EXPERT REVIEWS

Diagnosis and management of cardiovascular risk in nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as an important cardiovascular risk (CVR) factor. This is a narrative clinical review aimed at answering how diagnosis and management of CVR should be conducted in the individual patient with NAFLD. To this end, the authors performed an extensive search of the existing literature on PubMed (1993–2014) using pertinent keywords. To date, CVR among patients with NAFLD might be assessed with the Framingham risk score equation or other risk calculators, to be adapted to the true CVR in the specific population being assessed; however, the use of these CVR calculators needs to be validated by future studies in larger cohorts of NAFLD patients of various ethnic backgrounds in order to substantiate their clinical relevance as a foundation for the primary prevention of cardiovascular diseases in this group of patients. Early and aggressive drug treatment of CVR should be started in NAFLD patients with a history of cardiovascular events, established diabetes or who are at high (calculated) CVR. Whether such an aggressive pharmacological approach is also justified in patients with NAFLD, who are at intermediate or low CVR, remains debatable. Currently, there are no clinical trials showing that the treatment of NAFLD *per se* (either associated or unassociated with traditional CVR factors) will result in decreased risk of cardiovascular events. Accordingly, drug treatment should be better individualized, aiming at correcting all the coexisting cardio-metabolic risk factors of the individual patient with NAFLD. To this end, an overview of the lifestyle interventions and the available drugs is offered, emphasis being conveyed to statins and metformin, which promise to cover worrying complications of NAFLD such as the risk of developing hepatocellular carcinoma.

Keywords: cardiovascular risk • Framingham risk score • HCC • metformin • NASH • statins • steatosis

Background & review methodology

Our understanding of the link between liver disease and cardiovascular risk (CVR) has undergone a dramatic evolution over the last two decades. From a paradigm of non-steatotic (autoimmune or viral) liver disease being typically spared from cardiovascular disease (CVD) complications, we have moved to the recognition of steatotic (viral, alcoholic and non-alcoholic) liver disease as being particularly exposed to an increased CVR, which does not wane even at the more advanced stages of liver disease [1].

To date, the spectrum of CVD complications that are frequently associated with nonalcoholic fatty liver disease (NAFLD), that is, the most common liver disorder in developed countries [2], appears to be rapidly expanding. As shown in Figure 1, in addition to premature atherosclerosis [3], aortic valve sclerosis, left ventricular dysfunction/hypertrophy, cardiac autonomic dysfunction and the inherent risk of various types of cardiac arrhythmias (e.g., atrial fibrillation) are being increasingly identified in patients with NAFLD as a result of multiple extrahepatic systemic changes that are induced by this highly prevalent disease [4,5].

Reviews have specifically been devoted to the analysis of pathophysiological mechanisms of excess CVR in people with NAFLD [3,6,7]. Figure 2

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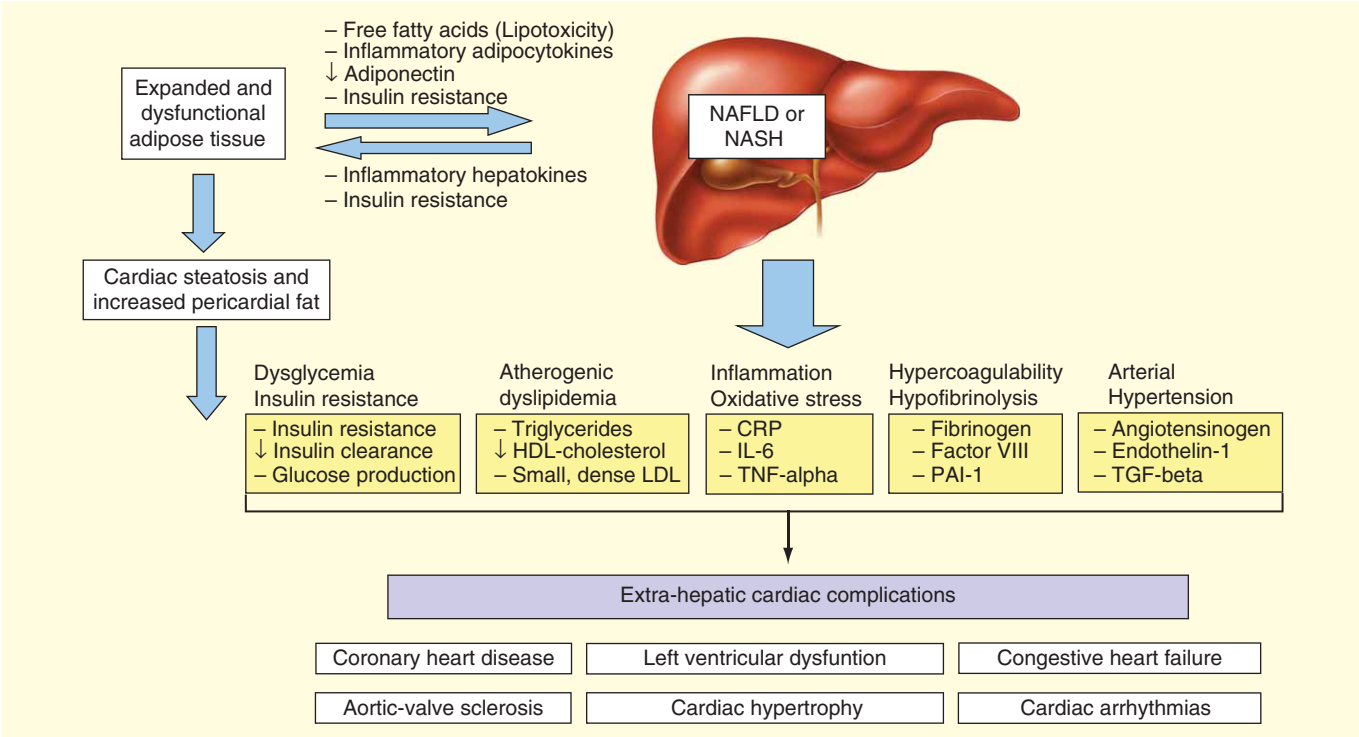

Figure 1. The enlarging spectrum of cardiovascular, cardiac and arrhythmogenic complications associated with nonalcoholic fatty liver disease. Accelerated atherogenesis is only one among the various and serious cardiovascular complications, which are increasingly being identified in patients with NAFLD.
CRP: C-reactive protein; HDL: High-density lipoprotein; IL: Interleukin; LDL: Low-density lipoprotein; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; PAI: Plasminogen activator inhibitor; TGF: Transforming growth factor; TNF: Tumor necrosis factor.

summarizes the currently putative biological mechanisms by which the liver may contribute to the increased CVR observed in patients with NAFLD [7]. However, the possibility that both NAFLD and its associated cardiovascular complications may result from a common shared primary metabolic derangement should be also kept in mind.

The present review aims at providing evidence-based answers to a common key question in clinical practice: how should diagnosis and management of CVR be conducted in the individual patient with NAFLD?

Although not a systematic review and meta-analysis, this is nevertheless a comprehensive clinical review of the existing literature. PubMed was extensively searched for pertinent articles published between 1993 and 2014 using the keywords 'nonalcoholic fatty liver disease' or 'fatty liver' combined with 'atherosclerosis', 'coronary heart disease', 'cardiovascular disease', 'cardiovascular risk', 'myocardial infarction', 'stroke', or with 'diagnosis' or 'management'. Articles published in languages other than English were excluded from the analysis.

Diagnosis of CVR in patients with NAFLD

As systematically and meta-analytically reviewed by Oni *et al.*, several cross-sectional studies have evaluated the association between NAFLD and subclinical CVD [8]. Such studies have used various markers of early, generalized atherosclerosis, such as carotid intima-media thickness (IMT), coronary artery calcification (CAC), endothelial dysfunction and arterial stiffness. Collectively, the findings of the study by Oni *et al.* provide further strong evidence that NAFLD is closely associated with subclinical CVD, independently of conventional CVR factors [8]. This information is of key pathophysiological significance and fully legitimates the recent recommendations of several scientific hepatological societies in encouraging the non-invasive assessment of CVR in patients with NAFLD [9].

However, there is an endless controversy concerning the true capacity of carotid IMT and CAC score to predict cardiovascular events, and clinical practice needs to be guided by evidence-based data. Therefore, the 'ideal' information that clinicians need may not be necessarily contained in the published studies reviewed by Oni *et al.* (Table 1). In particular, it would be important to base our medical practice and clinical decisions on the results of studies where prospectively registered 'hard' clinical CVD outcomes are evaluated in relation to histologically characterized NAFLD. We believe that what clinicians ideally need is a calculator of the global CVD risk in the individual patient with NAFLD; and such a risk calculator should ideally be applicable to different ethnic groups (Hispanics and Afro-Americans and not only limited to Caucasians or Asians) (Table 2), given that NAFLD represents a worldwide epidemic.

Is CVD mortality increased in patients with NAFLD?

