well established, including ~ 20% reduction in MACE (SELECT trial) [66] and reduced CKD progression (FLOW trial) [67], supporting its role as a first-line therapy in patients with MASLD and cardiometabolic disease.

Oral semaglutide is approved for type 2 diabetes and cardiovascular risk reduction, with the SOUL trial demonstrating a 14% reduction in MACE, though kidney outcomes were neutral [68]. Higher-dose oral formulations achieve ~ 13.6–15.1% weight loss in the OASIS trials [69]. Although observational data suggest improvements in liver enzymes, stiffness, and FIB-4 [70], histologic efficacy of oral semaglutide in MASH remains unproven.

Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP)/ glucagon-like peptide-1 (GLP-1) receptor agonist, has shown particularly promising hepatic and cardiometabolic effects. In the phase 2b SYNERGY-NASH trial, tirzepatide achieved dose-dependent improvements in MASH resolution (44–62% vs. 10% placebo) and fibrosis (51–55% vs. 30%) over 52 weeks [71]. It also produces substantial weight loss (> 20% in SURMOUNT-1) [72] and demonstrates cardiovascular safety (noninferior to dulaglutide in SURPASS-CVOT) with signals for renal benefit, including reductions in albuminuria [73, 74].

Sodium-Glucose Transport Protein 2 (SGLT2) Inhibitors

SGLT2 inhibitors reduce liver fat and improve metabolic parameters in MASLD, with consistent cardiovascular and renal benefits demonstrated in large trials [75, 76]. These agents are recommended as first-line therapy in patients with diabetes and CKD and form a key component of CKM management. In the phase 2 DEAN trial, dapagliflozin 10 mg for 48 weeks resulted in significant reductions in liver fat and higher rates of MASH resolution compared with placebo (23% vs. 8%), with fibrosis improvement observed in approximately 45% vs. 20% of patients [77]. Similarly, empagliflozin reduces liver fat and aminotransferase levels [78]. Other SGLT2 inhibitors, including canagliflozin [79], tofogliflozin [80], and ipragliflozin [81], have also demonstrated promising hepatoprotective effects.

Other Diabetes Therapies

Other diabetes therapies, such as metformin and dipeptidyl peptidase-4 (DPP-4) inhibitors, appear to have largely neutral or modest benefits with respect to CKM and liver outcomes [82]. In contrast, pioglitazone has demonstrated benefits in ASCVD and hepatic steatosis [45]. However, due to its association with worsening heart failure, it is not typically favored for diabetes management in patients with MASLD [83]. Sulfonylureas and insulin are generally not preferred as first-line therapies due to their propensity for weight gain and lack of cardiovascular benefit [34].

In summary, a GLP-1 receptor agonist (preferably semaglutide) or an SGLT2 inhibitor is recommended as first-line therapy for patients with type 2 diabetes mellitus and MASLD, selected based on comorbidities [34].

Lipid-Lowering Agents

Statins

Statins remain first-line therapy for cardiovascular risk reduction and are generally safe in MASLD, with preserved—and possibly greater—cardiovascular benefit in this population [84]. Although some studies suggest hepatic benefit [84], the evidence is inconsistent [85], and statins should be used primarily for cardiovascular risk reduction. In advanced or decompensated cirrhosis, adverse effects may be more common because of altered drug metabolism; in these patients, hydrophilic statins such as pravastatin or rosuvastatin are often preferred, and simvastatin doses > 20 mg/day should be avoided [86].

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

PCSK9 inhibitors (evolocumab and alirocumab) provide substantial cardiovascular benefit in the general population, achieving ~ 60% LDL cholesterol reduction and a 15–25% reduction in MACE [87, 88]. In patients with MASLD, dedicated cardiovascular outcome trials are lacking; however, available evidence supports that PCSK9 inhibitors are safe and effective, with similar lipid-lowering efficacy [89]. A small study found 72.7% (n = 8/11) of patients achieved complete resolution of hepatic steatosis on PCSK9 inhibitors, with significant ALT reductions [90]. Emerging evidence suggests that PCSK9 inhibition may reduce proteinuria, indicating a potential renal protective effect [91, 92].

CKD Management

For CKD management, ACE inhibitors and ARBs are first-line therapies for patients with CKD and diabetes or albuminuria, reducing progression to kidney failure by approximately 25–40% in those with severely increased albuminuria (urine albumin-creatinine ratio ≥ 300 mg/g) [93]. SGLT2 inhibitors provide robust cardiorenal protection regardless of diabetes status and are recommended when MASLD coexists with diabetes, CKD, or heart failure [94]. GLP-1 receptor agonists offer established cardiovascular and emerging renal benefits and confer dual hepatic and cardiorenal advantages in MASLD [95].

