Review article: non-alcoholic fatty liver disease and cardiovascular diseases - associations and treatment considerations

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Running title: NAFLD and CVD

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Funding declaration: There was no grant or financial support for this study.

Conflicts of interest: SAP, SK, EAT have no conflict of interest.

Abstract

Background: There are increasing data on association between non-alcoholic fatty liver disease (NAFLD) and cardiovascular diseases (CVD).

Aim: To summarize evidence on the association between NAFLD and CVD in the clinical setting and provide potential therapeutic implications.

Methods: A literature search was performed in PubMed. Evidence was primarily derived from meta-analyses, and, when data were not available, first, from clinical trials and, next, from observational studies.

Results: NAFLD has been linked to arterial hypertension, arterial stiffness, atherosclerosis, coronary artery disease, atrial fibrillation, and aortic valvular sclerosis. Advanced liver fibrosis is a crucial prognostic factor for end-stage liver disease, but also for cardiovascular and overall mortality. Weight loss through lifestyle modifications (diet and exercise) remains the cornerstone of the management of both NAFLD and CVD, but it is difficult to achieve and possibly more difficult to sustain for the long-term. Therefore, pharmacological management of NAFLD seems to be important, although no licenced medication currently exist. Pioglitazone, proposed for non-alcoholic steatohepatitis (NASH) by most guidelines, increases weight and should be avoided in congestive heart failure. Statins must not be avoided in NAFLD patients at risk for cardiovascular disease. Glucagon-like peptide 1 receptor agonists and sodium glucose cotransporter-2 inhibitors, two classes of anti-diabetic drugs, showed promising results in NAFLD and CVD, but more studies with hard end-points are needed. Obeticholic acid, a promising medication for NASH under investigation, should be carefully considered, owing to adverse effect on lipid profile.

Conclusions: NAFLD is associated with CVD, which may have certain clinical and therapeutic implications.

Keywords: cardiovascular disease; coronary artery disease; fibrosis; metabolic (dysfunction)-associated fatty liver disease; metabolic syndrome; non-alcoholic fatty liver disease; non-alcoholic steatohepatitis.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is closely associated with the epidemics of obesity and type 2 diabetes mellitus (T2DM).[1] NAFLD entails a spectrum of histopathological features that range from simple steatosis via establishment of inflammation and hepatocellular injury, i.e. non-alcoholic steatohepatitis (NASH), with or without fibrosis to cirrhosis with risk of development end-stage liver disease or hepatocellular carcinoma (HCC).[2] NAFLD shares common pathogenetic factors not only with obesity and T2DM, but also with other components of insulin resistance (IR) syndrome or metabolic syndrome (MetS), including dyslipidemia and arterial hypertension.[1, 2] NAFLD seems to interplay with the components of MetS in a dynamic way, i.e. it affects them and it is affected by them, and by this way NAFLD may add to the cardiovascular (CV) risk of affected individuals.[3] In this regard, when obesity, T2DM and/or other components of MetS coexist with NAFLD, there is higher risk of advanced liver disease and CV disease.[3] Although most NAFLD patients have BMI of >25 kg/m^2, a subset of individuals has BMI <25 kg/m^2, which is usually denoted as lean NAFLD. Most patients with lean NAFLD have excess visceral adiposity and IR, despite normal BMI, thus being on high CV risk.[4] Based on these considerations, the recent recommendation to change the nomenclature of NAFLD to metabolic (dysfunction)-associated fatty liver disease (MAFLD) seems rational.[5, 6] This recommendation does not refer to a simple change in the name of the disease, but also to a novel definition. Thus, although it has provoked a large-scale discussion,[7] it simultaneously brings to the surface the close relationship of NAFLD with CV diseases (CVD), being the key endpoint of MetS. This is immediately evident, if considering that CVD is the first cause of mortality in NAFLD patients.[8]

The aim of this review is to summarize evidence on the association between NAFLD and CVD in the clinical setting and provide potential therapeutic implication. Data were primarily derived from meta-analyses; however, when meta-analyses were not available, data from randomized controlled trials (RCTs), cohort, case-control, and cross-sectional studies were hierarchically selected, based on the principles of evidence-based medicine.

2. Literature Search

We performed a computerized literature search using the PubMed electronic database, not limited by publication time. The Medical Subject Heading (MeSH) database of the US National Center for Biotechnology Information (NCBI) was used as a terminological search filter. Subsequently, a query was created by combining MeSH terms: ("Non-alcoholic Fatty Liver Disease"[Mesh]) AND ("Cardiovascular Diseases"[Mesh] OR "Heart Failure"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Stroke"[Mesh] OR "Hypertension"[Mesh] OR "Atherosclerosis"[Mesh] OR "Coronary Artery Disease"[Mesh] OR "Atrial Fibrillation"[Mesh] OR "Heart Valve Diseases"[Mesh] OR "Percutaneous Coronary Intervention"[Mesh] OR "Coronary Artery Bypass"[Mesh]). This query totally provided 1345 results (last update: May 21, 2021). By applying the filters of "systematic review" and "meta-analysis", 34 articles were retrieved, which were studied in full text. When a topic was not sufficiently covered by these systematic reviews and meta-analyses, specific search was performed in PubMed, e.g. ("Non-alcoholic Fatty Liver Disease"[Mesh]) AND ("Stroke"[Mesh]), by applying the filter, first of "clinical trial" and, next, if available evidence was not satisfactory, the filter of "observational study". Since this was a narrative review, some more articles were added on the discretion of the authors, when this was considered necessary for the flow of this review.