We believe that this question can be better answered by analyzing the results from six observational studies with a reasonably long duration of follow-up, which have addressed the natural course of patients with biopsy-proven NAFLD [10–15]. However, it should be noted that all of these studies were retrospective cohort studies with relatively small numbers of patients who were seen at tertiary care referral centers – features that limit the generalizability of the findings to a broader patient population. However, with those caveats in mind, data from these studies clearly suggested non-alcoholic steatohepatitis (NASH) to be closely associated with excess CVD and liver-related mortality compared with the matched control population. Interestingly, CVD was the primary cause of mortality in NAFLD patients (Table 3). However, a meta-analytic review of five out of these six studies [10,12–15] led Musso *et al.* to conclude that NAFLD was significantly associated with a higher risk of CVD mortality but that, compared with simple steatosis, NASH did not confer an excess CVD mortality [16]. Although it conflicts with the experimental evidence showing that the gene expression in NASH livers is unbalanced toward a more atherogenic risk profile [17], this meta-analytic finding [16] suggests that, unless proven otherwise by future studies, liver biopsy is not necessary in assessing CVR in the individual patient with NAFLD.

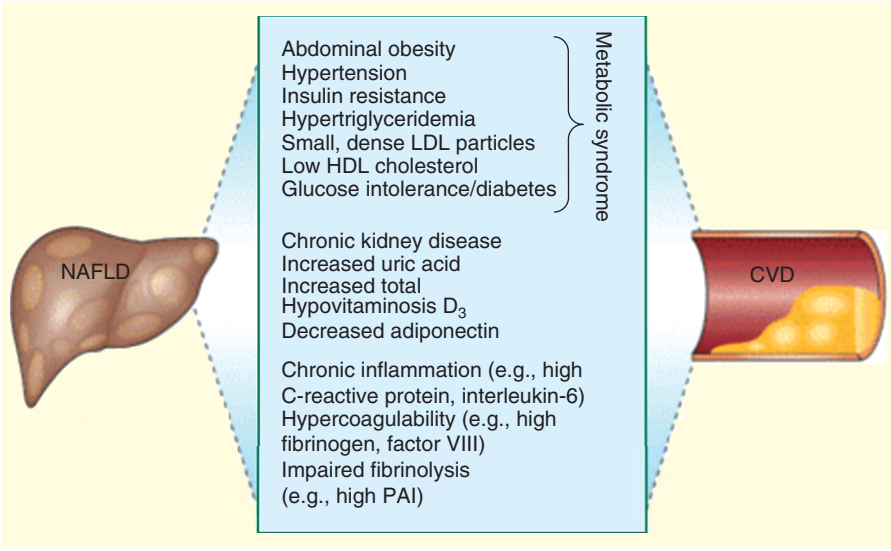

Figure 2. The wide array of physiopathological nonalcoholic fatty liver disease-associated derangements associated with premature atherosclerosis. Several cardiovascular risk factors appear to be either specifically triggered or amplified by NAFLD. CVD: Cardiovascular disease; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NAFLD: Nonalcoholic fatty liver disease; PAI: Plasminogen activator inhibitor. Reprinted with permission from [7].

Patient vignette

A 48-year old asymptomatic non-diabetic, overweight, teetotal man, who does not have a history of coronary heart disease (CHD), has been found to have fatty liver on ultrasonography [18]. Should this individual be submitted to CVR assessment, despite the fact that it remains unproven whether specific therapeutic interventions on NAFLD (associated or not with traditional CVR factors) will result in a decreased risk of cardiovascular events?

Presently, scientific societies agree that CVR should indeed be evaluated in NAFLD patients, including the case described above. However, how such a CVR assessment should be done remains controversial [9].

The following sections will provide to practising physicians a pragmatic view of the diagnosis and management of CVR of this case.

Can 10 -year risk of developing CHD events be predicted in the individual patient with NAFLD?

The most practical tool to calculate the 10-year risk of developing a CHD event in adults aged 20 years and older, who do not have CHD or diabetes, has been made available online by NIH [19]. This risk score uses information from the Framingham Heart Study to predict a person's chance of having a CHD event in the next 10 years, and is based on a set of only seven traditional risk factors (i.e., age, sex, total and high-density lipoprotein [HDL]-cholesterol, smoking, systolic blood pressure and hypertension treatment).

It is well known that a history of prior CHD and/or the presence of established diabetes increase CVR substantially, and that NAFLD markedly increases the risk of developing CVD in multiple sites (coronary, cerebral and peripheral disease) in patients with Type 2 diabetes [20,21]. Accordingly, these two subgroups of patients, irrespective of the coexistence of NAFLD, are thought to be at very high CVR and should be, therefore, routinely screened for traditional CVD risk factors and aggressively treated according to the international guidelines provided for patients in secondary prevention of CVD or those at high CVR [22,23].

Recently, Treeprasertsuk *et al.* [24] have prospectively registered the occurrence of incident CHD events in 309 US patients with NAFLD who were followed for a mean period of 11.5 years. Although NAFLD patients had a significantly higher 10-year CHD risk than the general population of the same age and sex, these patients were at low or intermediate CHD risk on the basis of the Framingham risk score (FRS) (overall mean 10-year risk score 11 ± 9%). Notably, at multivariate analysis, the FRS was the only variable significantly associated with new-onset CHD. A FRS cut-point of 11 in women and 6 in men had a high sensitivity of 80% and 74%, and a high negative predictive value of 97 and 93%, respectively in predicting new-onset CHD [24].

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Table 1. Evidence that nonalcoholic fatty liver disease is associated with surrogate markers of cardiovascular disease.

	Meaning of the test	Number of studies	Findings	Adjusted OR; 95% CI
Carotid IMT	Independent predictor of CVD events	16	NAFLD is associated with increased carotid IMT independent of traditional risk factors	OR from 8.38; CI: 2.39–29.43 to 1.35, 95% CI: 1.06–1.71
Coronary artery calcification	Associated with increased risk of multiple CVD outcomes	7	NAFLD increases the risk of coronary artery calcification independent of traditional risk factors	OR from 2.46, 95%; CI: 1.06–5.69 to 1.24; CI: 0.68–2.26
Endothelial dysfunction	Earliest marker of atherosclerosis	7	NAFLD is associated with endothelial dysfunction independent of traditional risk factors	OR: 11.7; 95% CI: 1.4–96.5
Arterial stiffness	Independent marker of symptomatic CVD and events	6	NAFLD is associated with arterial stiffness independent of traditional risk factors	OR from 1.50; 95% CI: 1.29–1.75 to 1.30; 95% CI: 1.11–1.51

CVD: Cardiovascular disease; IMT: Intima-media thickness; OR: Odds ratio; NAFLD: Nonalcoholic fatty liver disease.
Adapted from [8].

Although the FRS appears to be sufficiently accurate in predicting CHD risk among populations from the USA, Australia and New Zealand, it overestimates the prediction for CHD risk and requires adjustments when applied to European populations [25]. This implies that National authorities need to release specific CHD risk assessment tools that have been validated for a given population.

For example, the Istituto Superiore di Sanità, that is, the Italian Health National authority, has validated for Italian people without a history of CHD (or other clinical CVD complications) a new risk calculator available online [26–28] that uses the same set of risk factors of the FRS. It is reasonable to assume that this risk calculator might also accurately predict CVR in NAFLD patients without a history of CHD (or other clinical CVD complications) from Southern Europe. However, external validation for the use of this CVR calculator is certainly needed.

Table 2. The information practising clinicians need as opposed to evidence from published studies.

	Published studies	The *'ideal'* information clinicians need
Outcome: atherosclerosis	Subclinical disease	Clinical event
Diagnosis of NAFLD	Surrogate	Histological
Study design	Cross-sectional	Longitudinal
Indicators of outcome in the individual patient	None	Individual risk score calculator
Population evaluated	Caucasians & Asians	Hispanic and Afro-Americans included

NAFLD: Nonalcoholic fatty liver disease.

It is conceivable that the FRS and other CVR scoring systems may underestimate the CVR among patients with NAFLD, given that the subclinical inflammatory, insulin-resistant and hypertriglyceridemic states of NAFLD are not considered in any of these CVR scoring systems. Thus, we believe that the use and the accuracy of the FRS or other risk scoring systems in predicting CHD risk among patients with NAFLD need to be further validated by future prospective studies in larger cohorts of NAFLD patients of various ethnic backgrounds in order to substantiate their clinical relevance as a foundation for the primary prevention of atherosclerotic CVD in this group of patients.

When should CVD risk be re-measured?

Timing and frequency of the follow-up for the re-assessment of global CVR in patients in primary prevention of CVD (including those with NAFLD) is still poorly defined [21]. Interestingly, using data collected in two large observational studies, Bell *et al*. have estimated the probability of becoming high risk for CHD (according to the FRS) among approximately 15,000 people at low and intermediate risk and not being treated for high blood pressure or lipid levels. These authors concluded that decisions on the frequency of re-measuring for CVR should be made on the basis of baseline risk. Repeat risk estimation before 8–10 years is not warranted for most people initially not requiring treatment. However, re-measurement within a year seems warranted in those with an initial 15 to less than 20% risk [29].

Table 3. Evidence-based natural history of nonalcoholic fatty liver disease.

