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JACC STATE-OF-THE-ART REVIEW

Nonalcoholic Fatty Liver Disease and the Heart

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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) integrate the evidence for risk of cardiovascular disease (CVD) events and CVD mortality in patients with nonalcoholic fatty liver disease (NAFLD); 2) recognize barriers to screening patients for NAFLD (even for those who are high risk); 3) recommend statin therapy in patients with NAFLD because the cardiovascular and hepatic benefits outweigh the risk of hepatic toxicity; 4) consolidate the pathophysiological mechanisms that link NAFLD and CVD; and 5) summarize the potential therapies available to NAFLD patients to reduce their risk of CVD.

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD) are both manifestations of end-organ damage of the metabolic syndrome. Through multiple pathophysiological mechanisms, CVD and NAFLD are associated with each other. Systemic inflammation, endothelial dysfunction, hepatic insulin resistance, oxidative stress, and altered lipid metabolism are some of the mechanisms by which NAFLD increases the risk of CVD. Patients with NAFLD develop increased atherosclerosis, cardiomyopathy, and arrhythmia, which clinically result in cardiovascular morbidity and mortality. Defining the mechanisms linking these 2 diseases offers the opportunity to further develop targeted therapies. The aim of this comprehensive review is to examine the association between CVD and NAFLD and discuss the overlapping management approaches. (J Am Coll Cardiol 2019;73:948–63) © 2019 by the American College of Cardiology Foundation.

Nonalcoholic fatty liver disease (NAFLD) encompasses a continuum of liver disease progressing from steatosis (>5% of fatty infiltration of hepatocytes) to nonalcoholic steatohepatitis (NASH) (fatty infiltration plus necroinflammation), to fibrosis, and then finally to cirrhosis (1). Liver biopsy is the only method of assessing the degree of inflammation, cell injury, and fibrosis stage (2). Although the gold standard for identifying NASH is liver biopsy, imaging modalities such as ultrasound, computed tomography, and magnetic resonance imaging are safer and less expensive, without sacrificing significant sensitivity and specificity (2,3). NAFLD occurs in the absence of significant alcohol consumption. The worldwide prevalence of NAFLD is estimated to be 25.24% (4). In the United States, the prevalence of NAFLD diagnosed by ultrasound is estimated to be 24.1% (5). According to data from the most recent 1999 to 2012 NHANES (National Health and Nutrition Examination Survey), the prevalence of NAFLD (based on the U.S. Fatty Liver Index) is 30.0% (6). The prevalence of NAFLD increases with age and is higher in men compared with women (3,7). In the United States, Hispanics have a significantly higher prevalence than non-Hispanic white and non-Hispanic black individuals (6,7). In the Dallas Heart Study, the prevalence of NAFLD was 45% in Hispanics, 33% in Caucasians, and 24% in African Americans (8). In the United States, NASH is now ranked second behind hepatitis C virus (HCV) as the most common etiology of liver disease among those awaiting liver transplantation (3,9). As more patients are treated for HCV and the prevalence of NASH increases, NASH is expected to pass HCV as the leading indication for liver transplantation (3).

NAFLD is associated with cardiovascular disease (CVD), and the 2 disorders share several cardiometabolic risk factors (10). The specific contribution of NAFLD to increased CVD risk, especially in clinical studies, is difficult to discern from the combination of these shared risk factors. Furthermore, the population of NAFLD patients is probably heterogeneous. Numerous studies have evaluated the mechanisms of association between NAFLD and CVD. In some, the liver is particularly involved in the pathophysiology of the metabolic syndrome (MetS), and the subsequent development of CVD and other complications, whereas in others, NAFLD is a manifestation of end-organ damage due to MetS (11,12). Given the high burden of CVD, the relationship between NAFLD and cardiovascular events has generated significant interest from a standpoint of CVD prevention (13).

This comprehensive narrative review examines the association between CVD and NAFLD and discusses overlapping management approaches to reduce morbidity and mortality.

DIAGNOSIS AND SCREENING OF NAFLD

The diagnosis of NAFLD relies on 4 criteria (**Table 1**): 1) hepatic steatosis on imaging or histology; 2) absence of significant alcohol consumption; 3) absence of competing etiologies for hepatic

ABBREVIATIONS AND ACRONYMS

ALT = alanine aminotransferase

CVD = cardiovascular disease

DM = diabetes mellitus

GGT = γ-glutamyltranspeptidase

HDL = high-density lipoprotein

LDL = low-density lipoprotein

MetS = metabolic syndrome

NAFLD = nonalcoholic fatty liver disease

NASH = nonalcoholic steatohepatitis

steatosis; and 4) absence of coexisting causes of chronic liver disease (3).

The severity of NAFLD is determined by the presence of steatohepatitis and degree of fibrosis. Steatohepatitis requires ≥5% hepatic steatosis with inflammation and hepatocyte injury (ballooning). Fibrosis is categorized from stage 1 (involving perivenular, perisinusoidal, or periportal) to stage 2 (involving perivenular and periportal) to stage 3 (bridging fibrosis with nodularity) to stage 4 (cirrhosis) (3). Liver biopsy remains the gold standard for determining the presence of steatohepatitis and assessing fibrosis. Due to biopsy cost and procedure morbidity, a number of noninvasive tools have been developed to predict fibrosis stage (NAFLD Fibrosis Score, Fibrosis-4 index, aspartate transaminase to platelet ratio index, or imaging (transient elastography on magnetic resonance elastography) (14). Liver biopsy should only be considered in patients with NAFLD who are at increased risk of having advanced fibrosis (due to the presence of MetS or elevated noninvasive prediction tools) or to differentiate other etiologies of chronic liver disease (3). Confirming the presence of NASH and the degree of fibrosis should prompt more aggressive CVD risk reduction.

