World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i7.1724

World J Gastroenterol 2014 February 21; 20(7): 1724-1745
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (12): Fatty liver

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

Stefano Ballestri, Amedeo Lonardo, Stefano Bonapace, Christopher D Byrne, Paola Loria, Giovanni Targher

Stefano Ballestri, Division of Internal Medicine, Pavullo Hospital, 41026 Pavullo, Italy
Stefano Ballestri, Amedeo Lonardo, Paola Loria, Department of Biomedical, Metabolic and Neural Sciences, Division of Internal Medicine NOCSAE, University of Modena and Reggio Emilia and Azienda USL, Baggiovara, 41126 Modena, Italy
Stefano Bonapace, Division of Cardiology, "Sacro Cuore" Hospital, 37024 Negrar, Italy
Christopher D Byrne, Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton, Southampton SO16 6YD, United Kingdom
Giovanni Targher, Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata, 37126 Verona, Italy
Author contributions: Targher G conceived the hypothesis and the outline of the manuscript; Ballestri S, Lonardo A and Targher G researched the data, analyzed the data and wrote the manuscript; Bonapace S, Byrne CD and Loria P contributed to discussion and reviewed/edited the manuscript.
Supported by (in part) the Southampton National Institute for Health Research Biomedical Research Centre (Byrne CD); grants from the School of Medicine of the Verona University (Targher GT)
Correspondence to: Giovanni Targher, MD, Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata, Piazzale A. Stefani 1, 37126 Verona, Italy. giovanni.targher@univr.it
Telephone: +39-45-8123748 **Fax:** +39-45-8027314
Received: September 30, 2013 **Revised:** October 30, 2013
Accepted: November 18, 2013
Published online: February 21, 2014

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.

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 arrhythmogenic complications.

Ballestri S, Lonardo A, Bonapace S, Byrne CD, Loria P, Targher G. Risk of cardiovascular, cardiac and arrhythmic complications in patients with non-alcoholic fatty liver disease. *World J Gastroenterol* 2014; 20(7): 1724-1745 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i7/1724.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i7.1724

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 atherogenesis[3-6] 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[7,8]. The finding that NAFLD is associated with an increased risk of AF in people without evidence of co-existing valvular heart disease[9,10] 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[11-16].

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[12-14].

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[5]. 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 identical results were reported by some investigators in other ethnic groups[27].

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*[28] 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 transthoracic 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[31-45].

Recent data from the Valpolicella Heart Diabetes Study of 2839 unselected 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[31].

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*[38] 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*[36] 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*[41] confirmed that NAFLD on ultrasonography was associated with a greater angiographic severity of CHD, defined as the presence of ≥ 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[33,35,37,40,43-45]. 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[47-50,53]. 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 cardiometabolic risk factors, among NAFLD patients with and without type 2 diabetes (as shown in Table 2)[56-58,61,63,65]. In the only study having CHD as a pre-specified study outcome, Treeprasertsuk *et al*[65] confirmed that patients

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*[31], 2005	2088 male workers undergoing an 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*[32], 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
Arslan *et al*[33], 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*[34], 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*[35], 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
Akabame *et al*[36], 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*[37], 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*[38], 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*[39], 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, medication use, hemoglobin A1c, and albuminuria
Sun *et al*[40], 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*[41] 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*[42], 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*[43], 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)
Boddi *et al*[44], 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*[45], 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

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.

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*[11] also confirmed that the presence of NAFLD, as detected

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*[47], 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
Schindhelm *et al*[48], 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*[49], 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*[50], 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*[51], 2008	Population-based cohort, *n* = 11285 subjects (NHANES-Ⅲ)	8.7	Liver enzymes	All-cause and cause- 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*[52], 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*[53], 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*[54], 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*[55], 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*[56], 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
Targher *et al*[57], 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
Soler Rodriguez *et al*[58], 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*[59], 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*[60], 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*[61], 2012	Community-based cohort study, *n* = 3543 adult men and women	4.0	US	All-cause and CVD mortality	Increased rates of all-cause and CVD mortality in NAFLD
Younossi *et al*[62], 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
Haring *et al*[63], 2009	Population-based cohort, *n* = 4160 German subjects (Study of Health in Pomerania)	7.2	US and liver enzymes	All-cause and CVD mortality	Elevated serum GGT level was independently associated with increased all-cause and CVD mortality in men
Kim *et al*[64], 2013	Population-based cohort, *n* = 1154 (NHANES-Ⅲ)	14.5	US and advanced fibrosis score systems	All-cause and cause- specific mortality	NAFLD was not associated with increased all-cause mortality. However, NAFLD with advanced hepatic fibrosis (defined by NAFLD fibrosis score, APRI index or Fib-4) was independently associated with risk of all-cause mortality, of which the majority of deaths were due to CVD

Treeprasertsuk *et al*[65], 2012	Community-based cohort, *n* = 309 patients with NAFLD	11.5	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. Almost identical number of FRS-predicted and actual new CHD events
Matteoni *et al*[66], 1999	Patient-based cohort, *n* = 132 NAFLD	18.0	Histology	All-cause and cause-specific mortality	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
Dam-Larsen *et al*[67], 2004	Patient-based cohort (Danish national registry of patients), *n* = 109 subjects with non-alcoholic SS	16.7	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
Adams *et al*[68], 2005	Community-based cohort, *n* = 420 patients with NAFLD	7.6	US/CT and histology	All-cause and cause-specific mortality	Increased rate of age- and sex-adjusted all-cause mortality in NAFLD than in the general population with CHD being the second cause of death
Ekstedt *et al*[69], 2006	Patient-based cohort, *n* = 129 consecutive patients with NAFLD and elevated serum liver enzymes (55% NASH)	13.7	Histology	All-cause and cause-specific mortality	Increased rates of CVD and liver-related mortality in patients with NASH, but not in those with SS, compared with in the reference population
Rafiq *et al*[70], 2009	Patient-based cohort, *n* = 173 patients with NAFLD (41.6% NASH)	13.0	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
Söderberg *et al*[71], 2010	Patient-based cohort, *n* = 118 patients with NAFLD and elevated serum liver enzymes (43% NASH)	24.0	Histology	All-cause and cause-specific mortality	Increased mortality rates of CVD, malignancy and liver disease in patients with NASH, but not in those with SS, compared with the matched general population

AST: Alanine aminotransferase; CHD; Coronary heart disease; CT: Computed tomography; US: Ultrasonography; 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 Stated 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[59,60]. 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[64]. In addition, Younossi *et al*[62] 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[66-71]. However, only two studies reported specific data about CHD outcomes rather than dealing with general CVD outcomes. Adams *et al*[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*[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[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 histological severity of NAFLD did not increase CVD mortality[70]. However, further larger and longer prospective studies in patients with biopsy-confirmed NAFLD are needed to improve understanding of this issue.

Collectively, the current evidence from the published prospective studies supports that NAFLD, irrespective of the methodology used for diagnosing it, is significantly associated with an increased risk of fatal and non-fatal CHD/CVD events in both nondiabetic and type 2 diabetic individuals. However, uncertainty remains as to

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

	Ref.	Study characteristics	NAFLD diagnosis	Study measures	Main findings
Abnormalities in myocardial metabolism	Lautamaki *et al*[28], 2006	55 consecutive type 2 diabetic adults with known CHD	^{1}H-MRS	Cardiac PET using [15O]-water and [18F]-2-fluoro-2-deoxy-D-glucose	Decreased coronary functional capacity and myocardial glucose uptake in NAFLD. These abnormalities were worse in those with higher intra-hepatic fat content
	Perseghin *et al*[7], 2008	Case-control: 21 nondiabetic, nonobese, normotensive, young men with NAFLD and 21 age- and BMI-matched male controls	^{1}H-MRS	Cardiac ^{31}P-MRS and MRI	Impaired LV energy metabolism in NAFLD, independently of age, BMI, blood pressure, lipids, fasting glucose. LV mass and function were not different between the groups
	Rijzewijk *et al*[74], 2008	Case-control: 38 uncomplicated type 2 diabetic men without CHD and 28 age, sex- and BMI-matched healthy controls	^{1}H-MRS	Cardiac ^{1}H-MRS and MRI	Myocardial fat content, which was much higher in diabetics than in control subjects, was positively associated with intra-hepatic fat content in both groups. Myocardial steatosis was a strong predictor of LV diastolic dysfunction
	Rijzewijk *et al*[75], 2010	61 uncomplicated type 2 diabetic men without CHD (32 of whom with high intra-hepatic triglyceride content)	^{1}H-MRS	Cardiac MRI, ^{31}P-MRS and cardiac PET using [15O]-water, [11C]-palmitate, and [18F]-2-fluoro-2-deoxy-D-glucose	Decreased myocardial perfusion, glucose uptake and impaired LV energy metabolism in NAFLD. Cardiac fatty acid metabolism, LV mass and function were not different between the two groups
Cardiac structure and function in adults	Goland *et al*[76], 2006	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
	Fallo *et al*[77], 2009	Case-control: newly-diagnosed untreated hypertensive patients (non-obese, non-diabetic): 48 NAFLD *vs* 38 controls	US	Echocardiography	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
	Fotbolcu *et al*[78], 2010	Case-control: 35 nondiabetic, normotensive NAFLD patients and 30 age- and sex-matched healthy controls	US	Echocardiography with TDI	Increased LV mass and early impairment in systolic and diastolic function in NAFLD (no adjustment for potential confounders was made)
	Mantovani *et al*[79], 2011	116 consecutive older patients with hypertension and type 2 diabetes (53% of whom had NAFLD) without history of CHD and hepatic diseases	US	Echocardiography	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
	Bonapace *et al*[8], 2012	50 consecutive type 2 diabetic patients without CHD and hepatic diseases (32 patients had NAFLD)	US	Echocardiography with TDI (speckle tracking analyses)	Impairment in LV diastolic function (including global longitudinal diastolic strain) in NAFLD, independently of age, sex, BMI, hypertension 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
	Hallsworth *et al*[80], 2013	Case-control: 19 non-diabetic, overweight adults with NAFLD and 19 age-, sex- and BMI-matched healthy controls	^{1}H-MRS	Cardiac MRI and ^{31}P-MRS	Early impairment in systolic and diastolic function in NAFLD. Myocardial energy metabolism and LV mass were not altered in NAFLD
Cardiac structure and function in children or adolescents	Alp *et al*[81], 2013	Case-control: 400 obese children (93 with NAFLD) and 150 age- and sex-matched healthy controls	US	Echocardiography with TDI	Increased LV mass and early impairment in systolic and diastolic function in obese children with NAFLD independently of traditional cardiac risk factors. These abnormalities were worse in those with severe NAFLD on ultrasonography
	Singh *et al*[82], 2013	Case-control: 14 lean adolescents, 15 obese adolescents without NAFLD and 15 obese adolescents with NAFLD	^{1}H-MRS	Echocardiography with TDI (speckle tracking analyses)	Decreased rates of LV global longitudinal systolic strain and early diastolic strain in obese adolescents with NAFLD independently of traditional cardiac risk factors. LV mass was not different between the groups
	Sert *et al*[83], 2013	Case-control: 108 obese adolescents and 68 healthy controls	US	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

