Risk of cardiovascular, cardiac and arrhythmic complications in patients with non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has emerged as a public health problem of epidemic proportions worldwide. Accumulating clinical and epidemiological evidence indicates that NAFLD is not only associated with liver-related morbidity and mortality but also with an increased risk of coronary heart disease (CHD), abnormalities of cardiac function and structure (e.g., left ventricular dysfunction and hypertrophy, and heart failure), valvular heart disease (e.g., aortic valve sclerosis) and arrhythmias (e.g., atrial fibrillation). Experimental evidence suggests that NAFLD itself, especially in its more severe forms, exacerbates systemic/hepatic insulin resistance, causes atherogenic dyslipidemia, and releases a variety of pro-inflammatory, pro-coagulant and pro-fibrogenic mediators that may play important roles in the pathophysiology of cardiac and arrhythmic complications. Collectively, these findings suggest that patients with NAFLD may benefit from more intensive surveillance and early treatment interventions to decrease the risk for CHD and other cardiac/arrhythmic complications. The purpose of this clinical review is to summarize the rapidly expanding body of evidence that supports a strong association between NAFLD and cardiovascular, cardiac and arrhythmic complications, to briefly examine the putative biological mechanisms underlying this association, and to discuss some of the current treatment options that may influence both NAFLD and its related cardiac and arrhythmic complications.

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Key words: Non-alcoholic fatty liver disease; Cardiovascular disease; Cardiac complications; Coronary heart disease; Myocardial dysfunction; Valvular heart disease; Arrhythmias; Arrhythmic complications

Core tip: The purpose of this clinical review is to summarize the rapidly expanding body of evidence that supports a strong association between Nonalcoholic fatty liver disease (NAFLD) and cardiovascular, cardiac and arrhythmic complications, to briefly examine the putative biological mechanisms underlying this association, and to discuss some of the current treatment options that may influence both NAFLD and its related cardiac and arrhythmic complications.
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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a complex health condition with implications far beyond the liver. Over the last decade, it has been shown that the clinical burden of NAFLD is not only confined to liver-related morbidity or mortality, and the majority of deaths among these patients are due to malignancy, coronary heart disease (CHD) and other cardiovascular (CVD) complications.

Although the anecdotal concurrence of peripheral atherosclerosis and atrial fibrillation (AF) in a patient with diabetes and hepatic steatosis dates back to the early 50’s[1], the traditional paradigm of liver disease protecting against the development of CVD has only been recently challenged. The experimental observations that an atherogenic diet causes hepatic steatosis and gallstones in mice[2], and the pioneering clinical studies showing that NAFLD is a possible contributor to accelerated atherosclerosis[3-5] suggested that either the relationship between NAFLD and CVD is bidirectional or both diseases result from a common pathogenic ancestor. More recent work has identified NAFLD as a risk factor not only for premature CHD and CVD events, but also for early abnormalities in myocardial structure and function[6-9]. The finding that NAFLD is associated with an increased risk of AF in people without evidence of co-existing valvular heart disease[10] supports the assertion that NAFLD may also be an emerging risk factor for cardiac arrhythmias.

In this clinical review, we will discuss the clinical evidence linking NAFLD to an increased risk of structural and arrhythmogenic cardiac complications. We will also briefly review the putative biological mechanisms linking NAFLD to the development and progression of such complications, and discuss some of the current treatment options that may influence both NAFLD and its related structural and arrhythmogenic cardiac complications. The potential adverse impact of NAFLD on these complications deserves particular attention, especially with respect to screening and surveillance strategies for the growing number of patients with NAFLD.

Review criteria and evidence acquisition: this is a clinical, narrative review and not a systematic review and meta-analysis. PubMed was extensively searched for articles using the keywords “non-alcoholic fatty liver disease” or “fatty liver” combined with “cardiovascular disease”, “cardiovascular risk”, “cardiovascular mortality”, “cardiac complications”, “coronary heart disease”, “congestive heart failure”, “myocardial dysfunction”, “valvular heart disease”, “atrial fibrillation” or “cardiac arrhythmias” between 1990 and 2013. Articles published in languages other than English were excluded from the analysis.

CLINICAL EVIDENCE LINKING NAFLD TO RISK OF STRUCTURAL AND ARRHYTHMOGENIC CARDIAC COMPLICATIONS

NAFLD and risk of CHD

Over the last decade, the prognostic value of NAFLD as a risk factor for the development and progression of CHD has attracted considerable scientific interest. To date, there is a large body of clinical and epidemiological evidence supporting the assertion that NAFLD is strongly associated with an increased prevalence and incidence of CHD[11-13].

Subclinical and clinical CHD

Subclinical CHD: Abundant epidemiological data link NAFLD with markers of subclinical atherosclerosis (i.e., endothelial dysfunction, increased arterial stiffness, increased carotid intima-media thickness, elevated coronary calcium score) both in adults and in adolescents[14-16].

Some investigators have reported that NAFLD is associated with circulatory endothelial dysfunction, independently of obesity, hypertension and other established CVD risk factors[17-19]. A systematic review and meta-analysis of seven cross-sectional studies (involving a total of 3497 subjects) showed that NAFLD diagnosed on ultrasonography is strongly associated with increased carotid-artery intimal medial thickness and an increased prevalence of carotid atherosclerotic plaques[8]. Interestingly, two studies also found a positive, graded relationship between carotid-artery intimal medial thickness and the severity of NAFLD histology, independently of multiple cardiometabolic risk factors[20,21].

Accumulating evidence also suggests that NAFLD is associated with increased coronary artery calcium (CAC) score on cardiac computed tomography (CT), which is another marker of early coronary atherosclerosis[22]. A retrospective study showed that NAFLD, assessed by either CT or ultrasonography, was significantly associated with increased CAC score (i.e., CAC score > 100), independently of traditional CVD risk factors[23]. Another community-based study found that the presence of ultrasound-diagnosed NAFLD with increased serum ALT levels, but not hepatic steatosis alone, independently predicted a high CAC score[24]. In 2012, Sung et al[25] reported that in a South Korean occupational cohort of 10153 people, NAFLD on ultrasonography was associated with increased CAC score (i.e., CAC > 0), independently of conventional CVD risk factors, metabolic syndrome features, insulin resistance and pre-existing CVD. In the same year, another large community-based study of Korean people confirmed that increasing CAC scores were associated with NAFLD, independently of classical CVD risk factors, including visceral adiposity[26]. Almost identi-
cal results were reported by some investigators in other ethnic groups\[37\].

Notably, some studies reported an abnormal coronary flow reserve (CFR), an index of impaired coronary microcirculation, in patients with NAFLD. For example, Lautamäki et al\[36\] reported a strong association between higher intra-hepatic fat content and decreased CFR, as assessed by positron emission tomography, in patients with type 2 diabetes and known CHD, independently of whole-body insulin sensitivity, visceral adiposity and other common CVD risk factors. Other studies confirmed a significantly reduced CFR, assessed by either thoracic doppler echocardiography or cardiac magnetic resonance imaging, in patients with NAFLD, independently of conventional CVD risk factors and metabolic syndrome features\[29,30\]. Collectively, the presence of reduced CFR among NAFLD patients suggests that decreased CFR might represent an additional pathogenic mechanism involved in CHD mortality and morbidity in this group of patients.

### Clinical CHD:

Table 1 shows the main cross-sectional studies relating NAFLD to clinically manifest CHD in both nondiabetic and diabetic individuals\[31-44\]. Recent data from the Valpolicella Heart Diabetes Study of 2839 unscreened Italian patients with type 2 diabetes have shown that those with NAFLD had a remarkably greater prevalence of clinical CVD (CHD, cerebrovascular and peripheral vascular disease) than their counterparts without NAFLD, independently of classical CVD risk factors, use of medications, glycemic control and features of the metabolic syndrome\[32\]. Similar findings were also reported in adults with type 1 diabetes mellitus\[39\]. In a large community-based cohort of 2088 Taiwanese male workers, NAFLD was significantly associated with an increased prevalence of CHD, independently of obesity and other established CVD risk factors\[30\].