3. Epidemiologic evidence on the association between NAFLD and CVD

The global prevalence of NAFLD is approximately 25% in the general population.[9] The highest prevalence has been observed in the Middle East (32%) and South America (30%) and the lowest in Africa (13%).[9] The prevalence of NASH in the general population has been estimated to be 3-5%.[10] Patients with NAFLD have high rates of MetS (43%) and its components, including hyperlipidemia (69%), obesity (51%), arterial hypertension (39%), and T2DM (23%),[9] which all contribute to CV risk.

Vice versa, the prevalence of NAFLD in obesity and T2DM is higher than that observed in the general population. The prevalence of obesity among patients with NAFLD (including simple steatosis and NASH) has been reported to be 51% and specifically in NASH 81%, respectively.[9] In studies with morbidly obese populations, the prevalence of NAFLD has been reported to be even higher (over 90% in some studies).[11] Likewise, the global prevalence of NAFLD among patients with T2DM is 55%, with the highest rates being observed in Europe (68%).[12] The global prevalence of NASH and advanced fibrosis (F3-F4) among patients with T2DM is 37% and 17%, respectively,[12] much higher than those observed in the general population.[10] This is highly alarming, reflecting the high rates of advanced liver disease in patients with T2DM.

The prevalence of CVD is higher in patients with than without NAFLD (odds ratio [OR] 1.8; 95% CI 1.2-2.7).[13] In another meta-analysis, the OR of CV events (overall fatal and non-fatal) was 1.6 (95% CI 1.3-2.1) in NAFLD compared with non-NAFLD patients, being higher in patients with more severe disease (OR 2.6; 95% CI 1.8-3.8).[14] Data indicate higher prevalence of CVD in the regions of high NAFLD prevalence.[15] This is expected to a degree, since obesity, T2DM, dyslipidemia, and arterial hypertension, which are all observed in high rates among NAFLD patients,[9] are mutual risk factors of CVD, as mentioned above. For example, obese patients with NAFLD have higher incidence of new onset CVD (33.3 per 1000 person-years; 95% Confidence Interval [CI] 22.7-46.0);[16] importantly, non-obese or lean patients with NAFLD have also high, albeit lower, incidence of new onset CVD (18.7 per 1000 person-years; 95% CI 9.2-31.2).[16] It should also be highlighted that patients with T2DM and NAFLD have approximately double risk of CVD (OR 2.2; 95% CI 1.7-2.9), as compared with those with T2DM without NAFLD,[17] thus implying a synergistic effect of T2DM and NAFLD to CV risk. The association between NAFLD and CVD may be possibly modified by the race and ethnicity. For example, the Multi-Ethnic Study of Atherosclerosis showed that the African Americans with NAFLD had higher prevalence of abdominal aortic calcification compared with White Americans with NAFLD.[18] Interaction by race/ethnicity was also reported when comparing Chinese and African to White Americans, regarding the association

between NAFLD and the prevalence of increasing abdominal aortic calcification.[18] However, more data in a longitudinal basis and for other CVD are needed to reach secure conclusions for race/ethnicity as a modifier of the association between NAFLD and CVD.

The association between NAFLD and CVD becomes more apparent when considering causes of mortality in NAFLD patients. Importantly, CVD represent the first cause of death among NAFLD patients. In a prospective long-term follow-up study (22 ± 6 years), including biopsy-proven NAFLD patients, 43% of patients died from CVD, followed by non-gastrointestinal malignancies (19%).[8] HCC, other gastrointestinal malignancies, and liver cirrhosis accounted for 13% of overall mortality (5%, 4%, and 4%, respectively). Thus liver-related mortality was the third most common cause of death.[8] The hazard ratio (HR) of death from CVD was 1.6 (95% CI 1.1-2.2) in this study, being much higher for patients with advanced fibrosis/cirrhosis (fibrosis stages F3-F4): 4.4 (95% CI 2.3-8.3).[8]. These results were validated in another cohort study with biopsy-proven NAFLD patients, followed-up for 5.5 years, showing that advanced fibrosis/cirrhosis (fibrosis stages F3-F4) were also independently associated with incident CVD (HR 8.9; 95% CI 1.4-6.0).[19] In a multinational cohort with a mean follow-up of 5.5 years, it was also reported that the incidence of CV events was higher in patients with F3 fibrosis stage than F4 (7% vs. 2%, respectively), whereas, as expected, the incidence of hepatic decompensation (6% vs. 44%, respectively) and HCC (2% vs. 17%, respectively) were lower in F3 than F4 stage.[20] It should also be highlighted that overall mortality is higher specifically in NASH patients (26 per 1000 person-years) than in patients with NAFLD (sum of patients with simple steatosis and NASH: 15 per 1000 person-years)[9] and that overall mortality increases gradually with increasing stage of hepatic fibrosis.[21] Furthermore, mortality is higher in hospitalized patients with CVD with than without NAFLD (HR 2.1; 95% CI 1.6-2.6).[22]

Summarizing, NAFLD is a highly prevalent disease, closely associated with MetS and its components, such as T2DM, obesity, hyperlipidemia, and arterial hypertension, probably adding to the MetS-associated CV risk. Importantly, CV-mortality represents the

primary component of overall mortality in NAFLD patients and is closely associated with the stage of hepatic fibrosis.