	Pacifico *et al*[84], 2013	Case-control: 108 obese children (54 with NAFLD) and 18 lean healthy controls	MRI and biopsy (in 41 obese children)	Echocardiography with TDI	Early impairment in systolic and diastolic function in obese children with NAFLD independently of traditional cardiac risk factors. These abnormalities were more severe in those with NASH
Risk of atrial fibrillation	Sinner *et al*[87], 2013	Community-based cohort of 3744 adult individuals free of clinical HF (from the Framingham Heart Study original and Offspring cohorts)	Liver enzymes	Incidence of AF over up 10 yr of follow-up	Mildly elevated serum transaminases were associated with increased incidence of AF, independently of age, sex, BMI, systolic blood pressure, electrocardiographic PR interval, anti-hypertensive treatment, smoking, diabetes, valvular heart disease, alcohol consumption
	Targher *et al*[9], 2013	Hospital-based sample of 702 patients with type 2 diabetes without a history of hepatic diseases, or excessive alcohol intake (73% of them had NAFLD)	US	Prevalence of persistent or permanent AF	Increased prevalence of AF in those with NAFLD, independently of age, sex, systolic blood pressure, hemoglobin A1c, estimated glomerular filtration rate, total cholesterol, electrocardiographic left ventricular hypertrophy, chronic obstructive pulmonary disease, and prior history of heart failure, valvular heart disease or hyperthyroidism
	Targher *et al*[10], 2013	Random sample of 400 type 2 diabetic outpatients free from AF, moderate-to-severe heart valve disease and known causes of chronic liver diseases at baseline (70% of them had NAFLD)	US	Incidence of AF over 10 yr of follow-up	Increased incidence of AF in those with NAFLD, independently of age, sex, prior history of HF, BMI, systolic blood pressure, anti-hypertensive treatment, electrocardiographic LV hypertrophy, PR interval

BMI: Body mass index; CHD: Coronary heart disease; LV: Left ventricular; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; TDI: Tissue doppler imaging; US: Ultrasonography; E′: Mitral annular tissue doppler early diastolic velocity; NAFLD: Non-alcoholic fatty liver disease; AF: Atrial fibrillation; HF: Heart failure.

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[7,28,74,75] 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*[7] showed that nondiabetic, non-obese, normotensive, young men with newly diagnosed NAFLD, as detected by proton magnetic resonance spectroscopy (^{1}H-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*[74]. found that compared with those with lower intra-hepatic fat content, patients with higher intra-hepatic fat content on ^{1}H-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 ^{1}H-MRS.

Again, Rijzewijk *et al*[75] found that the frequency of myocardial steatosis as diagnosed by cardiac ^{1}H-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[75].

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)[8,76-80].

Goland *et al*[76] and Fotbolcu *et al*[78] 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 resolution 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*[80] 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*[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*[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[8]. 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[8].

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[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*[81] 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*[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[82]. Similar findings were reported by Sert *et al*[83] in a larger sample of obese adolescents.

Finally, Pacifico *et al*[84] 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[85,86].

In the original cohort of the 3544 Framingham Study participants, who were free of HF and myocardial infarction, Dhingra *et al*[85] 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*[86] 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[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[8,9,87].

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[88]. 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[10].

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 tachyarrhythmias, 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: 4-66, *P* = 0.021) even after adjusting for several established CVD risk factors, including kidney function parameters, C-reactive protein, serum ferritin, and white blood cells[99].

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)[13-16,100-109]. Moreover, the release of key components of the renin-angiotensin-aldosterone 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 intrahepatic 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[14-16,109]. 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[104].

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)[95] 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[9,10]. 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[110] and persistence or recurrence of AF after catheter ablation[111].

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)[13-16].

The primary role of insulin resistance in the development and progression of NAFLD has been recently challenged[112]. 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[113]. Accordingly, perturbed lipid homeostasis could play a key role in accelerated atherogenesis observed in patients with NAFLD/NASH. Further evidence for a specific

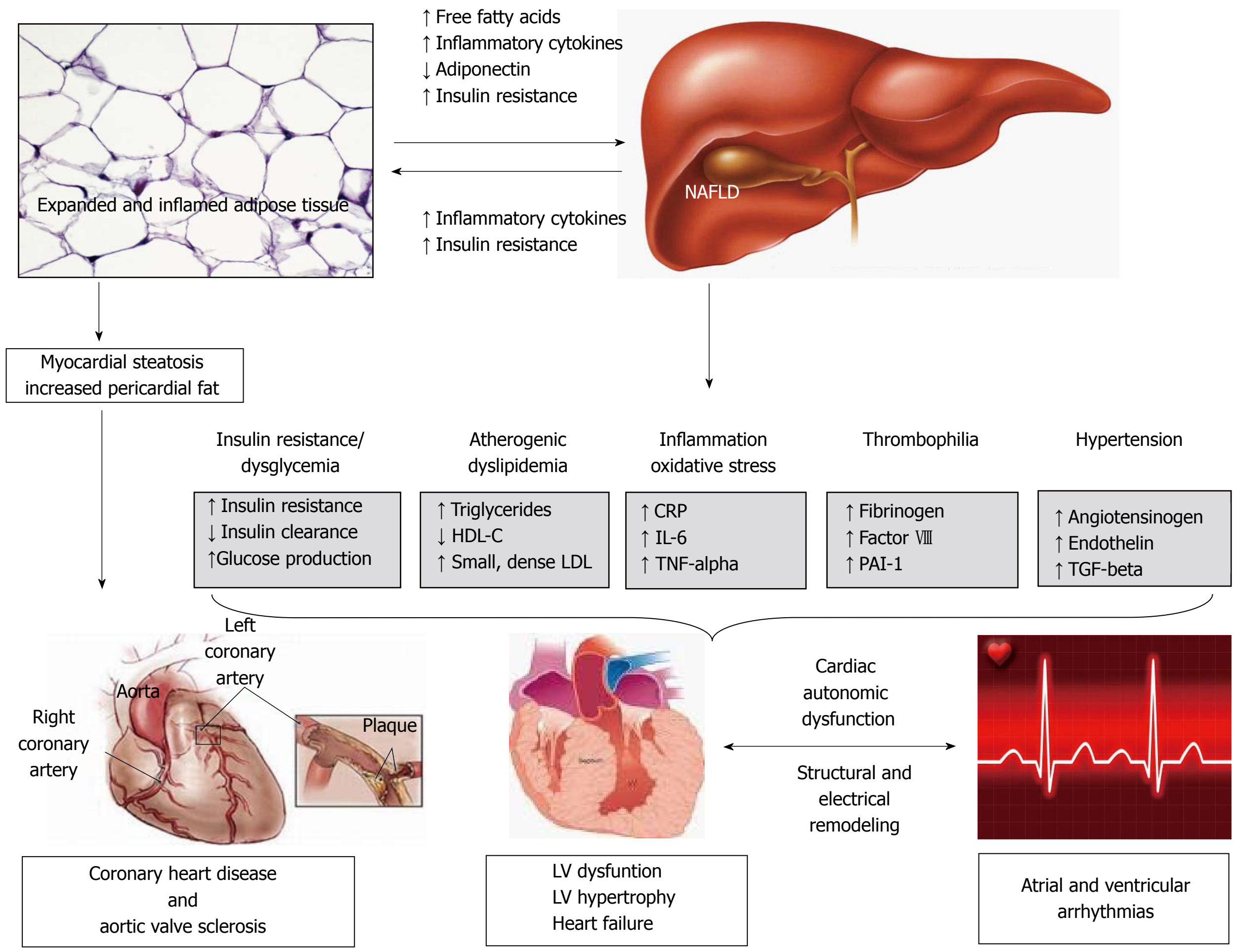

Figure 1 Possible mechanisms leading to cardiac and arrhythmogenic complications in non-alcoholic fatty liver disease. The close and complex interrelationships among non-alcoholic fatty liver disease (NAFLD), visceral obesity and insulin resistance make it extremely difficult to dissect out the specific 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.