Routine screening for NAFLD in high-risk patients is controversial (**Table 1**), mainly due to the absence of an effective treatment and a lack of cost-effective screening modality (15). Liver biochemistries can be normal in patients with NAFLD. Imaging, such as liver ultrasound, is highly sensitive but has higher costs. The American Association for the Study of Liver Diseases (AASLD) does not recommend routine screening for NAFLD even in high-risk groups due to uncertainties in diagnostic work up and limited treatment options (3). However, the European Association for the Study of the Liver recommends screening obese, MetS, and high CVD-risk patients for NAFLD with liver enzymes and/or ultrasound because of its prognostic implications (16) in spite of limited benefit in outcomes. The CardioMetabolic Heath Alliance has advocated for more comprehensive screening in the community to improve prevention of MetS (12). Such screening should focus on measurable biomarkers such as blood pressure, lipids, body mass index (BMI), and waist circumference. An important part of MetS screening is an assessment of abdominal obesity, but unfortunately, technology for measuring abdominal obesity is limited. Although screening for NAFLD using liver ultrasound may be too costly for even a high-risk population, it may offer important information about risk stratification and staging for patients at risk or for those who have already developed MetS. Before more definitive recommendations about screening for NAFLD are made, improvement in both cost-effectiveness and treatment outcomes must be achieved.

TABLE 1 Diagnosis and Screening for NAFLD

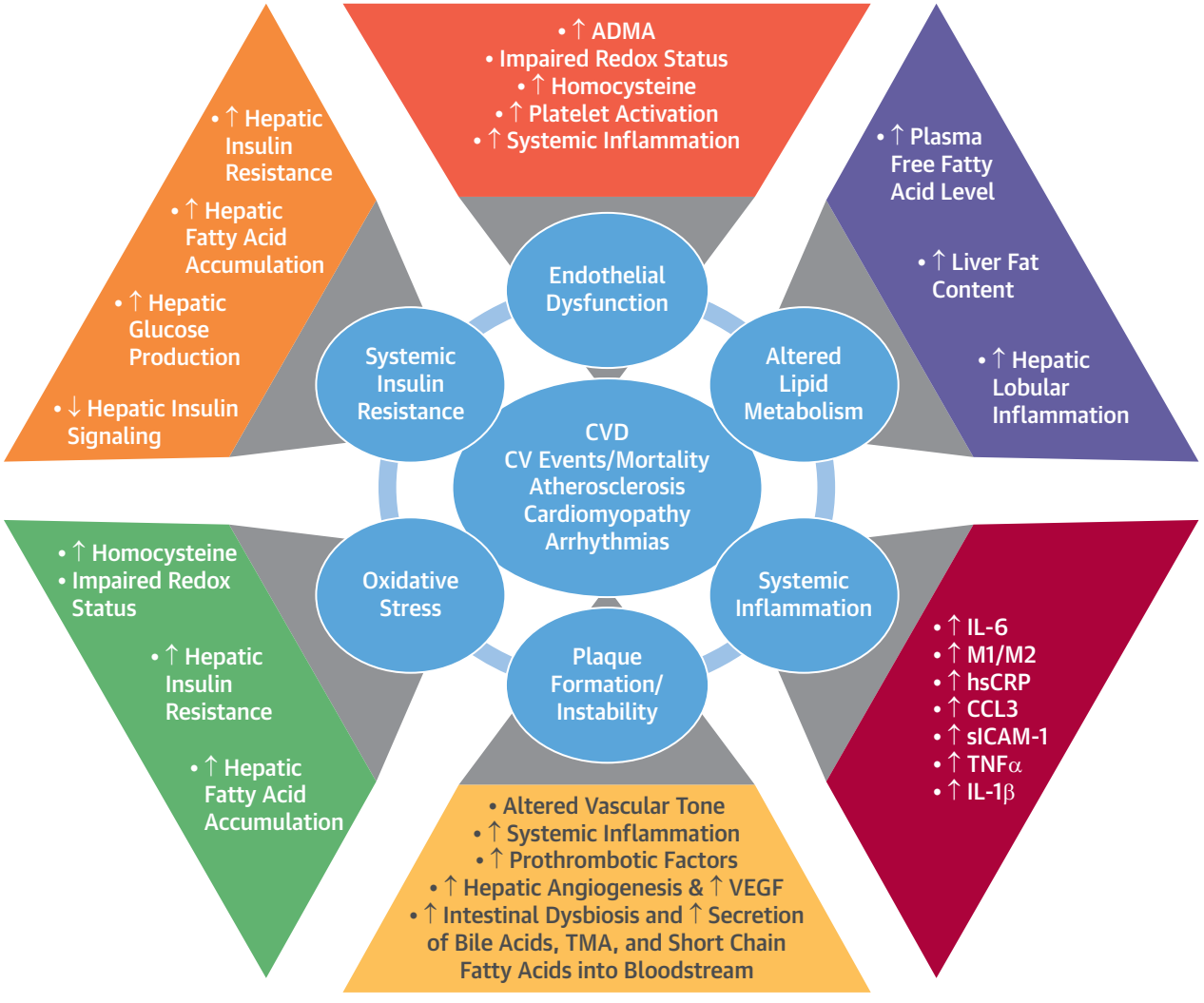
Criteria for Diagnosis of NAFLD	Potential Barriers to Screening for NAFLD
1. Hepatic steatosis on imaging or histology	Limited therapies with sustained benefits
2. Absence of significant history of alcohol consumption	Costs of imaging
3. Absence of competing etiologies for hepatic steatosis	Liver biochemistries can be normal
4. Absence of coexisting causes of chronic liver disease	Inheritability of NAFLD is variable

The criteria for diagnosis and potential barriers to screening nonalcoholic fatty liver disease (NAFLD). The American Association for the Study of Liver Diseases guidelines do not recommend routine NAFLD screening (3).

PATHOPHYSIOLOGICAL MECHANISMS LINKING NAFLD AND CVD

There are likely multiple underlying mechanisms by which NAFLD increases the risk of CVD (**Central Illustration**). A comprehensive review by Francque et al. (17) summarizes these mechanisms and their potential clinical impact. One of the early steps in the process of developing atherosclerosis is endothelial dysfunction. Increased levels of asymmetric dimethyl arginine, which is an endogenous antagonist of nitric oxide synthase, are typically observed in NAFLD patients (17–19). Elevated serum homocysteine levels are often seen in NAFLD, primarily due to changes in methionine metabolism, which disrupts the production and catabolism of homocysteine in the liver (20). Hyperhomocysteinemia is associated with increased intrahepatic vascular resistance, which impairs nitric oxide formation. Furthermore, elevated homocysteine levels cause oxidative stress, which enhances platelet activation. Last, circulating markers of systemic inflammation (interleukin 6, high sensitivity C-reactive protein, interleukin 1β, tumor necrosis factor [TNF]-α, chemokine [C-C motif] ligand 3, soluble intracellular adhesion molecule 1, and macrophage phenotype 1/2 ratio [M1/M2]) are often increased in patients with NAFLD (17). Obesity plays a direct role in M1/M2 Kupffer cell imbalance and the secretion of proinflammatory cytokines (21). Systemic inflammation increases endothelial dysfunction, alters vascular tone, and enhances vascular plaque formation. These mechanisms are supported by the clinical findings in a study of NAFLD patients that found significantly reduced flow-mediated vasodilation, compared with age- and

CENTRAL ILLUSTRATION **Nonalcoholic Fatty Liver Disease Increasing Risk of Cardiovascular Disease: Pathophysiological Mechanisms**



Stahl, E.P. et al. J Am Coll Cardiol. 2019;73(8):948-63.