Study (year)	Study cohort (% NASH)	Length of follow-up (years)	Main findings	Ref.
Matteoni *et al*. (1999)	132 (63)	Mean 8.2	NASH is associated with increased mortality	[10]
Dam-Larsen *et al*. (2004)	215 (49)	Median 16.7	Fatty liver has the same life expectancy as general population	[11]
Adams *et al*. (2005)	420 (49/61)	Mean 7.6	Survival was lower than that expected for age- and sex-matched general population	[12]
Ekstedt *et al*. (2006)	129 (55)	Mean 13.7	Survival of NASH patients was reduced ($p = 0.01$). These subjects more often died from cardiovascular ($p = 0.04$) and liver-related ($p = 0.04$) causes	[13]
Rafiq *et al*. (2009)	173 (41)	Median 10.5	NASH patients have increased liver-related mortality	[14]
Söderberg *et al*. (2010)	118 (43)	Median 24	Survival of NASH patients is reduced and CVD is the primary cause of death	[15]

As summarized in Table 4, simple clinical data (e.g., family history for premature CHD) and numerous CVD screening tests (e.g., measurement of carotid IMT or CAC score or other diagnostic parameters) may be useful for a more accurate reclassification of the individuals at intermediate risk [21]. For example, intermediate-risk patients with a CAC score >300 Hounsfield units have approximately a 28% risk of developing CHD over 10 years and may, therefore, be re-classified as patients at high risk [30]. However, it should be highlighted once more that the accuracy of surrogate CVD markers (and particularly carotid IMT) in predicting the true risk of developing cardiovascular events remains quite controversial. Finally, ethnicity-specific CVR calculators are necessary.

Management of CVR in patients with NAFLD

Diet

Lifestyle changes, through diet and physical exercise, are universally recommended as the first-line approach to the management of NAFLD [9].

Optimal nutrient composition of diet for individuals with NAFLD is still unknown. A meta-analysis of three small randomized controlled trials (RCTs) that compared the effect of low-carbohydrate versus low-fat caloric restriction has reported similar reductions in body weight, liver fat content (magnetic resonance spectroscopy-assessed) and serum alanine aminotransferase (ALT) levels as well as similar improvements in Homeostasis Model Assessment (HOMA)-estimated insulin resistance, plasma triglycerides and adiponectin levels with both dietary regimens [31]. However, low-carbohydrate diet reduced more significantly waist circumference and plasma glucose levels compared with low-fat diet, which conversely improved plasma lipid profile more consistently [31]. Dietary restrictions, therefore, should better be tailored based on the specific metabolic derangement of the individual patient.

Replacement of dietary saturated fatty acids with polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids may improve NAFLD and decrease CVR [32]. The ω-3 PUFA effects on NAFLD are discussed below (see section 'Management of dyslipidemia').

Dietary ω-6 PUFA intake (suggested above 5%, ideally 10% of the total energy) is associated with a reduction in low-density lipoprotein (LDL)-cholesterol levels, which may explain the observed decreased risk of CHD [33]. However, little is known about the effects of ω-6 PUFA intake on liver fat content. Previous observational studies found an increased dietary ω-6 PUFA intake and ω-6/ω-3 PUFA ratio as well as an increased hepatic ω-6/ω-3 PUFA ratio in patients with NASH compared with control subjects [34,35]. In contrast, a recent RCT showed that an iso-caloric ω-6 PUFA-enriched diet significantly reduced liver fat content and modestly improved metabolic status compared with saturated fatty acid-enriched diet, without concomitant weight loss [36]. Moreover, this RCT did not find any significant effect of ω-6 PUFA-enriched diet on biomarkers of inflammation or oxidative stress.

A recent large RCT reported a significant reduction in the incidence of CVD events in subjects consuming a 'Mediterranean' diet compared with those following a low-fat diet [37]. However, little is known about the benefit of Mediterranean diet in patients with NAFLD. A small trial on 12 patients with biopsy-proven NAFLD showed that the Mediterranean diet significantly reduced hepatic steatosis (as assessed by magnetic resonance) and improved insulin sensitivity compared with a control low fat-high carbohydrate diet, with no difference in weight loss [38]. A case–control study showed that a higher adherence to the Mediterranean diet was not associated with a lower risk of having NAFLD, but it was associated with a less severe degree of liver disease and insulin resistance in those with NAFLD [39]. An Italian study reported that an iso-caloric monounsaturated fatty acid-enriched diet compared with a diet enriched in carbohydrates and fibers was associated with a significant reduction in hepatic fat content in Type 2 diabetic patients, independent of aerobic training program [40].

Given the strong association of high fructose consumption with the metabolic syndrome, the development and the

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Table 4. Overview of 2010 American College of Cardiology Foundation/American Heart Association guideline for assessment of cardiovascular risk in asymptomatic adults.

Parameter	Recommendation	Class of evidence (level of evidence)
Family history	Family history of atherothrombotic CVD should be obtained for CVR assessment in all symptomatic adults	Class I (level of evidence: B)
Genomic testing	Genotype testing for CVR assessment in asymptomatic adults is not recommended	Class III: no benefit (level of evidence: B)
Lipoprotein and apolipoprotein	Measurement of lipid parameters, including lipoproteins, apolipoproteins, particle size and density, beyond a standard fasting lipid profile is not recommended for CVR assessment in asymptomatic adults	Class III: no benefit (level of evidence: C)
Natriuretic peptides	Measurement of natriuretic peptides is not recommended for CVR assessment in asymptomatic adults	Class III: no benefit (level of evidence: B)
C-reactive protein	In men 50 years of age or older or women 60 years of age or older with LDL-cholesterol <130 mg/dl; not on lipid-lowering, hormone replacement or immunosuppressant therapy; without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions or contraindications to statins, measurement of CRP can be useful in the selection of patients for statin therapy	Class IIa (level of evidence: B)
	In asymptomatic intermediate-risk men 50 years of age or younger or women 60 years of age or younger, measurement of CRP may be reasonable for CVR assessment	Class IIb (level of evidence: B)
	In asymptomatic high-risk adults, measurement of CRP is not recommended for CVR assessment In low-risk men younger than 50 years of age or women 60 years of age or younger, measurement of CRP is not recommended CVR assessment	Class III: no benefit – (level of evidence: B) – (level of evidence: B)
Hemoglobin A1C	Measurement of hemoglobin A1C may be reasonable for CVR assessment in asymptomatic adults without a diagnosis of diabetes	Class IIb (level of evidence: B)
Microalbuminuria	In asymptomatic adults with hypertension or diabetes, urinalysis to detect microalbuminuria is reasonable for CVR assessment In asymptomatic adults at intermediate risk without hypertension or diabetes, urinalysis to detect microalbuminuria might be reasonable for CVR assessment	Class IIa (level of evidence: B) Class IIb (level of evidence: B)
Lipoprotein-associated phospholipase A2	Lipoprotein-associated phospholipase A2 might be reasonable for CVR assessment in intermediate-risk asymptomatic adults	Class IIb (level of evidence: B)
Resting electrocardiogram	A resting ECG is reasonable for cardiovascular risk assessment in asymptomatic adults with hypertension or diabetes	Class IIa (level of evidence: C)
	A resting ECG may be considered for cardiovascular risk assessment in asymptomatic adults without hypertension or diabetes	Class IIb (level of evidence: C)
Transthoracic echocardiography	Echocardiography to detect LVH may be considered for CVR assessment in asymptomatic adults with hypertension Echocardiography is not recommended for CVR assessment of CHD in asymptomatic adults without hypertension	Class IIb (level of evidence: B) Class III: no benefit (level of evidence: C)

CAC: Coronary artery calcification; CHD: Coronary heart disease; CRP: C-reactive protein; CVD: Cardiovascular disease; CVR: Cardiovascular risk; IMT: Intima-media thickness; LDL: Low-density lipoprotein; LVH: Left ventricular hypertrophy; MPI: Myocardial perfusion imaging; MRI: magnetic resonance imaging.
Adapted from [21].

Table 4. Overview of 2010 American College of Cardiology Foundation/American Heart Association guideline for assessment of cardiovascular risk in asymptomatic adults (cont.).

Parameter	Recommendation	Class of evidence (level of evidence)
Carotid IMT on ultrasound	Measurement of carotid artery IMT is reasonable for CVR risk assessment in asymptomatic adults at intermediate risk. Published recommendations on required equipment, technical approach and operator training and experience for performance of the test must be carefully followed to achieve high quality results	Class IIa (level of evidence: B)
Brachial/Peripheral flow-mediated dilation	Peripheral arterial flow-mediated dilation studies are not recommended for CVR assessment in asymptomatic adults	Class III: no benefit (level of evidence: B)
Measures of arterial stiffness	Measures of arterial stiffness outside of research settings are not recommended for CVR assessment in asymptomatic adults	Class III: no benefit (level of evidence: C)
Measurement of Ankle Brachial Index	Measurement of ABI is reasonable for CVR assessment in asymptomatic adults at intermediate risk	Class IIa (level of evidence: B)
Exercise electrocardiography	An exercise ECG may be considered for cardiovascular risk assessment in intermediate-risk asymptomatic adults (including sedentary adults considering starting a vigorous exercise program), particularly when attention is paid to non-ECG markers such as exercise capacity	Class IIb (level of evidence: B)
Stress echocardiography	Stress echocardiography is not indicated for CVR assessment in low- or intermediate-risk asymptomatic adults. (Exercise or pharmacologic stress echocardiography is primarily used for its role in advanced cardiac evaluation of symptoms suspected of representing CHD and/or estimation of prognosis in patients with known coronary artery disease or the assessment of patients with known or suspected valvular heart disease.)	Class III: no benefit (level of evidence: C)
Myocardial perfusion imaging	Stress MPI may be considered for advanced CVR assessment in asymptomatic adults with diabetes or asymptomatic adults with a strong family history of CHD or when previous risk assessment testing suggests high risk of CHD, such as a CAC score of 400 or greater Stress MPI is not indicated for CVR assessment in low- or intermediate-risk asymptomatic adults (Exercise or pharmacologic stress MPI is primarily used and studied for its role in advanced cardiac evaluation of symptoms suspected of representing CHD and/or estimation of prognosis in patients with known CAD.)	Class IIb (level of evidence: C) Class III: no benefit (level of evidence: C)
Computed tomography for coronary calcium	Measurement of CAC is reasonable for CVR in asymptomatic adults at intermediate risk (10–20% 10-year risk) Measurement of CAC may be reasonable for CVR assessment in persons at low to intermediate risk (6–10% 10-year risk) Persons at low risk (<6% 10-year risk) should not undergo CAC measurement for cardiovascular risk assessment	Class IIa (level of evidence: B) Class IIb (level of evidence: B) Class III: no benefit (level of evidence: B)
Coronary computed tomography angiography	Coronary computed tomography angiography is not recommended for CVR assessment in asymptomatic adults	Class III: no benefit (level of evidence: C)
MRI of plaque	MRI for detection of vascular plaque is not recommended for CVR assessment in asymptomatic adults	Class III: no benefit (level of evidence: C)