Mirbagheri et al\[34\] reported that NAFLD was the strongest, positive predictor of angiographically detected CHD in patients who underwent elective coronary angiography, ranking even before sex and diabetes at multivariate analysis; interestingly, the adjustment for traditional CVD risk factors did not attenuate the strong association between NAFLD and CHD. Similarly, Assy et al\[36\] reported that patients with NAFLD had a much greater prevalence of both calcified and non-calcified coronary plaques than control subjects without hepatic steatosis, and that NAFLD predicted coronary atherosclerosis, independently of metabolic syndrome features and plasma C-reactive protein levels. Akabame et al\[30\] found that NAFLD was significantly associated with lower remodeling lesions or lipid core plaques of coronary arteries, thus suggesting NAFLD is a novel risk factor for vulnerable coronary plaques. Interestingly, in a large hospital-based sample of 612 Chinese patients with suspected CHD, Wong et al\[38\] confirmed that NAFLD on ultrasonography was associated with a greater angiographic severity of CHD, defined as the presence of $\geq 50\%$ stenosis in at least one coronary artery, independently of multiple risk factors for CVD.

As also shown in Table 1, a number of other studies have documented a positive and independent association between NAFLD and the angiographic severity of CHD among patients with acute coronary syndromes or suspected CHD\[33,35,37,40-43\]. Finally, NAFLD was associated with poor coronary collateral development in nondiabetic patients with severe CHD, independently of insulin resistance and other features of the metabolic syndrome\[46\].

### Fatal and non-fatal CHD events

As summarized in Table 2, several retrospective and prospective studies have investigated the relationship between NAFLD and the incidence of CHD or CVD events\[47-71\]. These studies have used either biochemical markers, such as elevated serum liver enzymes and fatty liver index (FLI), or radiological imaging or liver biopsy for diagnosing NAFLD.

With regard to biochemistry-diagnosed NAFLD, a systematic review and meta-analysis of 10 population-based cohort studies has shown a strong association between mildly elevated serum levels of gamma glutamyltransferase (GGT), a surrogate marker for NAFLD, and increased incidence of fatal and non-fatal CVD events, independently of alcohol consumption and classical CVD risk factors\[47\]. Conversely, although Schindhelm et al\[48\] found a significant and independent association between mildly increased serum alanine aminotransferase (ALT) levels and risk of incident CHD events among the Hoorn study participants, other large population-based cohort studies that have examined the association of serum ALT levels with adverse CVD outcomes have provided more conflicting results\[47-60,63\]. A recent large population-based cohort study of 2074 Italian subjects with a follow-up period of 15 years showed a significant, positive association between NAFLD as estimated by FLI (i.e., a proxy of fatty liver based on body mass index, waist circumference, serum triglyceride and GGT levels\[72\]) and increased CVD mortality that was mainly attributed to insulin resistance\[54\]. Again, Lerchbaum et al\[55\] confirmed that high FLI was independently associated with an increased risk of all-cause, CVD and non-CVD related mortality in a large cohort of consecutive patients with suspected CHD, who were routinely referred to coronary angiography. In contrast, a recent study, involving 713 consecutive Chinese patients with suspected CHD, did not find any significant association between FLI and angiographically detected CHD\[73\].

With regard to imaging-diagnosed NAFLD, several prospective studies reported an increased risk of fatal and non-fatal CVD events, independently of several cardio-metabolic risk factors, among NAFLD patients with and without type 2 diabetes (as shown in Table 2)\[58-58,63,64-65\]. In the only study having CHD as a pre-specified study outcome, Tveprasertsuk et al\[64\] confirmed that patients
with NAFLD had a significantly higher 10-year risk for CHD as calculated by the Framingham risk score (FRS) than the matched control population, and proved the clinical utility of the FRS among these patients, given that an almost identical number of FRS-predicted and actual new CHD events was registered during the follow-up period of the study. A recent meta-analysis by Musso et al also confirmed that the presence of NAFLD, as detected

ACS: Acute coronary syndrome; NAFLD: Non-alcoholic fatty liver disease; CAG: Coronary angiography; CT: Computed tomography; CVD: Cardiovascular disease; ECG: Electrocardiogram; MetS: Metabolic syndrome; NASH: Non-alcoholic steatohepatitis; US: Ultrasonography.

Table 1  Main cross-sectional study examining the association of non-alcoholic fatty liver disease with the presence and severity of clinical coronary heart disease, ordered by year

| Ref. | Study characteristics | NAFLD diagnosis | CHD diagnosis | Main findings |
|------|---------------------|-----------------|--------------|---------------|
| Lin et al [33], 2005 | 2088 male workers undergoing annual health examination screening; NAFLD in 29.5% | US Patient history, ECG | NAFLD associated with higher prevalence of CHD, independently of obesity and other traditional CVD risk factors. The odds for CHD increased progressively with ultrasonographic severity of NAFLD | |
| Targher et al [34], 2007 | 2839 type 2 diabetic outpatients; NAFLD in 69.5% | US Patient history, review of patient records, ECG, doppler ultrasound of carotid and lower limb arteries | NAFLD associated with higher prevalence of coronary, cerebrovascular and peripheral vascular disease than their counterparts without NAFLD, independently of traditional CVD risk factors, hemoglobin A1c, medication use and MetS features | |
| Anslan et al [35], 2007 | 92 consecutive Turkish patients admitted with ACS; NAFLD in 70% | US CAG (elective) | NAFLD was an independent predictor of CHD (> 50% stenosis of ≥ 1 major coronary artery) after adjustment for traditional CVD risk factors and MetS features | |
| Mirbagheri et al [36], 2007 | 317 Iranian patients admitted for either ACS, angina or suspected CHD; NAFLD in 54% | US CAG (elective) | NAFLD was an independent predictor of "clinically relevant" CHD (> 30% stenosis of ≥ 1 major coronary artery) after adjustment for CVD risk factors and MetS features | |
| Alper et al [37], 2008 | 80 Turkish patients with MS (stable or unstable angina, prognostic reasons); NAFLD in 54% | US CAG (acute and elective) | NAFLD was the only independent predictor of severe CHD (> 70% stenosis of ≥ 1 major coronary artery) after adjustment for established CVD risk factors and MetS features | |
| Akabarne et al [38], 2008 | 298 consecutive Japanese patients with suspected CHD; NAFLD in 20% | CT CT (elective) | NAFLD was independently associated with remodeling lesions or lipid core of coronary plaques but not with calcified coronary plaques or stenosis | |
| Açikel et al [39], 2009 | 355 consecutive Turkish patients admitted for ACS or CHD suspicion; NAFLD in 60% | US CAG (acute and elective) | NAFLD was an independent predictor of CHD (> 50% stenosis of ≥ 1 major coronary artery) after adjustment for conventional CVD risk factors | |
| Assy et al [40], 2010 | 29 Israeli patients with low or intermediate risk of CHD and NAFLD and 32 healthy controls matched for age and sex | CT CT (elective) | NAFLD was associated with greater prevalence of calcified and non-calcified coronary plaques, independently of the MetS and plasma C-reactive protein | |
| Targher et al [41], 2010 | 250 type 1 diabetic patients; NAFLD in 44.4% | US Patient history, chart review, ECG, doppler ultrasound of carotid and lower limb arteries | NAFLD was associated with higher prevalence of coronary, cerebrovascular and peripheral vascular disease than their counterparts without NAFLD, independently of traditional CVD risk factors and MetS features | |
| Sun et al [42], 2011 | 542 hospitalized Chinese patients with high suspicion of CHD; NAFLD in 46% | CT CAG (elective) | NAFLD was associated with greater severity of CHD, independently of traditional CVD risk factors | |
| Wong et al [43], 2011 | 612 Chinese patients with suspicion of CHD; NAFLD in 58% | US CAG (elective) | NAFLD was associated with CHD, independently of established CVD risk factors and MetS features | |
| Domanski et al [44], 2012 | 377 patients with NAFLD (retrospective chart review); 219 of these patients had NASH | Biopsy History of CVD (stroke, unstable angina, myocardial infarction, congestive heart failure, or need for coronary revascularization) | No increased prevalence of CVD in NASH patients compared with those with non-NASH fatty liver | |
| Agaç et al [45], 2013 | 80 Turkish patients with ACS; NAFLD in 81% | US CAG (acute) | NAFLD was independently associated with a greater severity of CHD (by Syntax score) | |
| Boddhi et al [46], 2013 | 95 consecutive non-diabetic Italian patients admitted for ACS; NAFLD in 87% | US CAG (acute) | Presence and severity of NAFLD was independently associated with a three-fold higher risk of multi-vessel CHD | |
| Inci et al [47], 2013 | 136 consecutive Turkish patients with CHD (stable angina or positive stress test results) | US CAG (elective) | NAFLD was associated with greater severity of CHD, independently of traditional CVD risk factors | |