4. Clinical evidence on the association between NAFLD and CVD

Based on evidence from meta-analyses, NAFLD has been linked to arterial hypertension,[13] arterial stiffness,[23] atherosclerosis,[13, 24-26] coronary artery disease,[13, 25, 27] atrial fibrillation,[28, 29] aortic valvular sclerosis,[30] and stroke.[31] The main results of these meta-analyses are summarized in Table 1. Specifically for atrial fibrillation, the meta-analysis of cross-sectional studies or the combination of cross-sectional and cohort studies provided statistical significant results (two meta-analyses; OR 2.1);[28, 29] however, the synthesis of only cohort studies provided non-significant association. This seemingly paradox is not rare in meta-analyses, in which the synthesis of cross-sectional or case-control studies tends to overestimate the association, whereas the synthesis of cohort studies usually provides a more conservative association. Regarding stroke, the above-mentioned meta-analysis was referred to the association between γ-glutamyltransferase with stroke;[31] however, another meta-analysis on the same topic, but with better characterized NAFLD populations, is ongoing.[32] Regarding the aortic valvular stenosis, meta-regression analysis in one of the above mentioned meta-analyses,[30] showed that obesity, T2DM, arterial hypertension and dyslipidemia partly accounted for the difference in the rates of aortic valvular stenosis between patients with and without NAFLD, thus implying an indirect association between NAFLD and aortic valvular stenosis.

There are also meta-analyses of observational studies showing association of NAFLD with altered cardiac function and structure. Two meta-analyses have shown that NAFLD is associated with diastolic cardiac dysfunction.[33, 34] A similar association with systolic cardiac dysfunction was not shown in one of them.[34] Importantly, significant associations were also shown between NAFLD and structural parameters, including greater left ventricular mass, left ventricle end-diastolic diameter, left atrial diameter, posterior wall thickness and septum thickness.[34] Based on these findings, we could hypothesize that functional and structural

changes may initially occur in NAFLD patients, which may remain to a degree silent and underdiagnosed. If NAFLD and associated metabolic conditions are not effectively managed, the aggravation of the above functional and structural changes may progress to clinically significant diseases. However, this hypothesis on the natural course of the association between NAFLD and CVD remains to be elucidated.

Although the above-mentioned meta-analyses on the association between NAFLD and structural or functional parameters may imply higher probability of cardiomyopathy and heart failure in NAFLD patients,[33, 34] these are referred mainly to subclinical alterations. Limited data from observational studies suggest an association between NAFLD and clinically overt heart failure. More specifically, higher fatty liver index (FLI), a non-invasive index of hepatic steatosis, was associated with new onset heart failure in a large cohort of apparently healthy individuals at baseline, followed-up for a median of 5.4 years.[35] Higher rehospitalization rate was also observed in NAFLD compared with non-NAFLD patients with heart failure, after a one-year follow-up.[36] Likewise, higher mortality was observed in NAFLD than non-NAFLD patients admitted for acute heart failure after a mean follow-up of approximately two years.[37] Higher NAFLD fibrosis score (NFS), a non-invasive index of hepatic fibrosis, was independently associated with overall mortality in a cohort study of hospitalized patients with heart failure with preserved ejection fraction at baseline, followed-up for a median of three years.[38] Thus, although no meta-analysis to-date exists on the association between NAFLD and clinically overt heart failure, existing data support this association.

An interesting meta-analysis of observational studies has shown that the epicardial adipose tissue (EAT) was thicker in NAFLD patients than controls; an association between thickness of EAT and severity of hepatic steatosis and fibrosis was also evident.[39] Notably, the rates of arterial hypertension and atherosclerotic CVD were higher in NAFLD patients with greater EAT.[39] Although a causative effect cannot be shown by this meta-analysis, we could speculate that thicker EAT may be associated with unfavorable adipokine and cytokine profile,[40] thus with a locally producing source of factors associated with both hepatic and

cardiac inflammation and fibrosis. However, any causative interplay among EAT, NAFLD and CVD remains to be established by future studies.

Regarding lean or "non-obese" NAFLD, a recent population-based study showed that patients with lean NAFLD had similar rates of CVD and malignancy compared with patients with obese NAFLD and, interestingly, higher overall mortality than obese NAFLD.[41] It was also shown that lean and obese NAFLD share common metabolic and CV risk factors, including IR, dyslipidemia, hypertension and high waist circumference, implying high visceral adiposity.[42]

Not all data support a positive association between NAFLD and CVD. For example, a meta-analysis of 10 observational studies provided opposite results on the association between the *transmembrane 6 superfamily 2* (*TM6SF2*) gene variant E167K (rs58542926 C/T) and circulating lipid profile or NAFLD.[43] More specifically, the carriers of the minor T allele (EK/KK) were shown to have higher probability of NAFLD (OR 2.1; 95% CI 1.4-3.3) and higher hepatic fat content compared with the homozygous for the C allele (EE). On the contrary, the former had lower circulating triglyceride, total cholesterol and low density lipoprotein-cholesterol (LDL-C) concentrations compared to the latter.[43] Although this meta-analysis cannot show causality, the authors hypothesized that the T allele variant may offer protection against CVD at the expense of an increased risk of NAFLD.[43] In any case, regardless if this hypothesis proves to be true or not, the traits of this variant do not imply this variant as a link between NAFLD and CVD. Likewise, a large cohort study performed together with a meta-analysis of two studies showed that the variant I148M (rs738409) of the *patatin-like phospholipase domain containing 3 protein* (*PNPLA3*) gene, which is strongly associated with NAFLD and advanced liver disease,[44] was not associated with coronary artery disease.[45] This lack of genetic association may imply that NAFLD and CVD may share only some common pathogenetic mechanisms, or both may be affected by confounding factors (e.g. obesity, T2DM, dyslipidemia).