CAC: Coronary artery calcification; CHD: Coronary heart disease; CRP: C-reactive protein; CVD: Cardiovascular disease; CVR: Cardiovascular risk; IMT: Intima-media thickness; LDL: Low-density lipoprotein; LVH: Left ventricular hypertrophy; MPI: Myocardial perfusion imaging; MRI: magnetic resonance imaging.
Adapted from [21].

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progression of NAFLD [41], the consumption of soft drinks should be discouraged in individuals with NAFLD [32,42]. By inference from hepatitis C virus (HCV)-infected patients, it may be discussed whether it is only industrial, as opposed to fruit fructose consumption, that is deleterious [43]. In other words, 'fruit' is much more than 'fructose'. Such a contention, however, requires direct assessment.

Consumption of foods rich in cereal fibers or mixtures of whole grains and bran may be also suggested, given a modest association of these foods with reduced risks of obesity, Type 2 diabetes and CVD reported by epidemiological studies [44,45].

Further to offering benefits, diets are not completely devoid of drawbacks and side effects. The more diets are hypo-caloric, the less they are palatable and long-term sustainable, the more they need medical supervision owing to inherent risk of electrolyte imbalance, ketosis, hypotension and gallstones [46].

Light-to-moderate alcohol consumption may exert some beneficial effect on the severity of NAFLD [47,48]. However, it is still unknown whether the potential cardiovascular benefits of a light-to-moderate alcohol consumption observed in the general population may be also extended to those with NAFLD. In the absence of large RCTs, current guidelines advise against prescribing low-to-moderate alcohol consumption as a preventive/therapeutic strategy for NAFLD [9]. A teetotal individual such as that depicted in the clinical vignette should not, in our view, be encouraged to start drinking, although some experts have suggested that light drinking (up to one drink per day) may be acceptable (except for patients with NASH-cirrhosis, in whom alcohol intake should be completely avoided) [42].

Smoking cessation should be also strongly encouraged considering that tobacco smoking, an established risk factor for CVD, has been blamed for the onset and histological severity of NAFLD in epidemiological studies [49,50].

Physical activity & exercise

Epidemiologic data show a strong, inverse relationship between NAFLD and physical activity [51,52].

A growing body of research demonstrates that increased physical activity *per se* significantly reduces hepatic steatosis and serum aminotransferase levels in individuals with NAFLD, independent of weight loss [51–53]. A recent meta-analysis (involving a total of 439 overweight or obese participants) that combined 12 studies on exercise intervention with or without diet (11 with randomized controlled design) has clearly documented a beneficial effect of physical exercise on liver fat content, which was already apparent with minimal or no concomitant weight loss and at exercise levels below the current exercise recommendations for obesity management [54]. Also short-term exercise (60 min/day of treadmill walking per 7 consecutive days) improved hepatic lipid composition and insulin sensitivity, probably via increased adiponectin levels, without any change in body weight [55]. A recent RCT showed that 4 months of resistance training and aerobic training were equally effective in reducing hepatic fat content (as measured by MRI) among sedentary patients with Type 2 diabetes and NAFLD [56].

Weight loss achieved through diet alone or combined with physical activity significantly reduces hepatic steatosis and necro-inflammatory changes of people with NAFLD in proportion to the entity of body weight reduction (a 5–10% weight loss reduces hepatic steatosis, while up to a 10% weight loss is required to improve the degree of hepatic necro-inflammation) [57,58]. However, no study of lifestyle modification has been able to demonstrate an improvement in hepatic fibrosis stage. In adults with NAFLD, exercise alone might reduce hepatic steatosis, but limited data are available on its ability to improve other aspects of liver histology [58]. It is of interest, therefore, that vigorous, but not moderate exercise nor total duration or volume of physical activity, was related to decreased odds of having NASH or advanced fibrosis in a recent retrospective study [59].

Lifestyle modifications have an established role in CVD risk reduction via improvements in cardio-metabolic risk factors and myocardial function [4]. Moreover, regular physical exercise may also exert some of its beneficial health effects by decreasing markers of inflammation and endothelial dysfunction [60] and, in principle, by affecting the levels of the recently discovered myokine irisin [61]. Authors have indeed suggested that a molecular integration occurs in the muscle of signals coming from both nutrients and physical exercise [62].

Patients with NAFLD should be, therefore, advised to participate in regular, aerobic exercise combined with diet, which can provide a valid, first-line and low-cost therapy for both NAFLD and CVD.

Pharmacologic & surgical treatment

Detailed reviews on pharmacological treatment of NAFLD have recently been published [31,63–65]. Emphasis is given here to those, among available pharmacological options, which specifically address CVR.

Antioxidants & vitamins

Based on the shared role of oxidative stress in the pathogenesis of both NASH and atherosclerosis [6], antioxidants and specific vitamins may in theory improve liver histology and reduce CVR. This speculation, unfortunately, is not sufficiently confirmed by studies and findings remain controversial.

From the hepatological side, a recent RCT reported that vitamin E was superior to placebo for NASH treatment in non-diabetic adults [66]. The findings from this trial raised the issue of whether insulin resistance had still to be considered the primary pathogenic event in NASH development [67]. However, it should be noted that vitamin E was not superior to placebo in children with NAFLD [68].

From the CVR side, more worryingly, the Copenhagen Cochrane Group investigators have warned that supplements with β-carotene, vitamin E and high doses of vitamin A may increase all-cause mortality [69], whereas the potential effects of vitamin C and selenium on mortality need further study.

In conclusion, incomplete and conflicting evidence of any hepato-protective benefit on the one hand; and concerns for potential excess mortality associated with vitamin/antioxidant supplements dictate the need for further studies.

Management of diabetes

NAFLD and Type 2 diabetes share insulin resistance as their chief pathogenic determinant, and literature data strongly support NAFLD as an emerging risk factor for the development of Type 2 diabetes which is, in turn, a major contributor to progressive liver disease [70]. Although there are, to date, no pharmacological agents approved for the treatment of NAFLD *per se*, many studies have evaluated the use of insulin sensitizers as a possible treatment for this disease.

Insulin sensitizers

Metformin

Metformin is a biguanide widely used as a first-line treatment for patients with Type 2 diabetes. Metformin has anorexigenic/weight-loss properties and improves glucose and lipid metabolism via activation of adenosine monophosphate-activated protein kinase (AMPK) [71]. Despite its beneficial effects on insulin resistance, metformin exerts only a marginal beneficial effect on serum aminotransferase levels and fails to improve liver histology in NAFLD [31]. Four RCTs comparing metformin plus lifestyle intervention versus lifestyle intervention alone among patients with NAFLD did not show any significant improvement in NAFLD histology in the metformin group (as meta-analytically reviewed in [29]). In a recent RCT performed on a pediatric population, the treatment with metformin was associated with some improvements in hepatocellular ballooning but not hepatic fibrosis, steatosis or NAFLD activity score [68]. A recent meta-analysis by Musso *et al.* [31] confirmed that metformin significantly reduced body weight and insulin resistance but did not improve NAFLD histology as compared with placebo.

Accordingly, metformin is not recommended in non-diabetic patients with NAFLD [9], although it may have important beneficial effects on other NAFLD-related complications/comorbidities, which may prove useful along the natural course of disease. In fact, metformin has been consistently reported to reduce the risk of developing hepatocellular carcinoma (HCC) in patients with Type 2 diabetes [72–75]. Additional RCTs being necessary, prescribing metformin with the specific aim of preventing HCC in diabetic patients is unwarranted at this time.

Interestingly, some animal studies have suggested that metformin protects mice against chemically induced liver tumors without increasing AMPK activation, often shown to be a metformin target, but rather metformin decreases hepatic lipogenesis by impairing the expression of several lipogenic enzymes [76], which may potentially account for the finding that metformin also reduces the risk of developing other cancer types such as pancreatic and colorectal cancers in which lipid synthesis is upregulated [71,76]. In contrast, sulfonylureas or insulin possibly increase HCC risk [72,73].

In addition, a meta-analysis showed that metformin significantly reduces the conversion rate of pre-diabetes to diabetes [77]. Moreover, metformin may exert a cardio-protective effect by decreasing arterial stiffness and improving markers of endothelial function which may contribute to further reduce CVR beyond its beneficial metabolic effects [78,79].

