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Cross-Talk Between Non-Alcoholic Fatty Liver Disease and Cardiovascular Disease: Implications for Future Trial Design

**Short Title:** NAFLD and Cardiovascular Disease.

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Abstract

The natural history of non-alcoholic fatty liver disease (NAFLD) is still not fully elucidated. Patients with NAFLD have a low risk of liver complications, unless substantial liver fibrosis has developed. On the other hand, NAFLD has been linked with excess metabolic and cardiovascular complications. Therapies targeting common pathways may benefit both NAFLD and underlying cardiometabolic risk. Therefore, there is a rationale for considering cardiovascular endpoints in the context of NAFLD trials and, vice-versa, to consider the concomitant presence of NAFLD in drug development for cardiometabolic disorders. This manuscript provides a framework for consideration for future trials examining the inter-relationship between cardiovascular disease and NAFLD.

Key words: NAFLD, NASH, trials, cardiovascular, endpoints
Introduction

Excess fat in the liver, or steatosis, in the absence of a history of pathological alcohol consumption, characterizes a heterogeneous metabolic condition referred to as non-alcoholic fatty liver disease (NAFLD)\(^1\). NAFLD has two principal phenotypes: (a) a nonalcoholic fatty liver (NAFL) which is characterized by excess macrovesicular steatosis alone or in combination with minimal inflammation, and (b) nonalcoholic steatohepatitis (NASH) which is defined by the presence of macrovesicular steatosis, lobular inflammation and hepatocellular ballooning typically in a centrilobular distribution\(^2\). The principal risk factors for NAFLD include obesity, type 2 diabetes mellitus (T2DM), hypertension, and hypertriglyceridemia\(^3\), the same risk factors that are also associated with cardio-metabolic disease and chronic kidney disease. The development of NAFLD, especially NASH, further leads to increased LDL-cholesterol due to continued synthesis of cholesterol in the liver despite increased hepatic free cholesterol concentrations\(^4\). It is therefore unsurprising that NAFLD and cardiometabolic disease frequently co-exist and the epidemiology of NAFLD closely tracks with that of obesity and T2DM\(^5-7\).

Furthermore, cardio-metabolic events are the most common cause of mortality in patients with NAFLD especially before the development of advanced fibrosis\(^8,9\).

While there is substantial literature on the importance of cardio-metabolic outcomes in patients with NAFLD\(^10,11\) and serious but silent liver disease in the T2DM population, the care of these patients is often siloed and suboptimal, ignoring the totality of the disease burden on the patient (Table 1). This is in part due to the lack of suitable, easy-to-deploy diagnostics and approved therapies for NAFLD. There is also an unmet need to increase awareness of NAFLD within populations at risk for cardio-metabolic outcomes. NAFLD may independently drive
cardiometabolic risk, especially when significant liver fibrosis has developed\textsuperscript{12}. Indeed, the development of progressive NAFLD includes metabolic perturbation, lipid overload, cell stress, inflammation and fibrosis, which are also seen in cardio-metabolic disorders\textsuperscript{13}. It is plausible that therapies targeting common pathways may yield benefits for both NAFLD and underlying cardio-metabolic disease providing strong rationale for consideration of NAFLD-related endpoints in the context of clinical trials for cardiovascular disease.

Many drugs are also metabolized in the liver and the pharmacokinetic profile of such agents could be substantially altered by the presence of NAFLD with advanced fibrosis\textsuperscript{14,15}. The possibility of unexpected toxicity due to altered drug exposure to the liver leading to drug-induced liver injury is another reason why it is important to consider the concomitant presence of NAFLD in drug development for cardiometabolic disorders.

In light of these intersecting issues, we provide a framework for consideration for future trials examining the inter-relationship between cardiovascular disease and NAFLD.

**Identifying NAFLD in Clinical Practice**

NAFLD is widely prevalent and approximately 25-30\% of the adult population have hepatic steatosis, worldwide\textsuperscript{9}. Of these, about 20-25\% might have NASH\textsuperscript{16}. The clinical outcomes in those with either NAFL or NASH with early stage disease are mainly cardio-metabolic and cancer related, whereas liver related outcomes become more prominent only when stage 2 fibrosis or higher stages of disease develop\textsuperscript{12,17}. It has also become clear that disease activity
drives fibrosis and that, even without therapeutic intervention, both disease activity and fibrosis can wax and wane\textsuperscript{18-20}. From a hepatological perspective, it is therefore important to identify those with NASH, especially those with high disease activity and fibrosis stage 2 or higher. The identification of those with cirrhosis, who can be clinically silent until a complication such as variceal hemorrhage or hepatocellular cancer occur, is also important.