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[93,94,118,119], 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[123].

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 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 arrhythmogenic 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 arrhythmogenic complications. An improved knowledge of the pathophysiological links of NAFLD with cardiac and arrhythmogenic 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[15,16,124-126]. 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[12].

The first step to be offered to all patients with NAFLD includes lifestyle modifications such as hypocaloric diet, increased physical activity and smoking cessation[124-127]. 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)[125,126,128]. 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[129-133]. 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[133].

Lifestyle changes may result in reduced CVD risk *via* improvements in atherogenic risk profile (*e.g.*, blood pressure, glycemia and lipids) and myocardial structure and function[134-136]. Regular exercise may also exert some of its beneficial health effects by inducing anti-inflammatory actions[137]. 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[138].

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[139].

Insulin sensitizers

Indications and limitations for the use of insulin-sensitizing drugs in patients with NAFLD/NASH have been reviewed in detail elsewhere[112,140]. 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[141-143], 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[144-146]; unfortunately, however, the hepato-protective effects of glitazones vanish after drug treatment discontinuation[147]. 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[144]. 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 depots), and increases the risk of congestive HF and bone fractures[148]. A slightly increased risk of bladder cancer has also recently led to pioglitazone being withdrawn from market in France[149]. Therefore, the potential benefits of glitazones on the liver are counterbalanced by their lack of benefits on cardiovascular system, suggesting that the reduction of CVD risk needs a more global approach than just glucose control[150].

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[151]. 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 ^{1}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[161].

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[164]. 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 cardiac mortality and sudden cardiac death in patients with previous acute myocardial infarction[165], 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[166].

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 levels 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[169]. 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[170].

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 evidence suggests that *via* effects in both adipose tissue and liver, low serum levels of vitamin D_3 may predispose to hepatic steatosis and necro-inflammation, contributing to the development and progression of NAFLD[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[174,178,179]. 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[180]. However, larger and longer randomized clinical trials are needed to ascertain whether vitamin D_3 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[15,127]. 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.

REFERENCES

1 Diabetes mellitus; auricular fibrillation; arteriosclerosis obliterans of the legs; gangrene of the 1st and 2d toes of the right foot; fatty degeneration of the liver. *Arq Bras Med* 1952; **42**: 212-216 [PMID: 14953851]

2 **Lonardo A**, Bellini M, Tondelli E, Frazzoni M, Grisendi A, Pulvirenti M, Della Casa G. Nonalcoholic steatohepatitis and the "bright liver syndrome": should a recently expanded clinical entity be further expanded? *Am J Gastroenterol* 1995; **90**: 2072-2074 [PMID: 7485040]

3 **Targher G**, Bertolini L, Padovani R, Zenari L, Zoppini G, Falezza G. Relation of nonalcoholic hepatic steatosis to early carotid atherosclerosis in healthy men: role of visceral fat accumulation. *Diabetes Care* 2004; **27**: 2498-2500 [PMID: 15451925 DOI: 10.2337/diacare.27.10.2498]

4 **Lonardo A**, Lombardini S, Scaglioni F, Ballestri S, Verrone AM, Bertolotti M, Carulli L, Ganazzi D, Carulli N, Loria P. Fatty liver, carotid disease and gallstones: a study of age-related associations. *World J Gastroenterol* 2006; **12**: 5826-5833 [PMID: 17007049]

5 **Sookoian S**, Pirola CJ. Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. *J Hepatol* 2008; **49**: 600-607 [PMID: 18672311 DOI: 10.1016/j.jhep.2008.06.012]

6 **Holt LJ**, Krutchinsky AN, Morgan DO. Positive feedback sharpens the anaphase switch. *Nature* 2008; **454**: 353-357 [PMID: 18552837 DOI: 10.1016/j.jhep.2008.05.024]

7 **Perseghin G**, Lattuada G, De Cobelli F, Esposito A, Belloni E, Ntali G, Ragogna F, Canu T, Scifo P, Del Maschio A, Luzi L. Increased mediastinal fat and impaired left ventricular energy metabolism in young men with newly found fatty liver. *Hepatology* 2008; **47**: 51-58 [PMID: 17955548 DOI: 10.1002/hep.21983]

8 **Bonapace S**, Perseghin G, Molon G, Canali G, Bertolini L, Zoppini G, Barbieri E, Targher G. Nonalcoholic fatty liver disease is associated with left ventricular diastolic dysfunction in patients with type 2 diabetes. *Diabetes Care* 2012; **35**: 389-395 [PMID: 22210573 DOI: 10.2337/dc11-1820]

9 **Targher G**, Mantovani A, Pichiri I, Rigolon R, Dauriz M, Zoppini G, Morani G, Vassanelli C, Bonora E. Non-alcoholic fatty liver disease is associated with an increased prevalence of atrial fibrillation in hospitalized patients with type 2 diabetes. *Clin Sci* (Lond) 2013; **125**: 301-309 [PMID: 23596966 DOI: 10.1042/CS20130036]

10 **Targher G**, Valbusa F, Bonapace S, Bertolini L, Zenari L, Rodella S, Zoppini G, Mantovani W, Barbieri E, Byrne CD. Non-alcoholic fatty liver disease is associated with an increased incidence of atrial fibrillation in patients with type 2 diabetes. *PLoS One* 2013; **8**: e57183 [PMID: 23451184 DOI: 10.1371/journal.pone.0057183]

11 **Musso G**, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med* 2011; **43**: 617-649 [PMID:

21039302 DOI: 10.3109/07853890.2010.518623]

12 **Maurantonio M**, Ballestri S, Odoardi MR, Lonardo A, Loria P. Treatment of atherogenic liver based on the pathogenesis of nonalcoholic fatty liver disease: a novel approach to reduce cardiovascular risk? *Arch Med Res* 2011; **42**: 337-353 [PMID: 21843565 DOI: 10.1016/j.arcmed.2011.08.004]

13 **Bhatia LS**, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? *Eur Heart J* 2012; **33**: 1190-1200 [PMID: 22408036 DOI: 10.1093/eurheartj/ehr453]

14 **Targher G**, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010; **363**: 1341-1350 [PMID: 20879883 DOI: 10.1056/NEJMra0912063]

15 **Anstee QM**, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 330-344 [PMID: 23507799 DOI: 10.1038/nrgastro.2013.41]

16 **Targher G**, Byrne CD. Clinical Review: Nonalcoholic fatty liver disease: a novel cardiometabolic risk factor for type 2 diabetes and its complications. *J Clin Endocrinol Metab* 2013; **98**: 483-495 [PMID: 23293330 DOI: 10.1210/jc.2012-3093]

17 **Villanova N**, Moscatiello S, Ramilli S, Bugianesi E, Magalotti D, Vanni E, Zoli M, Marchesini G. Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease. *Hepatology* 2005; **42**: 473-480 [PMID: 15981216 DOI: 10.1002/hep.20781]

18 **Salvi P**, Ruffini R, Agnoletti D, Magnani E, Pagliarani G, Comandini G, Praticò A, Borghi C, Benetos A, Pazzi P. Increased arterial stiffness in nonalcoholic fatty liver disease: the Cardio-GOOSE study. *J Hypertens* 2010; **28**: 1699-1707 [PMID: 20467324 DOI: 10.1097/HJH.0b013e32833a7de6]

19 **Pacifico L**, Anania C, Martino F, Cantisani V, Pascone R, Marcantonio A, Chiesa C. Functional and morphological vascular changes in pediatric nonalcoholic fatty liver disease. *Hepatology* 2010; **52**: 1643-1651 [PMID: 20890890 DOI: 10.1002/hep.23890]

20 **Targher G**, Bertolini L, Padovani R, Rodella S, Zoppini G, Zenari L, Cigolini M, Falezza G, Arcaro G. Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. *Diabetes Care* 2006; **29**: 1325-1330 [PMID: 16732016 DOI: 10.2337/dc06-0135]

21 **Colak Y**, Senates E, Yesil A, Yilmaz Y, Ozturk O, Doganay L, Coskunpinar E, Kahraman OT, Mesci B, Ulasoglu C, Tuncer I. Assessment of endothelial function in patients with nonalcoholic fatty liver disease. *Endocrine* 2013; **43**: 100-107 [PMID: 22661277 DOI: 10.1007/s12020-012-9712-1]

22 **Abdulla J**, Asferg C, Kofoed KF. Prognostic value of absence or presence of coronary artery disease determined by 64-slice computed tomography coronary angiography a systematic review and meta-analysis. *Int J Cardiovasc Imaging* 2011; **27**: 413-420 [PMID: 20549366 DOI: 10.1007/s10554-010-9652-x]

23 **Chen CH**, Nien CK, Yang CC, Yeh YH. Association between nonalcoholic fatty liver disease and coronary artery calcification. *Dig Dis Sci* 2010; **55**: 1752-1760 [PMID: 19688595 DOI: 10.1007/s10620-009-0935-9]

24 **Jung DH**, Lee YJ, Ahn HY, Shim JY, Lee HR. Relationship of hepatic steatosis and alanine aminotransferase with coronary calcification. *Clin Chem Lab Med* 2010; **48**: 1829-1834 [PMID: 20961204 DOI: 10.1515/CCLM.2010.349]

25 **Sung KC**, Wild SH, Kwag HJ, Byrne CD. Fatty liver, insulin resistance, and features of metabolic syndrome: relationships with coronary artery calcium in 10,153 people. *Diabetes Care* 2012; **35**: 2359-2364 [PMID: 22829522 DOI: 10.2337/dc12-0515]