Thiazolidinediones

Thiazolidinediones are peroxisome proliferator-activated receptor (PPAR)-γ agonists, which enhance whole body insulin sensitivity by protecting non-adipose tissues against excessive lipid overload and by balancing the secretion of adipocytokines [80]. Troglitazone and rosiglitazone have been withdrawn from the market because of their significant side effects (i.e., hepatoxicity and increased risk of non-fatal myocardial infarction), whereas pioglitazone is the only currently available thiazolidinedione for the clinical use in humans. Pioglitazone is recommended by current guidelines for the treatment of NASH patients [9]. Large RCTs reported a beneficial effect of pioglitazone on insulin sensitivity and NAFLD histology, although its beneficial effect on hepatic fibrosis, if any, is probably of scarce entity [31,81]. However, the hepato-protective effects of pioglitazone vanish after treatment discontinuation [82]. In addition, concerns have been also raised about its long-term safety. Pioglitazone only marginally reduces the risk of major CVD events in people with Type 2 diabetes, but it is associated with significant weight gain (owing to increased subcutaneous fat depots), and increases the risk of congestive heart failure and bone fractures [83]. Moreover, a slight excess of bladder cancer has also recently led to pioglitazone being withdrawn from market in France [84]. Therefore, the potential favorable effects of pioglitazone on the liver are counterbalanced by the lack of clear cardiovascular benefits, suggesting that CVD risk reduction needs a more global approach than just glycemic control [85].

Incretin-based therapy

Glucagon-like peptide-1 (GLP-1) is an incretin hormone released by the gastrointestinal tract in response to nutrients (especially to glucose), eliciting glucose-stimulated insulin secretion while suppressing glucagon secretion [86]. GLP-1 also slows gastric emptying, which contributes to decreased postprandial glycemic excursions, and suppresses appetite, thereby contributing to weight loss [86,87]. GLP-1 has a very short half-life due to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). Two new classes of drugs acting on the incretin system are available for the treatment of Type 2 diabetes [88]: GLP-1 analogs (e.g., exenatide and liraglutide), which are GLP-1 receptor agonists, resistant to DPP-4 degradation and thus have a longer half-life; and DPP-4 inhibitors (e.g., saxagliptin, sitagliptin, vildagliptin, linagliptin and alogliptin), which increase GLP-1 circulating half-life.

GLP-1 analogs

GLP-1 analogs reduce hepatic steatosis and necro-inflammation in animal models of NAFLD [89,90]. *In vitro* studies showed

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that GLP-1 receptors are present in human hepatocytes and their activation produces a direct effect on hepatic steatosis, increasing hepatic insulin sensitivity and reducing fatty acid accumulation and endoplasmic reticulum stress [91,92]. A recent study has shown that glucose-induced GLP-1 secretion is deficient in patients with NAFLD/NASH [93].

Only few studies are available on the clinical use of GLP-1 analogs in patients with NAFLD. In an open-label clinical trial adjunctive exenatide treatment for at least 3 years in obese patients with Type 2 diabetes resulted in sustained improvements in glycaemic control, CVD risk factors and serum liver enzyme levels, coupled with progressive body weight reduction [94]. Some other small intervention trials reported that GLP-1 analogs significantly improved magnetic resonance measured hepatic fat content and serum aminotransferase levels in obese patients with Type 2 diabetes [95,96]. A case series study with paired liver biopsy in patients with Type 2 diabetes and NASH showed that exenatide treatment significantly reduced serum aminotransferases, but did not ameliorate liver histology [97].

A recent meta-analysis of six RCTs, including 4442 patients with Type 2 diabetes, showed that liraglutide (1.8 mg/day for 6 months) improved serum ALT level and hepatic steatosis on computed tomography (CT), mainly by its beneficial effects on weight loss and glycaemic control [98]. In a small retrospective study, liraglutide improved serum ALT level, aspartate aminotransferase/platelet ratio index score of fibrosis and body weight in patients with Type 2 diabetes and NAFLD [99]. Another study showed that liraglutide promoted weight loss, reducing CT-assessed subcutaneous fat, and improved CT-measured hepatic steatosis in patients with Type 2 diabetes and NAFLD [100]. Finally, a small case–control study reported a beneficial effect of liraglutide on hepatic fibrosis markers in obese women with polycystic ovary syndrome and NASH [101].

Taken together, these data suggest that GLP-1 analogs are useful for NAFLD/NASH treatment. However, further larger and longer RCTs with histological primary endpoints are needed to establish a beneficial effect of these drugs for the treatment of NAFLD/NASH.

DPP-4 inhibitors

Studies in animal models suggest that DPP-4 inhibitors such as sitagliptin and linagliptin may ameliorate hepatic steatosis and inflammation [102,103]. However, very limited clinical data from non-randomized trials conducted in small groups of Type 2 diabetic patients indicate that sitagliptin improves surrogate and histological liver end points in Type 2 diabetic patients with NASH [104,105]. Therefore, although DPP-4 inhibitors may be a promising class of drugs for NAFLD treatment, the limited available data do not permit to draw any firm conclusions about this issue.

Incretin-based therapy is associated with beneficial effects on CVD risk factors, including body weight, blood pressure and plasma lipids [106]. Neither GLP-1 analogs nor DPP-4 inhibitors have been associated with an increased risk of major CVD events in a meta-analysis of small RCTs [106]. Although still not conclusive, studies in preclinical models and in patients with acute coronary syndrome(s) suggest a potential cardio-protective effect of native GLP-1 or GLP-1 analogs following myocardial ischemia [106,107]. Large RCTs designed to evaluate the long-term CV outcomes with incretin-based therapies among patients with Type 2 diabetes are in progress. However, the first two published RCTs on saxagliptin and alogliptin failed to show any cardioprotective effects of these two drugs compared with placebo and raised some concerns about a significantly increased risk of hospitalization for congestive heart failure after a short-term treatment with saxagliptin [108,109].

Management of dyslipidemia

Statins

The availability of statins, inhibitors of the cholesterol synthesis *in vivo*, has changed our view of atherosclerosis from an unpreventable consequence of aging to a preventable condition, wherein cholesterol-lowering agents significantly reduce CVD morbidity and mortality [110].

Efficacy of statins on CVR

A recent Cochrane review of the statin use for the primary prevention of CVD has evaluated data from 56,934 participants randomized in 18 RCTs, 14 of which enrolled patients with dyslipidemia, diabetes, hypertension or microalbuminuria. Data have clearly shown that rates of all-cause mortality, combined fatal and non-fatal CHD events, and combined fatal and non-fatal strokes and revascularization procedures were all significantly reduced by statin treatment [111]. Opponents would argue, nevertheless, that the number needed to treat is relatively high, (i.e., 50 treated individuals to avoid one cardiovascular event over 5 years) [111] and the number needed to harm is relatively low and that the potential benefits and harms both tend to increase as the threshold for intervention increases [112].

Of interest, indirect evidence (namely based on surrogate indices of NAFLD) from the GREACE trial suggested statins to improve symptom-free survival from CVD selectively in patients with CHD and suspected NAFLD rather than in NAFLD-free patients [113]. Indeed, the results of this trial revealed a 68% relative risk reduction of CVD events in statin-allocated patients compared with placebo. Interestingly, CHD patients with moderately elevated transaminase levels and suspected NAFLD had a significantly greater cardiovascular benefit than those with normal serum transaminase levels (39% relative risk reduction), with a number needed to treat of 5. More recently, Tikkanen *et al*. suggested that this risk reduction was greater among CHD patients with moderately elevated transaminase levels who were treated with intensive statin therapy (80 mg/day atorvastatin) compared with those treated with moderate statin regimens (20–40 mg/day simvastatin), with a 44% relative risk reduction [114]. These findings suggest that moderately abnormal transaminases may be a useful marker for identifying people at

particularly high CVR and thus specifically needing aggressive pharmacological intervention.

Treatment in normolipidemic NAFLD patients at high/moderate CVR (in primary prevention for CVD) is still uncertain and future research should attempt to evaluate statin use in this patient group.

Effects of statins on NAFLD histology

While there is strong evidence for efficacy of statins in reducing CVR, two meta-analytic studies found no evidence for the effectiveness of statins in improving 'hard' hepatic histological end points [64,115]. These data are of importance given that the NAFLD natural history critically depends on liver histological changes [3].

Effects of statins on risk of HCC

Evidence for a favorable effect of statins on the risk of developing HCC comes from four recent human studies, of which two are meta-analyses [116–119].

By analyzing 10 studies, involving 4298 cases of HCC in 1,459,417 patients, Singh *et al*. reported that statin users were associated with decreased risk of developing HCC compared with statin non-users [116]. However, the results of this meta-analysis were heterogeneous, owing to study location (Asian vs Western populations) and design (observational studies vs clinical trials) and, therefore, the authors concluded that future large RCTs in HCC high-risk populations (such as Asian ethnicities with HBV infection) were warranted [116]. Two further studies from Taiwan have specifically addressed this issue. Lai *et al.* evaluated in a population-based case–control study the association between statin use and risk of HCC. Cases were 3480 patients with newly diagnosed HCC compared with 13,920 age- and sex-matched controls without HCC. These authors found that statin users had a 28% decreased risk of HCC compared with statin non-users [117]. Tsan *et al*. in a population-based cohort study observed 27,883 HCC cases in the HCV cohort during the follow-up period. Among these HCV-infected patients, statin use was associated with a significantly lower HCC risk [118]. Again, another recent meta-analysis, involving 2574 cases of HCC, confirmed that statin use significantly decreased the risk of developing HCC, though in the absence of any significant relationship between duration of statin treatment and HCC risk reduction [119].