Nonalcoholic fatty liver disease (NAFLD) increases the risk of developing cardiovascular disease (CVD) through a number of proposed pathophysiological mechanisms. Multiple circulating systemic markers that are present in NAFLD increase systemic inflammation, alter vascular tone, and enhance plaque formation. NAFLD also causes hepatic insulin resistance, altered lipid metabolism, increased oxidative stress, platelet activation, and endothelial dysfunction. ↑ = increased; ADMA= asymmetric dimethyl arginine; CCL= chemokine ligand; CV= cardiovascular; hsCRP= high sensitivity C-reactive protein; IL= interleukin; M1/M2= macrophage phenotype 1/2 ratio; sICAM= soluble intracellular adhesion molecule; TMA= trimethylamine; TNF = tumor necrosis factor; VEGF= vascular endothelial growth factor.

sex-matched control subjects (although BMI matching was not performed) (22).

The liver plays a vital role in lipid metabolism via lipogenesis, lipid breakdown, and the uptake and secretion of serum lipoproteins (23). NAFLD alters serum lipid profiles, causing abnormally elevated triglyceride (TG), very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) levels, as well as abnormally decreased high-density lipoprotein (HDL) levels (24-26). Patients with obesity, type 2 diabetes mellitus (DM), and MetS have oversecretion of VLDL due to high plasma free fatty acid levels and high liver fat content (21). Elevated serum VLDL and LDL concentration has been linked to hepatic lobular inflammation, independent of steatosis (27). Further investigation of lipoprotein subclasses reveals that

patients with NASH have significantly smaller LDL particle size and peak diameter, higher particle concentration of LDL, higher levels of LDL-IVb, and decreased levels of HDL2b, suggesting a mechanism for potentially higher risk of CVD in individuals with more severe NAFLD (24,28). This altered serum lipoproteins composition is likely to contribute to the increased risk for CVD.

NAFLD is very closely associated with insulin resistance, which is a risk factor for CVD. Obesity and excess free fatty acids not only lead to muscle insulin resistance but also induce hepatic insulin resistance and reduce insulin clearance (21). In a prospective study of 1,051 participants from the Framingham Heart Study, Ma et al. (29) demonstrated that computed tomography defined liver fat was associated with an increased odds of incident type 2 DM (odds ratio [OR]: 1.43; 95% confidence interval [CI]: 1.09 to 1.88). A meta-analysis by Fraser et al. (30) has shown that ultrasound-diagnosed NAFLD is associated with a relative risk of incident DM of 2.52 (95% CI: 1.07 to 5.96). Similar findings were seen in a meta-analysis of 296,439 individuals in which those with NAFLD had a >2-fold increased risk of DM as compared to those without NAFLD (hazard ratio [HR]: 2.22; 95% CI: 1.84 to 2.60; $I^2 = 79.2\%$) with more advanced fibrosis scores conferring higher risk (HR: 4.27; 95% CI: 3.54 to 5.94) (31). Increased levels of alanine aminotransferase (ALT) and γ-glutamyltranspeptidase (GGT) are also predictors of insulin resistance and type 2 DM (30). An increase in 1 U of logged ALT or GGT was associated with an HR for DM of 1.83 (95% CI: 1.57 to 2.14) and 1.92 (95% CI: 1.66 to 2.21), respectively (30). However, the prevalence of NAFLD or NASH in diabetic patients with normal liver enzymes was >50% (32). The mechanism by which NAFLD is associated with hepatic insulin resistance is believed to be due to increased hepatic diacylglycerol, which activates protein kinase C, resulting in decreased insulin signaling (33). Fatty acid accumulation in the liver, primarily from adipose tissue lipolysis, also leads to a suppression of endogenous liver glucose production, further stimulating insulin resistance (32). Saturated fatty acids, in particular, produce intrahepatic oxidative stress, which further impairs hepatic insulin signaling (34). Importantly, the relationship between NAFLD and CVD appears to be in addition to the risk conferred by DM, as the prevalence of CVD in patients with DM and NAFLD is increased compared with the risk in individuals with DM without NAFLD (OR: 1.6; 95% CI: 1.2 to 1.8) (35). This association with NAFLD and CVD, independent of multiple cardiometabolic risk factors including DM, has been supported by multiple large population-based cohorts (36–40). In the Danish National Death Registry, mortality was similar between diabetic and nondiabetic individuals with NAFLD (41). However, other studies, including one of 4,412 outpatients, showed steatosis to be a risk factor for cardiovascular events, although not after controlling for DM and BMI after multiple logistic regression analysis (42). Currently, as evidenced in the data it is difficult to distinguish clear independence of association of NAFLD and CVD given the prevalence of NAFLD in individuals with DM, which approaches nearly 70% to 75% (43).

Additional factors that influence atherogenesis and plaque instability in NAFLD have been identified. In the early stages of NAFLD preceding fibrosis, centrozonal arteries and microvessels develop, suggesting active angiogenesis (44). Increased serum levels of vascular endothelial growth factor (VEGF) and increased hepatic expression of VEGF and VEGF receptor-2 have been demonstrated in NAFLD patients (45). However, another study has shown no difference in serum VEGF levels compared with control subjects (46). Although the theorized association between VEGF and atherogenesis and plaque instability would be suspected of contributing to CVD, the clinical significance remains limited (47). Patients with NAFLD may also be at increased risk for atherosclerosis due to an increase in prothrombotic factors (48). Finally, intestinal dysbiosis contributes to both NAFLD and CVD via secretion of bile acids, trimethylamine, and short-chain fatty acids (49,50).