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### Table 2  Main prospective studies relating non-alcoholic fatty liver disease to increased risk of incident coronary heart disease or cardiovascular events, ordered by methodology used for the diagnosis of non-alcoholic fatty liver disease

| Ref. | Study characteristics | Years of follow-up | NAFLD diagnosis | Study outcomes | Main findings |
|------|----------------------|--------------------|-----------------|---------------|---------------|
| Fraser et al[59], 2007 | Meta-analysis of 10 population-based cohort studies | 7.3 | Liver enzymes | Fatal and non-fatal CVD events | Elevated serum GGT level was associated with increased incidence of CVD events, independently of alcohol intake and traditional CVD risk factors and C-reactive protein |
| Schindhelm et al[60], 2007 | Population-based cohort, n = 1439 subjects (Hoorn Study) | 10.0 | Liver enzymes | Fatal and non-fatal CHD events | Elevated serum ALT level was associated with CHD events, independently of the MetS and traditional CVD risk factors |
| Goessling et al[61], 2008 | Community-based cohort, n = 2812 (Framingham Offspring Heart Study) | 20.0 | Liver enzymes | Fatal and non-fatal CVD events | Elevated serum ALT level was not associated with CVD events at multivariate analyses |
| Dunn et al[62], 2008 | Population-based cohort, n = 7574 (NHANES-Ⅲ) | 8.7 | Liver enzymes | All-cause and cause-specific mortality | Increased all-cause and CVD mortality rates in NAFLD but only in 45-54 year age group, independently of conventional CVD risk factors and C-reactive protein |
| Ong et al[63], 2008 | Population-based cohort, n = 11285 subjects (NHANES-Ⅲ) | 8.7 | Liver enzymes | All-cause and specific mortality | Increased rates of all-cause, CVD and liver-related mortality in NAFLD. Liver disease was the third leading cause of death among persons with NAFLD after CVD and cancer-related mortality |
| Ruhl et al[64], 2009 | Population-based cohort, n = 14950 (NHANES-Ⅲ) | 8.8 | Liver enzymes | All-cause and cause-specific mortality | Elevated serum GGT level was associated with mortality from all causes, liver disease but not from CVD causes. Serum ALT level was associated only with liver disease mortality |
| Yun et al[65], 2009 | Community-based cohort, n = 37085 (Health Promotion Center) | 5.0 | Liver enzymes | CVD or diabetes-related mortality | Elevated serum ALT level was independently associated with increased CVD or diabetes-related mortality |
| Calori et al[66], 2011 | Community-based-cohort, n = 2074 (Cremona study) | 15.0 | FLI index | All-cause and cause-specific mortality | FLI was independently associated with all-cause, hepatic, cancer and CVD mortality. When HOMA-insulin resistance was included in multivariate analyses, FLI retained its statistical association with hepatic-related mortality but not with all-cause, CVD and cancer-related mortality |
| Lerchbaum et al[67], 2013 | Consecutive sample of patients, n = 3270 subjects routinely referred to coronary angiography | 7.7 | FLI index | All-cause and cause-specific mortality | High FLI was independently associated with increased all-cause, CVD, non-cardiovascular and cancer mortality |
| Jepsen et al[68], 2003 | Population-based cohort, n = 1804 with hospital diagnosis of NAFLD (Danish national registry of patients) | 16.0 | US | All-cause and cause-specific mortality | Increased rates of all-cause, CVD and liver-related mortality in NAFLD, independently of sex, diabetes, and cirrhosis at baseline |
| Tagher et al[69], 2007 | Outpatient cohort, n = 2103 type 2 diabetic subjects (Valpolicella Heart Diabetes Study) | 6.5 | US | Fatal and non-fatal CVD | Increased rates of fatal and non-fatal CVD events in NAFLD, independently of age, sex, body mass index, smoking, diabetes duration, hemoglobin A1c, LDL-cholesterol, MetS features, medication use and cirrhosis at baseline |
| Soler Rodriguez et al[70], 2007 | Community-based cohort, n = 1637 healthy Japanese | 5.0 | US | Non-fatal CVD events | Increased rates of non-fatal CVD events in NAFLD, independently of age, sex, body mass index, alcohol intake, smoking, LDL-cholesterol, MetS features |
| Lazo et al[71], 2011 | Population-based cohort, n = 11371 (NHANES-Ⅲ) | 14.5 | US | All-cause and cause-specific mortality | NAFLD was not associated with increased all-cause and cause-specific (CVD, cancer and liver) mortality |
| Stepanova et al[72], 2012 | Population-based cohort, n = 11613 (NHANES-Ⅲ) | 14.2 | US | All-cause and cause-specific mortality | NAFLD was associated with increased prevalence of CVD, after adjusting for established CVD risk factors, but not with increased CVD mortality |
| Zhou et al[73], 2012 | Community-based cohort study, n = 3543 adult men and women with NAFLD (NHANES-Ⅲ) | 4.0 | US | All-cause and CVD mortality | Increased rates of all-cause and CVD mortality in NAFLD only among NAFLD patients with the MetS |
| Younossi et al[74], 2013 | Population-based cohort, n = 1448 with NAFLD (NHANES-Ⅲ) | 14.2 | US | All-cause and cause-specific mortality | NAFLD was independently associated with increased all-cause, CVD and liver-related mortality only among NAFLD patients with the MetS |
### Table 1: Published Studies Assessing CHD/Cardiovascular Risk of NAFLD Histology or Ultrasonography

| Study | Study Design | Cohort Characteristics | NAFLD Diagnosis Method | Risk Comparison | Risk of Cardiac and Arrhythmic Complications |
|-------|--------------|------------------------|------------------------|----------------|---------------------------------------------|
| Treeprasertsuk et al. (2012) | Community-based cohort, 309 patients with NAFLD | US and CT | Fatal and non-fatal CHD | NAFLD patients had a higher 10-year CHD risk by FRS than the general population of the same age and sex. | Increasing liver-related mortality with the severity of NAFLD histology (according to four different histological subtypes). All-cause mortality and other causes of mortality were not significantly different across histological subtypes. |
| Matteoni et al. (1999) | Patient-based cohort, 132 patients with NAFLD | Histology | All-cause and cause-specific mortality | All-cause and cause-specific mortality did not significantly differ between patients with non-alcoholic SS and the general population. | Increased rates of CVD and liver-related mortality in patients with NAFLD, but not in those with SS, compared with the reference population. |
| Dam-Larsen et al. (2004) | Patient-based cohort (Danish national registry of patients), 109 subjects with non-alcoholic SS | Histology | All-cause and cause-specific mortality | All-cause and cause-specific mortality was higher in NASH vs non-NASH. No comparison was provided with the general population. | Increased rates of CVD and liver-related mortality in patients with NAFLD, but not in those with SS, compared with the reference population. |
| Adams et al. (2005) | Community-based cohort, 420 patients with NAFLD | US/CT and histology | All-cause and cause-specific mortality | All-cause and cause-specific mortality did not significantly differ between patients with non-alcoholic SS and the general population. | Increased rates of CVD and liver-related mortality in patients with NAFLD, but not in those with SS, compared with the reference population. |
| Ekstedt et al. (2006) | Patient-based cohort, 129 consecutive patients with NAFLD and elevated serum liver enzymes | Histology | All-cause and cause-specific mortality | CHD was the first cause of death in NAFLD cohort with no difference between NASH and non-NASH. Liver-related mortality, but not all-cause mortality, was higher in NASH vs non-NASH. No comparison was provided with the general population. | Increased rates of CVD, malignancy and liver disease in patients with NASH, but not in those with SS, compared with the matched general population. |
| Rafiq et al. (2009) | Patient-based cohort, 173 patients with NAFLD (41.6% NASH) | Histology | All-cause and cause-specific mortality | CHD was the first cause of death in NAFLD cohort with no difference between NASH and non-NASH. Liver-related mortality, but not all-cause mortality, was higher in NASH vs non-NASH. No comparison was provided with the general population. | Increased rates of CVD, malignancy and liver disease in patients with NASH, but not in those with SS, compared with the reference population. |
| Söderberg et al. (2010) | Patient-based cohort, 118 patients with NAFLD and elevated serum liver enzymes (43% NASH) | Histology | All-cause and cause-specific mortality | CHD was the first cause of death in NAFLD cohort with no difference between NASH and non-NASH. Liver-related mortality, but not all-cause mortality, was higher in NASH vs non-NASH. No comparison was provided with the general population. | Increased rates of CVD, malignancy and liver disease in patients with NASH, but not in those with SS, compared with the reference population. |

AST: Alanine aminotransferase; CHD: Coronary heart disease; CT: Computed tomography; FLI: Fatty liver index; FRS: Framingham risk score; GGT: Gamma-glutamyltransferase; HOMA: Homeostasis model assessment; MetS: Metabolic syndrome; NASH: Non-alcoholic steatohepatitis; SS: Simple steatosis; CVD: Cardiovascular.