5. Screening for CV risk factors in patients with NAFLD

Based on the potential association between NAFLD and CVD, it seems rational that most expert committees have recommended regular screening for CVD in patients with NAFLD. The European Association for the Study of Diabetes (EASD)/European Association for the Study of the Liver (EASL)/European Association for the Study of Obesity (EASO) combined guidelines strongly recommend the screening for CVD in all NAFLD patients, at least by detailed assessment of CV risk factors.[46] The American Gastroenterological Association (AGA) suggests that all patients with NAFLD and co-existing metabolic conditions, such as obesity, T2DM, dyslipidemia and arterial hypertension, should be stratified for CV risk[47] as proposed per American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.[48] The Latin American Association for the study of the liver (ALEH) also suggests that CV risk should be performed in every follow-up visit of NAFLD patients; ALEH propose the use of the Framingham score as an efficient, simple and cost-effective tool that may result in early referral to a cardiologist of patients with high CV risk.[49] However, it should be noted that the Framingham score as well as other CV risk calculators have not yet been validated specifically for NAFLD populations. The Asia–Pacific Working Party (APWP) on NAFLD recommends that patients with NAFLD should be assessed for other components of MetS, including T2DM, dyslipidemia, and arterial hypertension, but they also underline that data to support screening for CVD are considered insufficient.[50]

Although screening for CV risk factors in NAFLD is recommended by most guidelines, given that CVD is the leading cause of mortality,[8] the recommendations mentioned above lie to the most at the level of expert opinion, since there are scarce well-designed studies evaluating the usefulness and the cost-effectiveness of the recommended screening in the long-term. Until more specific data emerge, we of course would agree with a regular assessment for CV risk factors (e.g. lifestyle, including eating and exercise habits, smoking and drinking alcohol), and measurement of at least blood pressure, weight, height, central adiposity (e.g. waist circumference), and serum glucose and lipid profile in all NAFLD patients, as other authors have also previously supported (Figure 1).[51]

6. Management considerations

Since patients with NAFLD are at high risk for CV morbidity and mortality, most guidelines recommend management of CV risk factors,[46, 47, 49, 52] targeting to reduce CV morbidity and mortality.

6.1. Diet and physical activity

All guidelines recommend weight loss through lifestyle modification (diet and physical activity), as an effective measure against both NAFLD[46, 47, 49, 52] and CVD.[48] It has been proposed that weight loss ≥3% is required to improve hepatic steatosis, ≥5% to improve hepatic inflammation and ≥10% to improve hepatic fibrosis.[3] Structured programs combining a healthy diet and regular physical activity, targeting to a gradual weight loss are recommended.[46, 47, 49, 52]

Hypocaloric diets with a daily deficit of 500–1000 kcal from baseline or with a daily consumption of 1200–1800 kcal should be advised.[46, 47, 49, 52] Regarding the diet type, the APWP guidelines do not recommend any specific diet type for NAFLD;[50] this is supported by two meta-analyses that did not show superiority of low fat or low carbohydrate diet on liver function tests and hepatic fat content.[53, 54] Although it seems that the calorie restriction rather than the macronutrient composition mainly drives the beneficial effect of dietary intervention in NAFLD,[3] another meta-analysis showed that the Mediterranean diet simultaneously improves NAFLD-related CV risk factors (IR, triglycerides, total cholesterol),[55] thus possibly offering additional benefits to NAFLD patients, with regard to CVD. This additional CV benefit is the reason why the Mediterranean diet is recommended for NAFLD by some guidelines.[46, 47, 49]

Physical activity is recommended by all guidelines for NAFLD;[46, 47, 49, 52] similarly, its beneficial role in CVD is established.[48] Regarding the type of exercise, two meta-analyses did not show that aerobic training was more effective than resistance training in reducing hepatic steatosis.[56, 57] Another meta-analysis showed that aerobic training improves more CV risk

factors (circulating triglycerides, total cholesterol, LDL-C, high density lipoprotein-cholesterol [HDL-C], body mass index [BMI]) than resistance training (triglycerides) in patients with NAFLD.[58] On the other hand, the effort and energy consumption needed to achieve a comparable result was lower for resistance than for aerobic training,[57] thus possibly rendering the former more suitable for NAFLD patients with poor cardiorespiratory fitness or those being unwilling to participate in aerobic programs. Therefore, most guidelines suggest a combination of aerobic and resistance exercise,[46, 47, 49, 52] albeit with minor variations. EASL/EASD/EASO and ALEH propose 150–200 min/week of moderate intensity in 3–5 sessions,[46, 49] tailored according to individual preferences, so as to increase the possibility of long-term maintenance;[46] APWP and AGA proposes 150-300 min/week of moderate intensity or 75-150 min/week of vigorous intensity aerobic exercise.[47, 50] Of note, AGA suggests resistance training as complementary to aerobic, but not as its substitution.[47] An exercise "prescription" consisting of the recommended type, frequency, intensity and duration is also recommended by ACC/AHA,[48] which may improve the compliance and adherence of patients to exercise programs.

6.2. Pharmacological management

Although lifestyle modifications targeting weight loss are effective as preventive and therapeutic measures against NAFLD, they are difficult to achieve and possibly more difficult to sustain in the long-term.[59] This renders the pharmacological treatment of NAFLD highly important, but currently there is no licensed medication for NAFLD.[60] Current guidelines suggest the off-label use of pioglitazone (30-45 mg/d) or vitamin E (800 IU/day) in selected non-cirrhotic patients with NASH.[46, 49, 52, 61] It seems rationale that pioglitazone may be preferred in NASH patients with T2DM, whereas vitamin E in NASH patients without T2DM;[62] however, pioglitazone has been also successfully used in NASH patients without T2DM.[63] Pioglitazone seems to act, at least partly, via upregulation of adiponectin,[64] which is closely related with both NAFLD and its severity.[65] Contrary to rosiglitazone, which also belongs to the same drug class (thiazolidinediones), shown to have an adverse effect on serum