Recent studies have reviewed the molecular mechanisms underlying the beneficial effects of statins on cell cycle and apoptosis, which may eventually result in chemoprevention against HCC [110,120]. Statins may suppress tumor initiation and growth by preventing post-translational prenylation of signaling Ras/Raf proteins, inhibiting the activation of the proteasome pathway, limiting the degradation of the cyclin-dependent kinase inhibitors p21 and p27 and blocking Myc phosphorylation and activation [120]. Further, it should be noted that, by inhibiting cholesterol synthesis, statins are potentially implicated in deep changes in the composition of bile acid pool [121]. This is of importance given that a novel pathophysiologic link between Gram-positive bacteria-dependent generation of deoxycholic acid and obesity-associated HCC growth has recently been reported [122]. Finally, statins may also exert their beneficial effect in preventing HCC via their 'aspirin-like' anti-inflammatory, TNF-α-lowering activity [123,124].

Safety profile of statins in NAFLD

The Cochrane review found no excess of combined adverse events, cancers, myopathy, rhabdomyolysis, hemorrhagic stroke, serum liver enzyme elevation, renal dysfunction and arthritis, although the reviewers warn that not all clinical trials reported fully on adverse events [111]. However, an excess of incident diabetes was reported by RCTs specifically addressing this adverse event [125,126]. High statin doses *versus* usual statin doses seem to be associated with an increased risk of Type 2 diabetes [126]. The mechanism(s) by which statins may be associated with an increased diabetes risk is presently unknown.

Evidence for hepato-safety of statins

Previous reports from our and other groups have summarized the evidence for statins to be safe even if used in patients with established liver disease [110,121,127]. Recent studies have further strengthened such a conclusion.

Younoszai *et al*. [128] have used the Third National Health and Nutrition Examination Survey-mortality linked files to assess the association between statin use and liver-related mortality. In this large cohort of 9207 US adults, the rate of liver-related mortality was significantly lower among statin users than among non-statin users over a median period of 14.5 years. This study represents a major progress in our understanding of statin effects on the liver, given that previous studies had shown a possible hepato-protective effect of statins only on surrogate NAFLD indices (biochemistry and imaging), but failed to address the possible effects of statins on liver-related mortality [129].

Clinicians should be also aware that the association of statins plus fenofibrate, compared with statins alone, might provide some additional cardiovascular benefits. However, increased risks of liver and kidney side effects suggest the need for a careful monitoring [130].

Collectively, therefore, statins have, in a sense, fulfilled their promise of being the stone 'killing two birds', namely CVR and NAFLD [131]. Of interest, rather than being the cure for NAFLD *per se* statins appear to be a very promising class of drugs active in preventing CVD and HCC, the two most worrisome extrahepatic and hepatic complications of NAFLD.

Fibrates

Fibrates reduce serum triglyceride levels while simultaneously increasing HDL-cholesterol levels, by activating PPAR-α [132]. A recent meta-analysis of five RCTs, involving 315 patients, showed that fibrates did not significantly improve body weight, waist circumference, glucose metabolism, LDL-cholesterol,

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serum aminotransferases, radiological hepatic steatosis or liver histology [31]. Fibrates reduce CVD morbidity and mortality only in patients with atherogenic dyslipidemia [133]. Fenofibrate, due to its lower myopathic potential, can be prescribed concomitantly with statins to improve the achievement of lipid goals in patients with atherogenic dyslipidemia, especially those with the metabolic syndrome and/or Type 2 diabetes [132]. Collectively, although fibrates have not been shown to improve NAFLD histology, they do offer a safe and effective treatment for dyslipidemic individuals with NAFLD.

ω-3 polyunsaturated fatty acids

At present, in westernized countries, the intake of ω-3 PUFAs fails to satisfy the recommended dietary guidelines. ω-3 PUFAs are useful for the treatment of mild-to-moderate hypertriglyceridemia, which is often associated with insulin resistance and NAFLD. The American Heart Association (AHA) recommends two portions of fatty fish per week to prevent hypertriglyceridemia; in the presence of hypertriglyceridemia, treatment with 2–4 g/day of eicosapentaenoic acid and docosahexaenoic acid is recommended, to decrease serum triglyceride levels by 20–50% [134].

Several studies have investigated the effects of ω-3 PUFAs in dyslipidemic subjects with NAFLD. In the only RCT with post-treatment histology, ω-3 PUFAs ameliorated hepatic steatosis without affecting other histological features of NAFLD [135]. A recent systematic review and meta-analysis have included nine RCTs, involving 355 individuals given either ω-3 PUFA or control treatment with a median duration of 6 months and a median PUFAs dose of 4 g/day (range: 0.8–13.7 g/day). The pooled data of these RCTs show a significant reduction in liver fat content with ω-3 PUFA supplementation (without any substantial side effects), although the effect size was relatively small [136]. However, the optimal dose and duration of this therapy need to be addressed in future larger RCTs before recommending ω-3 PUFA supplementation for NAFLD treatment. Meanwhile, if additional lipid-lowering therapy is needed beyond statins, ω-3 PUFAs can be given safely in dyslipidemic individuals with NAFLD.

ω-3 PUFAs reduce serum triglyceride levels by decreasing very low-density lipoprotein secretion from hepatocytes and affect several genes involved in lipid metabolism that could affect hepatic steatosis in NAFLD [133,137]. The ω-3 PUFAs may decrease hepatic lipogenesis by downregulating the sterol response element binding protein-1c in the liver and upregulating lipid oxidation by activation of PPAR-α [133,137]. Finally, ω-3 PUFAs may also favorably affect lipid metabolism and insulin sensitivity by activating AMPK in the liver and adipose tissue. However, a recent RCT conducted in diabetic patients with NASH has shown that supplements of ω-3 PUFA worsened liver histology and insulin resistance [138].

Accumulating evidence also suggests that ω-3 PUFAs further to improving lipid metabolism may exert other important cardio-metabolic effects [133]. They may exert antiplatelet activity, decrease blood pressure and reduce systemic inflammation in patients with one or more features of the metabolic syndrome [133]. Although ω-3 PUFAs may also reduce CVD mortality and sudden cardiac death in patients with previous acute myocardial infarction [139], their role in the primary prevention of CVD among high-risk patients has recently been challenged by the results of a large RCT [140].

Ezetimibe

Ezetimibe is a lipid-lowering agent, which reduces the intestinal uptake of dietary cholesterol by 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 [39]. Experimental and clinical evidence suggests a role for hepatic free cholesterol accumulation in the progression from steatosis to NASH [141,142]. Preliminary data in mice and humans have suggested that treatment with ezetimibe may exert some improvement in NAFLD histology [143,144]. To date, two small RCTs have evaluated the effects of ezetimibe in patients with NAFLD. Ezetimibe reduced magnetic resonance-assessed liver fat content and plasma inflammatory biomarkers in one RCT, and improved histological hepatic ballooning and fibrosis in the other [145,146]. However, in the latter study ezetimibe was associated with a significant increase in hemoglobin A1c compared with placebo [146], while in the first study it did not significantly affect insulin resistance [145]. Thus, larger RCTs are needed to confirm a beneficial role of ezetimibe for the treatment of NAFLD/NASH. Meanwhile, ezetimibe in combination with statins is a safe and valid therapeutic option to achieve lipid goals in dyslipidemic patients with NAFLD. CVD benefits of the combination of statins and ezetimibe have been largely reported in the literature [147].

Management of hypertension

Patients with NAFLD display an increased frequency of hypertension [148]. Angiotensin receptor blockers (ARBs) are widely used antihypertensive agents with a well-characterized safety profile. The renin–angiotensin–aldosterone system is involved in the modulation of insulin sensitivity, systemic inflammation, hepatic lipogenesis and fibrogenesis [149,150]. Preliminary evidence in animals and humans has suggested that ARBs may improve serum liver enzyme levels and histological features of NAFLD [151,152].

To date, three RCTs have been performed. One RCT conducted in hypertensive patients with NASH showed that telmisartan improved insulin resistance, serum lipids and all histological features of NASH more consistently than losartan, perhaps because by its specific PPAR-γ ligand effect [153]. In one RCT on hypertensive patients with NAFLD, losartan plus simvastatin significantly ameliorated ultrasonographic hepatic steatosis, visceral adiposity, insulin resistance and C-reactive protein level compared with amlodipine plus simvastatin [154]. In another RCT on hypertensive patients with NAFLD, telmisartan displayed a beneficial effect on CT-assessed liver fat compared with valsartan, although neither of these two drugs significantly

improved serum liver enzymes [155]. Finally, preliminary evidence in a rat model of NASH suggests that telmisartan can prevent hepatocarcinogenesis via inhibited hepatic angiogenesis [156].

It is well established that ARBs reduce blood pressure values and improve glucose metabolism, thus contributing to further reducing the risk of CVD events even through the prevention of new-onset Type 2 diabetes [157].