by either serum liver enzyme levels or ultrasonography, was strongly associated with an increased risk of fatal and non-fatal CVD events. In contrast, and surprisingly, two recent studies, using the data from the National Health and Examination Survey (NHANES)-Ⅲ database of over 11000 United States adults, have reported that NAFLD on ultrasonography did not significantly predict the risk of all-cause and cause-specific (CVD, cancer or liver) mortality over 14 years of follow-up period\(^\text{[64]}\). These two studies, however, were limited by the inclusion of individuals with mild hepatic steatosis within the control arm. Interestingly, the lastest analyses of the same NHANES-Ⅲ cohort found that patients with NAFLD and advanced hepatic fibrosis (as defined by either the NAFLD fibrosis score or Fib-4 score) were indeed at increased risk of CVD mortality after adjustment for established CVD risk factors\(^\text{[65]}\). In addition, Younossi et al.\(^\text{[66]}\) found that NAFLD was independently associated with increased all-cause, liver-specific and CVD mortality among patients with NAFLD who had the metabolic syndrome but not among those without this syndrome. With regard to biopsy-diagnosed NAFLD (as also shown in Table 2), some retrospective studies with a relatively small sample size but a reasonably long duration of follow-up, that have examined the natural history of patients with biopsy-confirmed NAFLD have consistently shown that the presence and severity of hepatic fibrosis on histology dictates all-cause and liver-related mortality in NAFLD, and that CVD is a common cause of death among such patients\(^\text{[66-71]}\). However, only two studies reported specific data about CHD outcomes rather than dealing with general CVD outcomes. Adams et al.\(^\text{[68]}\) found higher all-cause mortality in patients with NAFLD (as detected by radiological imaging or histology) than in the matched control population with CHD being the second cause of death in both populations. Again, Rafiq et al.\(^\text{[70]}\) reported that CHD was the first cause of death among patients with NAFLD but did not provide any comparison with the general population. Interestingly, two retrospective studies with a reasonably long duration of follow-up showed that patients with NASH, but not those with simple steatosis, were at substantially higher risk of CVD mortality compared with the reference population\(^\text{[69,71]}\). However, it should be noted that a complete adjustment for potentially confounding cardiometabolic factors was not performed in these retrospective studies. In addition, a recent meta-analysis concluded that patients with NAFLD (as detected by histology or ultrasonography) had a significantly greater risk of developing CVD events than the matched control population but that the historical severity of NAFLD did not increase CVD mortality\(^\text{[78]}\). However, further larger and longer prospective studies in patients with biopsy-confirmed NAFLD are needed to improve understanding of this issue.
| Ref.                             | Study characteristics                                                                 | NAFLD diagnosis         | Study measures                                                                 | Main findings                                                                                   |
|---------------------------------|---------------------------------------------------------------------------------------|-------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Ballestri S et al[77], 2013     | Case-control: 14 lean adolescents, 15 obese adolescents without NAFLD and 15 obese adolescents with NAFLD | Cardiac MRI and [31P]-MRS | Echocardiography with TDI (speckle tracking analyses)                        | Increased LV mass and impaired diastolic function in NAFLD. Decreased myocardial performance in obese adolescents with NAFLD. The presence of NAFLD was associated with LV hypertrophy independently of age and BMI. No differences in LV mass and systolic function between the groups. |
| Hallsworth et al[80], 2013      | Case-control: 19 non-diabetic, overweight adults with NAFLD and 19 age- and sex-matched healthy controls | [31P]-MRS and [1H]-MRS | Echocardiography with TDI (speckle tracking analyses) | Early impairment in systolic and diastolic function in NAFLD. Myocardial energy metabolism and LV mass were not altered in NAFLD. |
| Sert et al[85], 2013            | Case-control: 108 obese adolescents and 68 healthy controls                           | [1H]-MRS and [31P]-MRS | Echocardiography with TDI (speckle tracking analyses) | Increased LV mass and impaired diastolic function and altered global systolic and diastolic myocardial performance in obese adolescents with NAFLD. |
| Manzoni et al[89], 2011         | Case-control: newly-diagnosed untreated hypertensive patients (non-obese, non-diabetic): 48 NAFLD vs 38 controls | US and biopsy (29% of cases) | Echocardiography with TDI | Increased prevalence of diastolic dysfunction in NAFLD (according to its severity on ultrasound). LV mass was not different between the groups. Diastolic dysfunction and insulin resistance were independently associated with NAFLD. |
| Fallo et al[90], 2009           | Case-control: 35 non-diabetic, normotensive NAFLD patients and 30 age- and sex-matched healthy controls | US and biopsy (29% of cases) | Echocardiography with TDI | Increased LV mass and early impairment in systolic and diastolic function in NAFLD (no adjustment for potential confounders was made). |
| Bonapace et al[91], 2012        | Case-control: 21 non-diabetic, normotensive adults with CHD and hepatic diseases       | US and biopsy (29% of cases) | Echocardiography with TDI | Increased prevalence of LV hypertrophy in NAFLD. NAFLD was associated with LV hypertrophy independently of age, sex, BMI, systolic blood pressure, kidney function parameters and other diabetes-related variables. These abnormalities were worse in those with severe NAFLD on ultrasonography. No differences in LV mass and systolic function between the groups. |
| Mantovani et al[92], 2011       | Case-control: 38 non-diabetic, normotensive NAFLD patients and 25 age- and sex-matched healthy controls | US and biopsy (29% of cases) | Echocardiography with TDI | Increased LV mass and increased prevalence of diastolic dysfunction in NAFLD. Reduced E' wave only independent parameter associated with NAFLD on multivariate analysis. |
| Goland et al[93], 2006          | Case-control: 61 uncomplicated type 2 diabetic men without CHD (32 of whom with high intra-hepatic triglyceride content) | US and biopsy (29% of cases) | Echocardiography with TDI | Increased LV mass and increased prevalence of diastolic dysfunction in NAFLD. Reduced E' wave only independent parameter associated with NAFLD on multivariate analysis. |
| Rijzewijk et al[94], 2010       | Case-control: 38 uncomplicated type 2 diabetic men without CHD and 28 age, sex- and BMI-matched healthy controls | [31P]-MRS and [18F]-2-fluoro-2-deoxy-D-glucose | Echocardiography with TDI | Increased LV mass and increased prevalence of diastolic dysfunction in NAFLD. Reduced E' wave only independent parameter associated with NAFLD on multivariate analysis. |

Table 3  Cardiac imaging studies relating -non-alcoholic fatty liver disease to structural and arrhythmogenic cardiac complications

Abnormalities in myocardial metabolism

Perseghin et al[95], 2008  Case-control: 21 nondiabetic, nonobese, normotensive, young men with NAFLD and 21 age- and BMI-matched male controls

Rijzewijk et al[96], 2006  Case-control: 38 uncomplicated type 2 diabetic men without CHD and 28 age, sex- and BMI-matched healthy controls

Rijzewijk et al[97], 2008  Case-control: 38 uncomplicated type 2 diabetic men without CHD and 28 age, sex- and BMI-matched healthy controls

Rijzewijk et al[98], 2008  Case-control: 38 uncomplicated type 2 diabetic men without CHD and 28 age, sex- and BMI-matched healthy controls

Cardiac structure and function in adults

Goland et al[99], 2006  Case-control: 38 non-diabetic, normotensive NAFLD patients and 25 age- and sex-matched healthy controls

Fallo et al[100], 2009  Case-control: newly-diagnosed untreated hypertensive patients (non-obese, non-diabetic): 48 NAFLD vs 38 controls

Fotbolcu et al[101], 2010  Case-control: 35 non-diabetic, normotensive NAFLD patients and 30 age- and sex-matched healthy controls

Manzoni et al[102], 2011  Case-control: 116 consecutive older patients with hypertension and type 2 diabetes (53% of whom had NAFLD) without history of CHD and hepatic diseases

Bonapace et al[103], 2012  Case-control: 50 consecutive type 2 diabetic patients without CHD and hepatic diseases (32 patients had NAFLD)

Cardiac structure and function in children or adolescents

Hallsowth et al[104], 2013  Case-control: 19 non-diabetic, overweight adults with NAFLD and 19 age-, sex- and BMI-matched healthy controls

Alp et al[105], 2013  Case-control: 400 obese children (93 with NAFLD) and 150 age- and sex-matched healthy controls

Singh et al[106], 2013  Case-control: 14 lean adolescents, 15 obese adolescents without NAFLD and 15 obese adolescents with NAFLD

Sert et al[107], 2013  Case-control: 108 obese adolescents and 68 healthy controls
whether NAFLD poses an independent risk above and beyond known CVD risk factors. There is a suggestion in that direction, but studies are too few and methodologically not rigorous. Additional large-scale prospective studies of a more extensive panel of known risk factors are needed to draw a firm conclusion about any independent hepatic contribution to the increased risk of CHD/CVD events observed among patients with NAFLD.