26 **Kim D**, Choi SY, Park EH, Lee W, Kang JH, Kim W, Kim YJ, Yoon JH, Jeong SH, Lee DH, Lee HS, Larson J, Therneau TM, Kim WR. Nonalcoholic fatty liver disease is associated with coronary artery calcification. *Hepatology* 2012; **56**: 605-613 [PMID: 22271511 DOI: 10.1002/hep.25593]

27 **Liu J**, Musani SK, Bidulescu A, Carr JJ, Wilson JG, Taylor HA, Fox CS. Fatty liver, abdominal adipose tissue and atherosclerotic calcification in African Americans: the Jackson Heart Study. *Atherosclerosis* 2012; **224**: 521-525 [PMID: 22902209 DOI: 10.1016/j.atherosclerosis.2012.07.042]

28 **Lautamäki R**, Borra R, Iozzo P, Komu M, Lehtimäki T, Salmi M, Jalkanen S, Airaksinen KE, Knuuti J, Parkkola R, Nuutila P. Liver steatosis coexists with myocardial insulin resistance and coronary dysfunction in patients with type 2 diabetes. *Am J Physiol Endocrinol Metab* 2006; **291**: E282-E290 [PMID: 16478772 DOI: 10.1152/ajpendo.00604.2005]

29 **Yilmaz Y**, Kurt R, Yonal O, Polat N, Celikel CA, Gurdal A, Oflaz H, Ozdogan O, Imeryuz N, Kalayci C, Avsar E. Coronary flow reserve is impaired in patients with nonalcoholic fatty liver disease: association with liver fibrosis. *Atherosclerosis* 2010; **211**: 182-186 [PMID: 20181335 DOI: 10.1016/j.atherosclerosis.2010.01.049]

30 **Nakamori S**, Onishi K, Nakajima H, Yoon YE, Nagata M, Kurita T, Yamada T, Kitagawa K, Dohi K, Nakamura M, Sakuma H, Ito M. Impaired myocardial perfusion reserve in patients with fatty liver disease assessed by quantitative myocardial perfusion magnetic resonance imaging. *Circ J* 2012; **76**: 2234-2240 [PMID: 22664721 DOI: 10.1253/circj.CJ-11-1487]

31 **Lin YC**, Lo HM, Chen JD. Sonographic fatty liver, overweight and ischemic heart disease. *World J Gastroenterol* 2005; **11**: 4838-4842 [PMID: 16097054]

32 **Targher G**, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, Day C, Arcaro G. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* 2007; **30**: 1212-1218 [PMID: 17277038 DOI: 10.2337/dc06-2247]

33 **Arslan U**, Türkoğlu S, Balcioğlu S, Tavil Y, Karakan T, Cengel A. Association between nonalcoholic fatty liver disease and coronary artery disease. *Coron Artery Dis* 2007; **18**: 433-436 [PMID: 17700213 DOI: 10.1097/MCA.0b013e3282583c0d]

34 **Mirbagheri SA**, Rashidi A, Abdi S, Saedi D, Abouzari M. Liver: an alarm for the heart? *Liver Int* 2007; **27**: 891-894 [PMID: 17696926 DOI: 10.1111/j.1478-3231.2007.01531.x]

35 **Alper AT**, Hasdemir H, Sahin S, Ontürk E, Akyol A, Nurkalem Z, Cakmak N, Erdinler I, Gürkan K. The relationship between nonalcoholic fatty liver disease and the severity of coronary artery disease in patients with metabolic syndrome. *Turk Kardiyol Dern Ars* 2008; **36**: 376-381 [PMID: 19155640]

36 **Akabame S**, Hamaguchi M, Tomiyasu K, Tanaka M, Kobayashi-Takenaka Y, Nakano K, Oda Y, Yoshikawa T. Evaluation of vulnerable coronary plaques and non-alcoholic fatty liver disease (NAFLD) by 64-detector multislice computed tomography (MSCT). *Circ J* 2008; **72**: 618-625 [PMID: 18362435 DOI: 10.1253/circj.72.618]

37 **Açikel M**, Sunay S, Koplay M, Gündoğdu F, Karakelleoğlu S. Evaluation of ultrasonographic fatty liver and severity of coronary atherosclerosis, and obesity in patients undergoing coronary angiography. *Anadolu Kardiyol Derg* 2009; **9**: 273-279 [PMID: 19666428]

38 **Assy N**, Djibre A, Farah R, Grosovski M, Marmor A. Presence of coronary plaques in patients with nonalcoholic fatty liver disease. *Radiology* 2010; **254**: 393-400 [PMID: 20093511 DOI: 10.1148/radiol.09090769]

39 **Targher G**, Bertolini L, Padovani R, Rodella S, Zoppini G, Pichiri I, Sorgato C, Zenari L, Bonora E. Prevalence of non-alcoholic fatty liver disease and its association with cardiovascular disease in patients with type 1 diabetes. *J Hepatol* 2010; **53**: 713-718 [PMID: 20619918 DOI: 10.1016/j.jhep.2010.04.030]

40 **Sun L**, Lü SZ. Association between non-alcoholic fatty liver disease and coronary artery disease severity. *Chin Med J*

(Engl) 2011; **124**: 867-872 [PMID: 21518594 DOI: 10.3760/cma.j.issn.0366-6999.2011.06.012]
41 **Wong VW**, Wong GL, Yip GW, Lo AO, Limquiaco J, Chu WC, Chim AM, Yu CM, Yu J, Chan FK, Sung JJ, Chan HL. Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease. *Gut* 2011; **60**: 1721-1727 [PMID: 21602530 DOI: 10.1136/gut.2011.242016]
42 **Domanski JP**, Park SJ, Harrison SA. Cardiovascular disease and nonalcoholic fatty liver disease: does histologic severity matter? *J Clin Gastroenterol* 2012; **46**: 427-430 [PMID: 22469639 DOI: 10.1097/MCG.0b013e31822fb3f7]
43 **Agaç MT**, Korkmaz L, Cavusoglu G, Karadeniz AG, Agaç S, Bektas H, Erkan H, Varol MO, Vatan MB, Acar Z, Mentese U, Celik S. Association between nonalcoholic fatty liver disease and coronary artery disease complexity in patients with acute coronary syndrome: a pilot study. *Angiology* 2013; **64**: 604-608 [PMID: 23439214 DOI: 10.1177/0003319713479155]
44 **Boddi M**, Tarquini R, Chiostri M, Marra F, Valente S, Giglioli C, Gensini GF, Abbate R. Nonalcoholic fatty liver in nondiabetic patients with acute coronary syndromes. *Eur J Clin Invest* 2013; **43**: 429-438 [PMID: 23480577 DOI: 10.1111/eci.12065]
45 **Inci MF**, Özkan F, Ark B, Vurdem ÜE, Ege MR, Sincer I, Zorlu A. Sonographic evaluation for predicting the presence and severity of coronary artery disease. *Ultrasound Q* 2013; **29**: 125-130 [PMID: 23609339 DOI: 10.1097/RUQ.0b013e318291580e]
46 **Arslan U**, Kocaoğlu I, Balcı M, Duyuler S, Korkmaz A. The association between impaired collateral circulation and nonalcoholic fatty liver in patients with severe coronary artery disease. *J Cardiol* 2012; **60**: 210-214 [PMID: 22738690 DOI: 10.1016/j.jjcc.2012.05.003]
47 **Fraser A**, Harris R, Sattar N, Ebrahim S, Smith GD, Lawlor DA. Gamma-glutamyltransferase is associated with incident vascular events independently of alcohol intake: analysis of the British Women's Heart and Health Study and Meta-Analysis. *Arterioscler Thromb Vasc Biol* 2007; **27**: 2729-2735 [PMID: 17932318 DOI: 10.1161/ATVBAHA.107.152298]
48 **Schindhelm RK**, Dekker JM, Nijpels G, Bouter LM, Stehouwer CD, Heine RJ, Diamant M. Alanine aminotransferase predicts coronary heart disease events: a 10-year follow-up of the Hoorn Study. *Atherosclerosis* 2007; **191**: 391-396 [PMID: 16682043 DOI: 10.1016/j.atherosclerosis.2006.04.006]
49 **Goessling W**, Massaro JM, Vasan RS, D'Agostino RB, Ellison RC, Fox CS. Aminotransferase levels and 20-year risk of metabolic syndrome, diabetes, and cardiovascular disease. *Gastroenterology* 2008; **135**: 1935-144, 1944.e1 [PMID: 19010326 DOI: 10.1053/j.gastro.2008.09.018]
50 **Dunn W**, Xu R, Wingard DL, Rogers C, Angulo P, Younossi ZM, Schwimmer JB. Suspected nonalcoholic fatty liver disease and mortality risk in a population-based cohort study. *Am J Gastroenterol* 2008; **103**: 2263-2271 [PMID: 18684196 DOI: 10.1111/j.1572-0241.2008.02034.x]
51 **Ong JP**, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. *J Hepatol* 2008; **49**: 608-612 [PMID: 18682312 DOI: 10.1016/j.jhep.2008.06.018]
52 **Ruhl CE**, Everhart JE. Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. *Gastroenterology* 2009; **136**: 477-85.e11 [PMID: 19100265 DOI: 10.1053/j.gastro.2008.10.052]
53 **Yun KE**, Shin CY, Yoon YS, Park HS. Elevated alanine aminotransferase levels predict mortality from cardiovascular disease and diabetes in Koreans. *Atherosclerosis* 2009; **205**: 533-537 [PMID: 19159884 DOI: 10.1016/j.atherosclerosis.2008.12.012]
54 **Calori G**, Lattuada G, Ragogna F, Garancini MP, Crosignani P, Villa M, Bosi E, Ruotolo G, Piemonti L, Perseghin G. Fatty liver index and mortality: the Cremona study in the 15th year of follow-up. *Hepatology* 2011; **54**: 145-152 [PMID: 21488080 DOI: 10.1002/hep.24356]
55 **Lerchbaum E**, Pilz S, Grammer TB, Boehm BO, Stojakovic T, Obermayer-Pietsch B, März W. The fatty liver index is associated with increased mortality in subjects referred to coronary angiography. *Nutr Metab Cardiovasc Dis* 2013; **23**: 1231-1238 [PMID: 23557879 DOI: 10.1016/j.numecd.2013.02.004]
56 **Jepsen P**, Vilstrup H, Mellemkjaer L, Thulstrup AM, Olsen JH, Baron JA, Sørensen HT. Prognosis of patients with a diagnosis of fatty liver--a registry-based cohort study. *Hepatogastroenterology* 2003; **50**: 2101-2104 [PMID: 14696473]
57 **Targher G**, Bertolini L, Rodella S, Tessari R, Zenari L, Lippi G, Arcaro G. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. *Diabetes Care* 2007; **30**: 2119-2121 [PMID: 17519430 DOI: 10.2337/dc07-0349]
58 **Soler Rodriguez F**, Miguez Santiyan MP, Pedrera Zamorano JD, Roncero Cordero V. An outbreak of lupinosis in sheep. *Vet Hum Toxicol* 1991; **33**: 492-494 [PMID: 1746145]
59 **Lazo M**, Hernaez R, Bonekamp S, Kamel IR, Brancati FL, Guallar E, Clark JM. Non-alcoholic fatty liver disease and mortality among US adults: prospective cohort study. *BMJ* 2011; **343**: d6891 [PMID: 22102439 DOI: 10.1136/bmj.d6891]
60 **Stepanova M**, Younossi ZM. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. *Clin Gastroenterol Hepatol* 2012; **10**: 646-650 [PMID: 22245962 DOI: 10.1016/j.cgh.2011.12.039]
61 **Zhou YJ**, Li YY, Nie YQ, Huang CM, Cao CY. Natural course of nonalcoholic fatty liver disease in southern China: a prospective cohort study. *J Dig Dis* 2012; **13**: 153-160 [PMID: 22356310 DOI: 10.1111/j.1751-2980.2011.00571.x]
62 **Younossi ZM**, Otgonsuren M, Venkatesan C, Mishra A. In patients with non-alcoholic fatty liver disease, metabolically abnormal individuals are at a higher risk for mortality while metabolically normal individuals are not. *Metabolism* 2013; **62**: 352-360 [PMID: 22999011 DOI: 10.1016/j.metabol.2012.08.005]
63 **Haring R**, Wallaschofski H, Nauck M, Dörr M, Baumeister SE, Völzke H. Ultrasonographic hepatic steatosis increases prediction of mortality risk from elevated serum gamma-glutamyl transpeptidase levels. *Hepatology* 2009; **50**: 1403-1411 [PMID: 19670414 DOI: 10.1002/hep.23135]
64 **Kim D**, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. *Hepatology* 2013; **57**: 1357-1365 [PMID: 23175136 DOI: 10.1002/hep.26156]
65 **Treeprasertsuk S**, Leverage S, Adams LA, Lindor KD, St Sauver J, Angulo P. The Framingham risk score and heart disease in nonalcoholic fatty liver disease. *Liver Int* 2012; **32**: 945-950 [PMID: 22299674 DOI: 10.1111/j.1478-3231.2011.02753.x]
66 **Matteoni CA**, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999; **116**: 1413-1419 [PMID: 10348825]
67 **Dam-Larsen S**, Franzmann M, Andersen IB, Christoffersen P, Jensen LB, Sørensen TI, Becker U, Bendtsen F. Long term prognosis of fatty liver: risk of chronic liver disease and death. *Gut* 2004; **53**: 750-755 [PMID: 15082596 DOI: 10.1136/gut.2003.019984]
68 **Adams LA**, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129**: 113-121 [PMID: 16012941]
69 **Ekstedt M**, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006; **44**: 865-873 [PMID: 17006923 DOI: 10.1002/

