

Nonalcoholic fatty liver disease and atrial fibrillation: possible pathophysiological links and therapeutic interventions

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Abstract

Atrial fibrillation (AF) and nonalcoholic fatty liver disease (NAFLD) share common risk factors and appear to have an association. Independently, the incidence and prevalence of both diseases are on the rise. Epidemiological evidence, experimental studies and various randomized clinical trials suggest a link between the 2 entities, delineating cumulative risks and clinical strategies to improve outcomes. Dyslipidemia, insulin resistance, inflammatory milieu, and activation of the renin-angiotensin system are likely common pathophysiological mechanisms linking AF and NAFLD. In this article we review the known pathways and pathophysiology that link the 2 conditions. This review also discusses therapies that target both NAFLD and AF, such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, metformin, and vitamin E. We further discuss other potential medications that have shown effects in NAFLD or AF through anti-inflammatory, antidiabetic, lipid-lowering, or renin-angiotensin system inhibiting effects. Future epidemiological studies are needed to establish a direct causal relationship between NAFLD and AF.

Keywords Non-alcoholic fatty liver disease, atrial fibrillation, treatment, intervention, pathophysiology

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the imaging or histologic evidence of an accumulation of triglycerides in hepatocytes in the absence of secondary causes, such as excessive alcohol intake, viral hepatitis, medications or other cause of liver injury. NAFLD includes

a spectrum of disease severity ranging from simple steatosis with minimal liver injury to hepatitis, defined as nonalcoholic steatohepatitis (NASH), with increasing levels of liver fibrosis eventually leading to cirrhosis [1]. The main risk factors for NAFLD are concomitant metabolic syndrome, type 2 diabetes mellitus (DM-2) and obesity. Both NAFLD and its risk factors are prevalent in the western world, where NAFLD is the most common cause of liver disease [2]. According to the Third National Health and Nutrition Examination Survey, roughly 10-40% of Americans have NAFLD [3]. Another concerning trend is that more adolescents are being diagnosed with NAFLD, with a prevalence of 3-18% [4]. As NAFLD is a progressive disease that leads to cirrhosis and adds to overall mortality, adolescents will experience significant cumulative morbidity and mortality in their lifetime [5].

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the elderly, coexisting with other comorbidities [6]. The prevalence of AF in the United States (US) was about 3 million in 2005 and is projected to increase to 7.5 million by 2050 [7]. Multiple risk factors, including hypertension, advanced age, obesity, DM-2, smoking and other components of metabolic syndrome (such as central obesity, dyslipidemia and insulin resistance), are contributing to an increasing incidence of AF [8]. In their review, Wasmer *et al* noted an increase in AF incidence in the younger population and proposed lifestyle changes leading

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The most likely explanation is the presence of common risk factors shared between the two conditions.

In 2013, Framingham Heart Study researchers evaluated 3744 AF patients over 10 years. After adjustment for risk factors such as age, body mass index (BMI), DM-2, etc., the researchers found that elevated levels of serum transaminases (regardless of the cause of liver disease) were independent risk factors for AF. This was still the case after the exclusion of patients with moderate to severe alcohol intake [13]. Although the Framingham study did not specifically investigate NAFLD, Clark *et al* illustrated that the etiology of transaminase in the US is NAFLD [14]; therefore, although weak, there is evidence that AF may be associated with NAFLD.