### NAFLD and abnormalities in cardiac structure and function

Table 3 show the relevant data from the principal cardiac imaging studies that have evaluated the relationship between NAFLD and abnormalities in myocardial metabolism[7,8,76-80] and cardiac structure and function, both in adults[8,76-80] and in children or adolescents[81-84].

#### Abnormalities in cardiac metabolism: As reported in Table 3, Perseghin et al[1] showed that nondiabetic, non-obese, normotensive, young men with newly diagnosed NAFLD, as detected by proton magnetic resonance spectroscopy (1H-MRS), had excessive fat accumulation in the epicardial area and impaired left ventricular (LV) energy metabolism [as measured by the phosphocreatine/adenosine triphosphate (PCr/ATP) ratio] compared with age-, sex- and body mass index (BMI)-matched control subjects without NAFLD. These myocardial metabolic alterations were detected despite normal LV morphological features and systolic and diastolic functions[7].

Similarly, in a study of uncomplicated type 2 diabetic men without CHD, Rijzewijk et al[10], found that compared with those with lower intra-hepatic fat content, patients with higher intra-hepatic fat content on 1H-MRS had significantly decreased myocardial perfusion, glucose uptake and high-energy phosphate metabolism (i.e., decreased PCr/ATP ratio) but similar values of myocardial fatty acid metabolism, LV mass and function.

Similar findings were also reported by Lautamäki et al[28] in patients with type 2 diabetes and known CHD. Interestingly, these investigators found that myocardial insulin resistance was more severe among those with higher intra-hepatic fat content on 1H-MRS.

Again, Rijzewijk et al[3] found that the frequency of myocardial steatosis as diagnosed by cardiac 1H-MRS was much higher in type 2 diabetic patients than in healthy controls matched for age and BMI, and that higher myocardial fat content was associated with higher intra-hepatic fat content. Notably, although the two groups of subjects did not significantly differ in terms of LV mass and ejection fraction, multivariable regression analyses revealed that myocardial steatosis was associated with LV diastolic dysfunction, independently of diabetic state, age, BMI, visceral adipose tissue, heart rate and blood pressure[3].

#### Abnormalities in cardiac structure and function in adults: As reported in Table 3, there is to date an increasing number of case-control studies that have evaluated the effect of NAFLD on cardiac structure and function in adults with or without co-existing established CVD risk factors (e.g., obesity, hypertension or diabetes)[87-88].

Goland et al[74] and Forbolcu et al[81] have shown a marked LV diastolic dysfunction and mild alterations in LV structure in patients with NAFLD, in the absence of hypertension, diabetes and severe obesity. Again, in a recent study examining cardiac status by high resolu-
tion MRI and $^{31}$P-MRS in a small group of NAFLD patients (defined as >5% intra-hepatic lipid on $^1$H-MRS), Hallsworth et al.\cite{88} have demonstrated significant changes in cardiac structure and evidence of early LV diastolic dysfunction compared with age-, sex- and BMI-matched controls, in the absence of cardiac metabolic changes or overt cardiac disease.

In a study of 86 never-treated hypertensive patients, who were subdivided in two subgroups according to the presence or absence of NAFLD on ultrasonography, Fallo et al.\cite{77} reported that patients with NAFLD had a three-fold greater prevalence of LV diastolic dysfunction than their counterparts without NAFLD.

In a study of older hypertensive patients with type 2 diabetes, who did not have a pre-existing history of CHD and hepatic diseases, Mantovani et al.\cite{79} found that the prevalence of LV hypertrophy on conventional echocardiography was four-fold greater among patients with NAFLD than among those without this disease.

In a recent study, involving 50 consecutive type 2 diabetic adults without history of CHD, excessive alcohol consumption or other known hepatic diseases, we found that early features of LV diastolic dysfunction could be detected by tissue doppler imaging in those with ultrasound-diagnosed NAFLD, even if the LV morphology and systolic function were preserved\cite{81}. Measurements of LV global longitudinal strain and strain rate by speckle tracking analyses further confirmed these findings. Notably, there was a positive, graded relationship between the ultrasonographic severity of NAFLD and LV diastolic dysfunction, independently of hypertension and other co-existing cardio-metabolic risk factors\cite{82}.

Abnormalities in cardiac structure and function in children and adolescents: As reported in Table 3, some recent published papers have addressed the relationship between NAFLD and changes in cardiac structure and function also in the pediatric population\cite{81-84}.

In a study including 93 obese children with ultrasound-diagnosed NAFLD, 307 obese subjects without liver involvement, and 150 age- and sex-matched healthy controls, Alp et al.\cite{86} showed that subclinical systolic and diastolic impairment could be detected by tissue doppler imaging in obese children with NAFLD. Also, cardiac dysfunction progressively increased with ultrasonographic scores of hepatic steatosis.

Recently, Singh et al.\cite{82} measured by 2-D speckle tracking echocardiography myocardial function in three small groups of age-, sex- and Tanner-matched adolescents and showed that obese adolescents with NAFLD had greater abnormalities of cardiac function, manifested by decreased systolic and diastolic myocardial strain and strain rate than obese adolescents without NAFLD. These myocardial functional abnormalities were independent of conventional CVD risk factors and insulin resistance\cite{83}. Similar findings were reported by Sert et al.\cite{84} in a larger sample of obese adolescents.

Finally, Pacifico et al.\cite{86} found that obese children with histologically confirmed non-alcoholic steatohepatitis (NASH) had more severe abnormalities in LV systolic and diastolic functions compared with those without NASH, independently of underlying cardio-metabolic abnormalities.

Risk of congestive heart failure: From the data of the available literature, it is plausible to assume that patients with NAFLD have changes in cardiac substrate metabolism (e.g., myocardial insulin resistance, impaired high-energy phosphate metabolism, and reduced mitochondrial ATP production), producing myocardial functional and structural consequences (e.g., LV dysfunction and hypertrophy) that are potentially linked to an increased rate of congestive heart failure (HF) in this patient population.

As regards to this, two recent large population-based cohort studies that used elevated serum liver enzyme levels, as proxy markers of NAFLD (and should therefore be interpreted cautiously) have shown that this disease is associated with an increased risk of incident congestive HF, independently of alcohol consumption and several established CVD risk factors\cite{31,32}.

In the original cohort of the 3544 Framingham Study participants, who were free of HF and myocardial infarction, Dhingra et al.\cite{77} reported that higher serum GGT concentrations within the “normal” range were independently associated with greater risk of incident HF (i.e., each SD increase in log-GGT was associated with a 1.4-fold risk of HF) and incrementally improved prediction of HF risk during a mean follow-up period of 24 years.

Similarly, in a population-based cohort study of 3494 British men aged 60 to 79 years with no diagnosed HF or myocardial infarction followed up for a mean period of 9 years, Wannamethee et al.\cite{80} reported that elevated serum GGT level (top quartile, ≥ 38 U/L) was associated with significantly increased risk of incident HF, especially in men aged <70 years. The increased risk of HF associated with elevated serum GGT level persisted after adjustment for a wide range of established and novel risk factors for HF, including also lung function, plasma C-reactive protein and N-terminal pro-brain natriuretic peptide levels. Other liver function markers showed no significant associations with the risk of HF after similar adjustments\cite{86}.

NAFLD and cardiac arrhythmias

Table 3 shows the relevant data from the published studies that have examined the association between NAFLD and the risk of cardiac arrhythmias, specifically AF\cite{88-91}.

To date, AF is the most common sustained arrhythmia seen in clinical practice, and its prevalence and incidence are expected to increase substantially over the next few decades because of ageing population and improvements in cardiovascular treatments\cite{92}. This underscores the urgent need for primary prevention strategies against the development of AF.

Increased risk of AF: As reported in the Table 3, the
investigators of the Framingham Heart Study have shown that elevated serum ALT or aspartate aminotransferase (AST) levels (> 40 U/L for either marker) were closely associated with an increased risk of incident AF over a 10-year follow-up period among 3744 United States white adults, who were free from clinical HF at baseline[87]. During follow-up, 383 subjects developed AF and both serum transaminases were found to be significantly associated with a greater risk for incident AF (hazard ratio expressed per SD of natural logarithmically transformed biomarker: ALT hazard ratio 1.19, 95%CI: 1.07-1.32, P = 0.002; AST hazard ratio 1.12, 95%CI: 1.01-1.24, P = 0.03) after adjusting for a broad number of clinical AF risk factors. The association between serum transaminases and incident AF remained consistent even after the exclusion of participants with moderate to heavy alcohol consumption[87].