hep.21327]
70 **Rafiq N**, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, Younossi ZM. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin Gastroenterol Hepatol* 2009; **7**: 234-238 [PMID: 19049831 DOI: 10.1016/j.cgh.2008.11.005]
71 **Söderberg C**, Stål P, Askling J, Glaumann H, Lindberg G, Marmur J, Hultcrantz R. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. *Hepatology* 2010; **51**: 595-602 [PMID: 20014114 DOI: 10.1002/hep.23314]
72 **Bedogni G**, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, Tiribelli C. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 2006; **6**: 33 [PMID: 17081293 DOI: 10.1186/1471-230X-6-33]
73 **Jiang ZY**, Xu CY, Chang XX, Li WW, Sun LY, Yang XB, Yu LF. Fatty liver index correlates with non-alcoholic fatty liver disease, but not with newly diagnosed coronary artery atherosclerotic disease in Chinese patients. *BMC Gastroenterol* 2013; **13**: 110 [PMID: 23834773 DOI: 10.1186/1471-230X-13-110]
74 **Rijzewijk LJ**, van der Meer RW, Smit JW, Diamant M, Bax JJ, Hammer S, Romijn JA, de Roos A, Lamb HJ. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. *J Am Coll Cardiol* 2008; **52**: 1793-1799 [PMID: 19022158 DOI: 10.1016/j.jacc.2008.07.062]
75 **Rijzewijk LJ**, Jonker JT, van der Meer RW, Lubberink M, de Jong HW, Romijn JA, Bax JJ, de Roos A, Heine RJ, Twisk JW, Windhorst AD, Lammertsma AA, Smit JW, Diamant M, Lamb HJ. Effects of hepatic triglyceride content on myocardial metabolism in type 2 diabetes. *J Am Coll Cardiol* 2010; **56**: 225-233 [PMID: 20620743 DOI: 10.1016/j.jacc.2010.02.049]
76 **Goland S**, Shimoni S, Zornitzki T, Knobler H, Azoulai O, Lutaty G, Melzer E, Orr A, Caspi A, Malnick S. Cardiac abnormalities as a new manifestation of nonalcoholic fatty liver disease: echocardiographic and tissue Doppler imaging assessment. *J Clin Gastroenterol* 2006; **40**: 949-955 [PMID: 17063117 DOI: 10.1097/01.mcg.0000225668.53673.e6]
77 **Fallo F**, Dalla Pozza A, Sonino N, Lupia M, Tona F, Federspil G, Ermani M, Catena C, Soardo G, Di Piazza L, Bernardi S, Bertolotto M, Pinamonti B, Fabris B, Sechi LA. Non-alcoholic fatty liver disease is associated with left ventricular diastolic dysfunction in essential hypertension. *Nutr Metab Cardiovasc Dis* 2009; **19**: 646-653 [PMID: 19278843 DOI: 10.1016/j.numecd.2008.12.007]
78 **Fotbolcu H**, Yakar T, Duman D, Karaahmet T, Tigen K, Cevik C, Kurtoglu U, Dindar I. Impairment of the left ventricular systolic and diastolic function in patients with non-alcoholic fatty liver disease. *Cardiol J* 2010; **17**: 457-463 [PMID: 20865675]
79 **Mantovani A**, Zoppini G, Targher G, Golia G, Bonora E. Non-alcoholic fatty liver disease is independently associated with left ventricular hypertrophy in hypertensive Type 2 diabetic individuals. *J Endocrinol Invest* 2012; **35**: 215-218 [PMID: 22490991]
80 **Hallsworth K**, Hollingsworth KG, Thoma C, Jakovljevic D, MacGowan GA, Anstee QM, Taylor R, Day CP, Trenell MI. Cardiac structure and function are altered in adults with non-alcoholic fatty liver disease. *J Hepatol* 2013; **58**: 757-762 [PMID: 23178979 DOI: 10.1016/j.jhep.2012.11.015]
81 **Alp H**, Karaarslan S, Selver Eklioğlu B, Atabek ME, Altın H, Baysal T. Association between nonalcoholic fatty liver disease and cardiovascular risk in obese children and adolescents. *Can J Cardiol* 2013; **29**: 1118-1125 [PMID: 23040432 DOI: 10.1016/j.cjca.2012.07.846]
82 **Singh GK**, Vitola BE, Holland MR, Sekarski T, Patterson BW, Magkos F, Klein S. Alterations in ventricular structure and function in obese adolescents with nonalcoholic fatty liver disease. *J Pediatr* 2013; **162**: 1160-118, 1168.e1 [PMID: 23260104 DOI: 10.1016/j.jpeds.2012.11.024]
83 **Sert A**, Aypar E, Pirgon O, Yilmaz H, Odabas D, Tolu I. Left ventricular function by echocardiography, tissue Doppler imaging, and carotid intima-media thickness in obese adolescents with nonalcoholic fatty liver disease. *Am J Cardiol* 2013; **112**: 436-443 [PMID: 23642511 DOI: 10.1016/j.amjcard.2013.03.056]
84 **Pacifico L**, Di Martino M, De Merulis A, Bezzi M, Osborn JF, Catalano C, Chiesa C. Left ventricular dysfunction in obese children and adolescents with nonalcoholic fatty liver disease. *Hepatology* 2013 Jul 11; Epub ahead of print [PMID: 23843206 DOI: 10.1002/hep.26610]
85 **Dhingra R**, Gona P, Wang TJ, Fox CS, D'Agostino RB, Vasan RS. Serum gamma-glutamyl transferase and risk of heart failure in the community. *Arterioscler Thromb Vasc Biol* 2010; **30**: 1855-1860 [PMID: 20539015 DOI: 10.1161/ATVBAHA.110.207340]
86 **Wannamethee SG**, Whincup PH, Shaper AG, Lennon L, Sattar N. Γ-glutamyltransferase, hepatic enzymes, and risk of incident heart failure in older men. *Arterioscler Thromb Vasc Biol* 2012; **32**: 830-835 [PMID: 22223732 DOI: 10.1161/ATVBAHA.111.240457]
87 **Sinner MF**, Wang N, Fox CS, Fontes JD, Rienstra M, Magnani JW, Vasan RS, Calderwood AH, Pencina M, Sullivan LM, Ellinor PT, Benjamin EJ. Relation of circulating liver transaminase concentrations to risk of new-onset atrial fibrillation. *Am J Cardiol* 2013; **111**: 219-224 [PMID: 23127690 DOI: 10.1016/j.amjcard.2012.09.021]
88 **Lip GY**, Tse HF, Lane DA. Atrial fibrillation. *Lancet* 2012; **379**: 648-661 [PMID: 22166900 DOI: 10.1016/S0140-6736]
89 **Kleiger RE**, Stein PK, Bigger JT. Heart rate variability: measurement and clinical utility. *Ann Noninvasive Electrocardiol* 2005; **10**: 88-101 [PMID: 15649244 DOI: 10.1111/j.1542-474X.2005.10101.x]
90 **Algra A**, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation* 1991; **83**: 1888-1894 [PMID: 2040041 DOI: 10.1161/01.CIR.83.6.1888]
91 **Straus SM**, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH, Witteman JC. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol* 2006; **47**: 362-367 [PMID: 16412861 DOI: 10.1016/j.jacc.2005.08.067]
92 **Okin PM**, Devereux RB, Lee ET, Galloway JM, Howard BV. Electrocardiographic repolarization complexity and abnormality predict all-cause and cardiovascular mortality in diabetes: the strong heart study. *Diabetes* 2004; **53**: 434-440 [PMID: 14747295]
93 **Liu YC**, Hung CS, Wu YW, Lee YC, Lin YH, Lin C, Lo MT, Chan CC, Ma HP, Ho YL, Chen CH. Influence of non-alcoholic fatty liver disease on autonomic changes evaluated by the time domain, frequency domain, and symbolic dynamics of heart rate variability. *PLoS One* 2013; **8**: e61803 [PMID: 23626730 DOI: 10.1371/journal.pone.0061803]
94 **Newton JL**, Pairman J, Wilton K, Jones DE, Day C. Fatigue and autonomic dysfunction in non-alcoholic fatty liver disease. *Clin Auton Res* 2009; **19**: 319-326 [PMID: 19768633 DOI: 10.1007/s10286-009-0031-4]
95 **Otto CM**, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. *Circulation* 1994; **90**: 844-853 [PMID: 7519131 DOI: 10.1161/01.CIR.90.2.844]
96 **Otto CM**, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 1999; **341**: 142-147 [PMID: 10403851 DOI: 10.1056/NEJM199907153410302]
97 **Barasch E**, Gottdiener JS, Marino Larsen EK, Chaves PH, Newman AB. Cardiovascular morbidity and mortality in