Zhang *et al* studied 1688 Chinese adults to determine the association between AF and NAFLD. NAFLD diagnosis was based on sonographic criteria. Most of the associative factors, including age, sex, BMI, systolic and diastolic blood pressures, and lipid profile, were adjusted for as confounders and the results showed a statistically significant correlation between NAFLD and AF (odds ratio [OR] 1.95, 95% confidence interval [CI] 1.03-3.69) [15]. You *et al* performed the largest longitudinal study to date on 232,979 adult Korean subjects from 2009 to 2013, with a mean follow-up period of 3.7 years. After adjusting for confounders such as age, sex, heart failure, chronic kidney disease, obesity, impaired fasting glucose and systolic blood pressure, the hazard ratio (HR) for AF associated with NAFLD was 1.13 (95%CI 1.03-1.24; $P=0.01$). Moreover, for every 10-unit increase in the fatty liver index (a score based on anthropometric and laboratory values for prediction of the fatty liver), the risk of AF increased by 4% [16]. Karajmaki *et al* performed a prospective study on 958 middle-aged Finnish individuals from the OPERA (Oulu Project Elucidating Risk of Atherosclerosis) cohort with a 16-year follow-up period. The researchers found a 2-fold greater incidence of AF in NAFLD patients (14.9% vs. 7.9%, $P<0.001$). NAFLD was a risk factor for AF after adjustment for confounders, including age, sex, diabetes, BMI, serum alanine aminotransferase, systolic blood pressure, left ventricular mass index, left atrial diameter, coronary artery disease and C-reactive protein (CRP) (adjusted OR 1.88, 95%CI 1.03-3.45) [17]. The same group studied the gradient correlation of liver stiffness (a surrogate of liver fibrosis) with AF using transient elastography (TE) and echocardiography. In a cross-sectional study, they divided 76 subjects from the OPERA study into 4 subgroups with and without NAFLD or AF. Left atrial diameter was used as a surrogate of AF severity. They concluded that patients with AF had higher TE values, with a proportional increment relation between TE value and left atrial diameter (by TE tertiles: 39, 45 and 48 mm, $P<0.001$) [18]. The results of this study suggest a gradient relationship between NAFLD and AF.

Though most studies have consistently shown a positive relationship between NAFLD and AF, some have presented negative results. Mantovani *et al* conducted a meta-analysis on 364,919 patients from 5 cross-sectional and 4 longitudinal studies. Their analysis of the 5 cross-sectional studies found NAFLD to be increasingly associated with the prevalence of AF, after adjustment for confounders such as age, sex, BMI and hypertension (HTN) (adjusted OR 2.07, 95%CI 1.38-3.10;

$P=54.7\%$). However, the analysis of 4 longitudinal studies (including You *et al* and Karajmaki *et al*) showed NAFLD as a predictor for 10-year increased risk of incident AF only in DM-2 patients (HR 4.96, 95%CI 1.42-17.28) [12].

In order to search for a missing link between AF and NAFLD other than metabolic syndrome (including HTN, DM-2, or obesity), Mahfouz *et al* hypothesized that interatrial septal thickness (IAST) and left atrial stiffness (LAsT) cause AF in patients with NAFLD. They performed an echocardiography and speckle-tracking assessment of left atrial function to determine IAST and LAsT in 180 patients with NAFLD. The study findings suggested that high values of IAST and LAsT were associated with a greater incidence of AF in NAFLD. IAST and LAsT are independent risk factors and can serve as a mechanistic link between the 2 diseases [19]. The authors hypothesized that myocardial steatosis might exert local adverse effects leading to cardiac autonomic changes, as well as structural and electrical remodeling, causing the heart to become pro-arrhythmogenic. However, we believe the link that Mahfouz *et al* hypothesized was questionable. Although the authors performed multivariate regression analysis to determine the independence of IAST and LAsT from confounding factors, there are proinflammatory cytokines from NAFLD livers that may promote AF [20]. Other investigators have also found LAsT to be an independent risk factor for AF; however, they did not control for NAFLD or for proinflammatory cytokines as confounding factors [21]. Another link between AF and obesity is pericardial fat. It has been shown that there is a gradient relationship between the two, and that therapies that reduce pericardial fat can reduce the risk of AF. The proposed pathology is that pericardial fat tissue is a source of proinflammatory cytokines that exert local arrhythmogenic effects and cause AF [22].

An important limitation to consider is the fact that some studies did not take into account possible confounders. Future studies should be conducted to assess the role of confounders in the pathophysiological link between AF and NAFLD.

