Circulation

IN DEPTH

Cardiovascular-Liver-Metabolic Health: Recommendations in Screening, Diagnosis, and Management of Metabolic Dysfunction-Associated Steatotic Liver Disease in Cardiovascular Disease via Modified Delphi Approach

Nicholas W.S. Chew, MBChB*; Anurag Mehta, MD*; Rachel Sze Jen Goh, MBBS; Audrey Zhang, MBBCh BAO; Yiming Chen, MBBS; Bryan Chong, MBBS; Han Shi Jocelyn Chew, PhD; Asim Shabbir, FRCS; Adrian Brown, PhD; Georgios K. Dimitriadis, PhD; Daniel Q. Huang, MMed; Roger Foo, MBBS; Carel W. le Roux, PhD; Gemma A. Figtree, DPhil; Marat Fudim, MD, MHS; Ambarish Pandey, MD; Mamas A. Mamas, MBBCh; Derek J. Hausenloy, PhD; A. Mark Richards, PhD; Stephen J. Nicholls, PhD; Mark Y. Chan, PhD; Mark D. Muthiah, MMed; Arun Sanyal, MD; Laurence S. Sperling, MD

ABSTRACT: There is a new awareness of the widespread nature of metabolic dysfunction–associated steatotic liver disease (MASLD) and its connection to cardiovascular disease (CVD). This has catalyzed collaboration between cardiologists, hepatologists, endocrinologists, and the wider multidisciplinary team to address the need for earlier identification of those with MASLD who are at increased risk for CVD. The overlap in the pathophysiologic processes and parallel prevalence of CVD, metabolic syndrome, and MASLD highlight the multisystem consequences of poor cardiovascular–liver–metabolic health. Metabolic dysfunction and associated insulin resistance, together with the predilection for ectopic fat deposition in the liver and surrounding tissues, are associated with elevated risk of endothelial dysfunction, systemic inflammatory response, and ectopic fat deposition in the epicardium. This complex pathophysiology can accelerate atherogenic dyslipidemia, atherogenesis, diastolic dysfunction, valvular calcification, and cardiac arrhythmias. Despite the mounting evidence of mechanistic pathways underpinning MASLD and CVD, current recommendations have not clearly focused upon MASLD as a risk factor or target for intervention in CVD. We have brought together a diverse range of international experts committed to promoting cardiovascular–liver–metabolic health and related outcomes across the globe. The overarching goal of this document is to offer a construct for clinicians in the cardiovascular field with regards to (1) diagnosis and screening of MASLD through the use of noninvasive serum and imaging tests; (2) screening for CVD in all individuals with MASLD regardless of established atherosclerotic risk factors; and (3) the approach to management of MASLD with respect to prevention of CVD through lifestyle, as well as pharmacologic and surgical strategies. To achieve this, the modified Delphi method was applied and a series of evidence-based quality standard recommendations have been identified.

Key Words: atherosclerosis ■ cardiovascular diseases ■ fatty liver ■ liver diseases ■ metabolic syndrome ■ risk factors

Correspondence to: Nicholas W.S. Chew, MBChB, Department of Cardiology, National University Heart Centre, National University Health System, 5 Lower Kent Ridge Rd, Singapore, 119074, Email nicholas_ws_chew@nuhs.edu.667; or Laurence S. Sperling, MD, Emory University School of Medicine, 1440 Clifton Rd, Atlanta, GA 30322, Email lsperli@emory.edu
*N.W.S. Chew and A. Mehta contributed equally.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.124.070535.
For Sources of Funding and Disclosures, see page 116.

Circulation is available at www.ahajournals.org/journal/circ

Nonstandard Abbreviations and Acronyms

ASCVD	atherosclerotic cardiovascular disease
CLMH	cardiovascular–liver–metabolic health
CVD	cardiovascular disease
ELF	Enhanced Liver Fibrosis
FIB-4	Fibrosis-4 Index
GLP1-RA	glucagon-like peptide-1 receptor agonist
MASH	metabolic dysfunction–associated steatohepatitis
MASLD	metabolic dysfunction–associated steatotic liver disease
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NIT	noninvasive test
T2D	type 2 diabetes
VCTE	vibration-controlled transient elastography

The Nomenclature Consensus Group[1] proposed a nomenclature change from nonalcoholic fatty liver disease (NAFLD) to metabolic dysfunction–associated steatotic liver disease (MASLD) in 2023. This represented a shift away from the previous exclusion-based, negatively-defined NAFLD diagnosis that required the exclusion of excess alcohol intake and other chronic liver diseases, to a more positive MASLD criteria that encapsulate the presence of concomitant cardiometabolic diseases.[1] MASLD affects approximately 38.0% of adults worldwide.[2] It is present in more than one-half of those with type 2 diabetes (T2D).[3] In Eastern and Western regions, the prevalence of MASLD in the T2D population is 58.84% and 72.65%, respectively. T2D is an important driver of MASLD progression, with more than one-third of people with concurrent T2D and MASLD affected by clinically significant fibrosis.[3,4] Of concern, global MASLD prevalence is anticipated to reach 55.4% by 2040,[5] alongside epidemics of obesity and metabolic dysfunction.

Cardiovascular disease (CVD) is the most frequent cause of death in patients with MASLD.[6] An important mediating role underscoring the bidirectional association between liver and CVD has been ascribed to excess and dysfunctional adipose tissue (including hepatic fat), promoting metabolic, inflammatory, and other systemic effects that increase CVD risk.[4] However, underdiagnosis of MASLD remains a significant barrier to effective medical treatment and prevention of cardiovascular-related complications, in part reflecting the lack of awareness of MASLD among patients and clinicians.

Herein, we provide the cardiology perspective supporting enhanced CVD prevention in people with MASLD; notably, the need for earlier identification and more effective prevention, especially in those at greater risk for incident CVD, morbidity, and mortality. We assembled an international team consisting of cardiologists, hepatologists and endocrinologists, and a wider multidisciplinary team to offer a construct for clinicians in the cardiovascular field with regards to the (1) diagnosis and screening of MASLD through the use of noninvasive tests; (2) screening for CVD in individuals with MASLD; and (3) the approach to management of MASLD with respect to CVD prevention. A modified Delphi method was applied and a series of evidence-based quality standard recommendations have been identified. The overarching goal of this document is to offer a holistic construct for cardiologists and nonhepatologists in improving cardiovascular–liver–metabolic health (CLMH) globally.

METHODS

A systematic review was conducted of clinical practice guidelines and reviews on NAFLD and MASLD published in the last 20 years, with the dual purpose of examining existing evidence and generating the preliminary draft checklist of quality standard recommendations. A PubMed search on January 27, 2024, including key terms such as *nonalcoholic fatty liver disease*, *metabolic dysfunction–associated steatotic liver disease,* and *cardiovascular disease*, identified 165 relevant articles (Table S1), of which 54 were clinical practice guidelines. The remaining articles were systematic reviews and meta-analysis. Inclusion criteria were articles discussing the relationship between MASLD and CVD, CVD subtypes, or cardiovascular complications.

Three blinded authors (N.W.S.C., R.G., A.Z.) screened through the full text of the articles. Any discrepancies were resolved by a fourth author (A.M.). For systematic reviews and meta-analysis, articles assessed to be of higher quality with stronger levels of evidence were prioritized for inclusion (Supplemental Methods 1).[7] After the quality assessment, 18 articles were excluded because updated meta-analyses had been published on similar topics. An additional 81 articles were excluded because they did not discuss the relationship between MASLD and CVD, CVD subtypes, or their complications. Ultimately, a total of 54 clinical practice guidelines, and 12 systematic reviews and meta-analyses were selected for inclusion in this review.[6,8–18] The included articles were reviewed in a blinded fashion. In addition, the core steering committee voted on whether the preliminary statements should be included in the Delphi process via anonymous online surveys (Table 1).

Panel Generation

Subsequently, the study's 5 co-chairs (N.C.W.S., A.M., M.M., A.S., L.S.S.) adopted an iterative approach using purposive, snowball, targeted sampling to generate a larger global panel for this Delphi study (Figure 1). Based on publication record, engagement with the fatty liver disease agenda, and involvement in relevant clinical practice guidelines, the co-chairs identified 20 internationally recognized professionals in the fields of cardiology, hepatology, endocrinology, bariatric surgery, dietetics and nursing (Tables S2 and S3). The panelists were asked to review the studies selected for inclusion, and to recommend clinical

Table 1. Preliminary Statements on the Diagnosis and Management of MASLD in CVD, Before Inclusion in the Delphi Process

Preliminary statements	Included in the Delphi process
Screening and diagnosis of MASLD in CVD by cardiology clinicians	
Cardiovascular services should implement an agreed local clinical pathway for the screening of MASLD in CVD, that involves screening for liver fibrosis using imaging and/or serum noninvasive tests.	Y
Screening for MASLD and fibrosis in individuals with type 2 diabetes is recommended.	Y
Screening for MASLD and fibrosis in individuals with the metabolic syndrome is recommended.	Y
Screening for MASLD and fibrosis in individuals with overweight/obesity is recommended.	Y
Screening for MASLD as a cardiovascular risk–enhancing factor is recommended in individuals with borderline or intermediate ASCVD risk, that can guide primary preventative strategy.	Y
In individuals who are at normal weight with metabolic diseases, the screening of MASLD should be considered, given the prevalence of MASLD in lean individuals.	Y
The diagnostic criterion of MASLD should be used instead of the former nonalcoholic fatty liver disease criterion.	Y
For the detection of hepatic steatosis in the MASLD diagnostic criterion, liver ultrasound-based imaging techniques may be considered, although it has relatively low sensitivity in detecting lesser degrees of hepatic steatosis.	Y
For the detection of hepatic steatosis in the MASLD diagnostic criterion, serum liver biomarkers and its scoring system may be considered as alternatives to liver imaging, although they have relatively low sensitivity in the diagnosis of hepatic steatosis.	Y
Consideration of MASLD should not be dependent on the presence of abnormal liver serum tests. However, persistently unexplained abnormal liver serum tests must be evaluated.	Y
Assessments recommended for individuals with diagnosed MASLD, by cardiology clinicians	
Individuals with MASLD should be evaluated for additional causes of hepatic steatosis (such as alcohol), and undergo investigations for secondary causes of liver disease (such as hepatitis screen).	Y
Detailed alcohol, illicit drug, smoking history should be performed and documented.	Y
Detailed dietary habits and physical activity should be performed and documented.	Y
Both serum and imaging-based non-invasive tests can be used for risk stratification of individuals with MASLD.	N
Use widely available validated serum (eg, FIB-4) and imaging-based non-invasive tests with high negative predictive value to risk stratify for hepatic fibrosis in individuals with MASLD.	Y
The FIB-4 score can be used as a first-line point-of-care test for the screening of advanced fibrosis.	Y
An FIB-4 score <1.3 indicates a low probability of advanced fibrosis.	Y
An FIB-4 score ≥1.3 indicates an intermediate probability of advanced fibrosis, which warrants secondary assessment and/or hepatology referral.	Y
An FIB-4 ≥2.67 indicates a high probability of advanced fibrosis, which warrants secondary assessment and/or hepatology referral.	Y
Combining 2 or more noninvasive tests, using either serum or imaging-based tests, may be considered in patients at intermediate or high risk of hepatic fibrosis.	Y
Repeated non-invasive tests can be done for longitudinal disease/treatment monitoring. It is reasonable to perform FIB-4 surveillance every 2 years in low-risk and annually in high-risk individuals (with type 2 diabetes or established CVD).	Y
Patients stratified as high risk for advanced fibrosis or cirrhosis should be referred to a hepatologist.	Y
Screening for CVD in individuals with MASLD	
It is recommended to screen for CVD in all individuals with MASLD, regardless of the presence of traditional atherosclerotic risk factors, with detailed risk factor evaluation at a minimum	Y
Patients with MASLD should be screened annually for type 2 diabetes mellitus, hypertension, hyperlipidemia, and overweight/obesity.	Y
Cardiovascular risk assessment should be performed using standard atherosclerotic cardiovascular disease prediction tools.	Y
CT coronary artery calcium scoring may be beneficial in predicting future CVD risk in individuals with mild hepatic steatosis.	N
In selected patients with more significant hepatic steatosis, coronary computed tomography angiography may be considered given its high sensitivity and specificity.	N
MASLD should be considered a risk-enhancing factor for atherosclerotic CVD.	Y
Management of individuals with MASLD in CVD by cardiology clinicians.	
NITs can be a useful alternative to biopsy in the evaluation of treatment response in MASLD	N
The management of individuals with MASLD, assessed to be at low risk of hepatic fibrosis based on FIB-4 score, can be managed by clinicians within the cardiovascular specialty, with the focus on lifestyle management, cardiovascular risk reduction, and regular reassessment of hepatic fibrosis.	Y
Target weight loss of 3–5% to improve hepatic steatosis	Y
Target weight loss of ≥10% in the treatment of MASH or fibrosis, and reduction of cardiovascular risk.	Y
Individuals with MASLD should be referred to obesity management services if weight loss goals have not been met despite lifestyle interventions.	Y

(*Continued*)

Table 1. Continued

Preliminary statements	Included in the Delphi process
Referral for bariatric surgery should be considered for individuals with MASLD who meet the national recommendations and eligibility criteria for bariatric surgery.	Y
Dietary recommendations include the Mediterranean diet, as well as vegetables, fruits, nuts, whole grains, lean animal protein, and fish. The intake of trans fats, red meat and processed red meats, refined carbohydrates, as well as fructose and sugar-sweetened beverages should be minimized.	Y
Regular moderate exercise for at least 150 minutes per week, or 75 minutes of vigorous-intensity aerobic physical activity is recommended. Resistance exercise in addition to aerobic activity, for ≥2 days/week, should be considered.	Y
Reduce sedentary time and engage in at least light activity throughout the day.	Y
Prescriptions of exercise regime should be tailored according to the biological age, exercise experience, functional capacity, safety, and aging trajectories, especially in vulnerable populations.	Y
Abstinence from alcohol should be recommended in individuals with MASLD, fibrosis or cirrhosis.	Y
Individuals with MASLD, with concomitant hypertension, should be managed with blood pressure-lowering agents according to current clinical practice guidelines.	Y
Individuals with MASLD, with concomitant T2D, should be managed with glucose-lowering agents that promote weight loss and improved cardiometabolic profile according to current clinical practice guidelines.	Y
In the special population with normal-weight MASLD, lifestyle intervention is the key recommendation. Although the recommended use of GLP1-RA and SGLT2i may be premature in this group, these agents may be considered to reduce cardiovascular events in individuals with high ASCVD risk.	Y
Resmetirom should be initiated early in patients with MASLD with elevated CVD risk	N
The multidisciplinary management of individuals with MASLD should be recommended, involving expertise in hepatology, cardiology, endocrinology, bariatric surgery, dietetics, physiotherapists, and nursing.	Y
Recommendations on MASLD-specific therapies in CVD	
SGLT2 inhibitor	
Who should get the intervention: Individuals with MASLD, and concomitant type 2 diabetes mellitus, chronic kidney disease, heart failure, and/or atherosclerotic CVD.	Y
Surveillance: Serial assessment of renal function, liver function, body weight, blood pressure, glycemic control, and symptoms.	Y
Stopping rules: Renal injury (generally eGFR <30 mL/[min·1.73 m^2]), symptomatic (genital/perineal infection, hypoglycemia, diabetic ketoacidosis, volume depletion).	Y
Incretin analogues	
Who should get the intervention: Individuals with MASLD, and concomitant type 2 diabetes and/or obesity.	Y
Surveillance: Serial assessment of serum glucose and HbA1c, renal function, triglycerides and weight. Monitor for signs and symptoms of pancreatitis.	Y
Stopping rules: Diabetic ketoacidosis, end-stage renal failure, decompensated cirrhosis and pancreatitis. Recommended against use in individuals with personal or family history of medullary thyroid cancer or MEN2 syndrome.	Y
PPAR agonist	
Who should get the intervention: Used as second or third line therapy for management of type 2 diabetes, or with co-existing MASLD.	Y
Surveillance: Serial assessment of serum glucose, HbA1c and liver function test. Monitor for signs of heart failure.	Y
Stopping rules: Heart failure or evidence of fluid overload, history of fracture or at high risk for fracture, pregnancy, active or history of bladder cancer, macular edema and active liver disease (transaminases >2.5× ULN unless MASH is known to be the underlying cause of the elevation).	Y
Statin therapy	Y
Who should get the intervention: Used for primary prevention guided by cardiovascular disease risk assessment, or in secondary prevention in individuals with previous atherosclerotic cardiovascular disease.	Y
Surveillance: Consider baseline lipid panel, liver function test and creatine kinase. If elevated ALT, to recheck liver enzymes in 4–6 weeks. If ALT remains elevated, check for other etiologies, and consider hepatology referral.	Y
Stopping rules: If ALT <3× ULN, to consider continuation of therapy with surveillance of liver enzymes. If ALT ≥3× ULN, stop lipid-lowering therapy or reduce dose, recheck liver enzymes within 4–6 weeks, and consider hepatology referral. Cautious reintroduction of therapy may be considered after ALT normalizes. Consider cessation in myositis or rhabdomyolysis. Statins should not be withheld from individuals with MASLD, including individuals with mild transaminitis or compensated cirrhosis, as its cardiovascular benefits significantly outweigh its risk.	Y
Additional consideration: The identification of MASLD, as a risk-enhancing factor, can guide statin initiation decision in individuals at borderline or intermediate ASCVD risk. If further guidance is required on refining the individual's ASCVD risk, CT coronary artery calcium scoring may be considered.	N

ALT indicates alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; CT, computed tomography; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MASLD, metabolic dysfunction–associated steatotic liver disease; MEN2, multiple endocrine neoplasia type 2; N, No; ULN, upper limit of normal; and Y, Yes.