The role of genetic factors linking NAFLD and CVD has yet to be defined, but much has been documented (51). Two missense genetic variants have been identified by genome-wide association studies of NAFLD: patatin-like phospholipase domain containing protein 3 (PNPLA3) and transmembrane 6 superfamily member 2. PNPLA3 modulates the morphology and physiology of lipid droplets and appears to be related to TG metabolism (52). Carriers of this mutation have been shown to have increased atherosclerosis (53), but paradoxically lower serum TG levels (54). In a cohort study of the Danish general population, using Mendelian randomization testing a genetic variant in the gene encoding PNPLA3, genetically high liver fat content was not found to be causally associated with increased risk of ischemic heart disease (OR: 0.95; 95% CI: 0.86 to 1.04; $p = 0.46$) (55). Transmembrane 6 superfamily member 2 is the other protein with genetic variants that have been studied and modulates secretion of TG and cholesterol in the liver via VLDL excretion (56). Carriers of this mutation are at risk for

NAFLD due to increased retention of TG and lipids in the liver but may experience some degree of cardioprotection with subsequently reduced levels of serum TG, LDL cholesterol, and total cholesterol (57).

Structural changes that occur early in NAFLD can impose effects on the heart left ventricular remodeling, increased mass, and diastolic dysfunction. Increased portal pressure occurs in NAFLD due to changes in sinusoidal morphology, reduction in sinusoidal flow, and increased intrahepatic resistance, particularly as disease severity progresses with increased fibrosis (58). NAFLD causes an increased body surface area, which further increases left ventricular filling pressures, cardiac output, and volume overload (59,60).

INCREASED RISK OF CVD IN NAFLD PATIENTS

CARDIOVASCULAR EVENTS. Whether NAFLD is an independent risk factor for cardiovascular mortality and other cardiovascular events has been studied but remains controversial. A number of cohort studies have demonstrated increased cardiovascular mortality in NAFLD patients (38,61-69), although other studies have not shown an association (70,71). In a systematic review and meta-analysis of 11 prospective studies, Fraser et al. (72) found that an elevated serum GGT level was an independent predictor of cardiovascular events in both men and women. However, GGT level is a poor surrogate marker for NAFLD. The question remains whether NAFLD independently contributes to cardiovascular mortality and morbidity.

Three meta-analyses have been performed to evaluate this association (73-75). Targher et al. (73) published a meta-analysis of 34,043 individuals from 16 observational, prospective, and retrospective studies with a primary outcome of CVD events (death, myocardial infarction, stroke, or coronary revascularizations). NAFLD was diagnosed by imaging or by histology in a single study. Patients with NAFLD had a higher risk of fatal and/or nonfatal CVD events than those without NAFLD (OR: 1.64; 95% CI: 1.26 to 2.13). However, when the analysis was restricted to studies with CVD mortality as the primary outcome, the association between NAFLD and fatal CVD events was not statistically significant. In 6 studies, patients with more "severe" NAFLD were even more likely to develop fatal and nonfatal CVD events (OR: 2.58; 95% CI: 1.78 to 3.75). Severe NAFLD was defined as the presence of hepatic steatosis on imaging plus elevated serum GGT level, high NAFLD fibrosis score, high hepatic FDG uptake on positron emission tomography, or increasing fibrosis stage on liver histology.

Haddad et al. (74) published a meta-analysis of 25,837 patients from 6 studies. They found that patients with NAFLD (diagnosed via ultrasound) had a significantly higher risk of clinical CVD events compared with those without (relative risk: 1.77; 95% CI: 1.26 to 2.48). CVD events were defined as myocardial infarction, angina, stroke, transient ischemic attack, CVD death, coronary or peripheral revascularization, symptomatic peripheral vascular disease, clinically driven angiography demonstrating >50% stenosis of epicardial coronaries, or composite endpoints.

Wu et al. (75) conducted a large meta-analysis of nearly 165,000 participants from 34 studies. NAFLD was defined by ultrasound, CT, histology, or liver enzymes. In this study, NAFLD was associated with an increased risk of prevalent CVD (OR: 1.81; 95% CI: 1.23 to 2.66) and incident CVD (HR: 1.37; 95% CI: 1.10 to 1.72). Severity of disease did appear to be associated with an increase in events, as NASH was associated with increased incident CVD risk (HR: 2.97; 95% CI: 1.03 to 8.52). However, the meta-analysis did not indicate any significant association with either overall mortality or CVD mortality in both NAFLD and NASH. Importantly, the association with other adverse cardiovascular risk factors, namely CVD, hypertension (pooled OR: 1.24; 95% CI: 1.14 to 1.36), and atherosclerosis (pooled OR: 1.32; 95% CI: 1.07 to 1.62) between NAFLD and the non-NAFLD population was seen in this study (13).

These studies demonstrate an association between NAFLD and increased CVD events, especially for those with severe NAFLD or NASH. Association with overall or CVD mortality is less evident, especially given the discordant studies used in the meta-analyses. Collectively, these meta-analyses must be interpreted with caution due to their variability, particularly with regard to diagnostic modalities and heterogeneity among studies included in the meta-analysis. Additionally, these meta-analyses are based on observational studies, which leave the possibility of confounding factors. Also, many of these meta-analyses suffered from limited studies in several subgroup analyses, which may lead to low statistical power in these analyses. Further studies are clearly needed to further clarify the relationship between CVD and NAFLD.