Putative mechanisms

One mechanism linking AF and NAFLD in obese individuals is the inflammatory and oxidative system. Inflammation and oxidative stress are closely connected, as the innate arm of the immune system produces reactive oxidation species via the myeloperoxidase enzyme [23]. Obesity leads to decreased release of an anti-inflammatory mediator called adiponectin and increased release of inflammatory mediators such as interleukin (IL)-6, tumor necrosis factor (TNF)- α , and CRP from adipose tissue, leading to a proinflammatory milieu and oxidative stress [24]. Cell death and the ensuing fibrosis from oxidative radicals and inflammatory infiltration lead to the progression of both AF and NAFLD [25]. Cardiac myocytes show both cellular (modification of ion currents) and structural (fibrosis) alterations, leading to AF [26]. For example, a case-control study by Ozveren *et al* showed a longer interatrial electromechanical delay and conduction abnormality in NAFLD patients, after adjustment for HTN and heart disease [27]. This is due to both increased fibrosis and the cellular ion channelopathies observed

in the cardiomyocytes of NAFLD patients. To close the causation loop, a liver with NAFLD produces atherogenic lipids and inflammatory proteins like CRP, leading to a proinflammatory and pro-oxidant milieu [28,29].

The renin-angiotensin system (RAS) is activated in patients with NAFLD [30]. The RAS contributes to HTN and can also lead to heart fibrosis. Angiotensin II is a proinflammatory component that causes an increase in cytokines, such as IL-6 and TNF- α , that worsen NAFLD through hepatic infiltration of inflammatory cells [31]. Angiotensin II leads to fatty accumulation in the liver via an altered metabolism of fatty acids and very-low-density lipoproteins [32]. In addition, angiotensin II promotes oxidative stress and leads to insulin resistance [33]. Angiotensin II leads to transforming growth factor (TGF)- β -mediated cardiac fibrosis, resulting in left atrial electrical and mechanical remodeling that can lead to AF [34]. Interestingly, although evidence is limited, AF can itself further produce an inflammatory state and sustain it, rendering the relationship bidirectional. Evidence of AF-mediated inflammation is that cardioversion can lead to a decrease in CRP level; the proposed mechanism is myocyte calcium overload in the heart with AF and cell death [35].

Potential therapies targeting NAFLD and AF

Lifestyle interventions

No studies have investigated the effects of lifestyle on AF and NAFLD concurrently. A weight loss of 5-7% through lifestyle modification with diet and exercise is the mainstay of the management of overweight patients with NAFLD and the only treatment for fibrosis regression [36]. Regarding AF, the LEGACY and REVERSE-AF studies have shown a decrease in the progression of AF, or even reversal, after weight loss [37,38]. Obesity leads to inflammatory mediator release from adipose tissue, increasing AF and NASH [24,25]. Khanna *et al* showed that a low-calorie diet and exercise-induced weight loss led to a decrease in inflammatory markers (IL-6 and TNF- α) [39]. A meta-analysis of 116 studies by Askarpour *et al* found significant improvement in CRP ($P < 0.001$), IL-6 ($P < 0.001$), and TNF- α ($P = 0.031$) in obese patients after bariatric surgery [40]. Further studies have shown that exercise leads to improvement in lipid profile, glycemic index and blood pressure, and a decrease in systemic inflammatory markers (CRP) [41]. Colbert *et al*, in a study involving over 3000 subjects, found evidence that exercise causes a decrease in IL-6 and CRP ($P < 0.05$). Interestingly, the effect was still present even after adjustment for weight loss; thus, exercise exerts its effects through other mechanisms than just weight loss alone [42].

Pharmacological interventions

Unfortunately, many patients find it challenging to institute lifestyle changes over the long term [43]. Many medications that act on AF are also seen to be effective for NAFLD, and *vice versa*, because of the suggested common pathophysiological pathway (Table 1 and Fig. 2). Medications effective for the conditions

target the 4 pathways: namely RAS, hyperglycemia, dyslipidemia, and inflammation. The medications with a proven effect on both conditions are angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) (only animal studies), pioglitazone, dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1) analogs, statins, and vitamin E. In addition to the well-established medications, we highlight a list of developing/novel therapies for NAFLD that have potential to be effective for AF (Table 1). Following are the established and proposed experimental medications categorized based on their mechanism of action. Note that some of the medications are known to have multiple mechanisms. Unfortunately, we were unable to account for baseline therapies for AF, such as anticoagulants and/or antiarrhythmics, as they can be a potential confounder in treatment for AF and NAFLD.