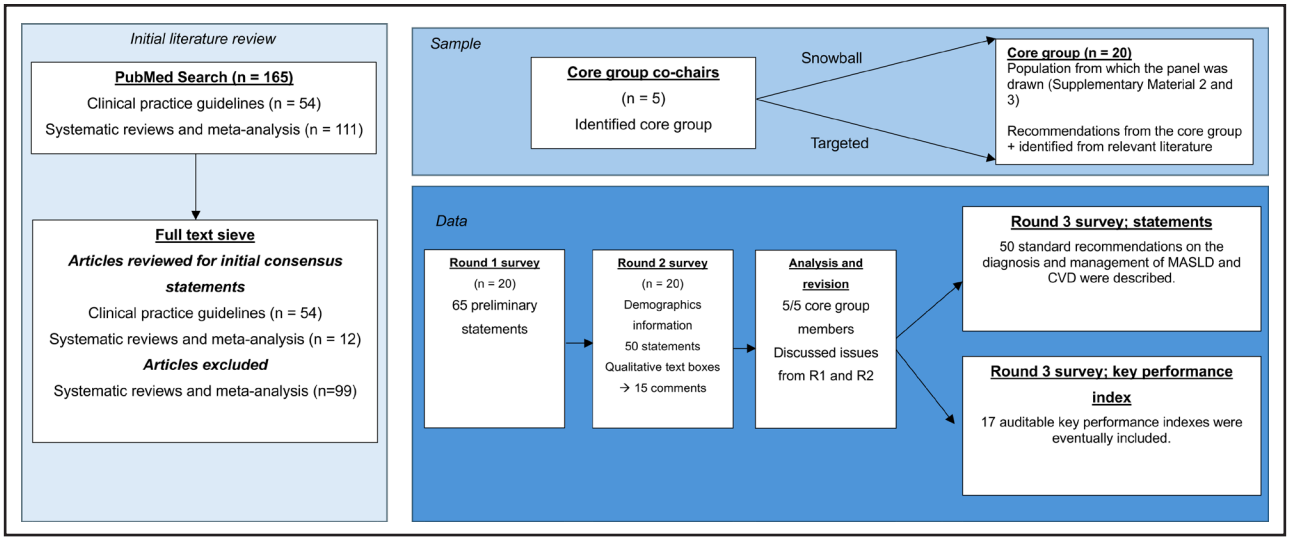

Figure 1. Summary of methodology.

pathways for the diagnosis and management of MASLD in CVD. As described in the ACCORD protocol, there have been no generally accepted standards for the panel size in Delphi studies, although a panel size of 20 is common.[19] A 2-step modified Delphi method was adopted to facilitate the agreement on the incorporation of input from the literature on the investigations and management strategies of MASLD to be included in the clinical pathway. Panel members convened electronically between February and May 2024.

Data Collection

The Delphi process comprised 4 fundamental areas identified by the steering committee, namely: (1) screening and diagnostic pathways for MASLD in CVD, and vice versa; (2) role of MASLD in CVD risk stratification; (3) key considerations in the approach to MASLD management in CVD; and (4) key performance indicators for cardiovascular services to benchmark their practices. This process consisted of online data collection and in-person discussions, including a first round survey (March 1 to March 31, 2024), and second round survey (April 1 to May 1, 2024), which included additional panelists. Two in-person discussions (including 5 co-chairs) were conducted before the first round survey, and one discussion occurred before the second round survey. During the first round survey, the core steering committee proposed additional areas based on their knowledge and expertise. These were then voted on in the second round survey, and preliminary draft statements were revised and approved by the steering committee.

Quantitative analyses were performed on the survey responses in the modified Delphi study, detailed in Supplemental Methods 2. From the finalized list of statements, auditable key performance indicators were selected based on their impact potential on patient outcomes and its measurability, in order to allow services to benchmark their practice. After the Delphi voting process and the review of evidence, 50 quality standard recommendations on the diagnosis and management of MASLD in CVD were described. Of which, 17 auditable key performance indicators have been selected (Tables 2 and 3).

Change From NAFLD to MASLD Diagnostic Criteria

MASLD diagnostic criterion should be used, which includes (1) evidence of hepatic steatosis identified by imaging or biopsy, and (2) presence of ≥1 of 5 cardiometabolic criteria[1] (Table S4), instead of the former NAFLD criterion (Recommendation 1.1; Table 2). Individuals with MASLD should be evaluated for additional causes of hepatic steatosis (such as alcohol), and undergo investigations for secondary causes of liver disease (such as hepatitis screen) (Recommendation 2.1, Table 2; Figure 2). Detailed alcohol, illicit drug, smoking history should also be performed and documented (Recommendation 2.2; Table 2). In the absence of overt cardiometabolic risk factors, with other etiologies excluded, cryptogenic steatotic liver disease may be considered; although early MASLD should remain a differential based on clinical judgement, that may prompt additional testing such as fasting insulin and oral glucose tolerance tests.[1] This is important as patients can exhibit insulin resistance and steatosis without meeting the specified cardiometabolic risk criteria, particularly in younger individuals.[1]

DIAGNOSIS, SCREENING OF MASLD, AND RISK PREDICTION

Screening MASLD should be considered when the presence of MASLD guides management (ie, statin initiation in individuals with intermediate atherosclerotic CVD [ASCVD]).[1] The consideration of MASLD should not be dependent on the presence of abnormal liver serum tests, although persistently unexplained abnormal liver serum tests must be evaluated (Recommendation 1.2; Table 2). Although moderate to severe steatosis can be reliably determined with liver ultrasound, with good sensitivity (84.8%) and specificity (93.6%);[20] in lesser degrees of steatosis, the sensitivity (65%) and specificity (81%) of ultrasound appear to be insufficient—especially in individuals with concomitant

Table 2. Diagnosis and Management of MASLD in CVD Quality Standard Recommendations

	Recommendation	Grade*	Responses	
			Agreement†	NQ, n
1	Screening and diagnosis of MASLD in CVD by cardiology clinicians			
1.1	The diagnostic criterion of MASLD should be used instead of the former nonalcoholic fatty liver disease criterion	U	60.0% SA, 40.0% A	0
1.2	Consideration of MASLD should not be dependent on the presence of abnormal liver serum tests. However, persistently unexplained abnormal liver serum tests must be evaluated.	U	65.0% SA, 35.0% A	0
1.3	For the detection of hepatic steatosis in the MASLD diagnostic criterion, liver ultrasound–based imaging techniques may be considered, although it has relatively low sensitivity in detecting lesser degrees of hepatic steatosis.	A	47.1% SA, 47.1% A, 5.8% D	3
1.4	For the detection of hepatic steatosis in the MASLD diagnostic criterion, serum liver biomarkers and its scoring system may be considered as alternatives to liver imaging, although they have relatively low sensitivity in the diagnosis of hepatic steatosis.	A	36.8% SA, 57.9%, 5.3% D	1
1.5	Screening for MASLD and fibrosis in individuals with type 2 diabetes is recommended.	U	80.0% SA, 20.0% A	0
1.6	Screening for MASLD and fibrosis in individuals with the metabolic syndrome is recommended.	U	70.0% SA, 30.0% A	0
1.7	Screening for MASLD and fibrosis in individuals with overweight/obesity is recommended.	U	75.0% SA, 25.0% A	0
1.8	Cardiovascular services should implement an agreed local clinical pathway for the screening of MASLD in CVD, that involves screening for liver fibrosis using imaging and/or serum noninvasive tests.	U	80.0% SA, 20.0% A	0
1.9	In individuals who are at normal weight with metabolic diseases, the screening of MASLD should be considered, given the prevalence of MASLD in lean individuals.	A	52.6% SA, 42.1% A, 5.3% D	1
2	Assessments recommended for individuals with diagnosed MASLD, by cardiology clinicians			
2.1	Individuals with MASLD should be evaluated for additional causes of hepatic steatosis (eg, alcohol), and undergo investigations for secondary causes of liver disease (eg, hepatitis screen).	U	70.0% SA, 30.0% A	0
2.2	Detailed alcohol, illicit drug, smoking history should be performed and documented.	U	85.0% SA, 15.0% A	0
2.3	Use widely available validated serum (eg, FIB-4) and imaging-based noninvasive tests with high negative predictive value to risk stratify for hepatic fibrosis in individuals with MASLD.	U	70% SA, 30% A	0
2.4	FIB-4 ≥2.67 indicates a high probability of advanced fibrosis, which warrants secondary assessment and/or hepatology referral	U	63.2% SA, 36.8% A	1
2.5	Combining ≥2 noninvasive tests, using either serum or imaging-based tests, may be considered in patients at intermediate or high risk of hepatic fibrosis.	U	65.0% SA, 35.0% A	0
2.6	Patients stratified as *high risk* for advanced fibrosis or cirrhosis should be referred to a hepatologist.	U	80.0% SA, 20.0% A	0
2.7	Repeated noninvasive tests can be done for longitudinal disease/treatment monitoring. It is reasonable to perform FIB-4 surveillance every 2 years in low-risk and annually in high-risk individuals (with type 2 diabetes or established CVD).	B	61.1% SA, 27.8% A, 11.1% D	2
2.8	FIB-4 score can be used as a first-line point-of-care test for the screening of advanced fibrosis.	U	52.6% SA, 47.4% A	1
2.9	FIB-4 <1.3 indicates a low probability of advanced fibrosis	U	57.9% SA, 42.1% A	1
2.10	FIB-4 ≥1.3 indicates an intermediate probability of advanced fibrosis, which warrants secondary assessment and/or hepatology referral	U	47.4% SA, 52.6% A	1
2.11	Detailed dietary habits and physical activity should be performed and documented.	U	80.0% SA, 20.0% A	0
3	Screening for CVD in individuals with MASLD			
3.1	It is recommended to screen for CVD in all individuals with MASLD, regardless of the presence of traditional atherosclerotic risk factors, with detailed risk-factor evaluation at a minimum.	U	60.0% SA, 40.0% A	0
3.2	Cardiovascular risk assessment should be performed using standard atherosclerotic cardiovascular disease prediction tools.	U	70.0% SA, 30.0% A	0
3.3	Patients with MASLD should be screened annually for type 2 diabetes, hypertension, hyperlipidemia, and overweight/obesity.	U	80.0% SA, 20.0% A	0
3.4	MASLD should be considered a risk-enhancing factor for atherosclerotic CVD.	U	75.0% SA, 25.0% A	0

(*Continued*)

Table 2. Continued

	Recommendation	Grade*	Responses	
			Agreement†	NQ, n
4	Management of individuals with MASLD in CVD by cardiology clinicians			
4.1	The management of individuals with MASLD, assessed to be at low risk of hepatic fibrosis based on FIB-4 score, can be managed by clinicians within the cardiovascular specialty, with the focus on lifestyle management, cardiovascular risk reduction, and regular reassessment of hepatic fibrosis.	U	70.0% SA, 30.0% A	0
4.2	The multidisciplinary management of individuals with MASLD should be recommended, involving expertise in hepatology, cardiology, endocrinology, bariatric surgery, dietetics, physiotherapists, and nursing.	U	73.7% SA, 26.3% A	1
4.3	Target weight loss of 3–5% to improve hepatic steatosis.	A	60.0% SA, 30.0% A, 5.0% D, 5.0% SD	0
4.4	Target weight loss of ≥10% in the treatment of MASH or fibrosis, and reduction of cardiovascular risk.	U	65.0% SA, 35.0% A	0
4.5	Dietary recommendations include the Mediterranean diet, as well as vegetables, fruits, nuts, whole grains, lean animal protein, and fish. The intake of trans fats, red meat and processed red meats, refined carbohydrates, as well as fructose and sugar-sweetened beverages should be minimized.	A	85.0%, 10.0% A, 5.0% D	0
4.6	Abstinence from alcohol should be recommended in individuals with clinically significant liver fibrosis or cirrhosis.	A	90.0% SA, 5.0% A, 5.0% D	0
4.7	Regular moderate exercise for at least 150 min/week, or 75 minutes of vigorous-intensity aerobic physical activity is recommended. Resistance exercise in addition to aerobic activity, for ≥2 days/week, should be considered.	B	85.0% SA, 5.0% A, 5.0% D, 5.0% SD	0
4.8	Reduce sedentary time and engage in at least light activity throughout the day.	A	75.0% SA, 20.0% A, 5.0% SD	0
4.9	Prescriptions of exercise regime should be tailored according to the biologic age, exercise experience, functional capacity, safety, and ageing trajectories, especially in vulnerable populations.	A	80.0% SA, 15.0% A, 5.0% SD	0
4.10	Referral for bariatric surgery should be considered for individuals with MASLD who meet the national recommendations and eligibility criteria for bariatric surgery.	U	90.0% SA 10.0% A	0
4.11	Individuals with MASLD, with concomitant hypertension, should be managed with blood pressure–lowering agents according to current clinical practice guidelines.	U	85.0% SA, 15.0% A	0
4.12	Individuals with MASLD, with concomitant type 2 diabetes, should be managed with glucose-lowering agents, such as GLP1-RA, dual GIP/GLP1 receptor agonist (including tirzepatide), PPAR agonist (including pioglitazone), and SGLT2i, that promote weight loss and improved cardiometabolic profile according to current clinical practice guidelines.	U	85.0% SA, 15.0% A	0
4.13	In the special population with normal-weight MASLD, lifestyle intervention is the key recommendation. Although the recommended use of GLP1-RA and SGLT2i may be premature in this group, these agents may be considered to reduce cardiovascular events in individuals with high ASCVD risk.	U	63.2% SA, 36.8% A	1
4.14	Individuals with MASLD should be referred to obesity management services if weight loss goals have not been met despite lifestyle interventions.	U	70.0% SA, 30.0% A	0
5	Recommendations on MASLD-specific therapies in CVD			
5.1	Incretin analogues			
5.1.1	Who should get the intervention: Individuals with MASLD, and concomitant type 2 diabetes and/or obesity.	U	80.0% SA, 20.0% A	0
5.1.2	Surveillance: Serial assessment of serum glucose and HbA1c, renal function, triglycerides and weight. Monitor for signs and symptoms of pancreatitis.	U	75.0% SA, 25.0% A	0
5.1.3	Stopping rules: Diabetic ketoacidosis, end-stage renal failure, decompensated cirrhosis and pancreatitis. Recommended against use in individuals with personal or family history of medullary thyroid cancer or MEN2 syndrome.	A	70.0% SA, 25.0% A, 5.0% SD	0
5.2	PPAR agonist			
5.2.1	Who should get the intervention: Used as second or third line therapy for management of type 2 diabetes, or with co-existing MASLD	U	66.7% SA, 33.3% A	2
5.2.2	Surveillance: Serial assessment of serum glucose, HbA1c and liver function test. Monitor for signs of heart failure.	U	57.9% SA, 42.1% A	1
5.2.3	Stopping rules: Heart failure or evidence of fluid overload, history of fracture or at high risk for fracture, pregnancy, active or history of bladder cancer, macular edema and active liver disease (transaminases >2.5× ULN unless MASH is known to be the underlying cause of the elevation).	U	78.9% SA, 21.1% A	1
5.3	SGLT2 inhibitor			
5.3.1	Who should get the intervention: Individuals with MASLD, and concomitant type 2 diabetes, chronic kidney disease, heart failure, and/or atherosclerotic CVD	U	75.0% SA, 25.0% A	0

(*Continued*)

Table 2. Continued

	Recommendation	Grade*	Responses	
			Agreement†	NQ, n
5.3.2	Surveillance: Serial assessment of renal function, liver function, body weight, blood pressure, glycemic control, and symptoms	U	75.0% SA, 25.0% A	0
5.3.3	Stopping rules: Renal injury (generally eGFR <30 mL/[min·1.73 m^2]), symptomatic (genital or perineal infection, hypoglycemia, diabetic ketoacidosis, volume depletion)	U	70.0% SA, 30.0% A	0
5.4	Statin therapy			
5.4.1	Who should get the intervention: Used for primary prevention guided by cardiovascular disease risk assessment, or in secondary prevention in individuals with previous atherosclerotic cardiovascular disease.	U	85.0% SA, 15.0% A	0
5.4.2	Surveillance: Consider baseline lipid panel, liver function test and creatine kinase. If elevated ALT, recheck liver enzymes in 4–6 weeks. If ALT remains elevated, check for other etiologies, and consider hepatology referral.	U	78.9% SA, 21.1% A	1
5.4.3	Stopping rules: If ALT <3× ULN, to consider continuation of therapy with surveillance of liver enzymes. If ALT ≥3× ULN, stop lipid-lowering therapy or reduce dose, recheck liver enzymes within 4–6 weeks, and consider hepatology referral. Cautious reintroduction of therapy may be considered after ALT normalizes. Consider cessation in myositis or rhabdomyolysis. Statins should not be withheld from individuals with MASLD, including individuals with mild transaminitis or compensated cirrhosis, as its cardiovascular benefits significantly outweigh its risk.	U	68.4% SA, 31.6% A	1

A indicates agree; ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; D, disagree; eGFR, estimated glomerular filtration rate; FIB-4, Fibrosis-4 Index; MASH, MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MEN2, multiple endocrine neoplasia type 2; NQ, not qualified to respond; SA, strongly agree; SD, strongly disagree; U, unanimous agreement; and ULN, upper limits of normal.