More recently, in an observational study, involving 702 hospitalized patients with type 2 diabetes (73% of whom had NAFLD and 12% had persistent or permanent AF), we found that NAFLD on ultrasonography was associated with a about 3-fold higher prevalence of AF, independently of multiple established risk factors for AF[9].

Additionally, in another recent study, we have shown that type 2 diabetic patients with NAFLD were also more likely to develop incident AF over a 10-year follow-up period than their counterparts without NAFLD. In particular, NAFLD on ultrasonography was strongly associated with an increased risk of incident AF (adjusted OR = 4.96, 95%CI: 1.4-17.0, P < 0.01), independently of age, sex, BMI, hypertension and other variables that were included in the 10-year Framingham Heart Study-derived AF risk score[9].

Increased risk of ventricular arrhythmias: To date, there is a paucity of published data regarding the association between NAFLD and risk of ventricular arrhythmias, which are an established risk factor for sudden cardiac death in the general population.

However, it is plausible that various mechanisms that have been proposed to explain the specific contribution of NAFLD to CVD risk (including hepatic insulin resistance, systemic low-grade inflammation and a pro-thrombotic state)[9,10,13-16], might be, at least in part, implicated in the pathogenesis of ventricular arrhythmias.

Heart rate variability, which is a measure of the balance of the sympathetic and parasympathetic mediators of heart rate, and QTc interval prolongation on standard electrocardiograms have been proposed as useful tools in identifying patients at risk for sudden cardiac death[89]. For instance, QTc interval prolongation is a powerful predictor of ventricular tachyarhythmias, and predicts increased cardiac and all-cause mortality both in patients with type 2 diabetes and in those without diabetes[90-92].

Recently, in a study of 497 non-diabetic subjects without a history of previous CVD, Liu et al[93] reported that patients with ultrasound-diagnosed NAFLD had early cardiac autonomic dysfunction as detected by some parameters of heart rate variability measured during a 5-min Holter monitoring examination compared with those without NAFLD. The reduction in these Holter-derived parameters was independent of conventional cardiovascular risk factors, insulin resistance and circulating leptin levels[93]. Additionally, in a small study of non-diabetic people comprising a group of people with histologically proven, non-cirrhotic NAFLD and an age-, sex- and BMI-matched control group, there was evidence of cardiac autonomic dysfunction, presenting as orthostatic hypotension, vasovagal syncope (during head up tilt testing) and/or a relative nocturnal hypotension[94].

More recently, we examined whether NAFLD was associated with longer QTc intervals on standard electrocardiograms in 400 randomly selected patients with type 2 diabetes without a documented history of AF, moderate-to-severe heart valve disease, hepatic diseases or excessive alcohol consumption. Notably, we found that the presence and severity of NAFLD on ultrasonography was associated with prolonged QTc interval (adjusted OR = 2.27, 95%CI: 1.4-3.7, P < 0.001), independently of age, sex, hypertension, electrocardiographic LV hypertrophy, hemoglobin A1c and other potential confounders (manuscript under submission).

Collectively, although the arrhythmogenic potential of NAFLD requires further testing and confirmation in larger studies, we believe that this is a promising field of research to explore, and that the pathways that involve the contribution of NAFLD itself to systemic/hepatic insulin resistance and the systemic release of several pro-inflammatory, pro-coagulant and pro-fibrogenic mediators from the steatotic and inflamed liver[13-16], might provide a potential therapeutic target for the treatment and prevention of cardiac remodelling and electrophysiological abnormalities of the myocardium in people with NAFLD.

NAFLD and aortic valve sclerosis

Until recently, aortic valve sclerosis (AVS), defined as focal or diffuse thickening and calcification of the aortic leaflets without restriction of leaflet motion, was considered an incidental echocardiographic finding of no clinical significance, as it does not obstruct left ventricular outflow.

However, it is known that AVS shows some epidemiologic and histopathologic similarities to coronary atherosclerosis[95]. In addition, large prospective studies have suggested a strong, positive association between AVS and adverse CVD outcomes, independently of conventional CVD risk factors, both in nondiabetic and diabetic individuals[96-98]. The prevalence of AVS increases progressively with advancing age and is approximately 20%-30% in individuals aged ≥ 65 years[96,97].

Notably, Markus et al[99] have examined for the first time the association between NAFLD and AVS in a community-based cohort study of 2212 German men and women aged ≥ 45 years. In this cross-sectional study,
NAFLD diagnosed by ultrasonography was significantly associated with an increased risk of prevalent AVS on echocardiography (OR = 1.32, 95%CI: 1.3-7.3, P = 0.01), even after adjusting for several established CVD risk factors, including kidney function parameters, C-reactive protein, serum ferritin, and white blood cells.

Although these results are still unpublished, we have recently confirmed and expanded to patients with type 2 diabetes the interesting observations of the Markus’s study, providing further strong evidence that NAFLD and AVS are two inter-related pathologic conditions, in part independent from traditional CVD risk factors and diabetes-related variables. In such preliminary study, involving 180 consecutive type 2 diabetic outpatients without a history of prior CHD, hepatic diseases or excessive alcohol consumption, we found that ultrasound-diagnosed NAFLD was strongly associated with AVS (adjusted OR = 3.04, 95%CI: 1.3-7.3, P = 0.01), independently of multiple established CVD risk factors and diabetes-related variables.

However, future research is needed to corroborate these findings in independent samples, to elucidate the responsible mechanisms for this association, and to determine whether NAFLD predicts the development and progression of AVS.

PUTATIVE MECHANISMS LINKING NAFLD WITH STRUCTURAL AND ARRHYTHMOGENIC CARDIAC COMPLICATIONS

The pathophysiological mechanisms that link NAFLD with CHD, AVS, myocardial dysfunction/hypertrophy and cardiac arrhythmias are incompletely understood.

The complex interactions among NAFLD, insulin resistance and visceral obesity make it extremely difficult to dissect out the precise causal relationships responsible for the increased risk of CHD and other cardiac and arrhythmic complications observed in patients with NAFLD. Different pathogenetic theories and mechanisms, not mutually exclusive, may be put forward (as also schematically reported in Figure 1) and some key research questions remain to be addressed.

To date, it remains debatable whether NAFLD is merely a risk marker of co-existing metabolic disorders and ectopic fat deposition in other organs (such as visceral adipose tissue, myocardium and pericardium) in people at increased risk for cardiac and arrhythmic complications, or is an independent risk factor for the development and progression of such cardiac complications. Another unanswered question is whether the risk of cardiac and arrhythmic events is also increased in patients with simple steatosis or whether the hepatic necro-inflammatory milieu of NASH is a necessary pro-atherogenic and pro-thrombotic stimulus.

Accumulating evidence suggests that within the spectrum of disease encapsulated by NAFLD, the presence of NASH exacerbates systemic and hepatic insulin resistance and causes atherogenic dyslipidemia (typically characterized by high triglycerides, low HDL-cholesterol and increased small, dense LDL particles). In NASH there is also increased production of a variety of pro-inflammatory markers (e.g., C-reactive protein, interleukin-6, tumor necrosis factor-alpha), pro-coagulant factors (e.g., fibrinogen, factor VIII, plasminogen activator inhibitor-1), pro-oxidant molecules (e.g., oxidized low-density lipoprotein cholesterol, thiobarbituric acid-reacting substances, nitrotyrosine), and pro-fibrogenic mediators (e.g., tumor growth factor-beta, insulin-like growth factor-1, endothelin-1). Moreover, the release of key components of the renin-angiotensin-aldoosterone system, that may contribute to the pathophysiology of hypertension, is also increased in patients with NASH. The experimental findings that NASH is associated with abnormal intra-hepatic messenger RNA expression of these potential mediators of cardiac and vascular injury, further support the conclusion that the increased circulating levels of the aforementioned biomarkers result from the up-regulation of their own synthesis in the steatotic and inflamed liver. Some experimental studies have also shown that a number of the genes involved in fatty acid metabolism, lipolysis, monocyte and macrophage recruitment, coagulation, and inflammation are over-expressed in livers of patients with NASH.