lipid profile and being associated with an increased risk of myocardial infarction,[66] pioglitazone has a rather neutral effect on serum lipid profile.[64] However, pioglitazone should be avoided in patients with congestive heart failure, mainly due to an increase in body weight (2.0-3.5 kg on average) and fluid retention.[64, 67] Furthermore, it seems somehow oxymoron to recommend a weight-increasing medication in a patient that is counselled to lose weight. There may also be a possible small increase in the risk of bladder cancer with long-term pioglitazone treatment, needing further investigation, but the benefit in terms of NASH improvement seems to be much greater.[68] Of course, pioglitazone should be avoided in patients with bladder cancer.[60] The way of action of vitamin E on NASH has not been fully elucidated, but it may be partly achieved via its anti-oxidative effect.[60] Nonetheless, vitamin E in high dose (≥400 IU/day) for long-term, as required for NASH treatment, has been associated with a dose-dependent higher overall mortality.[69] Furthermore, there is a possible risk of prostate cancer, therefore, vitamin E should be avoided in male patients with a personal or family history of prostate cancer.[70] Thus, it seems to be prudent that vitamin E is not administered for longer than the duration of the PIVENS study (2 years),[63] a key study for the treatment of NASH with vitamin E and pioglitazone.

Another relevant topic is the use of statins in patients with NAFLD. Dyslipidemia is very common in NAFLD, with an estimated prevalence of 70%.[9] The use of statins is recommended for the management of dyslipidemia in NAFLD patients, thus reducing the increased CV risk observed in NAFLD patients.[71] Despite the notion of their detrimental effect in patients with elevated liver function tests in the past (many NAFLD patients have elevated liver function tests), statins were shown to decrease liver function tests and decrease CV mortality more in patients with mild-to-moderately abnormal liver function tests than in those with normal liver function tests.[72] Moreover, a meta-analysis of studies with histological endpoints reported a reduction of hepatic steatosis, but no significant effect on hepatic fibrosis.[73] Accordingly, the use of statins should not be avoided in NAFLD patients, at least for the prevention of CVD, although their definite effect on hepatic histology remains to be fully clarified by larger and mainly longer clinical trials.

Glucagon-like peptide 1 receptor agonists (GLP-1 RA) and sodium glucose cotransporter-2 inhibitors (SGLT-2i) are two classes of anti-diabetic drugs having shown promising results in NAFLD and CVD, which are both commonly encountered in patients with T2DM.[74] Despite their different mode of action, they both result in weight loss, so their beneficial effect on NAFLD and CVD may be mediated, at least partly, through weight loss.[60] To-date, GLP-1RAs have more evidence based on RCTs with repeat liver biopsies, as compared with SGLT-2i. In a meta-analysis, GLP-1RA were shown to reduce hepatic steatosis and hepatocellular ballooning, the latter being the hallmark of hepatocellular injury; however, they showed no effect on hepatic fibrosis.[75] More specifically, liraglutide (1.8 mg/day), administered in NASH patients for 48 months, improved hepatic steatosis in higher rates than placebo (83% vs. 45%, respectively) and resulted in NASH resolution in higher rates (39% vs. 9%, respectively).[76] Although the worsening of hepatic fibrosis was less frequent in patients on liraglutide than on placebo (9% vs. 36%, respectively), liraglutide did not result in improvement of fibrosis in higher rates than placebo.[76] More recently, administration of semaglutide for 72 weeks in a phase IIb trial for patients with NASH, resulted in NASH resolution with no worsening of fibrosis in higher rates than placebo (40% in the 0.1 mg group, 36% in the 0.2 mg group, 59% in the 0.4 mg group and 17% in the placebo group).[77] Nonetheless, semaglutide did not improve hepatic fibrosis in higher rates than placebo.[77] Likewise, two meta-analyses on SGLT-2i in NAFLD reported decrease in liver function tests and hepatic fat;[78, 79] however, studies with SGLT-2i and histological endpoints are scarce. Importantly, a large network meta-analysis of RCTs in patients with T2DM showed that both GLP-1RA and SGLT-2i decrease overall mortality, CV mortality, non-fatal myocardial infarction, and kidney failure,[80], thus adding CV and renal benefits. It should be highlighted that NAFLD is associated with chronic kidney disease, with the risk being higher in those with NASH and/or hepatic fibrosis.[81] It is noteworthy that SGLT-2i decreased mortality and admission to hospital for heart failure more than GLP-1RA, whereas GLP-1RA decreased non-fatal stroke more than SGLT-2 inhibitors, with the latter having no effect on this endpoint.[80] The main adverse events of GLP-1RA are nausea, vomiting, reduced

appetite, abdominal pain and diarrhea, which, however, tend to be resolved within a few weeks of treatment.[75] The main adverse events of SGLT-2i are genito-urinary tract infections, hypotension, dehydration, and increased appetite, as shown in a meta-analysis of studies with T2DM patients;[82] no difference was found in serious adverse events between SGLT-2i and placebo.[82] Rare cases of ketoacidosis and leg or toe amputation have been reported in T2DM patients and should be considered in the follow-up of patients. However, it should be underlined that both GLP-1RA and SGLT-2i are licensed for T2DM, therefore, their use in NASH patients without T2DM remains off label. It is important to note that GLP-1RA, and more specifically liraglutide, may be considered for the management of obesity; liraglutide has been approved for obesity in higher dose than that suggested for T2DM (3.0 mg vs. 1.8 mg [maximum], respectively) and has also provided some favorable results in hepatic histology in NASH patients,[76] as mentioned above.