Antidiabetic medications

Metformin

Metformin has been extensively studied in NAFLD. In a meta-analysis of 9 randomized controlled trials (RCTs) and 417 participants by Li *et al*, it was shown that metformin has beneficial metabolic effects but no histological effects in NAFLD [44]. In a nationwide study of a cohort of 645,710 patients, Chang *et al* showed that metformin decreases the chance of AF [45]. Metformin decreases hepatic gluconeogenesis and is the primary initial medication in diabetes mellitus [46]. Metformin has been shown to exert anti-inflammatory and antioxidant effects after adjustment for glycemic results. Metformin lowers serum CRP levels and increases nitric oxide, leading to anti-inflammatory effects [47].

Pioglitazone

In a meta-analysis of 4 RCTs from 3 continents, pioglitazone, a thiazolidinedione, was shown to significantly improve fibrosis in the liver of NASH patients compared to controls (OR 1.7, 95%CI 1.0-2.8) [48]. A meta-analysis by Zhang *et al* of 3 RCTs and 4 observational studies including 130,854 patients showed that thiazolidinedione-treated patients have a 30% lower risk of developing AF compared to controls (OR 0.73, 95%CI 0.62-0.87) [49]. In an RCT that included 23 DM-2 patients, pioglitazone was shown to reduce insulin resistance, free fatty acids and TNF- α , which translates to an improved inflammatory and hypercoagulable environment [50].

DPP-4 inhibitors and GLP-1 analogs

DPP-4 inhibitors and GLP-1 are medications for diabetes that exert their effect via the activation of GLP-1 receptors. GLP-1 has been shown to have protective effects on cardiomyocyte contractility, glucose uptake and survival [51]. Clinically, GLP-1 has been shown to improve patients' ejection fraction and functional status [52]. Liraglutide (a GLP-1

Table 1 Medications with effects on non-alcoholic fatty liver disease and atrial fibrillation

Drug	NAFLD effects	AF effects	Mechanism of action
ACEI/ARB*	+ ^a	+	RAS and TGF- β inhibition
Ezetimibe	+	+/0	Intestinal cholesterol absorption inhibition
DPP-4 inhibitor and GLP-1 analogs*	+	+ ^a	Insulin release and cardio-protection
Metformin	+/0	+	Decrease gluconeogenesis
Obeticholic acid	+	0	FXR agonist
Orlistat	+	0	Intestinal lipase inhibitor
Pentoxifylline	+	+/0	Phosphodiesterase inhibitor
Pioglitazone*	+	+	Stimulates PPAR- γ
Propranolol	+ ^a	+	β_1 and β_2 inhibition
Statins*	+	+	Inhibit HMG-CoA reductase and TGF- β
Silymarin	+	0	Antioxidant and anti-inflammatory
Ursodeoxycholic acid	+	+/0	Stimulates excretion of bile acids
Vitamin E*	+	+	Anti-inflammatory activity
Experimental medications			
Aramchol	+	0	Lipid synthesis inhibitor
Belapectin	+	0	Galectin-3 inhibitor
DUR-928	+ ^a	0	LXR inhibitor
Elafibranor	+	0	Agonist of PPAR- α and PPAR- δ
Pradigastat	+	0	DGAT-1 inhibitor
Quercetin	+ ^a	0	Antioxidant
Tropifexor/Cenicriviroc	+ ^a	0	FXR agonist/ CCR2 and 5 inhibitor

+, positive results; 0, no results / unknown effects due to lack of studies; +/-, equivocal results

*indicates proven benefit of medication in both AF and NAFLD, ^a indicates medications studied in animals and not in humans

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; CCR, C-C motif chemokine receptor; DGAT, Acyl-CoA diacylglycerol acyltransferase; FXR, farnesoid X receptor agonist; HMG-CoA reductase, 3-hydroxy-3-methyl-glutaryl-CoA reductase; LXR, liver X receptor; NAFLD, non-alcoholic fatty liver disease; PPAR- α , peroxisome proliferator-activated receptor- α ; PPAR- δ , peroxisome proliferator-activated receptor delta; PPAR- γ , peroxisome proliferator-activated receptor gamma; TGF- β , transforming growth factor- β

agonist) has been proven to reduce AF inducibility in animal models (P=0.02) [53]. The SCALE trial showed that liraglutide also causes significant weight loss in obese patients [54] and reduces obstructive sleep apnea [55], 2 major risk factors for AF. Liraglutide has been shown to downregulate TNF- α -induced oxidative stress [56] and endothelial inflammation [57]. The Liraglutide Efficacy and Action in NASH (LEAN) trial, which included 52 patients with NASH, showed a reduction in fibrosis progression from 36% in controls to 9% in the liraglutide group (relative risk 0.2, 95%CI 0.1-1.0) [58].