ATHEROSCLEROTIC DISEASE. Atherosclerosis, the main contributor to coronary artery disease (CAD), has been linked to fatty liver disease, and recently, there have been a number of studies quantifying this relationship. Carotid intima-media thickness (CIMT)

and coronary artery calcification (CAC) have been the 2 main studied measures of atherosclerosis. Studies have shown that NAFLD is independently associated with increased CIMT (76,77) and CAC (78–83). Compared with patients who do not have any steatosis, patients with NAFLD have been shown to have impaired flow-mediated vasodilation, increased CIMT, and increased carotid atherosclerotic plaques independent of metabolic syndrome characteristics (84,85). One meta-analysis of 3,497 participants from 7 studies addressed the association between NAFLD and CIMT (85). Not only was a significant independent association found, but NAFLD patients were noted to have a 13% increase in CIMT. Another meta-analysis evaluating CAC in 16,433 NAFLD patients (and 41,717 control subjects) from 16 studies demonstrated that NAFLD is significantly associated with both a CAC score >0 and a CAC score >100 (86). A larger meta-analysis, involving 85,395 participants, 29,493 of whom had NAFLD, also showed an increased risk of subclinical atherosclerosis compared with individuals without NAFLD (OR: 1.60; 95% CI: 1.45 to 1.78) with subgroup analyses showing increased CIMT (OR: 1.74; 95% CI: 1.47 to 2.06), arterial stiffness (OR: 1.56; 95% CI: 1.24 to 1.96), CAC (OR: 1.40; 95% CI: 1.22 to 1.60), and endothelial dysfunction as measured by flow-mediated dilation (OR: 3.73; 95% CI: 0.99 to 14.09) (87). Importantly, a longitudinal study of 8,020 adult men without carotid atherosclerosis who were followed over 8 years found that the HR of carotid atherosclerosis in those with regression of NAFLD compared with those with persistent NAFLD over this time was 0.82 (95% CI: 0.69 to 0.96; $p = 0.013$), which was explained by metabolic factors that may be potential mediators of persistent NAFLD (88).

In addition to subclinical atherosclerosis, patients with NAFLD are at increased risk of clinically significant atherosclerosis requiring percutaneous coronary intervention (89,90). In a study of individuals randomized to coronary CT angiography, high-risk plaque features (positive remodeling, napkin-ring sign, spotty calcium, CT attenuation <30 HU) were more frequent in patients with than in patients without NAFLD (59.3% vs. 19.0%, respectively; $p < 0.001$) (91). The association between NAFLD and high-risk plaque (OR: 2.13; 95% CI: 1.18 to 3.85) persisted after adjusting for the extent and severity of coronary atherosclerosis and traditional risk factors. While NAFLD patients are at increased risk of CAD, they may additionally have worse outcomes if they should experience acute coronary syndrome. In a study of 360 patients who had an ST-segment elevation myocardial infarction, those with higher severities of fatty liver disease experienced higher in-hospital and 3-year mortality (92). In another study of 186 nondiabetic patients who received percutaneous coronary intervention for ST-segment elevation myocardial infarction, those with more severe fatty liver disease were more likely to have absent myocardial perfusion (by myocardial blush grade), absent ST-segment resolution, and a higher in-hospital major cardiac event rate (93).

RISK FOR CARDIOMYOPATHY. Cardiac structural changes appear to occur in patients with NAFLD, as well. In 2 studies, left ventricular wall thickness and myocardial mass were demonstrated to be greater in patients with NAFLD (60,94). VanWagner et al. (59) studied comprehensive echocardiography in 2,713 participants and found that those with NAFLD had lower early diastolic relaxation velocity (10.8 ± 2.6 cm/s vs. 11.9 ± 2.8 cm/s), higher LV filling pressure (E/e′ ratio: 7.7 ± 2.6 vs. 7.0 ± 2.3), and worse absolute global longitudinal strain (14.2 ± 2.4% vs. 15.2 ± 2.4%) than those without NAFLD.

NAFLD has also been shown to be independently associated with valvular heart disease, specifically aortic valve sclerosis (AVS) and mitral annulus calcification (MAC). In a large cross-sectional study of 2,212 participants in the SHIP (Study of Health in Pomerania) study, individuals with hepatic steatosis had 33% higher odds (after adjusting for confounders) of having AVS compared with those without steatosis (95). A more recent study of 180 patients with type 2 DM showed that NAFLD was strongly associated with increased risk of AVS (adjusted OR: 3.04; 95% CI: 1.3 to 7.3) (96). Last, a similar cross-sectional study of 247 patients with type 2 DM examined both AVS and MAC and found that NAFLD was significantly associated with at least 1 of these valvular calcifications (adjusted OR: 2.70; 95% CI: 1.23 to 7.38) (97).

Patients with NAFLD also experience changes in epicardial fat distribution. Not only is epicardial adipose tissue (EAT) independently associated with NAFLD, but increasing steatosis grades correlate with increasing thickness of EAT (98). Furthermore, those with NAFLD and thicker EAT (>3.18 mm) are at increased risk for coronary calcification (CAC score >0) (99).

CARDIAC ARRHYTHMIAS. There is growing evidence that NAFLD patients are at increased risk for cardiac arrhythmias, specifically atrial fibrillation, QTc prolongation, and ventricular arrhythmias (100–107). Given the multiple shared risk factors, an association of NAFLD with arrhythmias may not be unexpected. A

study by the Framingham Heart Study Researchers demonstrated that 3,744 participants who had increased levels of ALT or aspartate transaminase were at increased independent risk for developing atrial fibrillation at 10-year follow-up (101). A number of studies have more closely evaluated the NAFLD and atrial fibrillation association. Targher et al. (102,103) published 2 studies involving type 2 DM patients who had an independent association between NAFLD and the development of atrial fibrillation (adjusted OR: 5.88; 95% CI: 2.72 to 12.7 [102] and 6.38; 95% CI: 1.7 to 24.2 [103]). Similarly, Käräjämäki et al. published a prospective cohort study of 958 hypertensive patients, which demonstrated an independent association between NAFLD and atrial fibrillation (adjusted OR: 1.88; 95% CI: 1.03 to 3.45) (104). However, in a community-based longitudinal study of the Framingham Heart Study participants, compared with placebo, NAFLD was not significantly associated with increased prevalence (4% vs. 3%) or incidence (8.7 cases vs. 7.8 cases per 1,000 person-years) of atrial fibrillation (108).

Hung et al. (105) investigated whether patients with NAFLD in the general population had an associated QTc prolongation. They found that increased severity of NAFLD was associated with an increased risk for QTc prolongation, even with adjustment for risk factors and comorbidities.

In a recent cross-sectional study of 330 patients with type 2 DM who underwent 24-h outpatient Holter monitoring, those with NAFLD had a significantly higher prevalence of nonsustained ventricular tachycardia, >30 premature ventricular contractions/h, or both, than those without NAFLD (106). This association was independent of age, sex, BMI, smoking, hypertension, ischemic heart disease, valvular heart disease, chronic kidney disease, chronic obstructive pulmonary disease, serum GGT levels, medication use, and left ventricular ejection fraction.