Obeticholic acid (OCA) is a farnesoid X receptor (FXR) agonist, approved for the treatment of primary biliary cholangitis.[83] OCA has provided some of the most encouraging results in clinical trials with NASH and fibrosis.[83] A 72-week treatment, with OCA (25 mg) improved hepatic steatosis, inflammation and, most importantly, fibrosis in higher rates than placebo (phase 2b RCT).[84] An 18-month interim analysis of a phase 3, ongoing RCT in NASH patients without cirrhosis, OCA (25 or 10 mg) improved fibrosis with no worsening of NASH in higher rates than placebo (23% vs. 18% vs. 12%, respectively).[85]. In a network meta-analysis of emerging medications under evaluation for NAFLD, only OCA was shown to substantially improve hepatic histology.[86] Nonetheless, OCA increased LDL-C and decreased HDL-C, resulting in treatment discontinuation in some patients.[84] To address this issue of a presumably increased CV risk in a population with already high CV risk, atorvastatin (10 mg with subsequent titration as needed) initiated four weeks after OCA (5, 10 or 25 mg) was shown to reduce the adverse effect of OCA on LDL-C, but not on HDL-C.[87] OCA represents an example of a medication whose beneficial effect on NASH and fibrosis may be limited by its adverse effect on lipid profile, at least in terms of CVD. Future studies are expected to show whether OCA will be co-administered with statins or will be replaced

by another FXR agonist without adverse effect on lipid profile. Beyond the CV adverse effect, OCA results in high rates of pruritus (23-50%) that may also lead to its discontinuation in some patients.[84,85]

Regarding the management of arterial hypertension in patients with NAFLD, the above-mentioned guidelines recognize it as an important risk factor that should be managed accordingly, but they do not suggest specific drug classes.[46, 47, 49, 52] Although head-to-head comparative studies for the management of arterial hypertension specifically in NAFLD are scarce, angiotensin II type 1 receptor blockers (ARB) may be considered as first line options in NAFLD patients: some ARB provided favorable histological results in clinical trials[88, 89] and they also constitute first line option in T2DM. However, more data are needed to reach mare secure conclusions for the management of arterial hypertension specifically in NAFLD patients. All the above considering, we propose an algorithm for the management of NAFLD and related co-morbidities in patients with co-existent CVD (Figure 2).

6.3. Bariatric surgery

Bariatric surgery may be considered in selected morbidly obese NAFLD patient, wehn lifestyle modifications and pharmacotherapy fail, as proposed by most guidelines.[3] A network meta-analysis supported that all bariatric interventions lead to more effective weight loss compared with standard care.[90] The most frequently performed techniques are currently the adjustable gastric banding (AGB) and the Roux en-Y gastric bypass (RYGB).[90] RYGB has higher weight loss efficacy than AGB, but also leads to more serious adverse effects, since it is more amputational.[90] A meta-analysis of cohort studies with morbidly obese NAFLD patients, reported that bariatric surgery resulted in resolution of hepatic steatosis, ballooning and fibrosis in 66%, 50% and 40% of patients, respectively,[91] possibly rendering bariatric surgery the most effective to-date management of NAFLD, but also the most risky regarding its complications.[3] Other meta-analyses showed that bariatric surgery reduces CV risk factors, including T2DM, hypertension and dyslipidemia,[92], as well as major CV events.[93] The above considering, bariatric surgery may be an alternative management of both NAFLD

and CVD in carefully selected morbidly obese individuals. However, studies having evaluated the effect of weight loss on both NAFLD and CVD are scarce. In a study from the US Nationwide Inpatient Sample database with a large sample (over 45,000 patients with NAFLD and morbid obesity), prior bariatric surgery was independently associated with lower risk of myocardial infarction and stroke, compared with no bariatric surgery.[94] However, more and specifically designed prospective studies are required to evaluated the effect of different bariatric surgery techniques on NAFLD and CVD in the long-term.

7. Closing remarks

NAFLD is closely associated with the epidemics of obesity and T2DM, as well as other components of the MetS.[9] It is of utmost importance that CVD represents the first cause of mortality in NAFLD patients.[8] However, the existing meta-analyses on this association are consisted of observational studies (cross-sectional and/or cohort studies) (Table 1). It should be also underlined that there are scarce meta-analyses of exclusively prospective cohort studies (e.g. in Fraser et al. study[31]), which usually provide the evidence of the higher quality on the association between NAFLD and specific CVD; existing meta-analyses of cohort studies included a small number of both prospective and retrospective cohorts, the latter considered to be more prone to bias (e.g. record or recall) and to be of lower quality. Other important issues, when translating the results of existing meta-analyses, are the high heterogeneity of most of them and the small number of included studies in some of them (Table 1). Therefore, considering these two characteristics, the results of most meta-analyses should be cautiously interpreted. Furthermore, since these meta-analyses are of observational studies, a cause-effect association could not be established, which would require meta-analyses of studies of different design. Therefore, their data cannot show either causality or the direction of the association, i.e. whether NAFLD predisposes to CVD, or CVD predisposes to NAFLD (reverse causality), or both (bi-directional causality). Apart from limited data showing that obesity, T2DM, hypertension and dyslipidemia may mediate the association between NAFLD and aortic valvular stenosis,[30] as above mentioned, current

evidence does not generally allow secure conclusions on whether NAFLD may directly affect CVD or whether co-morbidities closely related to NAFLD, e.g. hypertension, obesity, T2DM and dyslipidemia, may indirectly affect CVD, and to what extent each co-morbidity contributes to CVD. Even more, based on existing data, the presence of common denominators (confounding factors) predisposing to both NAFLD and CVD, without a direct association between NAFLD and CVD, cannot be excluded. For example, obesity, T2DM or dyslipidemia may result in both NAFLD and CVD; so NAFLD and CVD may seem to be associated, but without having a direct link between NAFLD and CVD. In other words, it should be elucidated whether the presence of NAFLD is an independent risk factor for CVD or an epiphenomenon, i.e. this seeming risk is just the sum of risks of common denominators (i.e. obesity, T2DM, dyslipidemia, arterial hypertension). In this regard, we need large well-designed cohort studies with NAFLD patient without CVD at baseline that will be followed-up in the long-term; hard CV endpoints should be set, i.e. major CV events (myocardial infarction, stroke, hospitalization due to CVD, percutaneous coronary intervention, coronary artery bypass graft, death from CVD).