*_U_ indicates 100% agreement; _A_, 90–99% combined agreement; _B_, 78–89% combined agreement; and _C_, 67–77% combined agreement.

†Alphanumeric data expressed as percentage (%) and degree of agree or disagreement (_A, SA, UA, D, SD_).

obesity (Recommendation 1.3; Table 2).[21] Moreover, liver ultrasound only provides a semiquantitative liver fat assessment, and the absence of steatosis on ultrasound does not exclude the presence of metabolic dysfunction-associated steatohepatitis (MASH) or fibrosis.[21] Non-imaging biomarkers that are used in steatosis scoring systems, such as the Fatty Liver Index or Hepatic Steatosis Index, have been proposed as alternatives in the identification of hepatic steatosis, but are all limited by the relatively low sensitivity (Recommendation 1.4; Table 2).[20,22] In line with current guidance from the American Association for the Study of Liver Disease (AASLD),[21] the routine use of liver ultrasound is questionable as the vast majority of people with obesity and/or T2D already have steatosis, but rather towards screening for clinically significant fibrosis in the higher risk population (those with T2D, obesity with metabolic complications, ≥2 cardiometabolic risk factors) with the use of Fibrosis-4 Index (FIB-4) given its strong negative predictive value (Recommendations 1.2–1.4, 2.3; Table 2).[21] It remains to be proven that the determination of hepatic steatosis in individuals at risk of ASCVD is cost-effective beyond the current standards of care for managing obesity and/or T2D. Hence, liver ultrasound for the detection of hepatic steatosis cannot presently be recommended in routine clinical practice for ASCVD risk stratification. Further studies evaluating the cost-effectiveness of fat measurements by ultrasound as a cardiovascular risk factor equivalent, may be an important next step.

In individuals with diagnosed MASLD, the key approach is the examination of MASLD disease activity, referring to the biologic processes resulting in liver injury and inflammation, and fibrosis stage, defined by the amount of hepatic scarring and hence cirrhosis risk. Disease activity can be assessed using the NAFLD Activity Score (NAS), which is a biopsy-based semi-quantitative scoring system for the grading and staging of hepatic lesions (steatosis, lobular inflammation and ballooning).[23] NAS correlating well with homeostasis model assessment of insulin resistance and liver transaminases, although it demonstrates a low prognostic value.[23] More importantly, fibrosis staging is the strongest predictor of liver-related and cardiovascular-related outcomes.[24] Steatohepatitis and fibrosis were classically identified through histology via a liver biopsy. However, invasiveness and bleeding risk, especially in the CVD population who are often taking antiplatelet agents, limit the use of liver biopsy.

Because of the risks associated with liver biopsy, noninvasive tests (NIT) have emerged as validated tools for early risk stratification in MASLD. It is important to note, however, that current NIT were initially developed to identify significant fibrosis, while the tools to assess disease activity are limited apart from liver biopsy.[25] NITs can be categorized into serum-based and imaging-based biomarkers, and they have been widely used in diagnosis, prognostication, and monitoring of disease progression and treatment response. With advanced fibrosis being a key predictor of liver and cardiovascular-related outcomes, various indices have been developed to screen for the presence of fibrosis, which include the NAFLD Fibrosis Score, FIB-4, and aspartate transaminase–to-platelet ratio index. The FIB-4 is the most validated, shown to outperform other indices in its ability to identify individuals

Table 3. Auditable Key Performance Indicators for the Diagnosis and Management of Patients With Suspected or Diagnosed MASLD in Cardiovascular Services

Key performance indicators
Cardiovascular services should implement an agreed local clinical pathway for the screening of MASLD in CVD, that involves screening for liver fibrosis using imaging and/or serum noninvasive tests.
Screening for MASLD in individuals with type 2 diabetes is recommended.
Screening for MASLD in individuals with the metabolic syndrome is recommended.
Screening for MASLD in individuals with overweight/obesity is recommended.
Individuals with MASLD should be evaluated for additional causes of hepatic steatosis (eg, alcohol), and undergo investigations for secondary causes of liver disease (eg, hepatitis screen).
Detailed alcohol, illicit drug, smoking history should be performed and documented.
Detailed dietary habits and physical activity should be performed and documented.
Use widely available validated serum (eg, FIB-4) and imaging-based noninvasive tests with high negative predictive value to risk stratify for hepatic fibrosis in individuals with MASLD.
It is recommended to screen all individuals with MASLD for CVD, regardless of the presence of traditional atherosclerotic risk factors, with detailed risk factor evaluation at a minimum
Patients with MASLD should be screened annually for type 2 diabetes, hypertension, hyperlipidemia, and overweight/obesity.
Target weight loss of 3% to 5% to improve hepatic steatosis
Target weight loss of ≥10% in the treatment of MASH or fibrosis, and reduction of cardiovascular risk.
Individuals with MASLD and concomitant hypertension should be managed with blood pressure–lowering agents according to current clinical practice guidelines.
Individuals with MASLD and concomitant type 2 diabetes should be managed with glucose-lowering agents (eg, GLP1-RA, dual GIP/GLP1-RA[including tirzepatide], PPAR agonist [including pioglitazone], and SGLT2i) that promote weight loss and improved cardiometabolic profile according to current clinical practice guidelines.
Individuals with MASLD should be referred to obesity management services if weight loss goals have not been met despite lifestyle interventions.
Referral for bariatric surgery should be considered for individuals with MASLD who meet the national recommendations and eligibility criteria for bariatric surgery.
The multidisciplinary management of individuals with MASLD should be recommended, involving expertise in hepatology, cardiology, endocrinology, bariatric surgery, dietetics, physiotherapists, and nursing.

CVD indicates cardiovascular disease; FIB-4, Fibrosis-4 Index; GIP, gastric inhibitory polypeptide; GLP1, glucagon-like peptide 1; GLP1-RA, glucagon-like peptide 1 receptor agonist; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; PPAR, peroxisome proliferator-activated receptor; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

with low probability of fibrosis. The FIB-4 algorithm takes advantage of readily available variables, including age, alanine aminotransferase (ALT), aspartate aminotransferase, and platelet count.[23,26] An FIB-4 score <1.3 is associated with a strong negative predictive value for advanced fibrosis, and may be a useful threshold to exclude advanced fibrosis in the CVD population.[26] On the other end of the spectrum, the FIB-4 score ≥2.67 has a high likelihood of advanced fibrosis (AUROC, 0.83).[26] An FIB-4 ≥2.67 indicates a high probability of advanced fibrosis, which warrants secondary assessment and/or hepatology referral (Recommendation 2.4; Table 2). Moreover, the FIB-4 adds to the stratification of CVD risk in patients with MASLD, with FIB-4 ≥2.67 shown to be associated with a 40% increase in cardiovascular mortality, enhancing the prediction of major adverse cardiovascular events.[27] These FIB-4 thresholds should be used with caution, especially in younger and older populations. FIB-4 has been shown to perform poorly for the diagnosis of advanced fibrosis in individuals aged ≤35 years, and the specificity of FIB-4 declines with age to an unacceptably low level of 35% in those aged ≥65 years resulting in high false-positive rates.[28] Age-specific FIB-4 thresholds should be used in those aged ≥65 years, with the revised FIB-4 threshold >2.0 demonstrating improved sensitivity (77%) and specificity (70%) for fibrosis. In those aged ≤35 years, it has been proposed that alternative fibrosis assessment should be considered.[28]

Because of the heterogeneity of MASLD across diverse population groups, reliance on one NIT may reduce sensitivity in identifying individuals at risk of fibrosis and cirrhosis within the CVD population. A combination ≥2 NITS, including serum- or imaging-based biomarkers, is recommended in the staging and risk stratification of individuals with MASLD with FIB-4 score >1.3 (Recommendation 2.5; Table 2).[24] Individuals at moderate or high risk for advanced fibrosis determined by FIB-4 should undergo secondary risk assessment. The Enhanced Liver Fibrosis (ELF) test is recognized as a second-line NIT option, used for prognostication when advanced fibrosis is suspected. ELF testing has shown equivalence to vibration-controlled transient elastography (VCTE) and is useful in some settings where the availability of VCTE is limited.[21] ELF scoring ≥11.3 has been shown as a predictor of future CVD and liver-related events in the general population.[21] An elevated FIB-4 followed by increased ELF can be used as a sequential strategy to determine high risk of fibrosis, and these individuals should be referred to hepatology for further evaluation and management[21] (Recommendation 2.6; Table 2). The sequential use of serum-based and imaging-based modalities, such as VCTE and magnetic resonance elastography, has been shown to improve sensitivity and specificity in the diagnosis of fibrosis and cirrhosis.[29] Although magnetic resonance elastography is the flagship of imaging technique, its use is limited by its availability and the required level of expertise in many centers. Magnetic resonance elastography is not the first-line approach for risk stratification in individuals with MASLD,[21] and should be ordered by the hepatologists for the assessment of hepatic fibrosis. On the other hand, VCTE is widely available, inexpensive, and easy to perform, but is less reliable in individuals with increased body

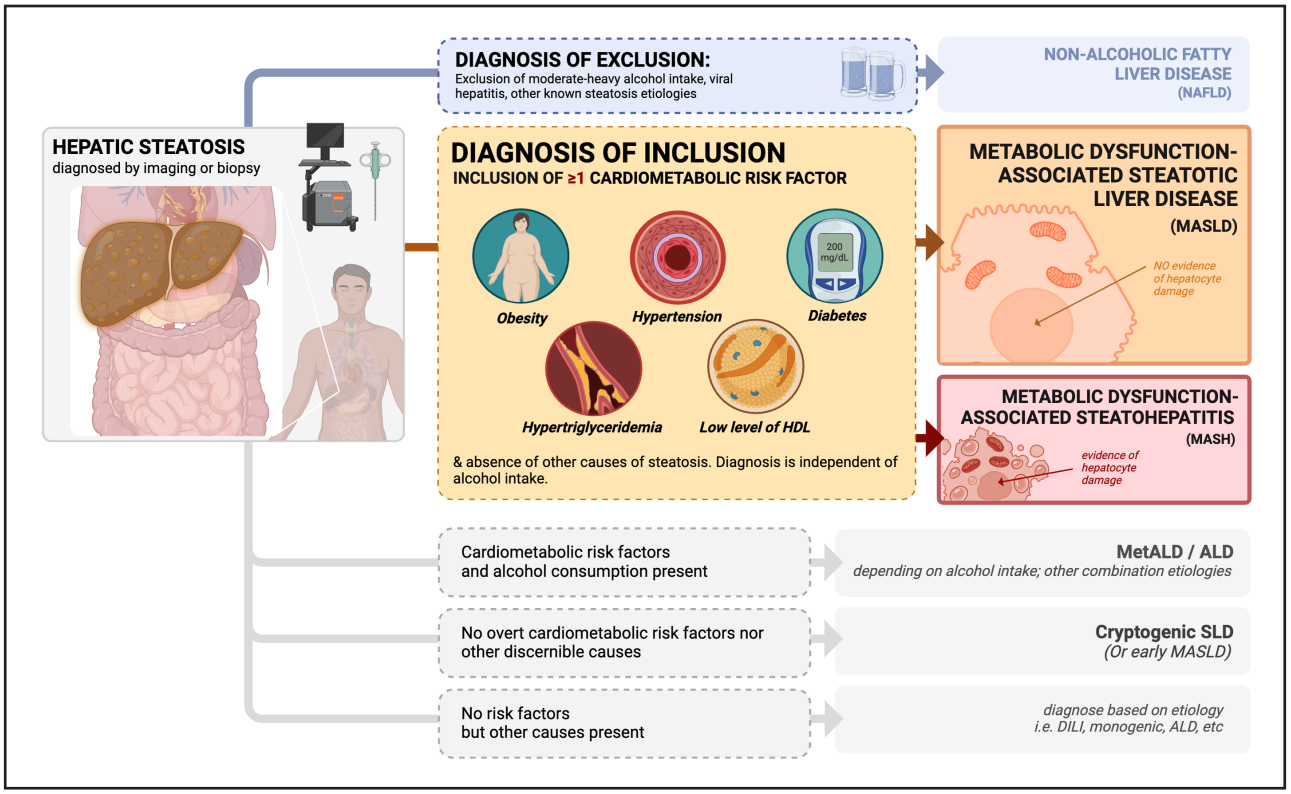

Figure 2. Comparison of the diagnostic criteria for NAFLD and MASLD.
If additional etiologies of hepatic steatosis are identified, a combination diagnosis should be considered. In the case of increased alcohol intake (weekly intake ≥210 g [or 21 units for males] or ≥140 g [or 14 units for females]), this can be defined as *MetALD* or *ALD*. ALD indicates alcoholic liver disease; DILI, drug-induced liver injury; HDL, high-density lipoprotein cholesterol; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol–associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; and SLD, steatotic liver disease.

mass.[21] Other ultrasound-based methods (eg, acoustic radio force impulse elastography) have shown to demonstrate good diagnostic accuracy for liver fibrosis, and can be ordered at the time of a standard liver ultrasound in the evaluation of patients with abnormal biochemical tests or altered biochemical indices.[28] Importantly, in individuals with indeterminate or discordant NITs, liver biopsy may be considered to confirm diagnosis and stage severity of fibrosis.

Cardiovascular services should implement an agreed local clinical pathway for the screening of MASLD in CVD, that involves screening for liver fibrosis using imaging and/or serum non-invasive tests (Recommendation 1.8; Table 2). In individuals identified to be at risk of advanced fibrosis by NITs, timely hepatology review for the identification of corroborative clinical, biochemical and/or radiographic characteristics of fibrosis can improve the positive predictive value in determining fibrosis and cirrhosis.[30] It is reasonable to perform annual FIB-4 surveillance in high-risk populations such as those with T2D or established CVD, and FIB-4 screening every 2 years in low-risk individuals who are young with few cardiovascular risk factors (Recommendation 2.7; Table 2).[26] In terms of disease and treatment monitoring, serial NITs should be performed for longitudinal disease monitoring to assess for disease progression or regression, as this will inform clinical management.[24]

More than half of individuals with MASH are asymptomatic, and most of the cases are incidentally detected by abnormal liver function tests.[21,27] A clinical consequence of identifying higher risk of fibrosis is the initiation of more aggressive CVD risk reduction strategies. As such, the screening for MASLD in patients with obesity, metabolic syndrome, T2D, or those with high risk for CVD, is recommended.[31] The proposed screening process for fibrosis involves the use of the FIB-4 as the first-line point-of-care test (Recommendation 2.8; Table 2). Low cardiometabolic risk and FIB-4 <1.3 can exclude advanced fibrosis with high negative predictive value (Recommendation 2.9; Table 2). In an intermediate-risk group of patients with FIB-4 ≥1.3, further assessment using VCTE may be performed (Recommendation 2.10; Table 2). In the high-risk group of individuals with prediabetes, T2D, or high cardiometabolic risk, sequential evaluation with a second NIT is recommended[26,31] (Figure 3). These NITs may be repeated at intervals from 1 to 2 years in accordance with the patient's fibrosis stage and response to treatment.