community-dwelling elderly individuals with calcification of the fibrous skeleton of the base of the heart and aortosclerosis (The Cardiovascular Health Study). *Am J Cardiol* 2006; **97**: 1281-1286 [PMID: 16635596 DOI: 10.1016/j.amjcard.2005.11.065]
98 **Rossi A**, Targher G, Zoppini G, Cicoira M, Bonapace S, Negri C, Stoico V, Faggiano P, Vassanelli C, Bonora E. Aortic and mitral annular calcifications are predictive of all-cause and cardiovascular mortality in patients with type 2 diabetes. *Diabetes Care* 2012; **35**: 1781-1786 [PMID: 22699285 DOI: 10.2337/dc12-0134]
99 **Markus MR**, Baumeister SE, Stritzke J, Dörr M, Wallaschofski H, Völzke H, Lieb W. Hepatic steatosis is associated with aortic valve sclerosis in the general population: the Study of Health in Pomerania (SHIP). *Arterioscler Thromb Vasc Biol* 2013; **33**: 1690-1695 [PMID: 23685558 DOI: 10.1161/ATVBAHA.112.300556]
100 **Verrijken A**, Francque S, Mertens I, Prawitt J, Caron S, Hubens G, Van Marck E, Staels B, Michielsen P, Gaal LV. Prothrombotic factors in histologically proven NAFLD and NASH. *Hepatology* 2013 May 23; Epub ahead of print [PMID: 23703589 DOI: 10.1002/hep.26510]
101 **Simonen M**, Männistö V, Leppänen J, Kaminska D, Kärjä V, Venesmaa S, Käkelä P, Kuusisto J, Gylling H, Laakso M, Pihlajamäki J. Desmosterol in human nonalcoholic steatohepatitis. *Hepatology* 2013; **58**: 976-982 [PMID: 23447451 DOI: 10.1002/hep.26342]
102 **Musso G**, Cassader M, De Michieli F, Rosina F, Orlandi F, Gambino R. Nonalcoholic steatohepatitis versus steatosis: adipose tissue insulin resistance and dysfunctional response to fat ingestion predict liver injury and altered glucose and lipoprotein metabolism. *Hepatology* 2012; **56**: 933-942 [PMID: 22684858 DOI: 10.1002/hep.25739]
103 **Musso G**, Cassader M, Bo S, De Michieli F, Gambino R. Sterol regulatory element-binding factor 2 (SREBF-2) predicts 7-year NAFLD incidence and severity of liver disease and lipoprotein and glucose dysmetabolism. *Diabetes* 2013; **62**: 1109-1120 [PMID: 23274901 DOI: 10.2337/db12-0858]
104 **Sookoian S**, Gianotti TF, Rosselli MS, Burgueño AL, Castaño GO, Pirola CJ. Liver transcriptional profile of atherosclerosis-related genes in human nonalcoholic fatty liver disease. *Atherosclerosis* 2011; **218**: 378-385 [PMID: 21664615 DOI: 10.1016/j.atherosclerosis.2011.05.014]
105 **Ndumele CE**, Nasir K, Conceiçao RD, Carvalho JA, Blumenthal RS, Santos RD. Hepatic steatosis, obesity, and the metabolic syndrome are independently and additively associated with increased systemic inflammation. *Arterioscler Thromb Vasc Biol* 2011; **31**: 1927-1932 [PMID: 21546603 DOI: 10.1161/ATVBAHA.111.228262]
106 **Papatheodoridis GV**, Chrysanthos N, Cholongitas E, Pavlou E, Apergis G, Tiniakos DG, Andrioti E, Theodossiades G, Archimandritis AJ. Thrombotic risk factors and liver histologic lesions in non-alcoholic fatty liver disease. *J Hepatol* 2009; **51**: 931-938 [PMID: 19726097 DOI: 10.1016/j.jhep.2009.06.023]
107 **Assy N**, Bekirov I, Mejritsky Y, Solomon L, Szvalb S, Hussein O. Association between thrombotic risk factors and extent of fibrosis in patients with non-alcoholic fatty liver diseases. *World J Gastroenterol* 2005; **11**: 5834-5839 [PMID: 16270394]
108 **Targher G**, Bertolini L, Rodella S, Lippi G, Franchini M, Zoppini G, Muggeo M, Day CP. NASH predicts plasma inflammatory biomarkers independently of visceral fat in men. *Obesity* (Silver Spring) 2008; **16**: 1394-1399 [PMID: 18369343 DOI: 10.1038/oby.2008.64]
109 **Targher G**, Byrne CD. Diagnosis and management of nonalcoholic fatty liver disease and its hemostatic/thrombotic and vascular complications. *Semin Thromb Hemost* 2013; **39**: 214-228 [PMID: 23397556 DOI: 10.1055/s-0033-1334866]
110 **Nyrnes A**, Njølstad I, Mathiesen EB, Wilsgaard T, Hansen JB, Skjelbakken T, Jørgensen L, Løchen ML. Inflammatory biomarkers as risk factors for future atrial fibrillation. An eleven-year follow-up of 6315 men and women: the Tromsø study. *Gend Med* 2012; **9**: 536-547.e2 [PMID: 23046763 DOI: 10.1016/j.genm.2012.09.001]
111 **Liu T**, Li G, Li L, Korantzopoulos P. Association between C-reactive protein and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis. *J Am Coll Cardiol* 2007; **49**: 1642-1648 [PMID: 17433956 DOI: 10.1016/j.jacc.2006.12.042]
112 **Lonardo A**, Bellentani S, Ratziu V, Loria P. Insulin resistance in nonalcoholic steatohepatitis: necessary but not sufficient - death of a dogma from analysis of therapeutic studies? *Expert Rev Gastroenterol Hepatol* 2011; **5**: 279-289 [PMID: 21476922 DOI: 10.1586/egh.11.19]
113 **Razani B**, Chakravarthy MV, Semenkovich CF. Insulin resistance and atherosclerosis. *Endocrinol Metab Clin North Am* 2008; **37**: 603-621, viii [PMID: 18775354 DOI: 10.1016/j.ecl.2008.05.001]
114 **DeFilippis AP**, Blaha MJ, Martin SS, Reed RM, Jones SR, Nasir K, Blumenthal RS, Budoff MJ. Nonalcoholic fatty liver disease and serum lipoproteins: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis* 2013; **227**: 429-436 [PMID: 23419204 DOI: 10.1016/j.atherosclerosis.2013.01.022]
115 **Liu J**, Fox CS, Hickson D, Bidulescu A, Carr JJ, Taylor HA. Fatty liver, abdominal visceral fat, and cardiometabolic risk factors: the Jackson Heart Study. *Arterioscler Thromb Vasc Biol* 2011; **31**: 2715-2722 [PMID: 21885852 DOI: 10.1161/ATVBAHA.111.234062]
116 **Pastromas S**, Terzi AB, Tousoulis D, Koulouris S. Postprandial lipemia: an under-recognized atherogenic factor in patients with diabetes mellitus. *Int J Cardiol* 2008; **126**: 3-12 [PMID: 17689745 DOI: 10.1016/j.ijcard.2007.04.172]
117 **Goldberg IJ**, Eckel RH, McPherson R. Triglycerides and heart disease: still a hypothesis? *Arterioscler Thromb Vasc Biol* 2011; **31**: 1716-1725 [PMID: 21527746 DOI: 10.1161/ATVBAHA.111.226100]
118 **Newton JL**, Jones DE, Henderson E, Kane L, Wilton K, Burt AD, Day CP. Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. *Gut* 2008; **57**: 807-813 [PMID: 18270241 DOI: 10.1136/gut.2007.139303]
119 **Newton JL**. Systemic symptoms in non-alcoholic fatty liver disease. *Dig Dis* 2010; **28**: 214-219 [PMID: 20460914 DOI: 10.1159/000282089]
120 **Jakovljevic DG**, Hallsworth K, Zalewski P, Thoma C, Klawe JJ, Day CP, Newton J, Trenell MI. Resistance exercise improves autonomic regulation at rest and haemodynamic response to exercise in non-alcoholic fatty liver disease. *Clin Sci* (Lond) 2013; **125**: 143-149 [PMID: 23458257 DOI: 10.1042/CS20120684]
121 **Ahmed MH**, Byrne CD. Obstructive sleep apnea syndrome and fatty liver: association or causal link? *World J Gastroenterol* 2010; **16**: 4243-4252 [PMID: 20818807 DOI: 10.3748/wjg.v16.i34.4243]
122 **Musso G**, Cassader M, Olivetti C, Rosina F, Carbone G, Gambino R. Association of obstructive sleep apnoea with the presence and severity of non-alcoholic fatty liver disease. A systematic review and meta-analysis. *Obes Rev* 2013; **14**: 417-431 [PMID: 23387384 DOI: 10.1111/obr.12020]
123 **Kohler M**, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. *Nat Rev Cardiol* 2010; **7**: 677-685 [PMID: 21079639 DOI: 10.1038/nrcardio.2010.145]
124 **Ratziu V**, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol* 2010; **53**: 372-384 [PMID: 20494470 DOI: 10.1016/j.jhep.2010.04.008]
125 **Loria P**, Adinolfi LE, Bellentani S, Bugianesi E, Grieco A, Fargion S, Gasbarrini A, Loguercio C, Lonardo A, Marchesini G, Marra F, Persico M, Prati D, Baroni GS. Practice guide-