The potential pathophysiological links between NAFLD and CVD have been reported elsewhere[95] and are beyond the scope of this review. Briefly, a) systematic and hepatic IR as well as related aberrations (dylipidemia, dysglycemia, atrerial hypertension), b) vasoactive and thrombogenic factors (e.g. fibrinogen, transforming growth factor-β, plasminogen activator inhibitor), c) inflammatory factors (e.g. cytokines, adipokines, hepatokines, C-reactive protein, fetuin-A), d) oxidative stress and the production of reactive oxygen species, e) mitochondrial dysfunction, f) gut-derived factors (lipopolysaccharide, products from intestinal dysbiosis) may all contribute to atherosclerosis, structural changes in the cardiac muscle and valves, but also to defects in the conduction system of the heart.[95] Based on the diversity of the putative links, it seems that there are multiple potential mechanisms that may affect to a different extent each patient, who may also carry different genetic predisposition or epigenetic modifications for NAFLD and CVD. Thus, similarly to the pathogenesis of NAFLD, which is a typically multifactorial,[96] the interplay of NAFLD with CVD seems to be

multifactorial too. However, these pathogenetic hypotheses cover mostly a direction from NAFLD to CVD and do not consider the above-mentioned reverse of bi-directional causality.

Regarding treatment of CVD in NAFLD patients, specific data are scarce. Therefore, CVD should be managed similarly in patients with or without NAFLD, until definite data support specific modifications. Summarizing the above-mentioned data, pioglitazone should be avoided in NAFLD patients with congestive heart failure due to weight gain and fluid retention[64, 67] and vitamin E should not be administered longer than the duration of the PIVENS trial (2 years),[63] due to a yet unclear increase in overall mortality. GLP-1RA and SGLT-2i seem to offer advantages in both NAFLD and CVD, but more studies with hepatic histological endpoints are required to reach secure conclusions. Notably, OCA, one of the most promising emerging medication for NASH, adversely affect lipid profile and should be cautiously administered in NAFLD patients with CVD, even in the setting of clinical trials.

Regarding lean NAFLD, there are not specific guidelines for its management. However, based on the common metabolic and CV risk factors in lean and obese NAFLD,[42] as well as the similar risk of CVD in patients with lean and obese NAFLD,[41] it seems rational that lean NAFLD may be managed in a similar way to obese NAFLD. This management includes lifestyle modifications that target to reduce visceral adiposity, which may be masked in lean patients with NAFLD, but does not include anti-obesity medications or bariatric surgery.

While waiting for the approval of medications for NASH, an individualized, diabetes-like approach may be possibly considered.[97, 98] In this regard, metabolic and non-metabolic CV risk factors (e.g. T2DM, obesity, dyslipidemia, arterial hypertension, smoking, excessive alcohol consumption, sedentary lifestyle) should be evaluated and appropriately managed in NAFLD patients in a similar way that are managed in patients with diabetes, so as to reduce the CV risk in the long-term in a multi-disciplinary setting. In the absence of treatment targets of NAFLD-related co-morbidity, we may adopt the respective targets proposed for patients with T2DM (Table 2),[99, 100] until novel data guide the global community to tailor these treatment targets specifically for patients with NAFLD. This may be rational, since NAFLD

and T2DM share common epidemiological trends and pathophysiological factors.[97]

In summary, NAFLD is associated with CVD, the latter being the leading cause of mortality in NAFLD patients, especially in those with NASH and advanced fibrosis. Since there is currently no approved medication specifically for NASH, the early identification and management of metabolic and non-metabolic risk factors of CVD among NAFLD patients seem to be important to reduce the CV risk.

Legend to figures

Figure 1. Proposed assessment of parameters related to CV risk at diagnosis and during the follow-up of patients with NAFLD. Lifestyle should be assessed at diagnosis and follow-up, including diet and exercise habits, smoking and alcohol consumption; the evaluation of lifestyle modifications during the follow-up is considered important. Simple clinical and biochemical tests are also recommended, including the measurement of systolic and diastolic blood pressure, weight, height, waist circumference, lipid profile and glucose levels to evaluate arterial hypertension, obesity, dyslipidemia and T2DM. In cases of intermediate results, e.g. impaired fasting glucose for the assessement of T2DM, other tests may be also considered, i.e. HbA1c and OGTT.

Abbreviations: BMI, body mass index; CV, cardiovascular; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; NAFLD, non-alcoholic fatty liver disease; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

Figure 2. **Proposed management of patients with NAFLD and CVD**. Diet and exercise is regarded as the standard care for all patients. Vitamin E or pioglitazone should be considered in carefully selected patients with NASH and fibrosis stage ≥2. Metabolic co-morbidities should also be managed appropriately. GLP-1RA may be considered in obese patients who fail to lose weight via lifestyle modifications; currently, liraglutide is the only GLP-1RA that is licensed for the management of obesity. In patients with coexisting T2DM, pioglitazone should be considered as a first line choice in patients without congestive heart failure; GLP-1RA and SGLPT-2i should also be considered for co-treatment or alternative treatment; to-date, GLP-1RAs have evidence of higher quality than SGLT-2i, so the use of GLP-1RAs may be qualified in patients with T2DM and NASH. Statins should be administered for dyslipidemia. ARB may be considered as first line choices for patients with arterial hypertension.