Although assessing abdominal obesity is a crucial aspect of MASLD screening, clinicians must remain cognizant that the burden of MASLD in lean individuals is

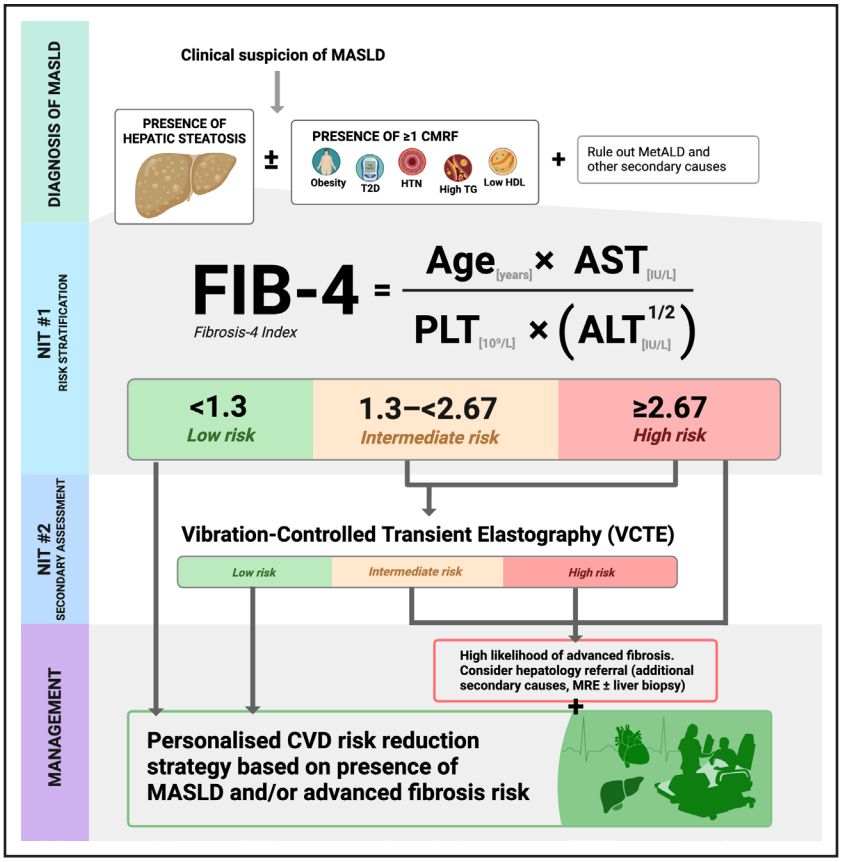

Figure 3. Proposed approach and diagnostic modalities in screening and identification of MASLD and advanced hepatic fibrosis. Screening for clinically significant fibrosis in the higher risk MASLD population (those with T2D, obesity with metabolic complications, ≥2 CMRFs) is recommended with the use of the FIB-4. Given the low sensitivity of detecting lesser degrees of steatosis, the routine use liver ultrasound or serum-based markers for the detection of hepatic steatosis cannot presently be recommended in routine clinical use for atherosclerotic cardiovascular disease risk stratification. This pathway is intended for the risk stratification of individuals with hepatic steatosis on imaging (either performed for abnormal liver function tests or other indication), or for populations at-risk for MASLD such as those with CMRFs. FIB-4 has been shown to perform poorly for the diagnosis of advanced fibrosis in younger (age ≤35 years) and older (aged ≥65 years) populations. An age-specific FIB-4 threshold >2.0 should be considered in individuals aged ≥65 years, while an alternative fibrosis assessment should be performed in individuals aged ≤35 years.[28] ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CMRF, cardiometabolic risk factor; CVD, cardiovascular disease; FIB-4, Fibrosis-4 Index; HDL, high-density lipoprotein; HTN, hypertension; MASLD, metabolic dysfunction–associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol–associated steatotic liver disease; MRE, magnetic resonance elastography; NIT, noninvasive test; T2D, type 2 diabetes mellitus; TG, triglyceride; and VCTE, vibration-controlled transient elastography.

not negligible. In those of normal weight with metabolic diseases, screening for MASLD using serum indices and imaging techniques for fibrosis staging and surveillance should be considered[32] (Recommendation 1.9; Table 2). Insulin resistance is the main pathophysiologic–mechanistic driver of MASLD even in the absence of obesity, with lean individuals sharing similar liver disease severity and clinical outcomes despite having fewer metabolic comorbidities.[33]

MASLD, Metabolic Syndrome, and CVD

There is an overlap in the pathophysiologic processes present in metabolic syndrome and MASLD, although patients can develop hepatic steatosis in the absence of metabolic syndrome and vice versa.[34] The associations between MASLD and cardiometabolic risk factors are often bidirectional, with the MASLD diagnosis conferring an increased risk of incident T2D.[34] MASLD can accelerate atherosclerosis, diastolic dysfunction, and valvular calcification through the intricate interplay of metabolic dysfunction, insulin resistance, and atherogenic dyslipidemia. Moreover, ectopic fat deposition in the liver and surrounding tissues has been associated with endothelial dysfunction, and a systemic inflammatory response. Together with ectopic fat deposition in the epicardium and pancreas, these responses can collectively potentiate atherogenesis and intramyocardial inflammation.[34] Increasing MASLD severity is associated with higher incidence of cardiometabolic risk factors and worse CVD severity.[35] Yet, MASLD remains an underappreciated risk factor for ASCVD. However, there are studies that have conflicting evidence in the relationship between MASLD and cardiovascular outcomes,

 Circulation. 2025;151:98–119. DOI: 10.1161/CIRCULATIONAHA.124.070535

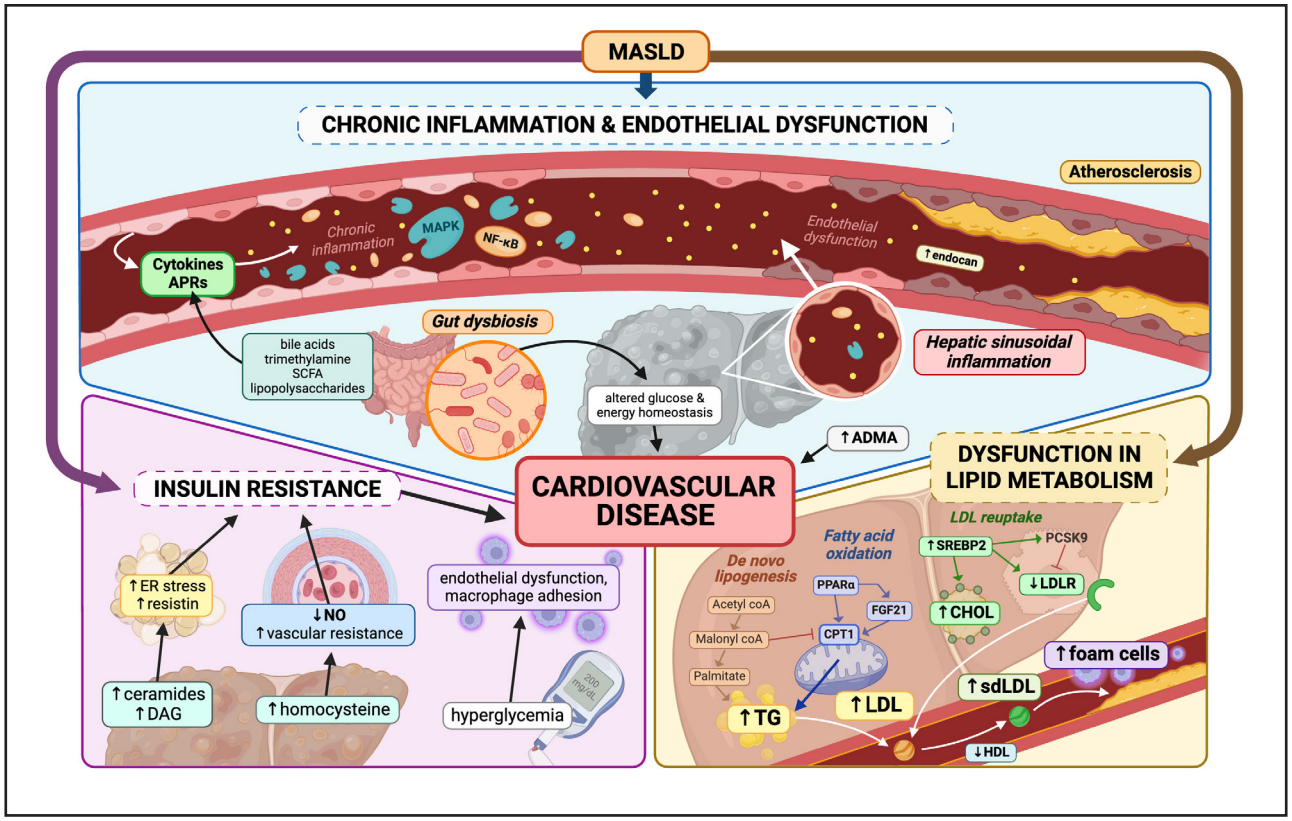

Figure 4. Pathophysiologic mechanisms contributing to CVD in MASLD.
Three main mechanistic pathways underlie the development of CVD in MASLD: (1) MASLD is a chronic inflammatory state, associated with increased release of cytokines and acute phase proteins. Coupled with mitochondrial dysfunction, this results in oxidative stress, activating proinflammatory pathways NFκB and MAPK. Gut dysbiosis in MASLD contributes to the chronic inflammatory state, through secretion of bile acids, trimethylamine, and short-chain fatty acids, as well as dysregulation in gut microbiome and the release of lipopolysaccharides that amplify inflammatory cytokine release. Endothelial dysfunction is related with heightened ADMA levels, owing to the liver's reduced capability in ADMA breakdown. (2) Hepatic insulin resistance is closely linked with Increased hepatic diacylglycerol that activates protein kinase C, resulting in a decline in insulin signaling. Homocysteine levels are often elevated in MASLD, inducing ER stress in adipose tissues, increasing resistin production in adipocytes, and aggravating insulin resistance. Homocysteine also reduces NO formation and increases intrahepatic vascular resistance, contributing to oxidative stress and cardiovascular diseases. (3) MASLD is characterized by atherogenic dyslipidemia, consisting of hypertriglyceridemia, elevated LDL and non-HDL cholesterol, and decreased HDL cholesterol. Impaired insulin signaling exacerbates lipolysis, leading to increased conversion of triglycerides to free fatty acids, and the increased release of very low–density lipoprotein. Small-dense LDL cholesterol particles permeate endothelial fenestrations, instigating inflammation and formation of atherosclerotic plaques. ADMA indicates asymmetric dimethyl arginine; APR, acute phase response; CHOL, cholesterol; coA, coenzyme A; CPT1, carnitine palmitoyltransferase; DAG, diacylglycerol; ER, endoplasmic reticulum; FGF21, fibroblast growth factor 21; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; MAPK, mitogen-activated protein kinases; MASLD, metabolic dysfunction–associated steatotic liver disease; NFκB, nuclear factor κ light-chain-enhancer of activated B cells; NO, nitric oxide; PCSK9, proprotein convertase subtilisin/kexin type 9; PPARα, peroxisome proliferator–activated receptor alpha; SCFA, short chain fatty acids; sdLDL, small dense low-density lipoprotein; SREBP2, sterol regulatory element–binding protein 2; and TG, triglyceride.

suggesting that these associations may be attributed to confounding or reverse causation. A Mendelian randomization study described a stepwise association of increased ischemic heart disease risk with increasing hepatic fat content and the presence of MASLD, but did not support genetically high hepatic fat content as being causally related to risk of ischemic heart disease.[12] Other reports indicate visceral adipose tissue and hepatic fat as differentially associated with CVD and T2D outcomes. Increased visceral adipose tissue, irrespective of liver fat status, has been closely related with both CVD and T2D, while high liver fat alone was associated with T2D, but not CVD.[36] The biologic underpinnings and clinical outcomes of MASLD are beyond the scope of the review, but have been briefly summarized in Figure 4 and Table S5, respectively.

SCREENING FOR CVD IN MASLD

Current primary preventative risk scoring tools focus on standard risk factors, that only provide modest discrimination for ASCVD events, and are often associated with underestimation of ASCVD risk in MASLD.[37] As cardiovascular complications often determine the clinical outcomes of MASLD, current guidelines emphasize the screening for CVD using standard ASCVD

prediction tools, in all individuals with MASLD regardless of the presence of atherosclerotic risk factors, with detailed risk factor evaluation at a minimum[31,34] (Recommendation 3.1; Table 2). Standard ASCVD prediction tools include the Predicting Risk of Cardiovascular Disease Events (PREVENT) calculator, that also takes into account chronic kidney disease and metabolic comorbidities, for determining 10- and 30-year risk of ASCVD and heart failure[38] (Recommendation 3.2; Table 2). Patients with MASLD should also be screened annually for T2D, hypertension, hyperlipidemia, and overweight/obesity (Recommendation 3.3; Table 2). If further guidance is required on refining the individual's ASCVD risk or on guidance of treatment decisions, CT coronary artery calcium scoring can be considered to aid in prediction of CVD events in individuals with MASLD. MASLD has been reported as an independent risk factor for coronary artery plaques in the asymptomatic population, associated with adverse cardiac events, prompting timely medical therapy in the MASLD cohort.[8] In selected individuals with more severe MASLD, and symptoms suggestive of underlying coronary artery disease, coronary computed tomography angiography may be considered because of its high sensitivity and specificity.[39] However, routine CT coronary artery calcium scoring or coronary computed tomography angiography is not recommended based on the presence of MASLD alone.

The development and progression of cardiac structural abnormalities, including left ventricular hypertrophy, diastolic dysfunction, and valvular calcification, may be accelerated in MASLD. In symptomatic patients with MASLD, clinicians should have a higher index of suspicion for structural abnormalities. Echocardiography is useful for assessing early diastolic relaxation velocity, filling pressures, global longitudinal strain, regional wall motion abnormalities, valvular abnormalities,[10] and epicardial adipose tissue,[40] in symptomatic patients with MASLD.

MASLD is a Cardiovascular Risk Enhancer

Multivariable risk prediction tools for ASCVD yield individualized estimates of cardiovascular risk to guide the extent of preventive interventions.[41] For the past decade, risk-based prevention has primarily focused on 10-year risk of ASCVD, and this has recently been updated by the American Heart Association (AHA) with the PREVENT calculator that takes into account chronic kidney disease and metabolic disorders.[42]

Unlike chronic kidney disease, long-recognized as a risk-enhancing factor in primary prevention guidelines,[41] MASLD has been an underappreciated risk enhancer—although it is likely to move into the same category as chronic kidney disease. The existing risk assessment models, such as the Framingham risk score, may underestimate the cardiovascular risk in the MASLD population, given that these models do not incorporate MASLD-related risk factors such as insulin resistance, obesity and hypertriglyceridemia.[37,38] MASLD has not been incorporated into the pooled cohort equations because its lack of phenotyping in the derivation cohorts that have been used. This is contributed by the lack of inexpensive biomarkers of MASLD, that can be widely used and validated across different large-scale CVD cohorts, and in turn improve the discriminant value in current cardiovascular risk–prediction models. Some of these challenges in integrating NITs into current ASCVD risk scores are that the present NITs (1) may have physiologic variability across population groups, inadequate accuracy and potential sampling error to the reference standard; (2) were initially developed to screen for fibrosis in other disease conditions such as chronic hepatitis C, and later redirected to the MASLD population; and (3) do not differentiate the different stages of MASH, and the longitudinal dynamic changes in fibrosis or disease activity.[25] Understanding the limitations of NITs will allow for more cautious integration of these liver biomarkers in modified ASCVD risk scores.