Anti-inflammatory and antioxidants

Pentoxifylline

Pentoxifylline, a synthetic methylxanthine, is a phosphodiesterase inhibitor with cardiovascular protective effects achieved through smooth muscle relaxation, a decrease in neutrophil superoxide production, migration, and response to TNF- α and IL-1 [59]. A meta-analysis of 3 RCTs and 2 cohort studies showed that pentoxifylline treatment results in

weight loss, improved transaminases and improved histological parameters in patients with NASH [60].

Vitamin E

The American Association for the Study of Liver Diseases recommends vitamin E in patients with NASH [61]. Vitamin E decreases the levels of proinflammatory cytokines like IL-8 and CRP via protein kinase C and cyclooxygenase-2 pathways [62]. An RCT by Rodrigo *et al*, which included 152 cardiac surgery patients, showed a reduction of postoperative AF in cardiac surgery patients on vitamin E [63]. However, vitamin E has not been established as a standard of care for AF patients.

RAS inhibitors and sympatholytics

ACEI and ARBs

ACEIs and ARBs are groups of medications with direct effect on RAS. Treatment with ACEIs and ARBs leads to

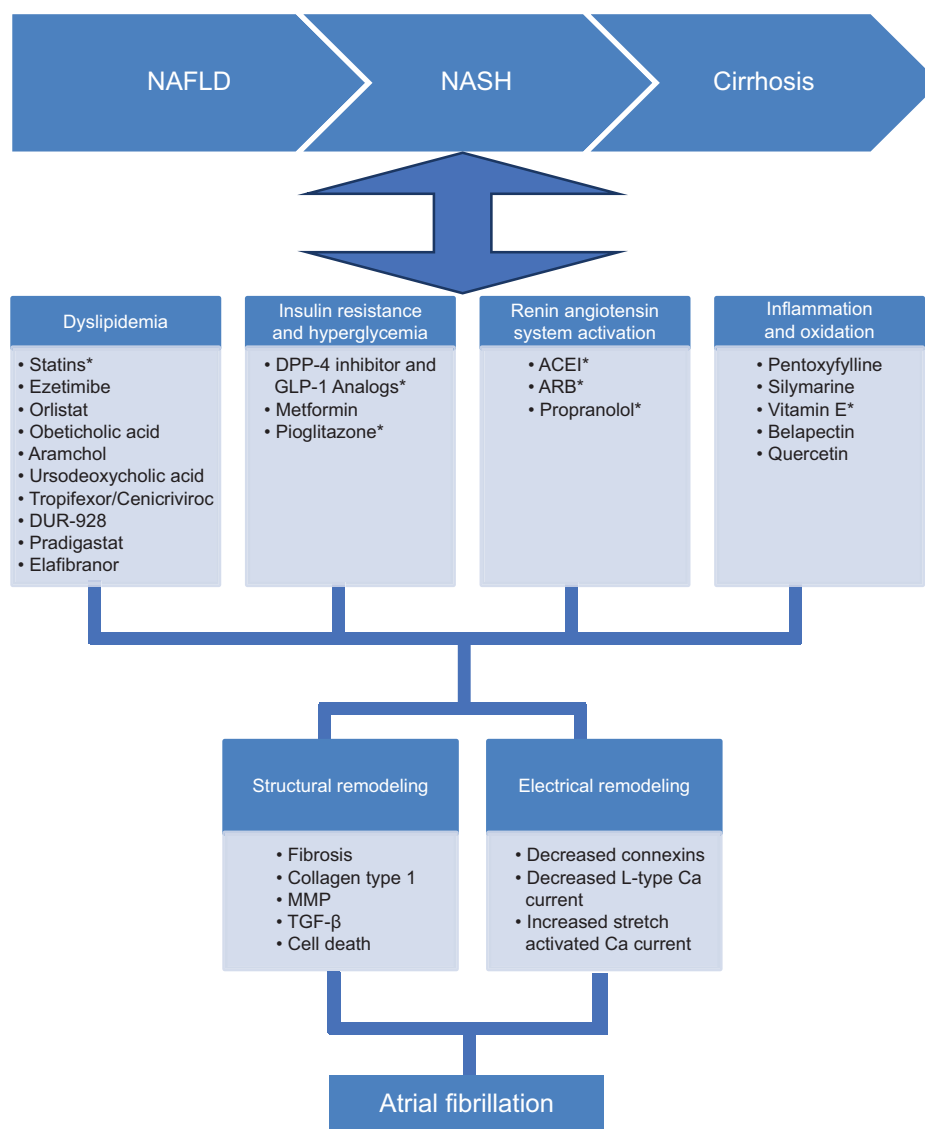


Figure 2 Drug therapy effects on pathways linking NAFLD and atrial fibrillation

MMP, matrix metalloproteinase; TGF- β , transforming growth factor- β ; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

attenuation of the RAS and beneficial effects on both NAFLD and AF in animal models [64]. There are other mechanisms apart from attenuating the RAS. Losartn, an ARB, inhibits Toll-like receptor-4 and TGF- β and reduces liver fibrosis in rats [65]. In animal models, valsartan ameliorates liver fibrosis by reducing TGF- β and TNF- α , in addition to its anti-apoptotic effects [66]. ACEI and ARBs also lead to a decrease in AF via a decrease in cardiac fibrosis, in addition to the other mechanisms [67].

Nonselective β -blockers

Propranolol is an example of a nonselective β -blocker with effects on β_1 and β_2 receptors [68]. β_1 -Blocking causes a