Finerenone is FDA-approved for CKD with type 2 diabetes and is associated with a 14% reduction in composite cardiovascular outcomes (cardiovascular death, MI, stroke, or heart failure hospitalization). Although no dedicated trials exist for finerenone in MASLD, its use is appropriate per standard CKD guidelines given the high prevalence of type 2 diabetes and CKD in this population [96]. Key therapeutic classes, including RAAS inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists, have been discussed in detail in prior sections.

Pharmacologic Interventions with Histologic Benefit in MASH

Several novel agents targeting metabolic and fibrotic pathways are under investigation for MASLD/MASH. The FDA employs a two-tiered approval framework: accelerated (conditional) approval is based on histologic surrogate endpoints (MASH resolution without worsening of fibrosis or ≥1 stage fibrosis improvement without MASH worsening), whereas full approval requires demonstration of clinical outcome benefits (e.g., mortality, liver transplantation or hepatic decompensation). Given the slow progression of liver-related outcomes and large population burden of disease, surrogate endpoints are used for initial approval.

To date, two medications, resmetirom and semaglutide, have received conditional approval for MASH with F2–F3 fibrosis with ongoing phase 3 trials (MAESTRO-NASH, ESSENCE), evaluating long-term clinical outcomes [97, 98].

Resmetirom

Resmetirom, a selective thyroid hormone receptor (THR) β agonist, was the first FDA-approved therapy for noncirrhotic MASH with F2-F3 fibrosis in March 2024. In the phase 3 MAESTRO-NASH trial ($n = 966$), resmetirom significantly improved MASH resolution (25.9%-29.9% vs. 9.7% placebo) and fibrosis by ≥ 1 stage (24.2%-25.9% vs. 14.2% placebo) over 52 weeks [99, 100]. It also reduced liver fat and improved atherogenic lipid parameters, including LDL cholesterol and apolipoprotein B, suggesting potential cardiovascular benefit [99, 100].

From a cardiology perspective, drug–drug interactions are clinically important. Resmetirom increases plasma concentrations of several statins (atorvastatin, pravastatin, rosuvastatin, simvastatin), requiring ~ 50% dose reduction and monitoring for myopathy and hepatotoxicity [99, 100]. Pitavastatin and fluvastatin may be alternatives, as they are not included in current FDA interaction warnings. Gemfibrozil is contraindicated due to effects on resmetirom metabolism [101].

Combination Cardiometabolic Therapy

Because MASLD exists within the broader CKM spectrum, many patients will appropriately receive combination therapy targeting complementary risk pathways. In practice, this may include a GLP-1 receptor agonist or SGLT2 inhibitor for diabetes, obesity, CKD, or heart failure; RAAS inhibition for hypertension, diabetes, CKD, or albuminuria; and statin therapy for ASCVD prevention [102]. However, dedicated MASLD trials testing additive or synergistic effects of specific combinations—such as SGLT2 inhibitors plus antihypertensive therapy or GLP-1 receptor agonists plus statins—are lacking. Therefore, combination therapy should currently be individualized according to standard cardiovascular, renal, metabolic, and hepatic indications rather than prescribed with the expectation of proven MASLD-specific synergy. Future studies should evaluate whether biologically complementary regimens can improve both fibrosis-related and cardiovascular outcomes.

Pipeline Therapies

Next-Generation Incretin-Based Therapies

Several next-generation incretin-based therapies are under investigation for MASLD. Dual GLP-1/glucagon receptor agonists have shown promising efficacy. In a phase 2b trial, survodutide achieved MASH resolution in 47–62% of patients versus 14% with placebo, with fibrosis improvement in 32–36% versus 18% over 48 weeks [103]. It also induces substantial metabolic and weight loss effects [104], though cardiovascular outcomes remain under evaluation.

Other multi-agonist incretin therapies—including cotadutide (GLP-1/glucagon) [105], pemvidutide (GLP-1/glucagon) [106], and retatrutide (GIP/GLP-1/glucagon) [107]—have demonstrated marked reductions in liver fat, improved glycemic control, and substantial

weight loss in early studies. While fibrosis data remain preliminary, their robust cardiometabolic effects suggest potential to reduce both hepatic and cardiovascular risk.

Pan-Peroxisome Proliferator-Activated Receptor (PPAR) Agonists

Lanifibranor, a pan-PPAR (α/δ/γ) agonist, has demonstrated antifibrotic efficacy in the phase 2 NATIVE trial, with higher rates of MASH resolution (41–49% vs. 22% placebo) and fibrosis improvement (34–48% vs. 29%), including combined endpoints [108]. It also improves insulin resistance, lipid profiles, and inflammatory markers, although mild weight gain has been observed. A phase 3 trial (NATiV3) is ongoing [109].