Moving forward, a novel CVD risk prediction equation incorporating MASLD indices will require a large sample that reflects a primary prevention population with diverse geographic, ethnic, socioeconomic demographics, spanning a wide age range across the life course, that encompass readily available predictive liver biomarkers in the primary care setting for easy implementation in clinical care.[43] Future studies are necessary to evaluate the improvements in discrimination and net reclassification with the incorporation of MASLD in modified risk assessment tools.[37] The recognition of MASLD as a cardiovascular risk–enhancing factor will be the next crucial step in promoting CLMH. More robust, large-scale prospective studies are warranted to examine the clinical utility and cost-effectiveness of using the presence of MASLD as a risk-enhancing factor to guide decisions on statin initiation, particularly in individuals at borderline or intermediate ASCVD risk.[30,31,34,44]

APPROACH TO MASLD MANAGEMENT IN CVD PREVENTION

The approach to the management of MASLD is mainly focused on lifestyle modifications and therapeutics that target weight loss in MASLD, with the goal of reducing liver fat content, inflammation, and preventing progress to fibrosis[33,35] (Figure 5). There is increasing emphasis on addressing the overall burden of cardiovascular risk factors, such as concomitant T2D, hypertension and hyperlipidemia, thus mitigating the risk of CVD. Detailed dietary habits and physical activity should be performed and documented in individuals with MASLD (Recommendation 2.11; Table 2). The management of individuals with MASLD, assessed to be at low risk of hepatic fibrosis based on FIB-4 score, can be managed by

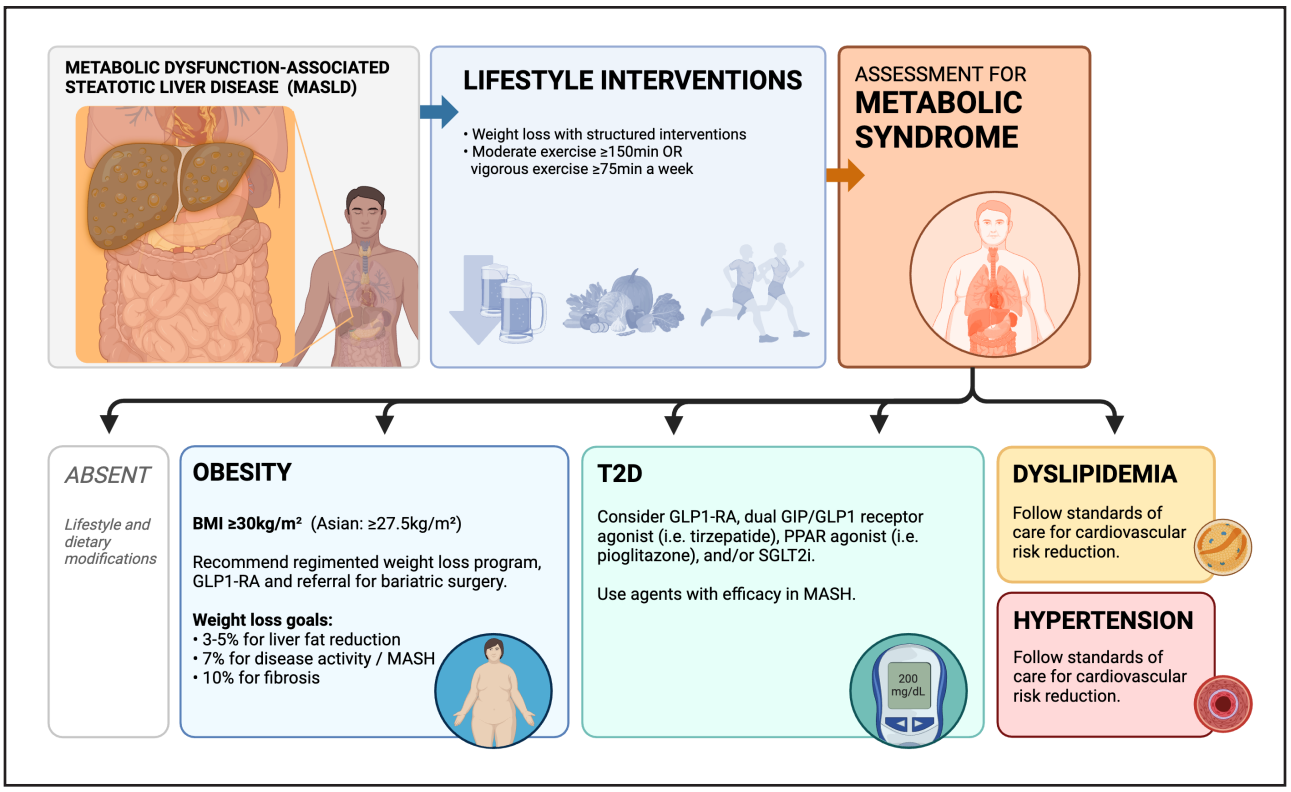

Figure 5. Treatment strategies for patients with MASLD.
BMI indicates body mass index; GIP, gastric inhibitory polypeptide; GLP1, glucagon-like peptide-1; GLP1-RA, glucagon-like peptide-1 receptor agonist; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; PPAR, peroxisome proliferator-activated receptor; SGLT2i, sodium-glucose cotransporter-2 inhibitors; and T2D, type 2 diabetes mellitus.

clinicians within the cardiovascular specialty, with the focus on lifestyle management, cardiovascular risk reduction, and regular reassessment of fibrosis[25,26,29,33] (Recommendation 4.1; Table 2). This management should also be shared broadly with cardiologists, hepatologists, endocrinologists, bariatric surgeons, and the wider multidisciplinary team[21] (Recommendation 4.2; Table 2).

Lifestyle and Psychosocial Interventions

Weight loss

Studies have shown that modest weight loss can be impactful, especially in early MASLD.[32] Weight loss of 3% to 5% improves steatosis. Greater weight loss of >10% with sustained weight control can improve steatohepatitis and fibrosis, and reverse cardiac abnormalities (Recommendations 4.3 and 4.4; Table 2).[32] Sustained weight loss is paramount in reducing adipose tissue stress, improving peripheral insulin sensitivity, and abrogating the drivers of liver injury in individuals with steatohepatitis.[32] Yet, achieving effective and sustained weight loss is often difficult. In the Look AHEAD study (Look AHEAD: Action for Health in Diabetes), participants were enrolled in intensive lifestyle intervention, supervised by a group of dieticians, exercise specialists, and psychologists, and managed to achieve 10% weight loss. However, only 42.2% of these participants were able to sustain the weight loss at 4 years.[45] Similarly, an observational cohort revealed that one-third of patients in the lifestyle intervention arm experienced weight loss of more than 5%; however, 21.2% regained the weight back to baseline within 1.5 years.[46] Obesity is viewed as a chronic relapsing condition as there is a increased tendency for individuals to regain weight once the weight management program has been stopped. Because of this, programs should remain readily available for individuals to re-engage, in order to sustain the initial weight advantage (and thereby the benefits on cardiometabolic health).[31,33,34,41] A multipronged strategy for sustained weight loss is necessary through exercise, controlled energy intake modifications and optimization of nutritional status, particularly so in adolescence and young adulthood; the World Health Organization forewarns that poor lifestyle choices can affect young people and contribute to 70% of global premature mortality.[47] Additionally, the use of incretin analogues have generated significant interest because of their superior weight loss effects compared with older weight loss drugs, as well as their weight loss–independent incretin effects on insulin resistance, hepatic steatosis, glycemic profile, lipid parameters, and blood pressure.[48] This offers a promising future because these drugs can induce weight loss and concomitantly improve components of the metabolic

milieu without the serious adverse effects that plagued previous efforts.[48] An integrated care model should include a community-based practice network, where public health and community stakeholders partner with health care practices to raise public health awareness of MASLD and promote healthy behaviors.[49] If weight loss goals, however, have not been met despite lifestyle interventions, individuals with MASLD should be referred to obesity management services (Recommendation 4.14; Table 2).

Dietary modifications

The current guidelines recommend a diet rich in vegetables, fruits, nuts, whole grains, lean animal protein, and fish. In addition, they recommend minimizing the intake of trans fats, red meat, refined carbohydrates, and sugar-sweetened beverages.[41] For patients with MASLD and overweight or obesity, AASLD guidelines[21] prioritize the need for weight loss and a tailored dietary plan that includes caloric deficit (ie, 500 kcal/day below the recommended amount), along with reduction in foods that have high calories, high glycemic index, and high fat. A Mediterranean dietary pattern (ie, high in fiber and unsaturated fats) is often recommended to patients with MASLD. It focuses on plant-based ingredients, such as fruits, vegetables, whole grains, and legumes, and only small portions of fish, meat, or eggs[50] (Recommendation 4.5; Table 2). It has been associated with improvements in cardiovascular health and reduction in liver fat. Compared with low-fat diets, this dietary approach is associated with a 30% lower risk for major adverse cardiovascular events.[51] In addition, dietary modifications with more polyunsaturated fatty acids—of which there are lower levels of with MASLD—may be beneficial: polyunsaturated fatty acids have been shown to reduce ALT, triglycerides, lipid synthesis, and inflammatory cytokines, as well as increase lipid oxidation in MASLD.[30] A randomized placebo-controlled trial examining the effects of polyunsaturated fatty acids in MASLD demonstrated reduction in serum GGT (gamma-glutamyl transpeptidase), liver fat, and weight, as well as improvement in plasma lipid profile, after 12 months.[52] Fructose- and sugar-sweetened beverages should be limited; they are associated with accelerated risk of MASLD.[31] Alcohol intake should be regularly assessed, with the recommendation of alcohol minimization in individuals with MASLD or F0 to F1 fibrosis. Because alcohol is a cofactor for progression of liver disease, patients with MASLD should be counseled about alcohol behaviors and how to account for alcohol-derived calories. Abstinence of alcohol is recommended in individuals with clinically significant liver fibrosis ([stage ≥F2[21]] see Recommendation 4.6; Table 2). A J-shaped relationship between alcohol intake and risk for CVD and mortality in individuals with isolated hepatic steatosis has been observed, with those drinking moderately portending the lowest mortality risk, while those with excessive alcohol consumption demonstrating the highest risk.[53]

Physical activity

Physical activity is considered a cornerstone of maintaining and improving CLMH, reflected through changes in energy balance, circulatory lipids, insulin resistance, and hepatic fat, although reduction in cardiovascular events has not yet been shown in randomized trials on exercise.[54] Despite physical activity having little impact on hepatic insulin sensitivity, it does improve peripheral insulin sensitivity, achieving an overall improvement in insulin action, insulin dependent glucose uptake, and reduction in hepatic de novo lipogenesis.[54] Both cardiology and hepatology guidelines recommend similar physical activity advice to reduce cardiovascular and MASLD risk, with regular moderate exercise ≥5 times per week, ≥150 minutes per week, or 75 minutes of vigorous-intensity aerobic physical activity (Recommendation 4.7; Table 2).[41] Although different forms of exercise, including aerobic, resistance, or high-intensity intermittent, have shown similar effects on hepatic fat reduction,[55] resistance exercise combined with aerobic physical activity lowers the risk of cardiovascular events and mortality. As such, engaging in resistance exercise, in addition to aerobic activity, ≥2 days per week is recommended.[55]

It is important to note that physical activity and sedentary behavior have independent effects on CLMH. Increased breaks in sedentary times have been linked with improved weight loss, glucose and triglyceride metabolism.[55] The reduction in sedentary time improves the cardiometabolic profile, independent of physical activity, and should be a target for lifestyle interventions. It is recommended to engage in at least light activity throughout the day to reduce cardiovascular mortality and morbidity (Recommendation 4.8; Table 2).[55]

In vulnerable populations, such as the elderly or those with multiple comorbidities (eg, sarcopenia, cirrhosis), prescribed exercise regimen should be tailored to biologic age, exercise experience, functional capacity, safety, and aging trajectories, and monitored by physicians or trained physiotherapists[33,34,41,46] (Recommendation 4.9; Table 2). However, weight reduction leads to more pronounced hepatic fat reduction than exercise. This is clinically important, especially for individuals with physical limitations, as the emphasis on weight management through dietary, nutritional and protein optimization should be prioritized.[54]

Surgical Interventions

The 2022 American Society for Metabolic and Bariatric Surgery and International Federation for the Surgery of Obesity and Metabolic Disorders use body mass index (BMI) ≥35 kg/m^2 as the criterion for bariatric surgery, irrespective of the presence or severity of comorbidities.[56] In individuals with BMI between 30 kg/m^2 to 34.9 kg/m^2, the American Society for Metabolic and Bariatric Surgery suggests a trial of nonsurgical therapy before

consideration of bariatric surgery (Recommendation 4.10; Table 2). BMI thresholds are adjusted for Asian populations, with ≥27.5 kg/m^2 being an indicator for bariatric surgery. MASLD regression has been associated with bariatric surgery, with a 40% reduction of fibrosis and a mean improvement of 2.39 in NAS.[51] Others have demonstrated that the resolution of steatohepatitis without worsening of fibrosis occurs in 80% of patients 1-year after bariatric surgery, and these beneficial effects were maintained at 5 years.[57]

Bariatric surgery lowers blood pressure by 4 mm Hg to 15 mm Hg in 1 to 2 years after surgery, lowers triglycerides and LDL, and improves glycemic control within days after the surgery.[58] Bariatric surgery can lower the risk of major adverse cardiovascular events and mortality in individuals with obesity, compared to usual care, although randomized controlled trial evidence is still awaited.

Pharmacologic Therapies

Dual treatments (eg, GLP1 [glucagon-like peptide-1] receptor agonists [GLP1-RA]; dual GIP [gastric inhibitory polypeptide]/GLP1-RA, including tirzepatide; PPAR [peroxisome proliferator-activated receptor] agonists, including pioglitazone; and SGLT2 [sodium glucose cotransporter-2] inhibitors), targeting MASLD and its metabolic comorbidities (ie, T2D and obesity),[21] should also be considered for the synergistic pathophysiologic processes between MASLD and cardiometabolic diseases (see Recommendations 4.11 and 4.12; Table 2).[21] These agents have demonstrated beneficial effects on blood pressure, glycemia, lipid panel, weight loss, cardiovascular outcomes, as well as hepatic steatosis and fibrosis reduction.

Incretin analogues

Recent evidence arising from GLP1-RA randomized trials point to cardiovascular, hepatic, and metabolic benefits. Beyond their glucose-lowering effects, semaglutide and liraglutide have been approved for the treatment of obesity. Semaglutide enhances weight reduction by 14.9% compared with the placebo group, as demonstrated in the STEP study (Semaglutide Treatment Effect in People with Obesity).[59] The SELECT trial[60] (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) compared the effects of weekly subcutaneous semaglutide 2.4 mg to placebo in nondiabetic patients with preexisting CVD together with overweight or obesity. Semaglutide was superior in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, compared to placebo, independent of the glucose-lowering effects. The SELECT trial (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) holds promise in the weight reduction effects of GLP1-RA in individuals with obesity, even in the absence of T2D.[60] Several trials have also demonstrated that GLP1-RA was associated with reductions in hepatic triglycerides on imaging,[61–65] as well as histologic improvement in individuals with MASH irrespective of T2D status,[66] compared with placebo.[67] Moreover, the ongoing phase 3 ESSENCE trial (Effect of Semaglutide in Subjects With Non-Cirrhotic Non-Alcoholic Steatohepatitis) seeks to examine the effects of semaglutide on resolution of steatohepatitis with no worsening of liver fibrosis, improvement in fibrosis with no worsening of steatohepatitis, and cirrhosis-free survival, as well as other cardiometabolic parameters at 72 weeks.[68] The indications, surveillance strategies and stopping rules for incretin analogues can be found in Table 2 (Recommendations 5.1.1–5.1.3).