decrease in heart rate. This effect makes β -blockers (selective or nonselective) an indication for AF according to American Heart Association guidelines [69]. In the landmark AFFIRM trial, β -blockers were the most effective medications for reducing heart rate, with 70% of patients achieving the target heart rate [70]. Blocking β_2 causes inhibition of the RAS, lipolysis, glycogenolysis, gluconeogenesis, noradrenaline release and some immune system modulation [68]. The above effects target pathways of ACEI, dyslipidemia and dysglycemia; hence, nonselective β -blockers may have potential against NAFLD. Indeed, propranolol has shown efficacy in a NAFLD rat model with improvement of serum triglycerides, TNF- α , transaminase, insulin resistance and liver histology ($P < 0.05$) [71]. Further human trials are warranted.

Lipid-lowering medications

Silymarin

Silymarin is a flavonoid extract from milk thistle seeds that exhibits antioxidant and anti-inflammatory properties [72]. Silymarin has shown beneficial anthropometric, biochemical, and histologic effects in NAFLD patients [73]. In a trial involving 102 patients undergoing cardiac surgery, silymarin was shown to decrease postoperative proinflammatory cytokines (IL-6 and TNF- α) [74]. Logistic regression analysis by Ishida *et al* of 39 patients undergoing cardiac surgery showed that elevated IL-6 after cardiac surgery was associated with a higher rate of AF (highest quartile with OR 7.63, 95%CI 1.06-54.9; P=0.04) [75]. Therefore, it is worthwhile to further investigate the role of this medication in AF.

Statins

Georgescu *et al* conducted an RCT that included 48 NAFLD patients receiving atorvastatin, losartan, pentoxifylline and ursodeoxycholic acid (UDCA). All groups showed improvement in transaminase and γ -glutamyl transferase (GGT) [76].

Statins are a group of medications effective against metabolic syndrome and have shown activity against NAFLD and AF. Statins are widely used and accepted in patients with NAFLD [77]. Statins improve NAFLD via various mechanisms. They increase adiponectin, which leads to an improvement in both AF and NAFLD [78]. Statins reduce TGF- β , improve peroxisomal β -oxidation and promote nitric oxide synthase [30]. This leads to an anti-inflammatory, anti-apoptotic, and anti-oxidative milieu that ameliorates fat accumulation and inflammation in the liver, according to a clinical trial involving 43 NASH patients [79]. A trial with 105 patients, confirmed by a meta-analysis of 13 studies, showed that statins improve AF through reducing oxidative stress and inflammatory markers such as CRP and TNF- α [80].