In aggregate, these studies offer significant evidence for an association between NAFLD and arrhythmias, independent of overlapping comorbidities and other risk factors, although the specific mechanisms remain unclear. NAFLD results in proinflammatory and pro-oxidative states, which may alter the electrophysiological myocardial substrate (100). As previously discussed, NAFLD can cause changes to the myocardial structure via valvular calcifications, diastolic dysfunction, or left ventricular hypertrophy. These myocardial changes are significant risks for arrhythmias. Last, NAFLD has been shown to be associated with autonomic dysfunction (109), which is another risk factor for arrhythmias.

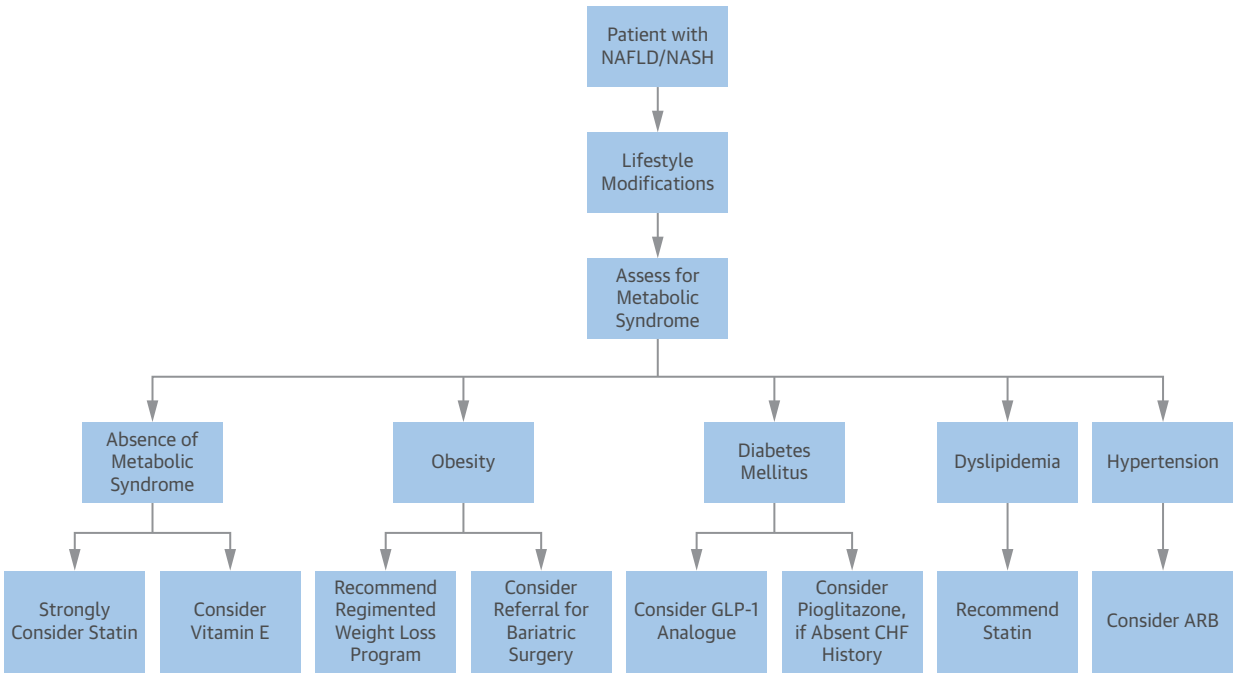
PRIMARY AND SECONDARY PREVENTION OF CVD IN NAFLD

PRIMARY PREVENTION. Primary prevention of NAFLD overlaps with cardiovascular prevention. Lifestyle modifications including weight loss, improved dietary patterns, and increased physical activity are the essential components of prevention (**Figure 1**). The American College of Cardiology and the American Heart Association have specific recommendations on lifestyle management to reduce the risk of CVD (110). A healthy dietary pattern should focus on vegetables, fruits, and whole grains, and also include low-fat dairy, fish, legumes, nontropical vegetable oils, and nuts. Sodium, sweets, sugar-sweetened beverages, and red meats should be limited. Physical activity should entail at least 2.5 h of moderate-intensity exercise or 75 min of vigorous-intensity exercise per week. Achieving and maintaining an optimal body weight is important. The prevalence of NAFLD was studied in participants performing varying degrees of physical activity (111). NAFLD prevalence was lower with higher levels of reported physical activity (45% in the low activity group, 38% in the moderate activity group, and 30% in the high activity group).

An important component of primary prevention is cardiovascular risk assessment. The Framingham Risk Score (FRS) is a validated measure of CV risk within the general population as well as in individuals with NAFLD (39). Importantly, the degree of liver fibrosis does seem to play an important role in cardiovascular risk. The FRS was shown to correlate with the degree of fibrosis, as measured by the NAFLD fibrosis score, with higher fibrosis scores correlating with a higher risk of CVD, as calculated by the FRS (112). This correlates with data seen in the meta-analysis by Wu et al. (13), in which individuals with NASH were found to be at higher risk of CVD. The FRS should be routinely included in patients with NAFLD without DM by clinicians to risk-stratify patients and guide treatment of risk factors.

SECONDARY PREVENTION. Lifestyle modification remains an essential aspect of treatment for those with NAFLD. A prospective study of 293 patients with NASH adopted lifestyle modifications (low-fat hypocaloric diet [750 kcal/day less than their daily energy need] and 200 min of weekly walking) for 52 weeks (113). Participants had a mean weight loss of 4.6 ± 3.2 kg. Resolution of steatohepatitis and regression of fibrosis was achieved in 25% and 19% of participants, respectively. The proportion of those who experienced resolution of steatohepatitis and regression of

FIGURE 1 Potential Therapeutic Approach to NAFLD/NASH Patients to Reduce the Risk of CVD



The management of patients with nonalcoholic fatty liver disease (NAFLD) to reduce the risk of cardiovascular disease (CVD) has yet to be defined. This potential therapeutic approach is formulated to target the pathophysiological mechanisms that associate NAFLD and CVD. ARB = angiotensin II receptor blockers; CHF = congestive heart failure; GLP = glucagon-like peptide; NASH = nonalcoholic steatohepatitis.

fibrosis increased with increasing amount of weight loss, particularly for those with ≥10% weight loss. Importantly, the degree of weight loss (even a modest loss of ≥7%) was independently associated with reversal of these NASH parameters.