Management of obesity

Lifestyle modifications through hypo-caloric diet and increased physical activity are the mainstay of the treatment of obesity. Antiobesity drugs have raised safety concerns. Orlistat, an inhibitor of pancreatic lipase, remains the only safe pharmacological treatment available on the market but conferred no additional cardio-metabolic or histological benefit over lifestyle intervention alone [31]. In selected obese patients, other endoscopic or surgical options are available.

Bioenterics intragastric balloon

Bioenterics intragastric balloon (BIB) is the intragastric balloon most widely used to treat severe obesity. The safety and efficacy of BIB placement for 6 months, within a multidisciplinary weight management program, in reducing body weight and improving obesity-associated comorbidities has been proven in the short-term [158,159]. Its long-term efficacy is still under investigation.

Recent evidence suggests that the patient's compliance and behavior change from the very early stages of BIB treatment is a strong predictor of its long-term effects. Patients losing either 80% of body weight during the first 3 months or 5% in the first month after BIB placement are more likely to have stable weight-loss after BIB removal [160,161]. Moreover, the maintenance of body weight loss appears critically dependent on supplemental strategies, such as lifestyle modifications or pharmacotherapy, being established after BIB removal [162].

The limited data available in severely obese patients with NAFLD suggest a beneficial effect of BIB on insulin resistance, serum liver enzymes and histological degrees of hepatic steatosis and necro-inflammation [163]. BIB placement may result in reduced CVR via improved cardio-metabolic risk factors. However, specific RCTs on this topic are lacking.

Bariatric surgery

Bariatric surgery should be reserved only for morbidly obese patients [162]. Studies have shown bariatric surgery to provide sustained improvements of liver histology in people with NAFLD and non-cirrhotic NASH [164,165]. Accumulating evidence also suggests that bariatric surgery reduces CVD and overall long-term mortality through prevention of diabetes, reduced cardio-metabolic risk factors and improved cardiac morphology and function [166,167]. Bariatric surgery could be a valid therapeutic option in morbidly obese patients with NAFLD non-responders to lifestyle interventions; moreover, it provides strong cardiovascular benefits [9,168].

Expert commentary

NAFLD is increasingly recognized as an independent risk factor for CVD, with major vascular events representing the primary cause of mortality and morbidity in these patients [4,148]. However, uncertainty still exists about the prognostic value of NAFLD in risk stratification for CVD. Formal statistical analyses in large, long-term prospective studies should be performed to better elucidate if addition of NAFLD to the widely used risk prediction algorithms will result – as largely anticipated – in a better ability of such algorithms in predicting CHD/CVD risk than evaluation of conventional risk factors alone.

In respect to mechanisms how NAFLD impacts on CVD and other cardiac complications, it is important to underline that a clear understanding of the pathophysiological pathways that link NAFLD to the development of cardiovascular, cardiac and arrhythmic complications remains lacking because of the complex and intertwined inter-relationships among NAFLD, visceral obesity and insulin resistance [4,148]. A pathogenic cross-talk between the liver and the expanded adipose tissue is likely to occur. As shown in Figure 1, the putative underlying mechanisms that link NAFLD to CVD and other structural and arrhythmogenic cardiac complications may originate from the expanded and inflamed visceral adipose tissue, 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. In this dangerous scenario (as schematically depicted in Figure 1), epidemiological evidence also suggests that the coexistence of obesity-related increases in fat accumulation in the myocardium and the pericardium may additionally exert local adverse effects that result in structural changes and functional derangements in the myocardium and vasculature [4]. However, further research is required to define the major sources of proinflammatory and prothrombotic mediators (i.e., to determine the relative contributions of visceral adipose tissue and the liver itself), as well as to uncover other specific mechanisms by which NAFLD may contribute to the development and progression of cardiac and arrhythmic complications. An improved knowledge of the pathophysiological links of NAFLD with cardiovascular, cardiac and arrhythmic complications might also provide a potential target for the pharmacological treatment of these diseases.

In Figure 3, we propose a pragmatic algorithm for the diagnosis and management of CVR in NAFLD patients without a history of CHD or other clinical atherosclerotic complications. This clinical algorithm has been developed by the authors using both available evidence and guidelines and resorting to personal opinion, where uncertainty exists owing to lack of definite evidence. Obviously, future large, long-term prospective studies will be needed to validate the use and accuracy of this pragmatic algorithm for the diagnosis and management of CVR among NAFLD patients in primary prevention of CVD.

Despite being associated with many traditional and non-traditional CVD risk factors (as summarized in Figure 1) and independently raising risk scores on prediction models, it is

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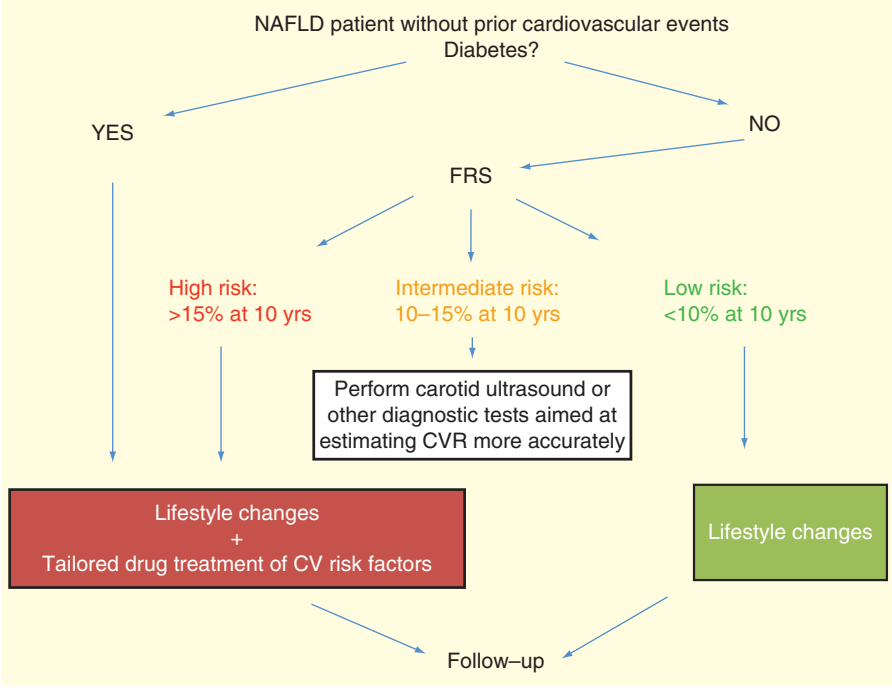

Figure 3. A pragmatic view of the diagnosis and management of cardiovascular risk in patients with nonalcoholic fatty liver disease in primary prevention for cardiovascular disease. This pragmatic flow-chart proposes tailored diagnosis and treatment of CVR of the individual patient with NAFLD without a history of previous cardiovascular events, which is based on a preliminary CVR assessment by using the FRS. In all patients with NAFLD traditional risk factors for CVD that are used to calculate the FRS should be assessed at least annually. In a low-risk patient (i.e., FRS <10% at 10 years), we believe that lifestyle changes without drug treatment appear to be a reasonable first therapeutic option. In a high-risk patient (FRS >15% at 10 years) or with established diabetes, we believe that immediate, intensive, drug intervention aimed at correcting all the associated cardio-metabolic risk factors is needed. In an intermediate-risk patient (FRS between 10 and 15% at 10 years), it is reasonable to consider drug intervention if CVR profile remains uncontrolled after intensive lifestyle intervention. In NAFLD patients at intermediate risk, we also suggest the use of some of the clinical and non-invasive CVD screening tests, which are listed in Table 4, to identify those individuals who, in fact, should be considered at higher CVR.
CHD: Coronary heart disease; CVD: Cardiovascular disease; CVR: Cardiovascular risk; FRS: Framingham risk score; NAFLD: Nonalcoholic fatty liver disease.

important to note that the inflammatory, insulin-resistant and hypertriglyceridemic states of NAFLD are not considered neither in the FRS nor in any other prediction algorithms. So, we believe that the FRS (and other 10-year CHD prediction algorithms) may underestimate the CHD risk in people with NAFLD. For example, one large cohort study found the FRS to underestimate CHD risk in patients with the metabolic syndrome, which has CVD risk factors similar to NAFLD [169].

We believe that current guidance to treat individuals with a 10-year CHD risk >20% based on the FRS may be too high for patients with NAFLD, and devising separate thresholds for close monitoring or treatment, such as >15%, may promote earlier intervention and decrease CHD events. Again, we believe that traditional risk factors that are used to calculate the FRS should be assessed at least annually in all patients with NAFLD. On the basis of our pragmatic algorithm, we believe that NAFLD patients with established diabetes or with a 10-year CHD risk >15% should be treated with a statin based on their absolute CHD risk, and not on their LDL-cholesterol concentration (*unless* LDL-cholesterol is <2.5 mmol/l [100 mg/dl] prior to treatment). Recent research suggests that reduced risk is not only attributable to the lipid-lowering capabilities of statins, but also to anti-inflammatory, antioxidative and antithrombotic properties of these agents, and given the pathogenesis of NAFLD, makes statin therapy a suitable option for CVR reduction. Despite previous hepatotoxicity concerns and a reluctance to prescribe statins in patients with NAFLD, statins are now considered safe in this patient group. Use of these agents has a significant positive benefit-to-risk ratio though in the absence of significant improvement in liver histology.