Obeticholic acid

Farnesoid X receptor (FXR) is a receptor in the liver that regulates cholesterol metabolism [81]. Obeticholic acid is an FXR agonist that has shown promise in NAFLD in a multicenter US clinical trial involving 141 NASH patients [82]. Animal studies have shown that FXR activation by obeticholic acid leads to a healthier lipid profile by reducing serum low-density lipoprotein (LDL) levels [83]. However, in humans this compound increases LDL and lowers high-density lipoprotein levels [84]. This may discourage its use in cardiovascular purposes; however, there is insufficient evidence to prove any cardiovascular benefits and/or drawbacks.

Ezetimibe

Ezetimibe is a drug that binds to the intestinal cholesterol transporter and inhibits cholesterol absorption [85]. According to a consensus panel in the United Kingdom, the addition of ezetimibe to statins reduces LDL by an additional 20% compared to statins alone [86]. In a meta-analysis of 5 trials involving a total of 199 NAFLD patients, NAFLD activity score was decreased; however, steatosis was not alleviated with ezetimibe [87]. In the landmark IMPROVE-IT trial, which included 18,000 patients with acute coronary syndrome, ezetimibe was associated with an improvement in cardiovascular profile when it was added to statins [88]. In the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) trial, which followed 1421 patients with aortic stenosis for 4.3 years, a combination of simvastatin and ezetimibe was not associated with a lower incidence of AF [89]. Moreover, although lipid-lowering effects were observed, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) RCT with 720 familial hypercholesterolemia patients, failed to show an improvement in carotid artery intima-media thickness (a surrogate of atherosclerosis) in familial hypercholesterolemia patients [90].

UDCA

UDCA is a hydrophilic bile acid that stimulates the excretion of other bile acids by liver cells [91]. Long-term UDCA has shown hepatoprotection in NASH patients [92]. After 12 months of UDCA therapy, in a pilot study involving 40 NASH patients, not only was there an improvement in liver enzymes, but there was also resolution of hepatic steatosis [93]. UDCA showed a benefit in lowering inflammatory markers in 17 male chronic heart failure patients in a single-center RCT [94]. Regarding arrhythmia and AF, *in vitro* studies have shown a reduction of arrhythmia in cardiomyocytes [95]. However, the efficacy has not been assessed *in vivo*.

Orlistat

Orlistat is an over-the-counter weight-loss medication that exerts its effect by inhibiting intestinal lipase [96]. A meta-analysis of 7 clinical trials by Wang *et al* showed an improvement in transaminase and lipid profile (P=0.01) in addition to weight loss [97]. In an observational study of 97 NAFLD patients by Khan *et al*, 4 months' use of orlistat reduced TNF- α in parallel with a reduction in grades of fatty liver [98]. In a multicenter RCT in 33 primary care centers in Sweden, orlistat was shown to lead to not only weight reduction but also a decrease in cardiovascular risks [99]. Orlistat's effects on AF need to be further investigated.

Novel/experimental therapies

There are novel medications whose effects have not all been fully studied in large multicenter RCTs. However,

preliminary studies have shown promise in NAFLD and further study is warranted in AF patients, as these medications target common pathways leading to AF and NAFLD.

Antidiabetic medications

Elafibranor

Peroxisome proliferator-activated receptors (PPAR)- α and PPAR- δ are involved in liver lipid metabolism and insulin sensitivity [100]. Some new medications are designed to utilize these receptors to treat NASH. Elafibranor is a novel agonist of PPAR- α and PPAR- δ that showed improvements in cardiometabolic parameters, such as lipid profile and insulin sensitivity, in an RCT involving 131 patients [101]. This medication has also been shown to improve hepatic steatosis, liver enzymes, lipid profile and inflammatory markers, such as haptoglobin, in NASH in a multicenter RCT ($P < 0.01$) [102]. Its effects on cardiovascular mortality and AF remain to be determined.