GLP1-RAs are postulated to reduce liver lipogenesis and fat content by reducing carbohydrate-responsive element-binding protein activation, which has a central role in lipogenesis in the liver. These agents decrease lipotoxicity, circulating free fatty acid levels and de novo lipogenesis in both fasting and non-fasting states. In addition, they have anti-inflammatory effects in reducing oxidative stress and macrophage influx into the liver potentiating the improvement of MASH inflammation and steatosis.[30,48,61,63–65]

Recently tirzepatide, a novel dual GIP receptor/GLP1-RA, has emerged as a therapeutic option in T2D treatment, with potential benefits in ameliorating metabolic dysfunction related to adipose tissue and hepatic fat accumulation. In the SURPASS trials (A Study of Tirzepatide in Participants with Type 2 Diabetes), greater weight loss was reported in participants who received tirzepatide as compared to placebo (SURPASS-1 [A Study of Tirzepatide (LY3298176) in Participants With Type 2 Diabetes Not Controlled With Diet and Exercise Alone]), semaglutide (SURPASS-2 [A Study of Tirzepatide (LY3298176) Versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants With Type 2 Diabetes]), insulin degludec (SURPASS-3 [A Study of Tirzepatide (LY3298176) Versus Insulin Degludec in Participants With Type 2 Diabetes]), and insulin glargine (SURPASS-4 [A Study of Tirzepatide (LY3298176) Once a Week Versus Insulin Glargine Once a Day in Participants With Type 2 Diabetes and Increased Cardiovascular Risk]).[69] Tirzepatide also showed reduction in liver fat content using magnetic resonance imaging (MRI)–proton density fat fraction) at week 52 in the SURPASS-3 trial.[70] In the phase 2 SYNERGY-NASH trial (A Study of Tirzepatide (LY3298176) in Participants With Nonalcoholic Steatohepatitis), which involved participants with MASH and moderate or severe hepatic fibrosis, individuals treated with tirzepatide for 52 weeks had higher rates of resolution of MASH without worsening of fibrosis compared with those receiving placebo (44% in 5-mg tirzepatide group, 56% in 10-mg tirzepatide group, and 62% in 15-mg tirzepatide group, vs 10% in placebo group; $P<0.001$ for all 3 comparisons).[71] In terms of the effects on cardiometabolic profile, the use of tirzepatide led to improvements in HbA1c, blood pressure, triglyceride, low-density

lipoprotein (LDL) and weight reduction without increase in major adverse cardiovascular events.[48] Furthermore, survodutide, a dual agonist of glucagon receptor and GLP-1 receptor, was evaluated in a 48-week, phase 2 trial involving individuals with biopsy-proven MASH and fibrosis stage F1 through F3. Survodutide was found to be superior to placebo in the improvement in MASH without worsening fibrosis, coupled with significant reduction in liver fat content by ≥30% and improvement in fibrosis by ≥1 stage.[72]

Although recommending GLP1-RA and SGLT2 inhibitors may be premature for the management of MASLD in normal-weight individuals, these agents may be considered to reduce cardiovascular events in individuals with T2D, ASCVD, and target organ damage[32,33] (Recommendation 4.13; Table 2).

PPAR agonists

Thiazolidinediones are ligands for PPAR-γ approved for the treatment of T2D. Although the use of thiazolidinediones in individuals with steatohepatitis is recommended in AASLD guidelines, caution is required in individuals with CVD[33] (Recommendations 5.2.1–5.2.3; Table 2). Pioglitazone reduces the risk of all-cause mortality, nonfatal myocardial infarction, and stroke in patients with T2D.[73] Pioglitazone has been shown to decrease coronary atheroma volume and increase high-density lipoprotein levels.[73] In MASH, pioglitazone can reduce the degree of hepatic steatosis, inflammation, and hepatocellular ballooning.[73–76] A randomized trial of 101 participants with prediabetes or T2D demonstrated 51% of individuals treated with pioglitazone had MASH resolution, compared to 19% in the placebo arm ($P<0.001$), with lower rates of fibrosis progression and reduction in mean fibrosis score.[74] However, the rates of fibrosis improvement did not reach statistical significance in the pioglitazone group.[74,75] In the PIVENS trial (Pioglitazone Versus Vitamin E Versus Placebo for the Treatment of Non-Diabetic Patients With Nonalcoholic Steatohepatitis), although pioglitazone treatment did not meet the primary end point (ie, ≥2-point reduction NAS without worsening of fibrosis), there were higher rates of MASH resolution with pioglitazone compared to placebo[77] (47% vs 21%, respectively; $P<0.001$). Combination therapy with vitamin E and pioglitazone in individuals with MASH and T2D demonstrated significantly higher rates of 2-point reduction in NAS without worsening of fibrosis, compared with placebo; however, this was not achieved with vitamin E alone.[76] Patients treated with combination therapy, as well as vitamin E, had improvements in resolution of MASH and steatosis assessed by histology, compared with placebo. Notably, improvements in inflammation and ballooning were only observed in the combination therapy arm[76]; however, the use of PPAR agonists remains controversial related to the potential side effects of weight gain, heart failure, and bone fractures. Pioglitazone has been shown to enhance left ventricular diastolic function in individuals without congestive heart failure,[78] but its use is contraindicated in individuals with advanced heart failure. PPAR agonists exacerbate heart failure via sodium and fluid retention, and should be used cautiously in individuals with preexisting CVD. In addition to agonists of any one specific isoform, lanifibranor is a pan-PPAR agonist that affects PPARα, -δ, and -γ in a balanced manner. Not only has it shown to cause MASH resolution and improvement of fibrosis in a 6-month trial, it has favorable lipid and inflammatory profiles compared with placebo.[79] Studies have highlighted the ability of lanifibranor to decrease liver and muscle insulin resistance, as well as improve unfavorable cardiometabolic profile (eg, hyperglycemia, hyperlipidemia, and high diastolic blood pressure) in indivduals with MASLD.[80] These benefits, however, are outweighed by increased rates of weight gain and peripheral edema with the use of lanifibranor.[79]

SGLT2 inhibitors

SGLT2 inhibitors are a promising therapeutic option with benefits in glycemic control, weight loss, renoprotection, cardioprotective effects, and liver-related outcomes. The recommendations of SGLT2 inhibitor use in specific population groups, surveillance strategies, and stopping rules can be found in Table 2 (see Recommendations 5.3.1–5.3.3). Patients with T2D at increased risk for cardiovascular events receiving SGLT2 inhibitors had lower rates of the major adverse cardiovascular events and all-cause mortality when compared to placebo.[33,67] Evidence on the hepato-protective effects of SGLT2 inhibitors are also emerging.[66] In trials examining MRI-measured changes in liver triglyceride content, SGLT2 inhibition with dapagliflozin,[67,81] empagliflozin,[82–84] or canagliflozin[85] has been associated with reduction of hepatic steatosis. The administration of SGLT2 inhibitors for 6 months in individuals with obesity has been associated with reduced liver transaminases and hepatic fat content, as well as improvements in liver triglyceride content and NAS.[86]

TRβ agonists

The U.S. Food and Drug Administration has approved its first treatment for MASH in 2024. The approved resmetirom is a TRβ (thyroid hormone receptor β) agonist, which decreases intrahepatic lipids via increased mitochondrial β oxidation and improved mitochondrial function. As reported by the randomized MAESTRO-NASH trial (A Phase 3 Study to Evaluate the Efficacy and Safety of MGL-3196 [Resmetirom] in Patients With NASH and Fibrosis), resmetirom has been shown to be superior to placebo in MASH resolution with no worsening of fibrosis (25.9% in the 80-mg resmetirom group and 29.9% in the 100-mg resmetirom group, vs 9.7% in the placebo group; $P<0.001$ for both comparisons with placebo). In addition, there was significant improvement in liver fibrosis by ≥1 stage without worsening of NAS in individuals treated with resmetirom compared to placebo (24.2% in the 80-mg resmetirom group and 25.9% in the 100-mg resmetirom group, vs 14.2% in

the placebo group; $P<0.001$ for both comparisons with placebo).[87] While data on cardiovascular outcomes are currently exploratory, resmetirom has been observed to lower blood pressure, LDL, triglycerides, apoB, apo C3, and lipoprotein (a).[88] Resmetirom use is indicated for the treatment of MASH with moderate to advanced fibrosis (stages F2–F3 fibrosis), but should be avoided in decompensated cirrhosis.[89] Close liver and endocrine safety monitoring, related to hepatotoxicity, thyroid axis or thyroid hormone effects, are recommended with the use of resmetirom.[88,90,91]

Lipid-lowering therapy

Statins are the cornerstone in the treatment of hyperlipidemia and are effective in primary and secondary prevention of coronary artery disease. However, statins remain underutilized related to concerns about transaminitis in MASLD. Several trials did not find any difference in the incidence of persistently elevated liver function tests between statin and placebo therapy.[92] The use of statin in the MASLD population actually results in liver enzyme reduction and has beneficial effects on steatohepatitis, with an AHA scientific statement recommending the use of statins in fatty liver disease with normal liver function.[34] While severe cases of drug-induced liver injury have been reported, the prevalence is rare (1.2 of 100 000 users).[93] A study reported that half of a population with moderately abnormal liver transaminases at baseline, treated with statin, observed improvement in liver function tests, whereas those who were not treated with statin demonstrated persistent worsening of liver function. Importantly, only 20% of the cohort receiving statins had an adverse cardiovascular event, compared to 60% in the nontreatment group.[94] Moreover, the clearance of statin by the liver depends on the hydrophobicity, with hydrophilic compounds (such as pravastatin and atorvastatin) leading to more pronounced active renal excretion, while lipophilic compounds (such as simvastatin and lovastatin) are predominantly excreted by the liver.[44] High-intensity hydrophilic statin therapy has been associated with increased risk of transaminase elevation and hepatotoxicity, compared with lipophilic therapy.[44] Apart from statin solubility, there are certain statin types associated with greater risk for liver-related adverse effects. Both simvastatin and atorvastatin have the highest documented hepatotoxicity cases, partly attributed by their higher frequency in prescription, and have been associated with fatality from statin-induced liver injury.[95] In terms of differential efficacy in CVD risk reduction for primary or secondary cardiovascular prevention, this is closely related to the potency of the statin in lowering LDL concentrations (with the highest potency in atorvastatin and rosuvastatin),[96] while the solubility profile of the statin is likely to play a secondary role in observed differences.[97] Regarding liver-related benefits, a large MASLD cohort study demonstrated lower risk of developing hepatocellular carcinoma with the initiation of both lipophilic and hydrophilic statin.[98]

The potential cardiovascular and hepatic benefits associated with statin use outweigh the risk for hepatotoxicity, and the education of physicians—particularly, nonhepatologists—is necessary to ensure individuals with MASLD and nonsevere elevation of transaminases may continue to receive statin therapy to reduce the risk of ASCVD.[99] Nevertheless, the need for vigilance surrounding the potential rare complications of severe statin-induced liver injury remains. Statins should not be initiated for primary cardiovascular prevention in patients with Child–Pugh class B or C cirrhosis, without the guidance of the hepatologist[100] (Recommendations 5.4.1–5.4.3; Table 2).

FUTURE DIRECTIONS FOR PROMOTING CLMH

Despite a vast body of evidence associating MASLD and CVD, present cardiology guidelines do not identify MASLD as a risk factor for CVD or target for intervention in the treatment of CVD.[41] With mounting evidence of mechanistic pathways underscoring the bidirectional dose–response relationship between these entities, independent of T2D, there is increasing impetus for clinicians to be proactive in earlier detection and intervention in MASLD. We recommend the consideration of MASLD as a cardiovascular risk factor (Recommendation 3.4; Table 2). Emerging metabolic pharmacotherapies have shown improvements in both liver- and cardiovascular-related end points in their respective specialty trials. Stronger collaborations between cardiologists, hepatologists, endocrinologists, and the wider multidisciplinary team are warranted in upcoming trials. It will also necessitate a shift in treatment paradigm that involves changes to clinical workflows, interdisciplinary care, integrated obesity management, and equitable access to pharmacotherapies particularly the antidiabetic agents approved for weight loss.[48]

To further the CLMH agenda both regionally and globally, a greater focus on the diagnosis and management of MASLD in CVD will be crucial to upcoming preventative cardiology policies, strategies, and guidelines. There is also need for ongoing surveillance and standardized evaluation of regional guidelines and policies related to the screening and management of MASLD in CVD. Research and audit efforts are recommended for monitoring, analyzing, and reporting MASLD, awareness of which is particularly useful for applicable patient populations, as well as professional societies outside of the field of hepatology, based on the multidisciplinary and multisectoral nature of promoting CLMH.

CONCLUSIONS

The intricate interrelationships between MASLD and CVD have important implications for cardiovascular morbidity and premature mortality. There is a sense of

optimism in improving cardiovascular and liver-related outcomes given the emerging evidence from newer therapies and healthcare strategies which may have synergistic benefits given the shared pathophysiologic–mechanistic pathways. The newly proposed MASLD definition is the first step in categorizing CLMH, and the diagnosis of MASLD should be considered among the cardiovascular risk-enhancing factors. Multidisciplinary efforts involving primary care clinicians, cardiologists, hepatologists, endocrinologists, and general physicians will be essential in laying down the critical framework with the concerted goal of improving MASLD-related outcomes and CVD prevention. The emergence of new and scalable treatments is likely to be the impetus that starts moving the needle.

ARTICLE INFORMATION

Affiliations

Department of Cardiology, National University Heart Centre (N.W.S.C., A.Z., R.F., M.Y.C.); and National University Centre for Organ Transplantation (D.Q.H., M.M.), National University Health System, Singapore. Alice Lee Centre for Nursing Studies (J.C.); and Yong Loo Lin School of Medicine (N.S.W.C., R.G., Y.C., B.C., D.Q.H., R.F., M.Y.C., M.M., D.J.H.), National University of Singapore, Singapore. Virginia Commonwealth University Health Pauley Heart Center, Division of Cardiology (A.M.); and Division of Gastroenterology, Hepatology and Nutrition (A.Sanyal), Department of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond. National University of Singapore, Department of Surgery (A. Shabbir); Division of Gastroenterology and Hepatology, Department of Medicine (D.Q.H., M.M.), National University Hospital, Singapore. University College London Centre for Obesity Research; Bariatric Centre for Weight Management and Metabolic Surgery, University College London Hospital NHS Trust; and National Institute of Health Research, UCLH Biomedical Research Centre, London, UK (A.B.). Department of Endocrinology ASO/EASO COM, King's College Hospital NHS Foundation Trust; and Faculty of Cardiovascular Medicine and Sciences, Department of Diabetes, Obesity, Type 2 Diabetes and Immunometabolism Research Group, School of Life Course Sciences, King's College, London, UK (G.K.D.). Diabetes Complications Research Centre, University College Dublin, Ireland (C.R.I.R.). Department of Cardiology, Royal North Shore Hospital, Australia (G.A.F.). Duke University Medical Center; and Duke Clinical Research Institute, Durham, NC (M.F.). Department of Internal Medicine, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas (A.P.). Keele Cardiovascular Research Group, School of Medicine, Keele University, UK (M.A.M.). Duke–NUS Medical School, Cardiovascular and Metabolic Disorders Programme; and National Heart Centre Singapore, National Heart Research Institute, Singapore (D.J.H.). University College London, The Hatter Cardiovascular Institute, UK (D.J.H.). Christchurch Heart Institute, University of Otago, New Zealand (A.M.R.). Cardiovascular Research Institute, National University Heart Centre Singapore, Singapore (A.M.R.). Victorian Heart Institute, Monash University, Australia (S.J.N.). Division of Cardiology, Department of Medicine, Emory Clinical Cardiovascular Research Institute; and Emory University School of Medicine, Atlanta, GA (L.S.S.).

Sources of Funding

National University Health System Seed Fund (NUHSRO/2022/RO5+6/Seed-Mar/03 to N.W.S.C.) and the National University Health System Clinician Scientist Program (NCSP2.0/2024/NUHS/NCWS). This article is based upon work supported by the Cardiovascular Disease National Collaborative Enterprise (CADENCE) National Clinical Translational Programme.