lines for the diagnosis and management of nonalcoholic fatty liver disease. A decalogue from the Italian Association for the Study of the Liver (AISF) Expert Committee. *Dig Liver Dis* 2010; **42**: 272-282 [PMID: 20171943 DOI: 10.1016/j.dld.2010.01.021]
126 **Chalasani N**, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012; **55**: 2005-2023 [PMID: 22488764 DOI: 10.1002/hep.25762]
127 **Nascimbeni F**, Pais R, Bellentani S, Day CP, Ratziu V, Loria P, Lonardo A. From NAFLD in clinical practice to answers from guidelines. *J Hepatol* 2013; **59**: 859-871 [PMID: 23751754 DOI: 10.1016/j.jhep.2013.05.044]
128 **Thoma C**, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. *J Hepatol* 2012; **56**: 255-266 [PMID: 21723839 DOI: 10.1016/j.jhep.2011.06.010]
129 **Johnson NA**, George J. Fitness versus fatness: moving beyond weight loss in nonalcoholic fatty liver disease. *Hepatology* 2010; **52**: 370-381 [PMID: 20578153 DOI: 10.1002/hep.23711]
130 **Hallsworth K**, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R, Day CP, Trenell MI. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. *Gut* 2011; **60**: 1278-1283 [PMID: 21708823 DOI: 10.1136/gut.2011.242073]
131 **Bae JC**, Suh S, Park SE, Rhee EJ, Park CY, Oh KW, Park SW, Kim SW, Hur KY, Kim JH, Lee MS, Lee MK, Kim KW, Lee WY. Regular exercise is associated with a reduction in the risk of NAFLD and decreased liver enzymes in individuals with NAFLD independent of obesity in Korean adults. *PLoS One* 2012; **7**: e46819 [PMID: 23110056 DOI: 10.1371/journal.pone.0046819]
132 **Keating SE**, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012; **57**: 157-166 [PMID: 22414768 DOI: 10.1016/j.jhep.2012.02.023]
133 **Bacchi E**, Negri C, Targher G, Faccioli N, Lanza M, Zoppini G, Zanolin E, Schena F, Bonora E, Moghetti P. Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 Randomized Trial). *Hepatology* 2013; **58**: 1287-1295 [PMID: 23504926 DOI: 10.1002/hep.26393]
134 **Bhupathiraju SN**, Tucker KL. Coronary heart disease prevention: nutrients, foods, and dietary patterns. *Clin Chim Acta* 2011; **412**: 1493-1514 [PMID: 21575619 DOI: 10.1016/j.cca.2011.04.038]
135 **Kardassis D**, Bech-Hanssen O, Schönander M, Sjöström L, Karason K. The influence of body composition, fat distribution, and sustained weight loss on left ventricular mass and geometry in obesity. *Obesity* (Silver Spring) 2012; **20**: 605-611 [PMID: 21566562 DOI: 10.1038/oby.2011.101]
136 **Frohlich J**, Al-Sarraf A. Cardiovascular risk and atherosclerosis prevention. *Cardiovasc Pathol* 2013; **22**: 16-18 [PMID: 22502868 DOI: 10.1016/j.carpath.2012.03.001]
137 **Mathur N**, Pedersen BK. Exercise as a mean to control low-grade systemic inflammation. *Mediators Inflamm* 2008; **2008**: 109502 [PMID: 19148295 DOI: 10.1155/2008/109502]
138 **Vepsäläinen T**, Soinio M, Marniemi J, Lehto S, Juutilainen A, Laakso M, Rönnemaa T. Physical activity, high-sensitivity C-reactive protein, and total and cardiovascular disease mortality in type 2 diabetes. *Diabetes Care* 2011; **34**: 1492-1496 [PMID: 21602429 DOI: 10.2337/dc11-0469]
139 **Rabl C**, Campos GM. The impact of bariatric surgery on nonalcoholic steatohepatitis. *Semin Liver Dis* 2012; **32**: 80-91 [PMID: 22418890 DOI: 10.1055/s-0032-1306428]
140 **Carulli L**, Maurantonio M, Hebbard L, Baldelli E, Loria P, George J. Classical and innovative insulin sensitizing drugs for the prevention and treatment of NAFLD. *Curr Pharm Des* 2013; **19**: 5280-5296 [PMID: 23394096 DOI: 10.2174/1381612811319290009]
141 **Singh S**, Singh PP, Singh AG, Murad MH, Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *Am J Gastroenterol* 2013; **108**: 881-91; quiz 892 [PMID: 23381014 DOI: 10.1038/ajg.2013.5]
142 **Zhang H**, Gao C, Fang L, Zhao HC, Yao SK. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients: a meta-analysis. *Scand J Gastroenterol* 2013; **48**: 78-87 [PMID: 23137049 DOI: 10.3109/00365521.2012.719926]
143 **Chen HP**, Shieh JJ, Chang CC, Chen TT, Lin JT, Wu MS, Lin JH, Wu CY. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. *Gut* 2013; **62**: 606-615 [PMID: 22773548]
144 **Ratziu V**, Caldwell S, Neuschwander-Tetri BA. Therapeutic trials in nonalcoholic steatohepatitis: insulin sensitizers and related methodological issues. *Hepatology* 2010; **52**: 2206-2215 [PMID: 21105109 DOI: 10.1002/hep.24042]
145 **Rakoski MO**, Singal AG, Rogers MA, Conjeevaram H. Meta-analysis: insulin sensitizers for the treatment of non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2010; **32**: 1211-1221 [PMID: 20955440 DOI: 10.1111/j.1365-2036.2010.04467.x]
146 **Musso G**, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia* 2012; **55**: 885-904 [PMID: 22278337 DOI: 10.1007/s00125-011-2446-4]
147 **Lutchman G**, Modi A, Kleiner DE, Promrat K, Heller T, Ghany M, Borg B, Loomba R, Liang TJ, Premkumar A, Hoofnagle JH. The effects of discontinuing pioglitazone in patients with nonalcoholic steatohepatitis. *Hepatology* 2007; **46**: 424-429 [PMID: 17559148 DOI: 10.1002/hep.21661]
148 **Lincoff AM**, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007; **298**: 1180-1188 [PMID: 17848652 DOI: 10.1001/jama]
149 **Neumann A**, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. *Diabetologia* 2012; **55**: 1953-1962 [PMID: 22460763 DOI: 10.1007/s00125-012-2538-9]
150 **Hiatt WR**, Kaul S, Smith RJ. The cardiovascular safety of diabetes drugs--insights from the rosiglitazone experience. *N Engl J Med* 2013; **369**: 1285-1287 [PMID: 23992603 DOI: 10.1056/NEJMp1309610]
151 **Wajcberg E**, Tavaria A. Exenatide: clinical aspects of the first incretin-mimetic for the treatment of type 2 diabetes mellitus. *Expert Opin Pharmacother* 2009; **10**: 135-142 [PMID: 19236187 DOI: 10.1517/14656560802611832]
152 **Trevaskis JL**, Griffin PS, Wittmer C, Neuschwander-Tetri BA, Brunt EM, Dolman CS, Erickson MR, Napora J, Parkes DG, Roth JD. Glucagon-like peptide-1 receptor agonism improves metabolic, biochemical, and histopathological indices of nonalcoholic steatohepatitis in mice. *Am J Physiol Gastrointest Liver Physiol* 2012; **302**: G762-G772 [PMID: 22268099 DOI: 10.1152/ajpgi.00476.2011]
153 **Zhang L**, Yang M, Ren H, Hu H, Boden G, Li L, Yang G. GLP-1 analogue prevents NAFLD in ApoE KO mice with diet and Acrp30 knockdown by inhibiting c-JNK. *Liver Int* 2013; **33**: 794-804 [PMID: 23432843 DOI: 10.1111/liv.12120]
154 **Klonoff DC**, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, Wintle ME, Maggs DG. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin* 2008; **24**: 275-286 [PMID:

18053320]
155 **Cuthbertson DJ**, Irwin A, Gardner CJ, Daousi C, Purewal T, Furlong N, Goenka N, Thomas EL, Adams VL, Pushpakom SP, Pirmohamed M, Kemp GJ. Improved glycaemia correlates with liver fat reduction in obese, type 2 diabetes, patients given glucagon-like peptide-1 (GLP-1) receptor agonists. *PLoS One* 2012; **7**: e50117 [PMID: 23236362 DOI: 10.1371/journal.pone.0050117]
156 **Sathyanarayana P**, Jogi M, Muthupillai R, Krishnamurthy R, Samson SL, Bajaj M. Effects of combined exenatide and pioglitazone therapy on hepatic fat content in type 2 diabetes. *Obesity* (Silver Spring) 2011; **19**: 2310-2315 [PMID: 21660077 DOI: 10.1038/oby.2011.152]
157 **Mundil D**, Cameron-Vendrig A, Husain M. GLP-1 receptor agonists: a clinical perspective on cardiovascular effects. *Diab Vasc Dis Res* 2012; **9**: 95-108 [PMID: 22496442 DOI: 10.1177/1479164112441526]
158 **Athyros VG**, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, Pagourelias ED, Theocharidou E, Karagiannis A, Mikhailidis DP. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *Lancet* 2010; **376**: 1916-1922 [PMID: 21109302 DOI: 10.1016/S0140-6736(10)61272-x]
159 **Tikkanen MJ**, Fayyad R, Faergeman O, Olsson AG, Wun CC, Laskey R, Kastelein JJ, Holme I, Pedersen TR. Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels. *Int J Cardiol* 2013; **168**: 3846-3852 [PMID: 24001698 DOI: 10.1016/j.ijcard.2013.06.024]
160 **Lonardo A**, Loria P. Potential for statins in the chemoprevention and management of hepatocellular carcinoma. *J Gastroenterol Hepatol* 2012; **27**: 1654-1664 [PMID: 22849701 DOI: 10.1111/j.1440-1746.2012.07232.x]
161 **Phan BA**, Dayspring TD, Toth PP. Ezetimibe therapy: mechanism of action and clinical update. *Vasc Health Risk Manag* 2012; **8**: 415-427 [PMID: 22910633 DOI: 10.2147/VHRM.S33664]
162 **Van Rooyen DM**, Gan LT, Yeh MM, Haigh WG, Larter CZ, Ioannou G, Teoh NC, Farrell GC. Pharmacological cholesterol lowering reverses fibrotic NASH in obese, diabetic mice with metabolic syndrome. *J Hepatol* 2013; **59**: 144-152 [PMID: 23500152 DOI: 10.1016/j.jhep.2013.02.024]
163 **Park H**, Shima T, Yamaguchi K, Mitsuyoshi H, Minami M, Yasui K, Itoh Y, Yoshikawa T, Fukui M, Hasegawa G, Nakamura N, Ohta M, Obayashi H, Okanoue T. Efficacy of long-term ezetimibe therapy in patients with nonalcoholic fatty liver disease. *J Gastroenterol* 2011; **46**: 101-107 [PMID: 20658156 DOI: 10.1007/s00535-010-0291-8]
164 **Parker HM**, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J. Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012; **56**: 944-951 [PMID: 22023985 DOI: 10.1016/j.jhep.2011.08.018]
165 **Marik PE**, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. *Clin Cardiol* 2009; **32**: 365-372 [PMID: 19609891 DOI: 10.1002/clc.20604]
166 **Roncaglioni MC**, Tombesi M, Avanzini F, Barlera S, Caimi V, Longoni P, Marzona I, Milani V, Silletta MG, Tognoni G, Marchioli R. n-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med* 2013; **368**: 1800-1808 [PMID: 23656645 DOI: 10.1056/NEJMoa1205409]
167 **Hsueh WA**, Wyne K. Renin-Angiotensin-aldosterone system in diabetes and hypertension. *J Clin Hypertens* (Greenwich) 2011; **13**: 224-237 [PMID: 21466617 DOI: 10.1111/j.1751-7176.2011.00449.x]
168 **Schuppan D**, Gorrell MD, Klein T, Mark M, Afdhal NH. The challenge of developing novel pharmacological therapies for non-alcoholic steatohepatitis. *Liver Int* 2010; **30**: 795-808 [PMID: 20624207 DOI: 10.1111/j.1478-3231.2010.02264.x]
169 **Kudo H**, Yata Y, Takahara T, Kawai K, Nakayama Y, Kanayama M, Oya T, Morita S, Sasahara M, Mann DA, Sugiyama T. Telmisartan attenuates progression of steatohepatitis in mice: role of hepatic macrophage infiltration and effects on adipose tissue. *Liver Int* 2009; **29**: 988-996 [PMID: 19386026 DOI: 10.1111/j.1478-3231.2009.02006.x]
170 **Yokohama S**, Yoneda M, Haneda M, Okamoto S, Okada M, Aso K, Hasegawa T, Tokusashi Y, Miyokawa N, Nakamura K. Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis. *Hepatology* 2004; **40**: 1222-1225 [PMID: 15382153 DOI: 10.1002/hep.20420]
171 **Scheen AJ**. Prevention of type 2 diabetes mellitus through inhibition of the Renin-Angiotensin system. *Drugs* 2004; **64**: 2537-2565 [PMID: 15516153]
172 **Mancia G**, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; **34**: 2159-2219 [PMID: 23771844 DOI: 10.1093/eurheartj/eht151]
173 **Makishima M**, Lu TT, Xie W, Whitfield GK, Domoto H, Evans RM, Haussler MR, Mangelsdorf DJ. Vitamin D receptor as an intestinal bile acid sensor. *Science* 2002; **296**: 1313-1316 [PMID: 12016314]
174 **Targher G**, Pichiri I, Lippi G. Vitamin D, thrombosis, and hemostasis: more than skin deep. *Semin Thromb Hemost* 2012; **38**: 114-124 [PMID: 22314609 DOI: 10.1055/s-0031-1300957]
175 **Eliades M**, Spyrou E, Agrawal N, Lazo M, Brancati FL, Potter JJ, Koteish AA, Clark JM, Guallar E, Hernaez R. Meta-analysis: vitamin D and non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2013; **38**: 246-254 [PMID: 23786213 DOI: 10.1111/apt.12377]
176 **Targher G**, Bertolini L, Scala L, Cigolini M, Zenari L, Falezza G, Arcaro G. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. *Nutr Metab Cardiovasc Dis* 2007; **17**: 517-524 [PMID: 16928437 DOI: 10.1016/j.numecd.2006.04.002]
177 **Targher G**, Scorletti E, Mantovani A, Byrne CD. Nonalcoholic fatty liver disease and reduced serum vitamin D(3) levels. *Metab Syndr Relat Disord* 2013; **11**: 217-228 [PMID: 23745619 DOI: 10.1089/met.2013.0044]
178 **Lee JH**, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vita-

min D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol* 2008; **52**: 1949-1956 [PMID: 19055985 DOI: 10.1016/j.jacc.2008.08.050]
179 **Lutsey PL**, Michos ED. Vitamin D, calcium, and atherosclerotic risk: evidence from serum levels and supplementation studies. *Curr Atheroscler Rep* 2013; **15**: 293 [PMID: 23232985 DOI: 10.1007/s11883-012-0293-5]
180 **Fall T**, Shiue I, Bergeå af Geijerstam P, Sundström J, Ärnlöv J, Larsson A, Melhus H, Lind L, Ingelsson E. Relations of circulating vitamin D concentrations with left ventricular geometry and function. *Eur J Heart Fail* 2012; **14**: 985-991 [PMID: 22723659 DOI: 10.1093/eurjhf/hfs091]

P- Reviewers: Basar O, Guerrero-Romero F, Vos MB
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Wu HL

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327

07>

9 771007 932045