Table 4 summarizes the 2010 American College of Cardiology Foundation/AHA guidelines and recommendations for the assessment of CVR in asymptomatic adults without clinical CVD [21]. Although controversy exists over such guidelines, we believe that some of the non-invasive CVD screening tests that are listed in this table may also be used for NAFLD patients, who are at intermediate risk (i.e., individuals with a 10-year CHD risk between 10 and 15%) to better estimate/reclassify the CHD risk of these individuals. Moreover, the FRS has recently been replaced by a – very criticized – new CVR calculator [170].

Finally, Table 5 provides a synthetically commented overview of the drug weaponry presently available against NAFLD.

Five-year view

Therapeutic research and drug development in NASH has only started, and will gain considerable traction given the clearly unmet medical needs. Although diet and lifestyle changes should always be the first-line therapy, current practice guidelines recommend the use of hepatic pharmacological therapy in patients with NASH and advanced fibrosis, without cirrhosis. Thiazolidinediones have the best evidence-based data for efficacy in NASH, but long-term adverse cardiovascular (e.g., congestive heart failure) and non-cardiovascular side effects (e.g., increased body weight, increased risk of bone fractures) side effects attributed to this class of drugs are a serious issue, and are likely to prevent licensing of thiazolidinediones as a treatment for NASH.

Table 5. Overview of the effects of lifestyle changes and available drug armamentarium on cardiovascular risk and nonalcoholic fatty liver disease.

	Effects on cardio-metabolic risk	Effects on the liver
Lifestyle changes (diet ± physical exercise)	Physical activity may decrease excess CVD morbidity/ mortality associated with raised C-reactive protein levels in Type 2 diabetes	A 5–10% weight loss reduces steatosis. Up to a 10% weight loss is needed to improve the necro-inflammation
Statins	Decrease CVD events of ~30% increase diabetes risk	Decrease hepatic steatosis and serum transaminases. Potential for HCC prevention
Ezetimibe	The CVD benefits of combining statins + ezetimibe have been largely reported in the literature	Not tested in RCTs. Preliminary evidence suggests some improvement in liver histology in NAFLD
Fibrates	Statins ± fibrates provides clinical benefits over treatment with statins alone but increased risks of hepatic or renal side effects	Improve serum liver enzymes without affecting liver histology
Vitamin D3	RCTs are needed	RCTs are needed
Ursodeoxycholic acid	None	Histological improvement of fibrosis remains unproven
Pentoxyphylline	No data on whether it decreases CVD events	Improvement of hepatic steatosis and lobular inflammation. No effects on hepatocellular ballooning or fibrosis
Sartans	Significantly decrease blood pressure and may improve glucose intolerance, thus decrease CVD events through prevention of new-onset Type 2 diabetes	Telmisartan was associated with some improvement in NASH histology in a small study
Insulin	Patients with diabetes who show pronounced weight gain during insulin therapy may have a less favorable cardio-metabolic risk profile. Severe hypoglycemic episodes may increase CV events	Possibly increases HCC risk as reported by independent studies
Metformin	The best available antidiabetic treatment based on CVR profiles. Cardio-protection mediated by the Reperfusion Injury Salvage Kinase pathway, AMPK and increase adenosine. Potential to improve CV outcome even in non-diabetic patients	Marginal benefit on aminotransferase levels without improving liver histology. Decreased HCC risk
Glytazones	The lack of benefits on cardiovascular system suggests that the decrease of CVD risk needs a more global approach than just glucose control	Decrease systemic insulin resistance and improve hepatic steatosis and necro-inflammation. These effects vanish after drug discontinuation
GLP-1 analogs	Unproved cardio-protective effects	Decrease steatosis and serum aminotransferases in diabetic patients
Vitamin E	Vitamin E supplementation associated with a decreased risk of myocardial infarction, only in RCTs in which supplements were supplied by the pharmaceutical industry	Superior to placebo for the treatment of biopsy-confirmed NASH in non-diabetic adults. Does not improve hepatic fibrosis

AMPK: Adenosine monophosphate-activated protein kinase; CVD: Cardiovascular disease; GLP-1: Glucagon-like peptide-1; HCC: Hepatocellular carcinoma; NAFLD: Nonalcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; RCTs: Randomized controlled trials.
Adapted from [4].

Future therapeutic research in NASH should focus on exploring innovative drug agents, rediscovering and chemically manipulating old drugs resulting in an enhanced efficacy and an improved safety profile. It is very likely that an individualized, dual approach of improving insulin resistance and conferring hepato-protective, anti-inflammatory and antifibrotic actions would be necessary for an effective treatment of NASH.

Mipomersen is an attractive nonsense apoB inhibitor administered via intramuscular route for possible use as an alternative to statins. Relatively little is known on its efficacy and, even less concerning its hepatic safety and efficacy. Preliminary data suggest that mipomersen may induce a self-limited hepatic steatosis, which is non-progressive and thus different from true NASH [171,172].

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To date, there are large, ongoing, Phase IIb RCTs in NASH patients without cirrhosis testing the efficacy of new pharmacological agents, such as obethicolic acid (i.e., a semi-synthetic farnesoid X receptor agonist), GFT505 (a dual PPAR-α and PPAR-δ agonist) and simtuzumab (a humanized anti-lysil oxidase homolog 2 monoclonal antibody) [63].

Very recently, the results of a small, multicenter, Phase Ib, RCT found that the inhibition of 11-hydroxysteroid dehydrogenase type 1 by oral RO5093151 was effective and safe in reducing intrahepatic triglyceride content assessed by magnetic resonance spectroscopy [173]. However, more data are necessary to confirm the efficacy of this intriguing therapy, proof-of-concept for a major role of endocrine derangements in the pathogenesis of NASH [174].

Moreover, the effects of both vitamin D and ω-3 PUFA supplementations continue to raise interest and several RCTs are underway [63,175,176].

Finally, further larger, long-term prospective studies are also needed to determine whether improvement in NAFLD (or future treatments for NAFLD) will ultimately delay or prevent the development and progression of CVD and other cardiac complications in patients with NAFLD. In this context, although too premature to be proposed for clinical use, the issues of antiplatelet and anticoagulation therapies, which may reduce the risk of developing HCC and thrombotic complications in patients with liver disease, and may also improve liver histology in experimental models of NAFLD [133], will have to be more extensively evaluated in RCTs in patients with NAFLD at high CVR.

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Key issues

- From a paradigm of non-steatotic liver disease being spared from cardiovascular disease (CVD), we have moved to the recognition of steatotic liver disease as being particularly exposed to increased cardiovascular risk. Nonalcoholic fatty liver disease (NAFLD), not a mere marker of CVD, but a key player in the pathogenesis of CVD, is associated with an increased risk of CVD independent of traditional risk factors. CVD risk does not wane even at the more advanced stages of liver disease and CVD is the primary cause of mortality in NAFLD patients.
- Liver biopsy is not necessary in assessing cardiovascular risk (CVR) in the individual NAFLD patient. Framingham Risk Score is accurate in predicting CVR in NAFLD patients from the USA, Australia and New Zealand but it is likely to overestimate this risk in European populations.
- Moreover, it is likely that Framingham Risk Score and other CVR scoring systems may underestimate the cardiovascular risk in NAFLD patients given that the subclinical inflamatory, insulin resistant and hypertriglycridemic states of NAFLD are not considered in any of these cardiovascular risk scoring systems. Data suggest that NAFLD patients may benefit from more intensive surveillance and early treatment interventions to decrease their risk of CVD.
- The frequency of re-measuring cardiovascular risk should be tailored according to baseline risk. Repeat risk estimation before 8-10 years is not warranted for most people initially not requiring treatment. However, re-measurement within a year seems warrantated in those with an initial 15-<20% risk.
- Lifestyle changes, through diet and physical exercise, are universally recommended as the first-line approach to the management of NAFLD. Pharmacological and surgical treatment of NAFLD includes a wide array of options such as antioxidant and vitamins, insulin sensitizers, lipid lowering agents, anti-hypertensives and endoscopic and surgical interventions against obesity.
- Metformin, widely used as a first-line treatment for patients with type 2 diabetes reduces body weight and insulin resistance. Although it does not improve NAFLD liver histology, it significantly reduces the conversion of pre-diabetes to diabetes, may exert a cardioprotective effect and has been consistently reported to reduce the risk of developing hepatocellular carcinoma in patients with type 2 diabetes.
- Statins effectively reduce various cardiovascular outcomes and NAFLD patients are probably those who benefit most from such a reduction of cardiovascular events. Although not associated with improved NAFLD liver histology, statin use reduces the risk of developing hepatocellular carcinoma in published studies confirming that the action of this class of drugs goes further to their lipid-lowering effect and may be attributable to their anti-inflammatory, antioxidant and antithrombotic activity.
- Uncertainty remains about the prognostic value of NAFLD in CVR stratification. Large, long-term, well designed prospective studies should be conducted in patients of various ethnic backgrounds to assess whether adding NAFLD to the currently used prediction algorithms will improve the prediction of cardiovascular outcomes in the specific population being assessed.
- Research seems appropriate on cardiovascular and hepatic outcomes of innovative drug agents such as mipomersen, obeticholic acid, 11-hydoxysteroid dehydrogenase type 1 inhibitors and of already available antiplatelet/anticoagulation treatment in NAFLD patients.

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