Disclosures

N.W.S.C reports research support from the National University Health System's Seed Fund (grant No. NUHSRO/2022/RO5+6/Seed-Mar/03) and Clinician Scientist Program (grant No. NCSP2.0/2024/NUHS/NCWS), National Medical Research Council Research Training Fellowship (grant No. MH 095:003/008-303), and National University of Singapore Yong Loo Lin School of Medicine's Academic Fellowship Scheme. A.M. reports research grants from Novartis and Amgen. G.K.D reports research grants from National Institute for Health and Care Research, Novo Nordisk UK Research Foundation, and DDM, as well as payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novo Nordisk, Rhythm Pharmaceuticals, Johnson & Johnson/Ethicon, and Medtronic. C.W.I.R reports grants from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board; serves on advisory boards of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Glia, and Boehringer Ingelheim; is a member of the Irish Society for Nutrition and Metabolism, outside the area of work commented on here; was Chief Medical Officer and Director of the Medical Device Division of Keyron in 2011 (both unremunerated positions); and was a previous investor in Keyron, which develops endoscopically implantable medical devices intended to mimic the surgical procedures of sleeve gastrectomy and gastric bypass. The product has only been tested in rodents and none of Keyron's products are currently licensed. They do not have any contracts with other companies to put their products into clinical practice. No patients have been included in any of Keyron's studies and they are not listed on the stock market. C.W.I.R was also gifted stock holdings in September 2021 and divested all stock holdings in Keyron in September 2021, and continues to provide scientific advice to Keyron for no remuneration. G.A.F. reports grants from National Health and Medical Research Council (Australia), Abbott Diagnostic, Sanofi, Janssen Pharmaceuticals, and NSW Health; reports honorarium from CSL, CPC Clinical Research, Sanofi, Boehringer-Ingelheim, Heart Foundation, and Abbott; serves as Board Director for the Australian Cardiovascular Alliance, Executive Committee Member for CPC Clinical Research, Founding Director and CMO for Prokardia and Kardiomics, and Executive Committee member for the CAD Frontiers A2D2 Consortium. In addition, G.A.F serves as Chief Medical Office of the nonprofit, CAD Frontiers, with industry partners including Novartis, Amgen, Siemens Healthineers, ELUCID, Foresite Labs LLC, HeartFlow, Cleerly, Caristo, Genetech, Artyra, Bitterroot Bio, and Allelica. G.A.F. reports the following patents: "Patent Biomarkers and Oxidative Stress" awarded May 2017 (US9638699B2), issued to Northern Sydney Local Health District; "Use of P2X7R antagonists in cardiovascular disease" (PCT/AU2018/050905), licensed to Prokardia; "Methods for treatment and prevention of vascular disease" (PCT/AU2015/000548), issued to The University of Sydney/Northern Sydney Local Health District; "Wound healing methods" (PCT/AU2022/050129), issued to The University of Sydney; "Wound healing compositions" (PCT/AU2022/050130), issued to The University of Sydney; "Methods for predicting coronary artery disease" (AU202290266), issued to The University of Sydney; and "Novel P2X7 Receptor Antagonists" (PCT/AU2022/051400 [November 23, 2022], International Application No. WO/2023/092175 [June 1, 2023]), issued to The University of Sydney. M.F reports support from the National Institutes of Health, Alleviant, Gradient, Reprieve, Sardocor, and Doris Duke; and is a consultant/has ownership interest in Abbott, Alleviant, xonTherapies, Merck, and NovoNordisk. A.P. has received research support from the National Institute of Health, American Heart Association, Applied Therapeutics, Roche, Ultromics, and ScPharmaceuticals; has received honoraria outside of the present study as an advisor/consultant for Tricog Health Inc, Lilly USA, Rivus, Cytokinetics, Roche Diagnostics, Axon therapies, Medtronic, Edward Lifesciences, Science37, Novo Nordisk, Bayer, Merck, Sarfez Pharmaceuticals, Emmi Solutions, Anumana, Semler Scientific, Ultromics, Merck, Encarda, Kieele Health, Acorai; and has received nonfinancial support from Pfizer and Merck. A.P. is also a consultant for Palomarin with stock options. D.J.H. is supported by the Duke-NUS Signature Research Programme funded by the Ministry of Health's National Medical Research Council under its Singapore Translational Research Investigator Award (MOH-STaR21jun-0003). M.D.M. is supported by the Singapore Ministry of Health through the National Medical Research Council (NMRC) Office, MOH Holdings Pte Ltd under the NMRC Clinician Scientist-Individual Research Grant (MOH-001228) and NMRC Clinician Scientist Award (MOH-001631), as well as the National Research Foundation, Singapore (NRF) under the NMRC Open Fund - Large Collaborative Grant (MOH-001325) and administered by the Singapore Ministry of Health through the NMRC Office, MOH Holdings Pte Ltd. M.D.M is a consultant/on the advisory panel or has paid speaking engagements in Roche, Astellas, Gilead, LernaBio, Boston Scientific, Olympus Medical, and Perspectum. M.M serves as an associate editor of Circulation: Cardiovascular Interventions. A.M.R is the New Zealand Heart Foundation Chair of Cardiovascular Studies; is on the advisory board for Roche Diagnostics; receives speakers fees from Roche Diagnostics; and receives research grant support, in cash or in mind, from Roche Diagnostics, Abbott Laboratories, Sphingotec, Thermo Fisher, Astra Zeneca, and Novo Nordisk. S.J.N reports research grant support from AstraZeneca, Amgen, Anthera, Cerenis, Eli Lilly, Esperion, InfraReDx, LipoScience, The Medicines Company, New Amsterdam Pharma, Novartis, Resverlogix, Roche, and Sanofi-Regeneron; and consulting fees from Akcea, Amarin, Anthera, AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Esperion, Omthera, Merck, Resverlogix, Sanofi-Regeneron, Takeda, and Vaxxinity. M.Y.C receives salary support from an National Medical Council Research Clinician Scientist Award (Senior Investigator Category; No. MOH-000280-00). The other authors report no conflicts.

Supplemental Material

Supplemental Methods 1 and 2
Tables S1–S5

REFERENCES

1. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, Romero D, Abdelmalek MF, Anstee QM, Arab JP. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *Ann Hepatol*. 2023;101133 doi: 10.1097/HEP.0000000000000520
2. Biswas S, Shalimar. Editorial: the tip of the non-alcoholic fatty liver disease iceberg-the more we know, the smaller it gets? *JGH Open*. 2023;7:671–673. doi: 10.1002/jgh3.12996
3. Qi X, Li J, Caussy C, Teng GJ, Loomba R. Epidemiology, screening, and co-management of type 2 diabetes mellitus and metabolic dysfunction-associated steatotic liver disease. *Hepatology*. Published online May 8, 2024. doi: 10.1097/hep.0000000000000913
4. Chew NW, Pan XH, Chong B, Chandramouli C, Muthiah M, Lam CS. Type 2 diabetes mellitus and cardiometabolic outcomes in metabolic dysfunction-associated steatotic liver disease population. *Diabetes Res Clin Pract*. 2024;211:111652. doi: 10.1016/j.diabres.2024.111652
5. Le MH, Yeo YH, Zou B, Barnet S, Henry L, Cheung R, Nguyen MH. Forecasted 2040 global prevalence of nonalcoholic fatty liver disease using hierarchical bayesian approach. *Clin Mol Hepatol*. 2022;28:841–850. doi: 10.3350/cmh.2022.0239
6. Fu CE, Ng CH, Yong JN, Chan KE, Xiao J, Nah B, Bong SHS, Win KM, Bwa AH, Lim WH, et al. A meta-analysis on associated risk of mortality in nonalcoholic fatty liver disease. *Endocr Pract*. 2023;29:33–39. doi: 10.1016/j.eprac.2022.10.007
7. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008. doi: 10.1136/bmj.j4008
8. Abosheaishaa H, Hussein M, Ghallab M, Abdelhamid M, Balassiano N, Ahammed MR, Baig MA, Khan J, Elshair M, Soliman MY, et al. Association between non-alcoholic fatty liver disease and coronary artery disease outcomes: a systematic review and meta-analysis. *Diabetes Metab Syndr*. 2024;18:102938. doi: 10.1016/j.dsx.2023.102938
9. Alon L, Corica B, Raparelli V, Cangemi R, Basili S, Proietti M, Romiti GF. Risk of cardiovascular events in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2022;29:938–946. doi: 10.1093/eurjpc/zwab212
10. Gong H, Liu X, Cheng F. Relationship between non-alcoholic fatty liver disease and cardiac arrhythmia: a systematic review and meta-analysis. *J Int Med Res*. 2021;49:3000605211047074. doi: 10.1177/03000605211047074
11. Mantovani A, Dauriz M, Sandri D, Bonapace S, Zoppini G, Tilg H, Byrne CD, Targher G. Association between non-alcoholic fatty liver disease and risk of atrial fibrillation in adult individuals: an updated meta-analysis. *Liver Int*. 2019;39:758–769. doi: 10.1111/liv.14044
12. Lauridsen BK, Stender S, Kristensen TS, Kofoed KF, Køber L, Nordestgaard BG, Tybjærg-Hansen A. Liver fat content, non-alcoholic fatty liver disease, and ischaemic heart disease: Mendelian randomization and meta-analysis of 279 013 individuals. *Eur Heart J*. 2018;39:385–393. doi: 10.1093/eurheartj/ehx662
13. Liu B, Li Y, Li Y, Liu Y, Yan Y, Luo A, Ren H, She Q. Association of epicardial adipose tissue with non-alcoholic fatty liver disease: a meta-analysis. *Hepatol Int*. 2019;13:757–765. doi: 10.1007/s12072-019-09972-1
14. Mantovani A, Petracca G, Csermely A, Beatrice G, Bonapace S, Rossi A, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of new-onset heart failure: an updated meta-analysis of about 11 million individuals. *Gut*. 2022;72:372–380. doi: 10.1136/gutjnl-2022-327672
15. Mantovani A, Csermely A, Petracca G, Beatrice G, Corey KE, Simon TG, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2021;6:903–913. doi: 10.1016/S2468-1253(21)00308-3
16. Tang ASP, Chan KE, Quek J, Xiao J, Tay P, Teng M, Lee KS, Lin SY, Myint MZ, Tan B, et al. Non-alcoholic fatty liver disease increases risk of carotid atherosclerosis and ischemic stroke: an updated meta-analysis with 135,602 individuals. *Clin Mol Hepatol*. 2022;28:483–496. doi: 10.3350/cmh.2021.0406
17. Wong MYZ, Yap JJL, Sultana R, Cheah M, Goh GBB, Yeo KK. Association between non-alcoholic fatty liver disease and subclinical atherosclerosis in Western and Asian cohorts: an updated meta-analysis. *Open Heart*. 2021;8:e001850. doi: 10.1136/openhrt-2021-001850
18. Zhou YY, Zhou XD, Wu SJ, Fan DH, Van Poucke S, Chen YP, Fu SW, Zheng MH. Nonalcoholic fatty liver disease contributes to subclinical atherosclerosis: a systematic review and meta-analysis. *Hepatol Commun*. 2018;2:376–392. doi: 10.1002/hep4.1155
19. Gattrell WT, Hungin AP, Price A, Winchester CC, Tovey D, Hughes EL, van Zuuren EJ, Goldman K, Logullo P, Matheis R, et al. ACCORD guideline for reporting consensus-based methods in biomedical research and clinical practice: a study protocol. *Res Integr Peer Rev*. 2022;7:3. doi: 10.1186/s41073-022-00122-0
20. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, Clark JM. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology*. 2011;54:1082–1090. doi: 10.1002/hep.24452
21. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE, Loomba R. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77:1797–1835. doi: 10.1097/hep.0000000000000323
22. Pirmoazen AM, Khurana A, El Kaffas A, Kamaya A. Quantitative ultrasound approaches for diagnosis and monitoring hepatic steatosis in nonalcoholic fatty liver disease. *Theranostics*. 2020;10:4277–4289. doi: 10.7150/thno.40249
23. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol*. 2016;64:1388–1402. doi: 10.1016/j.jhep.2015.11.004
24. Wattacheril JJ, Abdelmalek MF, Lim JK, Sanyal AJ. AGA Clinical Practice Update on the role of noninvasive biomarkers in the evaluation and management of nonalcoholic fatty liver disease: expert review. *Gastroenterology*. 2023;165:1080–1088. doi: 10.1053/j.gastro.2023.06.013
25. Patel K, Sebastiani G. Limitations of non-invasive tests for assessment of liver fibrosis. *JHEP Rep*. 2020;2:100067. doi: 10.1016/j.jhepr.2020.100067
26. Noureddin M, Mena E, Vuppalanchi R, Samala N, Wong M, Pacheco F, Polanco P, Sakkal C, Antaramian A, Chang D, et al. Increased accuracy in identifying NAFLD with advanced fibrosis and cirrhosis: independent validation of the Agile 3+ and 4 scores. *Hepatol Commun*. 2023;7:e0055. doi: 10.1097/HC9.0000000000000055
27. Pouwels S, Sakran N, Graham Y, Leal A, Pintar T, Yang W, Kassir R, Singhal R, Mahawar K, Ramnarain D. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. *BMC Endocr Disord*. 2022;22:1–9.
28. McPherson S, Hardy T, Dufour JF, Petta S, Romero-Gomez M, Allison M, Oliveira CP, Francque S, Van Gaal L, Schattenberg JM, et al. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. *Am J Gastroenterol*. 2017;112:740–751. doi: 10.1038/ajg.2016.453
29. Mózes FE, Lee JA, Selvaraj EA, Jayaswal ANA, Trauner M, Boursier J, Fournier C, Staufer K, Stauber RE, Bugianesi E, et al; LITMUS Investigators. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. *Gut*. 2022;71:1006–1019. doi: 10.1136/gutjnl-2021-324243
30. Chew NW, Ng CH, Muthiah MD, Sanyal AJ. Comprehensive review and updates on holistic approach towards non-alcoholic fatty liver disease management with cardiovascular disease. *Curr Atheroscler Rep*. 2022;24:515–532. doi: 10.1007/s11883-022-01027-5
31. Tacke F, Horn P, Wong VW-S, Ratziu V, Bugianesi E, Francque S, Zelber-Sagi S, Valenti L, Roden M, Schick F. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol*. 2024;81:492–542. doi: 10.1016/j.jhep.2024.04.031
32. Long MT, Noureddin M, Lim JK. AGA clinical practice update: diagnosis and management of nonalcoholic fatty liver disease in lean individuals: expert review. *Gastroenterology*. 2022;163:764–774.e1. doi: 10.1053/j.gastro.2022.06.023
33. Miller WG, Kaufman HW, Levey AS, Straseski JA, Wilhelms KW, Yu HY, Klutts JS, Hilborne LH, Horowitz GL, Lieske J. National Kidney Foundation Laboratory Engagement Working Group recommendations for implementing the CKD-EPI 2021 race-free equations for estimated glomerular filtration rate: practical guidance for clinical laboratories. *Clin Chem*. 2022;68:511–520. doi: 10.1093/clinchem/hvab278
34. Duell PB, Welty FK, Miller M, Chait A, Hammond G, Ahmad Z, Cohen DE, Horton JD, Pressman GS, Toth PP; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on