It is plausible that the liver-secreted factors, mentioned above, may also play a pathogenic role in the development and progression of AVS (i.e., a condition that shares some epidemiologic and histopathologic similarities with coronary atherosclerosis) as well as in the development and persistence of AF and other arrhythmias, possibly by inducing cardiac remodelling and electrophysiological abnormalities of the myocardium in people with NAFLD. For instance, some studies reported that increased inflammatory biomarkers, including elevated C-reactive protein levels, are associated with an increased risk of both new-onset AF and persistence or recurrence of AF after catheter ablation.

Overall, therefore, there is to date a growing body of evidence suggesting that NAFLD is not a simple epiphenomenon but is, at least in part, involved in the pathophysiology of CHD and other cardiac and arrhythmogenic complications, possibly through the contribution of NAFLD itself to systemic and hepatic insulin resistance and atherogenic dyslipidemia, and/or through the hepatic secretion of several pathogenic mediators (as schematically reported in Figure 1).

The primary role of insulin resistance in the development and progression of NAFLD has been recently challenged. Similarly, some evidence suggests that insulin resistance per se does not directly promote atherosclerosis but it does so principally by promoting atherogenic dyslipidemia and other cardiometabolic abnormalities. Accordingly, perturbed lipid homeostasis could play a key role in accelerated atherogenesis observed in patients with NAFLD/NASH. Further evidence for a specific
role of NAFLD in the development of atherogenic dyslipidemia has been also recently published\(^{114,115}\). Again, post-prandial lipemia might represent an additional, under-diagnosed lipid abnormality that further links NAFLD to accelerated atherogenesis\(^{102,116,117}\).

Recent research has also shown that patients with NAFLD exhibit cardiac autonomic dysfunction\(^{103,104,118,119}\), a pathophysiological derangement that is, at least in part, reversible following resistance exercise training\(^{120}\). It is plausible that cardiac autonomic dysfunction, resulting from the co-existing dysmetabolic and inflammatory milieu of NAFLD, may contribute together with abnormalities of myocardial structure and function to the development and persistence of AF and other cardiac arrhythmias.

Altered sleep physiology is another emerging risk factor for NAFLD\(^{121}\). Recent epidemiological and experimental data suggest a strong link between disturbed sleep physiology and the histological severity of NAFLD\(^{121,122}\). Obstructive sleep apnea (OSA) is a complex disorder typically characterized by repetitive apnea-hypopnea cycles during sleep, which are associated with chronic intermittent hypoxia and sleep fragmentation\(^{123}\). Symptomatic OSA (also known as obstructive sleep apnea syndrome, or OSAS) is very common in people with severe obesity or type 2 diabetes. Controlled trials have demonstrated that OSAS causes hypertension, and prospective epidemiological studies have indicated that OSAS might be an independent risk factor for incident stroke and CHD\(^{122}\).

Collectively, as also mentioned above, it is important to underline that a clear understanding of the pathophysiological pathways that link NAFLD to the development of structural and arrhythmogenic cardiac complications remains lacking because of the complex and intertwined

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**Figure 1** Possible mechanisms leading to cardiac and arrhythmogenic complications in non-alcoholic fatty liver disease. The close and complex inter-relationships among non-alcoholic fatty liver disease (NAFLD), visceral obesity and insulin resistance make it extremely difficult to dissect out the specific role of the liver and the underlying mechanisms responsible for the association between NAFLD and the risk of developing coronary heart disease (CHD), aortic valve sclerosis, left ventricular (LV) dysfunction/hypertrophy and arrhythmias. NAFLD might be associated with such complications either as a consequence of shared cardiometabolic risk factors and co-morbidities or as a marker of ectopic fat accumulation in other organs. For instance, myocardial steatosis and increased pericardial fat volume might exert local adverse effects that result in functional and structural derangements of the myocardium. Such myocardial remodelling will likely also result in pro-arrhythmogenic effects. The occurrence of cardiac arrhythmias is likely facilitated in remodeled heart by (local) pro-inflammatory cytokines, chemokines and concurrent cardiac autonomic dysfunction occurring on this dysmetabolic milieu. However, in this dangerous scenario, which may potentially account for premature CHD and increased risk of arrhythmias, NAFLD seems to be not simply a marker of cardiac and arrhythmogenic complications but also may play a part in their pathogenesis possibly via atherogenic dyslipidemia and the hepatic secretion of several pathogenic mediators into the bloodstream. HDL-C: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein; CRP: C reactive protein; IL: Interleukin; TNF: Tumor necrosis factor; PAI-1: Plasminogen activator inhibitor-1; TGF: Transforming growth factor.
inter-relationships among NAFLD, visceral obesity and insulin resistance. It is likely that there is a pathogenic cross-talk between the liver and the expanded adipose tissue. As shown in schematic Figure 1, the putative underlying mechanisms that link NAFLD to cardiovascular, cardiac and arrhythmic complications might originate from the expanded and inflamed visceral adipose tissue (which increases the rate of free fatty acids and releases multiple adipokines), with the liver functioning as both the target of the resulting systemic abnormalities and the source of several molecular mediators that amplify the cardiac and vascular damage. However, further research is required to define the major sources of some pro-inflammatory and pro-thrombotic mediators (i.e., to determine the relative contributions of visceral adipose tissue and the liver itself), as well as to uncover other specific mechanisms by which NAFLD may contribute to the development and progression of cardiac and arrhythmic complications. An improved knowledge of the pathophysiological links of NAFLD with cardiac and arrhythmic complications might also provide a potential target for the pharmacological treatment of these diseases.

POTENTIAL IMPACT OF NAFLD TREATMENT ON CARDIAC COMPLICATIONS

Presently, there is no licensed treatment for human NAFLD. Most interventions evaluated for the treatment of NAFLD are those commonly used for the treatment of type 2 diabetes and exert a rather indirect effect through improvement in insulin resistance and glycemia. The treatment of NAFLD has also been proposed as a tool to effectively reduce the CVD risk of this group of patients by treating the co-existing features of the metabolic syndrome through a tailored treatment four-step pyramid choice.

The first step to be offered to all patients with NAFLD includes lifestyle modifications such as hypocaloric diet, increased physical activity and smoking cessation. Pharmacotherapy for NAFLD should probably be reserved for patients with NASH or those with co-existing cardiometabolic disorders amenable to specific drug therapy such as obesity, dyslipidemia, hypertension and type 2 diabetes. Of concern, however, there appears to be a dissociation in the actions of some classes of drugs, benefits on the liver side being counter-balanced by (some) important extra-hepatic side effects.

Here, we will briefly discuss whether and how some specific treatment interventions for NAFLD might also beneficially affect the development and progression of cardiac and arrhythmic complications.

Lifestyle modifications

Weight loss obtained through diet alone or combined with physical exercise significantly reduces hepatic steatosis and necro-inflammatory changes of people with NAFLD in proportion to the entity of body weight reduction (5%-10% weight loss reduces hepatic steatosis, while up to a 10% weight loss is needed to improve the degree of hepatic necro-inflammation). However, no study of lifestyle modification has been able to demonstrate an improvement in hepatic fibrosis stage. Interestingly, physical exercise may improve hepatic steatosis and serum liver enzymes in patients with NAFLD, independent of any change in body weight. A recent randomized controlled trial reported that 4 mo of resistance training and aerobic training are equally effective in reducing intra-hepatic fat content among patients with type 2 diabetes and NAFLD.

Lifestyle changes may result in reduced CVD risk improvements in atherogenic risk profile (e.g., blood pressure, glycemia and lipids) and myocardial structure and function. Regular exercise may also exert some of its beneficial health effects by inducing anti-inflammatory actions. Interestingly, physical activity reduced all-cause and CVD mortality in patients with type 2 diabetes with mildly elevated plasma C-reactive protein levels, whereas this beneficial effect was not observed in those with normal C-reactive protein levels, suggesting that the decrease in CVD mortality in physically active patients may reflect an anti-inflammatory effect of exercise independent of traditional CVD risk factors.

Finally, bariatric surgery, which should be reserved to patients with severe obesity, has been associated with beneficial and sustained improvements of liver histology in people with NAFLD/NASH.

Insulin sensitizers

Indications and limitations for the use of insulin-sensitizing drugs in patients with NAFLD/NASH have been reviewed in detail elsewhere. Although metformin, which is the first-line choice in oral therapy for type 2 diabetes, has been reported to moderately reduce the risk of developing hepatocellular carcinoma, it exerts only a marginal beneficial effect on serum aminotransferase levels but does not improve liver histology in NAFLD.