Fibroblast Growth Factor 21 (FGF21) Analogs

FGF21 analogs represent another promising class targeting hepatic and systemic metabolism. These agents reduce hepatic lipogenesis and triglycerides via central and hepatic mechanisms [110]. In phase 2 trials, pegozafermin [111], efruxifermin [112, 113], and efimosfermin alfa [114] have demonstrated substantial reductions in steatosis, MASH resolution, and fibrosis improvement. For example, efruxifermin reduced fibrosis by 46–75% versus 24% with placebo in F2–F3 disease (HARMONY trial) [112], and by 29–57% versus 11% in MASH-related compensated cirrhosis (stage 4 fibrosis) over 96 weeks (SYMMETRY trial) [113]. These agents also improve triglycerides, insulin sensitivity, and body weight, suggesting potential cardiovascular benefits. Phase 3 clinical trials are ongoing to confirm clinical outcomes [115].

Perspectives and Future Directions

Substantial progress has clarified the relationship between MASLD and CVD, but the next decade will determine whether this translates into improved outcomes.

A central unresolved question is whether hepatic fibrosis should be incorporated into ASCVD risk prediction models. A pragmatic path forward may be a modeling strategy in which standard ASCVD risk estimates are evaluated in parallel with models that additionally incorporate noninvasive fibrosis markers such as FIB-4, liver stiffness measurement, ELF, or related fibrosis scores [116]. Large EHR-linked biobanks and health-system datasets provide an immediate opportunity to test whether fibrosis-enhanced models improve discrimination, calibration, risk reclassification, and clinical decision-making across diverse cardiometabolic populations. Such studies should also determine whether fibrosis-informed risk categorization changes preventive treatment intensity, including lipid-lowering, antihypertensive, antidiabetic, anti-obesity, and CKD-directed therapies. This approach could transition hepatic fibrosis from a selective clinical consideration into a validated cardiovascular risk enhancer.

Equally important is whether fibrosis regression reduces cardiovascular events. Demonstrating this would reposition liver-directed therapies as tools for cardiovascular prevention. However, traditional cardiovascular outcome trials in MASLD populations are likely impractical due to required sample size and follow-up. Pragmatic approaches, including pharmacoepidemiologic analyses of large real-world datasets, may offer the most feasible path forward.

Biomarker development should shift from validation of individual tests toward identifying clinically actionable phenotypes. Patients at risk for hepatic decompensation versus cardiovascular events may appear similar using current tools but require fundamentally different management strategies. Achieving this level of precision will require standardization and large-scale validation.

Refining screening algorithms represents an immediate opportunity. While FIB-4 remains widely used, newer tools such as MAF-5—incorporating waist circumference and metabolic variables—offer improved performance in high-risk populations. Broader adoption may require simple workflow changes, such as routine measurement of waist circumference in cardiometabolic assessment.

Therapeutic development is evolving toward noninvasive endpoints and combination strategies. Reductions in liver stiffness (e.g., ≥30% by VCTE or MRE) are emerging as potential surrogate endpoints, which could accelerate trials and reduce reliance on biopsy. Combination regimens targeting complementary pathways (e.g., THR-β agonists, GLP-1 receptor agonists, FGF21 analogs) are also being explored to address the multifactorial nature of MASH.

Finally, cost-effectiveness analyses are essential to support implementation of fibrosis-based screening at scale, as even the most effective algorithms require system-level adoption to impact outcomes.

Conclusion

MASLD is a systemic cardiovascular-kidney-metabolic disease rather than an isolated liver condition, with implications for risk assessment and management. Hepatic fibrosis stage is a key integrator of both liver injury and cardiovascular risk. Noninvasive fibrosis tools are scalable, low-cost, and increasingly supported as cardiovascular risk enhancers, supporting their broader use beyond hepatology. Management should prioritize cardiometabolic risk reduction, including optimization of blood pressure, glycemia, lipids,

and body weight. Therapies such as semaglutide and resmetirom offer dual hepatic and cardiovascular benefits, though definitive evidence linking histologic improvement to cardiovascular risk reduction remains limited. Ultimately, effective care requires multidisciplinary coordination. Identification of advanced fibrosis should prompt cardiovascular risk reassessment, and patients with cardiometabolic disease should be evaluated for MASLD. Bridging this gap in care delivery represents a critical opportunity to improve outcomes in this high-risk population.

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Authors' Contributions S.L., M.T., J.P. wrote the main manuscript text and prepared the figures and tables. L.V. provided oversight and critical revision of all steps of the process. All authors reviewed the manuscript.

Funding None.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

Disclosures L.B.V. consults for Gerson Lehrman Group, Atheneum Partners, Slingshot Insights, ThirdBridge, receives grant support from Madrigal, Akero, B.D. and W.L. Gore & Associates, and participates in medicolegal consulting outside the submitted work. All other authors have no relevant disclosures.

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