Hypertension; Council on the Kidney in Cardiovascular Disease; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease. Nonalcoholic fatty liver disease and cardiovascular risk: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2022;42:e168–e185. doi: 10.1161/ATV.0000000000000153
35. Chew NW, Muthiah MD, Sanyal AJ. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: pathophysiology and implications for cardiovascular disease. In: *Cardiovascular Endocrinology and Metabolism*. Elsevier; 2023:137–173.
36. Tejani S, McCoy C, Ayers CR, Powell-Wiley TM, Després JP, Linge J, Leinhard OD, Petersson M, Borga M, Neeland IJ. Cardiometabolic health outcomes associated with discordant visceral and liver fat phenotypes: insights from the Dallas Heart Study and UK Biobank. *Mayo Clin Proc*. 2022;97:225–237. doi: 10.1016/j.mayocp.2021.08.021
37. Wong ND, Budoff MJ, Ferdinand K, Graham IM, Michos ED, Reddy T, Shapiro MD, Toth PP. Atherosclerotic cardiovascular disease risk assessment: an American Society for Preventive Cardiology clinical practice statement. *Am J Prev Cardiol*. 2022;10:100335. doi: 10.1016/j.ajpc.2022.100335
38. Khan SS, Coresh J, Pencina MJ, Ndumele CE, Rangaswami J, Chow SL, Palaniappan LP, Sperling LS, Virani SS, Ho JE, et al; American Heart Association. Novel prediction equations for absolute risk assessment of total cardiovascular disease incorporating cardiovascular-kidney-metabolic health: a scientific statement from the American Heart Association. *Circulation*. 2023;148:1982–2004. doi: 10.1161/CIR.0000000000001191
39. Ngam PI, Ong CC, Chai P, Wong SS, Liang CR, San Teo LL. Computed tomography coronary angiography–past, present and future. *Singapore Med J*. 2020;61:109. doi: 10.11622/smedj.2020028
40. Fracanzani AL, Pisano G, Consonni D, Tiraboschi S, Baragetti A, Bertelli C, Norata GD, Dongiovanni P, Valenti L, Grigore L, et al. Epicardial adipose tissue (EAT) thickness is associated with cardiovascular and liver damage in nonalcoholic fatty liver disease. *PLoS One*. 2016;11:e0162473. doi: 10.1371/journal.pone.0162473
41. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
42. Larkin H. What to know about PREVENT, the AHA's new cardiovascular disease risk calculator. *JAMA*. 2024;331:277–279. doi: 10.1001/jama.2023.25115
43. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, Coresh J, Mathew RO, Baker-Smith CM, Carnethon MR, et al; American Heart Association. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*. 2023;148:1606–1635. doi: 10.1161/CIR.0000000000001184
44. Pastori D, Polimeni L, Baratta F, Pani A, Del Ben M, Angelico F. The efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease. *Dig Liver Dis*. 2015;47:4–11. doi: 10.1016/j.dld.2014.07.170
45. Wadden TA, Neiberg RH, Wing RR, Clark JM, Delahanty LM, Hill JO, Krakoff J, Otto A, Ryan DH, Vitolins MZ; The Look AHEAD Research Group. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity*. 2011;19:1987–1998. doi: 10.1038/oby.2011.230
46. Malespin MH, Barritt AS, Watkins SE, Schoen C, Tincopa MA, Corbin KD, Mospan AR, Munoz B, Trinh HN, Weiss LM, et al. Weight loss and weight regain in usual clinical practice: results from the TARGET-NASH observational cohort. *Clin Gastroenterol Hepatol*. 2022;20:2393–2395.e4. doi: 10.1016/j.cgh.2021.01.023
47. Chong B, Kong G, Shankar K, Chew HJ, Lin C, Goh R, Chin YH, Tan DJH, Chan KE, Lim WH, et al. The global syndemic of metabolic diseases in the young adult population: a consortium of trends and projections from the Global Burden of Disease 2000–2019. *Metabolism*. 2023;141:155402. doi: 10.1016/j.metabol.2023.155402
48. Pan XH, Tan B, Chin YH, Lee ECZ, Kong G, Chong B, Kueh M, Khoo CM, Mehta A, Majety P, et al. Efficacy and safety of tirzepatide, GLP-1 receptor agonists, and other weight loss drugs in overweight and obesity: a network meta-analysis. *Obesity (Silver Spring)*. 2024;32:840–856. doi: 10.1002/oby.24002
49. Sperling LS, Mechanick JI, Neeland IJ, Herrick CJ, Després JP, Ndumele CE, Vijayaraghavan K, Handelsman Y, Puckrein GA, Araneta MR, et al. The CardioMetabolic Health Alliance: working toward a new care model for the metabolic syndrome. *J Am Coll Cardiol*. 2015;66:1050–1067. doi: 10.1016/j.jacc.2015.06.1328
50. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. *Nutr Metab Cardiovasc Dis*. 2014;24:929–939. doi: 10.1016/j.numecd.2014.03.003
51. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, et al; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378:e34. doi: 10.1056/NEJMoa1800389
52. Šmíd V, Dvořák K, Šedivý P, Kosek V, Leníček M, Dezortová M, Hajšlová J, Hájek M, Vítek L, Bechyňská K, et al. Effect of omega-3 polyunsaturated fatty acids on lipid metabolism in patients with metabolic syndrome and NAFLD. *Hepatol Commun*. 2022;6:1336–1349. doi: 10.1002/hep4.1906
53. Van Kleef LA, de Knegt RJ, Brouwer WP. Metabolic dysfunction-associated fatty liver disease and excessive alcohol consumption are both independent risk factors for mortality. *Hepatology*. 2023;77:942–948. doi: 10.1002/hep.32642
54. Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. *J Hepatol*. 2017;67:829–846. doi: 10.1016/j.jhep.2017.05.016
55. Borges-Canha M, Neves JS, Libânio D, Von-Hafe M, Vale C, Araújo-Martins M, Leite AR, Pimentel-Nunes P, Carvalho D, Leite-Moreira A. Association between nonalcoholic fatty liver disease and cardiac function and structure-a meta-analysis. *Endocrine*. 2019;66:467–476. doi: 10.1007/s12020-019-02070-0
56. Khan TS, Ramji K, Boudreau V, Glazer S. Treatments and challenges. *Canadian J General Intern Med*. 2023;18:17–32.
57. Lassailly G, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J, Raverdy V, Leteurtre E, Dharancy S, Louvet A, et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. *Gastroenterology*. 2015;149:379–88; quiz e15. doi: 10.1053/j.gastro.2015.04.014
58. Poirier P, Cornier M-A, Mazzone T, Stiles S, Cummings S, Klein S, McCullough PA, Ren Fielding C, Franklin BA; American Heart Association Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Bariatric surgery and cardiovascular risk factors: a scientific statement from the American Heart Association. *Circulation*. 2011;123:1683–1701. doi: 10.1161/CIR.0b013e3182149099
59. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, Jódar E, Kandler K, Rigas G, Wadden TA, et al; STEP 5 Study Group. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. *Nat Med*. 2022;28:2083–2091. doi: 10.1038/s41591-022-02026-4
60. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, et al; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389:2221–2232. doi: 10.1056/NEJMoa2307563
61. Vanderheiden A, Harrison LB, Warshauer JT, Adams-Huet B, Li X, Yuan Q, Hulsey K, Dimitrov I, Yokoo T, Jaster AW, et al. Mechanisms of action of liraglutide in patients with type 2 diabetes treated with high-dose insulin. *J Clin Endocrinol Metab*. 2016;101:1798–1806. doi: 10.1210/jc.2015-3906
62. Frøssing S, Nylander M, Chabanova E, Frystyk J, Holst JJ, Kistorp C, Skouby SO, Faber J. Effect of liraglutide on ectopic fat in polycystic ovary syndrome: a randomized clinical trial. *Diabetes Obes Metab*. 2018;20:215–218. doi: 10.1111/dom.13053
63. Guo W, Tian W, Lin L, Xu X. Liraglutide or insulin glargine treatments improves hepatic fat in obese patients with type 2 diabetes and nonalcoholic fatty liver disease in twenty-six weeks: a randomized placebo-controlled trial. *Diabetes Res Clin Pract*. 2020;170:108487. doi: 10.1016/j.diabres.2020.108487
64. Flint A, Andersen G, Hockings P, Johansson L, Morsing A, Sundby Palle M, Vogl T, Loomba R, Plum-Mörschel L. Randomised clinical trial: semaglutide versus placebo reduced liver steatosis but not liver stiffness in subjects with non-alcoholic fatty liver disease assessed by magnetic resonance imaging. *Aliment Pharmacol Ther*. 2021;54:1150–1161. doi: 10.1111/apt.16608
65. Bizino MB, Jazet IM, de Heer P, van Eyk HJ, Dekkers IA, Rensen PC, Paiman EH, Lamb HJ, Smit JW. Placebo-controlled randomised trial with liraglutide on magnetic resonance endpoints in individuals with type 2 diabetes: a pre-specified secondary study on ectopic fat accumulation. *Diabetologia*. 2020;63:65–74. doi: 10.1007/s00125-019-05021-6
66. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurst JM, Guo K, Abouda G, Aldersley MA, et al; LEAN trial team. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet (London, England)*. 2016;387:679–690. doi: 10.1016/S0140-6736(15)00803-X
67. Genua I, Cusi K. Pharmacological approaches to nonalcoholic fatty liver disease: current and future therapies. *Diabetes Spectr*. 2024;37:48–58. doi: 10.2337/dsi23-0012

68. ClinicalTrials.gov. Research study on whether semaglutide works in people with non-alcoholic steatohepatitis (NASH). NIH National Library of Medicine; 2021. Updated October 31, 2024. Accessed July 8, 2024. https://clinicaltrials.gov/study/NCT04822181?tab=history&a=130.
69. McDermid E. A quick guide to the SURPASS and SURMOUNT trials; phase 3 trials of tirzepatide in type 2 diabetes and obesity [Internet]. 2022. Accessed March 2, 2024. https://diabetes.medicinematters.com/tirzepatide/type-2-diabetes/a-quick-guide-to-the-surpass-and-surmount-trials/18478154.
70. Gastaldelli A, Cusi K, Landó LF, Bray R, Brouwers B, Rodríguez A. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet Diabetes Endocrinol*. 2022;10:393–406. doi: 10.1016/S2213-8587(22)00070-5
71. Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, Yoneda M, Behling C, Cummings OW, Tang Y, et al. Tirzepatide for metabolic dysfunction–associated steatohepatitis with liver fibrosis. *N Engl J Med*. 2024;391:299–310. doi: 10.1056/nejmoa2401943
72. Sanyal AJ, Bedossa P, Fraessdorf M, Neff GW, Lawitz E, Bugianesi E, Anstee QM, Hussain SA, Newsome PN, Ratziu V, et al; 1404-0043 Trial Investigators. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N Engl J Med*. 2024;391:311–319. doi: 10.1056/NEJMoa2401755
73. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med*. 2006;355:2297–2307. doi: 10.1056/NEJMoa060326
74. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, Tio F, Hardies J, Darland C, Musi N, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med*. 2016;165:305–315. doi: 10.7326/M15-1774
75. Huang JF, Dai CY, Huang CF, Tsai PC, Yeh ML, Hsu PY, Huang SF, Bair MJ, Hou NJ, Huang CI, et al. First-in-Asian double-blind randomized trial to assess the efficacy and safety of insulin sensitizer in nonalcoholic steatohepatitis patients. *Hepatol Int*. 2021;15:1136–1147. doi: 10.1007/s12072-021-10242-2
76. Bril F, Biernacki DM, Kalavalapalli S, Lomonaco R, Subbarayan SK, Lai J, Tio F, Suman A, Orsak BK, Hecht J, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care*. 2019;42:1481–1488. doi: 10.2337/dc19-0167
77. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, et al; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med*. 2010;362:1675–1685. doi: 10.1056/NEJMoa0907929
78. Moody AJ, Molina-Wilkins M, Clarke GD, Merovci A, Solis-Herrera C, Cersosimo E, Chilton RJ, Iozzo P, Gastaldelli A, Abdul-Ghani M, et al. Pioglitazone reduces epicardial fat and improves diastolic function in patients with type 2 diabetes. *Diabetes Obes Metab*. 2023;25:426–434. doi: 10.1111/dom.14885
79. Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, Loomba R, Harrison SA, Balabanska R, Mateva L, et al; NATIVE Study Group. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. *N Engl J Med*. 2021;385:1547–1558. doi: 10.1056/NEJMoa2036205
80. Cooreman MP, Butler J, Giugliano RP, Zannad F, Dzen L, Huot-Marchand P, Baudin M, Beard DR, Junien J-L, Broqua P, et al. The pan-PPAR agonist lanifibranor improves cardiometabolic health in patients with metabolic dysfunction-associated steatohepatitis. *Nat Commun*. 2024;15:3962. doi: 10.1038/s41467-024-47919-9
81. Latva-Rasku A, Honka M-J, Kullberg J, Mononen N, Lehtimäki T, Saltevo J, Kirjavainen AK, Saunavaara V, Iozzo P, Johansson L, et al. The SGLT2 inhibitor dapagliflozin reduces liver fat but does not affect tissue insulin sensitivity: a randomized, double-blind, placebo-controlled study with 8-week treatment in type 2 diabetes patients. *Diabetes Care*. 2019;42:931–937. doi: 10.2337/dc18-1569
82. Kahl S, Gancheva S, Straßburger K, Herder C, Machann J, Katsuyama H, Kabisch S, Henkel E, Kopf S, Lagerpusch M, et al. Empagliflozin effectively lowers liver fat content in well-controlled type 2 diabetes: a randomized, double-blind, phase 4, placebo-controlled trial. *Diabetes Care*. 2020;43:298–305. doi: 10.2337/dc19-0641
83. Gaborit B, Ancel P, Abdullah A, Maurice F, Abdesselam I, Calen A, Soghomonian A, Houssays M, Varlet I, Eisinger M. Effect of empagliflozin on ectopic fat stores and myocardial energetics in type 2 diabetes: the EMPACEF study. *Cardiovasc Diabetol*. 2021;20:1–14. doi: 10.1186/s12933-021-01237-2
84. Elhini SH, Wahsh EA, Elberry AA, El Ameen NF, Abdelfadil Saedii A, Refaie SM, Elsayed AA, Rabea HM. The impact of an SGLT2 inhibitor versus ursodeoxycholic acid on liver steatosis in diabetic patients. *Pharmaceuticals (Basel, Switzerland)*. 2022;15:1516. doi: 10.3390/ph15121516
85. Cusi K, Bril F, Barb D, Polidori D, Sha S, Ghosh A, Farrell K, Sunny NE, Kalavalapalli S, Pettus J, et al. Effect of canagliflozin treatment on hepatic triglyceride content and glucose metabolism in patients with type 2 diabetes. *Diabetes Obes Metab*. 2019;21:812–821. doi: 10.1111/dom.13584
86. Han T, Fan Y, Gao J, Fatima M, Zhang Y, Ding Y, Bai L, Wang C. Sodium glucose cotransporter 2 inhibitor dapagliflozin depressed adiposity and ameliorated hepatic steatosis in high-fat diet induced obese mice. *Adipocyte*. 2021;10:446–455. doi: 10.1080/21623945.2021.1979277
87. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, Labriola D, Moussa SE, Neff GW, Rinella ME, et al; MAESTRO-NASH Investigators. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med*. 2024;390:497–509. doi: 10.1056/NEJMoa2309000
88. Harrison SA, Taub R, Neff GW, Lucas KJ, Labriola D, Moussa SE, Alkhouri N, Bashir MR. Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. *Nat Med*. 2023;29:2919–2928. doi: 10.1038/s41591-023-02603-1
89. Dutta D, Kamrul-Hasan A, Mondal E, Nagendra L, Joshi A, Bhattacharya S. Role of resmetirom, a liver-directed, thyroid hormone receptor beta-selective agonist, in managing non-alcoholic steatohepatitis: a systematic review and meta-analysis. *Endocr Pract*. 2024;30:631–638. doi: 10.1016/j.eprac.2024.04.016
90. Cusi K. Selective agonists of thyroid hormone receptor beta for the treatment of NASH. *N Engl J Med*. 2024;390:559–561. doi: 10.1056/NEJMe2314365
91. Sookoian S, Pirola CJ. Resmetirom for treatment of MASH. *Cell*. 2024;187:2897–2897.e1. doi: 10.1016/j.cell.2024.05.009
92. Chin YH, Lim O, Lin C, Chan YY, Kong G, Ng CH, Chong B, Syn N, Chan KE, Muthiah MD, et al. Meta-analysis of the placebo and nocebo effects associated with placebo treatment in randomized trials of lipid-lowering therapies. *Eur Heart J Qual Care Clin Outcomes*. 2023;9:511–519. doi: 10.1093/ehjqcco/qcac060
93. Björnsson E, Jacobsen EI, Kalaitzakis E. Hepatotoxicity associated with statins: reports of idiosyncratic liver injury post-marketing. *J Hepatol*. 2012;56:374–380. doi: 10.1016/j.jhep.2011.07.023
94. Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, Pagourelias ED, Theocharidou E, Karagiannis A, Mikhailidis DP; GREACE Study Collaborative Group. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study: a post-hoc analysis. *Lancet*. 2010;376:1916–1922. doi: 10.1016/S0140-6736(10)61272-X
95. Björnsson ES. Hepatotoxicity of statins and other lipid-lowering agents. *Liver Int*. 2017;37:173–178. doi: 10.1111/liv.13308
96. Yebyo HG, Aschmann HE, Kaufmann M, Puhan MA. Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: a systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. *Am Heart J*. 2019;210:18–28. doi: 10.1016/j.ahj.2018.12.007
97. Deedwania P, Stone PH, Bairey Merz CN, Cosin-Aguilar J, Koylan N, Luo D, Ouyang P, Piotrowicz R, Schenck-Gustafsson K, Sellier P, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease. *Circulation*. 2007;115:700–707. doi: 10.1161/CIRCULATIONAHA.106.654756
98. Zou B, Odden MC, Nguyen MH. Statin use and reduced hepatocellular carcinoma risk in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2023;21:435–444.e6. doi: 10.1016/j.cgh.2022.01.057
99. Chew NWS, Muthiah MD, Sanyal AJ. Chapter 6 - nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: pathophysiology and implications for cardiovascular disease. In: Krentz AJ, Chilton RJ, eds. *Cardiovascular Endocrinology and Metabolism*. Academic Press; 2023:137–173.
100. Moctezuma-Velazquez C, Abraldes JG. The role of statins in cirrhosis. *Curr Treat Options Gastroenterol*. 2022;20:316–335. doi: 10.1007/s11938-022-00394-x