Anti-inflammatories and antioxidants

Quercetin

Quercetin is a flavonoid present in vegetables and fruits and forms part of our daily diet [103]. Quercetin is an antioxidant and promotes relaxation of cardiovascular smooth muscle, with proven efficacy in reducing atherosclerosis in animal models [104]. Quercetin decreased abdominal obesity, hypertension, dyslipidemia, insulin resistance and hepatic steatosis, and improved cardiovascular remodeling in rats [105]. In animal models, it was found that quercetin exerts its anti-inflammatory and antioxidant activity through its prebiotic effects and by modulating the gut-liver axis [106]. These metabolic and anti-inflammatory effects have already proven beneficial in the cardiovascular system; however, quercetin's effects on AF need to be studied.

Belapectin

Belapectin is a complex carbohydrate molecule derived from a natural plant that inhibits galectin-3 and exerts antiapoptotic and immunomodulatory effects [107]. In animal models of NASH, the compound decreases hepatic steatosis, proinflammatory cytokines and infiltration, fatty acid oxidation, hepatocyte apoptosis, and fibrosis [108]. In a recent phase 2b trial involving patients with cirrhosis secondary to NASH, belapectin showed a clinical effect in reducing portal pressure [109]. At the time of writing this article, clinical cardiovascular effects have not been studied, but we postulate that the medication will have positive effects on AF.

Lipid-lowering medications

DUR-928

Liver X receptors (LXRs) are involved in liver lipid metabolism [100]. DUR-928 is a natural sulfated oxysterol that inhibits LXR and the inflammatory system, and has shown antisteatotic effects in animal models of NASH [110]. Since the compound decreases inflammation and improves metabolism, further studies in AF are warranted.

Tropifexor/cenicriviroc

Tropifexor is a non-bile acid FXR agonist that has been shown to reduce steatosis, inflammation and fibrosis in animal models of NASH [111]. Cenicriviroc is an antagonist of C-C Motif Chemokine Receptor types 2 and 5 (CCR2 and CCR5), involved in macrophage activation and the pathogenesis of NASH [112]. Cenicriviroc has shown anti-inflammatory and long-lasting antifibrotic activity in phase 2b trials in human subjects who had NASH with fibrosis [113]. The combination of tropifexor and cenicriviroc has shown promise in animal models of NASH, where it led to improvements in inflammation and histology [114]. A phase 2 randomized, double-blind, multicenter trial is underway to determine the efficacy of tropifexor and cenicriviroc in human subjects with NASH [115]. In light of the positive effects on both NASH and inflammatory markers, there is hope for concurrent effects of the combination of tropifexor and cenicriviroc in AF patients.

Aramchol

Aramchol, a bile acid conjugate that decreases lipid synthesis, has shown promise in NASH [116]. A phase 2b randomized clinical trial (ARREST) including 247 patients with NASH showed that aramchol therapy leads to resolution of NASH, a decrease in hepatic steatosis and improvement in glycemic control [116]. The medication was effective in improving metabolic activity in NASH patients; however, its clinical effects on the cardiovascular system need evaluation.

Pradigastat

Acyl-CoA diacylglycerol acyltransferase (DGAT) is an intestinal enzyme involved in the synthesis of triglycerides, especially the type destined for oxidation [117]. Pradigastat is a DGAT-1 inhibitor that showed promise in a small clinical trial that included 6 patients with familial chylomicronemia syndrome [118]. Studies in NAFLD patients have shown a decrease in liver fat content after 6 months of therapy; however, more than 4 out of 5 patients develop diarrhea due to fat malabsorption [119]. The effect of pradigastat in AF needs to be further investigated.

Concluding remarks

There is a multidirectional relationship between NAFLD and AF. The literature suggests that they are linked by proinflammatory, pro-oxidant and atherogenic effects, and a pro-fibrosis environment that stems from and leads to both conditions. There are further mechanisms, such as normal gut flora dysbiosis, effects of the pro-oxidant GGT, and anatomical complications of obesity, that contribute to the aforementioned conditions. Many medications used to treat NAFLD have proven efficacy in AF, as they target dyslipidemia, insulin resistance, the inflammatory system or the RAS. The novel experimental medications for NAFLD have potential for AF, as they target the components of metabolic syndrome or have anti-inflammatory effects. More research is still needed to unveil the pathophysiology, potential mechanisms, and ultimately treatment options targeting both disorders.

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