Although the AASLD states that there is insufficient evidence to make a recommendation on non-heavy alcohol consumption in NAFLD patients (3), there is emerging evidence that even a small amount of alcohol is harmful to NAFLD patients (114). Modest alcohol consumption has also been associated with less improvement in steatosis based on liver biopsy (115). It is probable that the risk of light alcohol consumption in NAFLD patients would outweigh the benefit of the well-known cardiovascular benefit (116).

The significant benefit of statins in reducing the risk of CVD is well-established, but concerns regarding adverse effects of muscle symptoms and increased transaminases are a factor leading to underutilization in patients with NAFLD. Although the role of statins in hepatotoxicity is now considered a "myth" (117,118), these medications continue to be underprescribed in patients with liver disease (119). Severe cases of drug-induced liver injury occurring 3 to 4 months after initiation of therapy have been reported, but are rare (1.2 of 100,000 users) (120), and the overall incidence of liver failure in patients on statins has not been significantly different from that in the general population (121). Several large randomized controlled trials did not find any difference in the incidence of persistently elevated liver function tests between statin and placebo therapy (122–124). A meta-analysis of 35 trials including 74,102 patients found that statins were associated with an absolute risk of elevated transaminases (risk difference per 1,000 patients: 4.2; 95% CI: 1.5 to 6.9) (125). Importantly, these abnormalities were reversible with dose reduction or termination of therapy, and progression to liver failure was rare. Additionally, Chalasani et al. (126) demonstrated that those patients with NAFLD who have elevated liver enzymes at baseline are not at increased risk for statin-induced hepatotoxicity. Therefore, routine monitoring of liver biochemistries while on statin therapy is no longer recommended (121,127,128).

The cardiovascular as well as hepatic benefits seen with statin use appears to heavily outweigh the risk

for hepatic toxicity (118). Hyogo et al. (129) found that pitavastatin improved NAFLD score in 54% and improved fibrosis stage in 42% of those with biopsy-proven NAFLD and dyslipidemia. Another small study of 20 biopsy-proven patients with NAFLD, metabolic syndrome, and dyslipidemia showed that after monotherapy with rosuvastatin 10 mg daily for 12 months, 19 of the 20 patients had complete resolution of NAFLD in repeat liver biopsy and ultrasound (130). The use of statins was also independently and negatively associated with both NAFLD (OR: 0.57; 95% CI: 0.32 to 1.01) and significant liver fibrosis (OR: 0.47; 95% CI: 0.26 to 0.84) in a cross-sectional study of 346 patients with biopsy-proven NAFLD and DM (131). Statins' reduction of inflammatory cytokines, such as TNF-α, as well as decreased production of reactive oxygen species in the liver have been proposed as potential mechanisms (130).

In addition to these histological benefits of statins in patients with NAFLD, statins have also been shown to have clinical benefits in this patient population (**Figure 1**) (132). Post hoc analysis of the GREACE (GREek Atorvastatin and Coronary heart disease Evaluation) study of 1,600 patients showed that those with abnormal liver tests at baseline (believed to be mostly due to NAFLD) who received therapy with atorvastatin (average dose of 24 mg/day) for 3 years had significant improvement in their liver tests and a reduction in cardiovascular events (3.2 events per 100 patient-years vs. 10.0 events per 100 patient-years) compared with those on usual care (133). Another post hoc analysis of the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study, a secondary prevention study, of 8,863 patients with high ALT levels found that high-dose atorvastatin (80 mg/day) had significant risk reduction compared with those on simvastatin (20 to 40 mg/day) (HR: 0.556; 95% CI: 0.367 to 0.843) (134). These findings were also replicated in the primary prevention ATTEMPT (Assessing The Treatment Effect in Metabolic syndrome without Perceptible diabeTes) study of patients with NAFLD on atorvastatin 30 mg/day (135). The major statin guidelines have yet to address the specific NAFLD population (136), but it may be reasonable to consider an approach similar to those with DM.

The cardiovascular benefits of aspirin have also been well-established. There is limited data on the use of aspirin in NAFLD patients. A cross-sectional study from NHANES III of 11,416 adults found that regular aspirin use was inversely associated with NAFLD identified on ultrasonography (OR: 0.62; 95% CI: 0.51 to 0.74) (137). Similarly to statins, aspirin is thought to be effective against NAFLD by inhibiting the production of TNF-α and stimulating the expression of endothelial nitric oxide synthase and VEGF, resulting in antioxidant activity (137). Liver injury from aspirin is rare, although adult cases of Reye syndrome have been reported (138).

Insulin resistance plays an important role in NAFLD, which is why insulin-sensitizing agents have been studied as possible therapies (**Figure 1**). Metformin improves insulin sensitivity, reduces hepatic gluconeogenesis, and in theory, should improve NAFLD (139). However, metformin has had limited clinical efficacy for NAFLD, as it has been shown to reduce liver enzyme levels, but not improve liver histology (140,141). Another insulin sensitizer that has been studied is the peroxisome proliferator-activated receptor (PPAR)-α agonist pioglitazone. Its effects on patients with DM has been established. It has been shown to reduce the risk of all-cause mortality, nonfatal myocardial infarction, and stroke in patients with type 2 DM with evidence of macrovascular disease (142,143) and to reduce the composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death among patients with insulin resistance or pre-DM (144). Pioglitazone's effect on insulin sensitivity appears to have benefit in patients with NAFLD as well. In patients with NASH and impaired glucose tolerance or type 2 DM, pioglitazone has been shown to decrease hepatic fat content; increase hepatic insulin sensitivity; decrease serum ALT levels; and improve fibrosis, steatosis, inflammation, and ballooning necrosis (145,146). In patients with NASH without DM, pioglitazone has been demonstrated to reduce steatosis, inflammation, and hepatocellular ballooning (147). In larger meta-analyses of patients with NASH and with or without DM, pioglitazone was associated with improvement in steatosis and fibrosis, and NASH resolution (148,149). While more robust confirmatory clinical outcomes studies are needed, the benefits of pioglitazone in patients with NAFLD appears significant. However, the risk of this drug, especially with regards to congestive heart failure, fluid retention, and weight gain, is a potential clinical concern (148,150). Last, there is strong evidence that glucagon-like peptide (GLP)-1 analogues reduce weight in obese diabetic patients, and they may be of benefit in patients with NAFLD. The LEAN (Liraglutide Efficacy and Action in NASH) trial, a randomized double-blinded controlled trial, demonstrated increased resolution of NASH in patients given liraglutide, a long acting GLP-1 analogue, compared with placebo (39% vs. 9%) (151). However, this benefit was not independent of weight loss. Liraglutide also appears to be beneficial from a cardiovascular

standpoint. Liraglutide has been shown to improve glycemic control; reduce total cholesterol, LDL, and TG; reduce systolic blood pressure; and decrease the incidence of nonfatal myocardial infarction, nonfatal stroke, heart failure admissions, and death due to any cardiovascular cause (152,153). GLP-1 analogues offer hope for reducing steatosis as well as for improving cardiovascular outcomes in patients with DM and NAFLD.