Abbreviations: ARB, angiotensin II type 1 receptor blockers; CVD, cardiovascular disease; F, fibrosis stage; GLP-1RA, glucagon-like peptide-1 receptor agonists; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SGLT-2i, sodium/glucose cotransporter-2 inhibitors; T2DM, type 2 diabetes mellitus.

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Authorship Statement

SAP: conception and design, acquisition of data, interpretation of data; drafting the manuscript and revising it critically for important intellectual content; final approval of the version to be published; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; guarantor of article.

SK: interpretation of data; revising the manuscript critically for important intellectual content; final approval of the version to be published; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

EAT: interpretation of data; revising the manuscript critically for important intellectual content; final approval of the version to be published; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Table 1. Association between NAFLD and specific CVD: data derived from meta-analyses

Reference	CVD (or condition)*	Number of included studies	Design of included studies	Metric (units, if necessary)	Tendency: metric (95% CI)	Heterogeneity (I^2 test)
Di Minno 2016 [30]	Aortic valvular sclerosis	3	Cross-sectional	OR	2.28 (1.22-4.28)	78%
Wu 2016 [13]	Arterial Hypertension	2	Cross-sectional	OR	1.24 (1.14-1.36)	0%
Wu 2016 [13]	Arterial Hypertension	3	Cohort	HR	1.16 (1.06-1.27)	56%
Jaruvongvanich 2017 [23]	Arterial stiffness (carotid-femoral PWV)	8	Cross-sectional	MD (m/sec)	0.75 (0.37-1.12)	89%
Jaruvongvanich 2017 [23]	Arterial stiffness (brachial-ankle PWV)	8	Cross-sectional	MD (m/sec)	0.82 (0.57-1.07)	92%
Jaruvongvanich 2017 [23]	Arterial stiffness (augmentation index)	7	Cross-sectional	MD (%)	2.54 (0.07-5.01)	73%
Wu 2016 [13]	Atherosclerosis	3	Cross-sectional	OR	1.32 (1.07-1.62)	57%
Madan 2015 [24]	Atherosclerosis (carotid)	13	Cross-sectional	OR	1.77 (1.21-2.58)	0%
Madan 2015 [24]	Atherosclerosis (carotid)	20	Cross-sectional	SMD (CIMT in mm)	0.94 (0.73-1.16)	0%
Madan 2015 [24]	Atherosclerosis (carotid)†	5	Cross-sectional	SMD (CIMT in mm)	1.08 (0.48-1.71)	0%
Ampuero 2015 [25]	Atherosclerosis (carotid)	10	Cross-sectional and cohort	OR	2.42 (1.98-2.96)	13%
Sookoian 2008 [26]	Atherosclerosis (carotid)	7	Cross-sectional	SMD (CIMT in mm)	1.44 (0.63-2.25)	98%
Sookoian 2008 [26]	Atherosclerosis (carotid)	5	Cross-sectional	OR	3.13 (1.76-5.58)	78%
Mantovani 2019 [28]	Atrial fibrillation	5	Cross-sectional	OR	2.07 (1.38-3.10)	55%
Mantovani 2019 [28]	Atrial fibrillation	4	Cohort	HR	1.34 (0.92-1.95)	65%
Wijarnpreecha 2017 [29]	Atrial fibrillation	5	Cross-sectional and cohort	RR	2.06 (1.10-3.85)	78%
Jaruvongvanich 2016 [27]	Coronary artery calcification	16	Cross-sectional	OR	1.41 (1.26-1.57)	66%
Wu 2016 [13]	Coronary artery disease	10	Cross-sectional	OR	1.87 (1.47-2.37)	80%
Ampuero 2015 [25]	Coronary artery disease	4	Cross-sectional and cohort	OR	3.31 (2.21-4.95)	38%
Fraser 2007 [31]	Stroke	6	Cross-sectional	HR	1.54 (1.19-1.99)	82%

* Data are sorted alphabetically according to the CVD (or condition).

†: Pediatric population

Abbreviations: CI, confidence interval; CIMT, carotid intimal medial thickness; CVD, cardiovascular disease; HR, hazard ratio; LVEF, left ventricle ejection fraction; MD, mean difference; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PWV, pulse wave velocity; RR, risk ratio; SMD, standardized mean difference.

Table 2. Treatment targets for NAFLD-related co-morbidity empirically proposed for patients with NAFLD

Co-morbidity of NAFLD	Treatment target(s)*	Comments
Obesity	Steatosis improvement: ≥3% weight loss Inflammation improvement: ≥5% weight loss Resolution of NASH: ≥7% weight loss Fibrosis improvement: ≥10% weight loss	Even minimal weight loss may have beneficial effects and should be encouraged.[3]
T2DM	HbA1c <7%	The target of HbA1c may be more stringent in younger patients with long life expectancy, lack of other co-morbidities and lack of vascular complications and in those with low risk associated with hypoglycemias.[99]
Dyslipidemia	LDL-C <70 mg/dl Triglycerides <150 mg/dl	Triglycerides >500 may increase the risk of acute pancreatitis.[100]
Arterial hypertension	<130/80 mmHg	The target may be <140/90 for patients at lower CV risk, i.e. when the 10-year risk of atherosclerotic cardiovascular disease <15%.[100]

* Treatment targets are mainly adopted from those proposed for patients with T2DM.
Abbreviations: CV, cardiovascular; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.