Glitazones (especially pioglitazone) reduce systemic insulin resistance and improve hepatic steatosis and necro-inflammation, but not hepatic fibrosis, in patients with biopsy-proven NASH; unfortunately, however, the hepato-protective effects of glitazones vanish after drug treatment discontinuation. Of concern, the use of glitazones is limited by their potential serious CVD side effects. Rosiglitazone has been withdrawn from the market because of increased risk of non-fatal myocardial infarction. Pioglitazone only marginally reduces the risk of major CVD events in people with type 2 diabetes but causes significant weight gain (by increased subcutaneous fat deposits), and increases the risk of congestive HF and bone fractures. A slightly increased risk of bladder cancer has also recently led to pioglitazone being withdrawn from market in France. Therefore, the potential benefits of glitazones on the liver are counterbal-
anced by their lack of benefits on cardiovascular system, suggesting that the reduction of CVD risk needs a more global approach than just glucose control\[109\].

**Glucagon-like peptide-1 analogues**

Glucagon-like peptide (GLP-1) analogues (exenatide and liraglutide) further to their hypoglycemic effects are potent appetite suppressants and promote body weight reduction\[160\]. Animal data suggest that GLP-1 analogues may be useful for the treatment of NAFLD\[152,153\]. Adjunctive exenatide treatment for at least 3 years in obese patients with type 2 diabetes resulted in body weight reduction and sustained improvements in glycemic control and serum liver enzyme levels\[154\]. Other small intervention trials reported that GLP-1 analogues significantly reduced intra-hepatic fat content on H-MRS and improved serum aminotransferase levels in obese patients with type 2 diabetes\[155,156\]. However, further larger and longer randomized clinical trials with histological endpoints are needed to establish a beneficial effect of these drugs for the treatment of NAFLD/NASH. Although still not conclusive, a possible cardio-protective effect of GLP-1 analogues has been recently supported by small animal and human studies\[157\].

**Statins**

Despite their limited benefits on NAFLD, where statins may produce some improvement in serum aminotransferases and hepatic steatosis (hepatic necro-inflammation and fibrosis remaining unaffected), statins represent a unique class of drugs\[125,126\]. Such a specificity results from the statin use having been shown to be associated with reduced CVD morbidity in patients with mildly-to-moderately abnormal liver function tests potentially attributable to NAFLD\[158,159\]. Moreover, statins are the most effective and widely used class of lipid-lowering drugs for the primary and secondary prevention of CVD, and may also exert a potentially beneficial role in primary and secondary chemoprevention of hepatocellular carcinoma\[160\].

Ezetimibe is another lipid-lowering agent, which reduces the intestinal uptake of dietary cholesterol through inhibiting Niemann-Pick C1-like 1 protein, the main transporter of intestinal cholesterol in jejunum, which is also expressed on hepatocytes at the level of canalicular membrane\[161\]. Although not tested in randomized clinical trials, preliminary evidence in mice and humans suggests that treatment with ezetimibe may exert some improvement in NAFLD histology\[162,163\].

The CVD benefits of the combination of statins and ezetimibe have been largely reported in the literature\[164\].

**Omega-3 polyunsaturated fatty acids**

Omega-3 polyunsaturated fatty acids (PUFA) are useful for the treatment of mild-to-moderate hypertriglyceridemia, which is often associated with insulin resistance and NAFLD. A recent systematic review has shown a significant reduction in hepatic fat content (without any substantial side effects), although the effect size was relatively small\[165\]. However, optimal dose and duration of this therapy need to be addressed in future large clinical trials before recommending omega-3 PUFA supplementation for the treatment of NAFLD.

Although omega-3 PUFAs have also shown to reduce cardiovascular system, angiogenesis in mice and sudden cardiac death in patients with previous acute myocardial infarction\[166\], however, their role in the primary prevention of CVD in at high-risk patients has recently been challenged by the results of a large randomized clinical trial\[167\].

**Angiotensin receptor blockers**

The renin-angiotensin-aldosterone system is involved in the pathogenesis of insulin resistance, NAFLD and target organ damage\[167\]. Angiotensin II increases insulin resistance, exacerbates the systemic inflammatory response by inducing reactive oxygen species and inflammatory cytokines, and stimulates the release of free fatty acids and triglycerides from the liver, thus further increasing systemic insulin resistance\[168\].

Some animal and human studies have suggested that angiotensin receptor blockers improve serum liver enzyme and histologic features of NAFLD. Specifically, telmisartan attenuated NASH progression in mice by suppressing the macrophage infiltration into the liver. Telmisartan also affected the reduction of adipocyte size and elevation of serum adiponectin in these animals\[159\]. Treatment with losartan for 48 wk was associated with some improvement in liver histology in a small sample of hypertensive patients with NASH. However, further larger clinical trials are needed to corroborate these findings\[153,154\].

It is well established that angiotensin receptor blockers reduce blood pressure values and also improve glucose tolerance and insulin sensitivity, thus contributing to further reduce the risk of CVD events even through the prevention of new-onset type 2 diabetes\[171,172\].

**Vitamin D**

Vitamin D\(_3\) has a key role in calcium homeostasis and bone mineralization, and has recently been implicated in the regulation of glucose and lipid metabolism, adipokine production and homeostasis of bile acids\[173\]. Vitamin D\(_3\)-deficiency is a highly prevalent condition worldwide, present in approximately 30%-60% of the general adult population\[174\].

A recent meta-analysis of 17 cross-sectional and case-control studies has shown that patients with NAFLD had about 0.35 ng/mL lower levels of serum 25-hydroxyvitamin D\(_{3}\) [25(OH)D\(_{3}\)] and were 1.3 times more likely to be vitamin D deficient than control subjects without NAFLD\[175\]. Our group also reported that serum 25(OH)D\(_{3}\) levels were inversely associated with the histological severity of hepatic steatosis, necro-inflammation and fibrosis, independently of age, sex, season measurement, metabolic syndrome features and kidney function parameters, among patients with histologically proven, non-cirrhotic NAFLD\[176\]. Preliminary experimental evi-
idence suggests that via effects in both adipose tissue and liver, low serum levels of vitamin D may predispose to hepatic steatosis and necro-inflammation, contributing to the development and progression of NAFLD.\cite{177}

Notably, accumulating evidence from observational, prospective studies suggests that lower serum 25(OH)D$_3$ levels were strongly associated with higher risks of developing type 2 diabetes, metabolic syndrome and CVD events.\cite{3,178,179,180} A recent community-based study also reported that lower serum 25(OH)D$_3$ levels were significantly associated with abnormalities in cardiac structure and function in elderly patients without a prior history of myocardial infarction, heart failure or valvular heart disease.\cite{181} However, larger and longer randomized clinical trials are needed to ascertain whether vitamin D supplementation may improve NAFLD and reduce the incidence of adverse CVD outcomes.

Given the increased risk for cardiovascular, cardiac and arrhythmic complications observed in patients with NAFLD and the strong association of NAFLD with the metabolic syndrome, we believe that all cardiometabolic risk factors should be carefully and routinely screened among patients with NAFLD, and that greater emphasis should be placed on both specific lifestyle modifications (i.e., weight loss, increased physical activity and smoking cessation) and aggressive pharmaceutical risk factor modification, which would not only reduce the risk of progressive liver disease, but could also positively impact on the risk of developing structural and arrhythmogenic cardiac complications in this patient population.

CONCLUSION

The relationship between NAFLD and an increased prevalence of clinical CHD appears to be robust, both in adults and in adolescents, and has been consistently replicated across different populations.

However, the specific and independent contribution of NAFLD per se to the development and progression of structural and arrhythmogenic cardiac complications is much more controversial. Whether NAFLD is simply a concurrent risk marker in people at increased risk for structural and arrhythmogenic cardiac complications, or is an independent risk factor for the development of such complications remains to be entirely ascertained. Moreover, uncertainty exists about the prognostic value of NAFLD in risk stratification for CHD/CVD. Clearly, more extensive and well-designed prospective studies are needed to answer these key research questions. In theory, such a line of research promises to promote our ability to delay or prevent the development and progression of cardiovascular, cardiac and arrhythmic complications in people with NAFLD.

In conclusion, far from being a benign and “para-physiological” condition, NAFLD should be viewed as a complex and multi-faceted disease often calling for multi-disciplinary intervention. Awareness of NAFLD in general appears to be disappointingly lacking in the medical community.\cite{15,127,121} Data reviewed here strongly support the conclusion that a certain proportion of patients with NAFLD, especially those with NASH, will develop major CVD events and will ultimately die from CVD before developing advanced liver disease. This implies the necessity for specific educational campaigns to be conducted in order to increase awareness of NAFLD as a novel cardiometabolic risk factor, necessitating appropriate diagnostic strategies, aggressive medical management and correct follow-up schedules.

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