Because the renin-angiotensin-aldosterone system plays a regulatory role in insulin sensitivity, the effects of angiotensin II receptor blockers (ARBs) on NAFLD have been studied in a limited number of clinical trials (154,155). Both of these trials have demonstrated a significant decrease in serum liver enzyme levels. In a small study, Yokohama et al. (154) found that patients with NAFLD and hypertension treated with losartan (50 mg/day) had improved hepatic necroinflammation and reduction of hepatic fibrosis (154). A larger, well-designed randomized controlled trial is still needed to better evaluate the effects of ARBs on patients with NAFLD.

Targeting oxidative stress has also been theorized as a potential therapy for hepatic injury. In the study by Sanyal et al. (147), compared with placebo, vitamin E was associated with a significant improvement in NASH but not in improvement of fibrosis (147). The meta-analysis by Said et al. (149), which incorporated the Sanyal et al. (147) study, also demonstrated significant improvements in steatosis, lobular inflammation, and ballooning, but not fibrosis. Although vitamin E is thought to potentially improve NASH, long-term use of this supplement has had no significant benefit in preventing major cardiovascular events (156–158).

Bariatric surgery is an extremely effective treatment for obesity, as well as NAFLD. It can lead to a significant improvement in liver histology and transaminases (159,160), as well as disappearance in NASH and reduction in fibrosis (160). Bariatric surgery was also shown to lead to a significant reduction or resolution in CVD risk factors. In a systematic review of 73 studies with 19,543 bariatric surgery patients, post-operative improvement of DM was reached in 73% of patients, of hyperlipidemia in 65% of patients, and of hypertension in 63% of patients (161). The presumed primary mechanism by which this surgery results in such improvement is by weight loss (162).

FUTURE DIRECTIONS

Although the treatment options for NAFLD may seem limited, there is optimism that future innovative safe and effective options for management will be available. A number of medications have emerged that target the pathophysiological mechanisms of NAFLD.

OBETICHOLIC ACID. Farnesoid X receptors (FXRs) are nuclear receptors that, when activated, increase insulin sensitivity, decrease hepatic gluconeogenesis, and protect against cholestasis-induced liver injury (163). Obeticholic acid is a bile acid derivative that can bind FXRs and take advantage of this pathway. A multicenter, double-blind, placebo-controlled, randomized phase IIb trial of patients with NASH found that patients on obeticholic acid had improvement in their liver histology at 18 months compared with placebo (relative risk: 2.2; 95% CI: 1.4 to 3.3) (163). One drawback for this medication was that it was associated with higher levels of total serum cholesterol and LDL, and a decrease in HDL level. In secondary analysis, the role of statin use on changes in LDL was assessed (164). Statin use from baseline through the treatment period did not prevent the LDL increase while on obeticholic acid. The addition of a statin during the treatment period resulted in a decrease in LDL, but not as significant as the placebo group. The clinical significance of these LDL changes has yet to be determined. This medication is undergoing large phase 3 clinical trials (REGENERATE [Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment]; NCT02548351; and REVERSE [Study Evaluating the Efficacy and Safety of Obeticholic Acid in Subjects With Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis]; NCT03439254) in patients with NASH and fibrosis. These trials will hopefully provide insight as to whether obeticholic acid reduces CVD risk overall, despite the increase in LDL.

ELAFIBRANOR. PPAR-α and PPAR-δ are nuclear receptors that activate anti-inflammatory changes in the liver (165,166). Elafibranor is a dual PPAR-α/δ agonist that, in addition to improving insulin sensitivity, glucose homeostasis, and lipid metabolism, also reduces hepatic inflammation. In a multicenter, randomized, placebo-controlled phase IIb trial, elafibranor was shown to be effective in resolving NASH without worsening fibrosis in patients with moderate to severe NASH (165). This medication is also undergoing a large phase 3 clinical trial (RESOLVE-IT [Phase 3 Study to Evaluate the Efficacy and Safety of Elfibranor Versus Placebo in Patients With Nonalcoholic Steatohepatitis (NASH)]; NCT02704403) in patients with NASH and fibrosis.

CENICRIVIROC. Cenicriviroc is an antagonist of C-C motif chemokine receptor (CCR) types 2 and 5, which promote anti-inflammatory and antifibrotic effects in

the liver (166,167). This medication has been studied with the goal of reducing hepatic fibrosis. A randomized, double-blind, phase IIb study found that this medication resulted in a significant improvement in fibrosis without worsening NASH after the first year (167) and second year (168) of treatment.

CONCLUSIONS

NAFLD and CVD share numerous risk factors as both are manifestations of end-organ damage of the MetS. Furthermore, NAFLD independently increases the risk of atherosclerosis, cardiomyopathy, and arrhythmia, which clinically result in cardiovascular morbidity and mortality. Although the pathophysiological mechanisms to elucidate the relationship between NAFLD and CVD are still being evaluated, treatments to target these mechanisms are under development. Further research is needed going forward. A genetic basis for the disease is under study with SNP associations that warrant further validation. The candidate medications under study for NAFLD should be thoroughly evaluated using cardiovascular endpoints and subclinical CVD. Also, given the heterogeneity of the disease process, the relationship of NAFLD with DM and CVD needs further elucidation, as NAFLD may precede and/or promote the development of MetS and its components (169). Analyses are needed between responders and nonresponders of the magnitude of improvement of NASH and the observed changes in cardiometabolic risk. At present, the core treatment for NAFLD-induced CVD should focus on lifestyle and risk factor modification.

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