The diagnostic approach for NAFLD is rapidly evolving although there is not one standard globally accepted algorithm. In routine clinical settings, an elevated aspartate transaminase (AST) and alanine aminotransferase (ALT) often is the first trigger for evaluation of NAFLD. The AST and ALT are classical measures of tissue injury and are widely available and used. However, they are severely limited by low sensitivity and specificity for NASH, the phenotype that is most likely to lead to cirrhosis\textsuperscript{21}. The full spectrum of NAFLD can be seen with normal AST and ALT and these are useful when positive but not very informative when normal. An elevated AST and ALT are also not necessarily reflective of NAFLD and may be due to other common conditions such as alcohol-or drug-induced liver disease or injury, hepatitis or iron overload. A mild elevation in liver enzymes is also commonly observed in patients with heart failure, frequently due to elevated central venous pressure\textsuperscript{22}. Prior to entering patients into cardiovascular clinical trials, which have often allowed patients with AST and ALT up to 1.5-2 times the upper limit of normal, it is both good clinical practice and prudent to evaluate such patients for the presence and cause of underlying liver disease.

The key questions to be addressed in the diagnostic evaluation for NAFLD include the presence of excess fat in the liver, assessment of disease activity and fibrosis stage.
How to diagnose excess liver fat and fibrosis?

There are now several well-validated tools for the measurement of excess hepatic lipid content. In routine clinical practice, their positive predictive values are high because the pre-test probability of a positive test is substantially enhanced in obese individuals with T2DM or other cardio-metabolic risk factors\textsuperscript{23}. A commonly used tool is the transient elastography which provides a measure of hepatic steatosis from the attenuation characteristics of sound waves in the liver; the continuous attenuation parameter (CAP) has both high sensitivity and specificity in detecting NAFLD but is not as good at differentiating grades of excess steatosis\textsuperscript{24}. Sonography can reveal an echogenic liver as a feature of hepatic steatosis but lacks relative sensitivity and specificity\textsuperscript{25}. MRI-based tools provide a more accurate and direct measurement of hepatic triglyceride content and their changes; the magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) is a widely used tool in the context of clinical trials\textsuperscript{26,27}. It is however limited by its cost and availability, and might not be suitable for every patient, for instance those unable to fit in the MRI machine or who have claustrophobia. In many clinical trials where fat content is a key outcome measure, a transient elastography is often used as a screening tool to reduce screen-fail rates inherent to the use of MRI-PDFF\textsuperscript{28}.

Measures of steatosis however are insufficient to provide information regarding underlying liver tissue injury, inflammation and fibrosis. There are currently no established non-invasive tools that outperform an AST and ALT for the assessment of disease activity. An ALT and AST over 40 IU/l has been associated with presence of steatohepatitis and fibrosis, respectively\textsuperscript{29}. Several simple laboratory aids such as the AST:platelet ratio (APRI) and the FIB-4 index (based on age,
AST, ALT, platelets) provide a high negative predictive value. Specifically, a FIB-4 index <1.3 can effectively exclude over 90% of individuals with stage 2 fibrosis or higher\textsuperscript{30}. Transient elastography or MRI-based tool such as two-dimensional magnetic resonance elastography (2D-MRE) are often used to gain specificity in the identification of those with fibrosis stage 2 or higher, but this approach is limited by their poor positive predictive value. Both transient elastography and MRI measure liver stiffness which can be affected by hepatic congestion, inflammation, fibrosis, cholestasis, and post-prandial blood flow\textsuperscript{31}. Ultrasound-based methods to measure liver stiffness are in development but have not been validated to the extent that transient elastography and 2D-MRE have.

Based on these considerations, while there remain areas of uncertainty, most patients can be identified to have NAFLD with low, intermediate, or high risk of liver-related outcomes and the use of a liver biopsy to evaluate the disease is increasingly being relegated to indeterminate cases and in clinical trials for NASH\textsuperscript{32}.

**Clinical profile and natural history of patients with NAFLD**

NAFLD has been reported at even young ages, but is usually first diagnosed in middle-aged individuals, frequently in the background of several comorbidities that substantially increase CV risk\textsuperscript{9}. Observational studies report that up to 50% of patients with NAFLD are obese, and rate of prevalent T2DM, hypertension, and hyperlipidemia might be as high as 70%. Smoking habits and coronary artery disease are less frequent\textsuperscript{33}; genetic predisposition has been implicated in up to 20% of patients with NAFLD\textsuperscript{34}. Over half of patients diagnosed to have NAFLD report to continue to drink, regularly or occasionally, a substantial amount of alcohol, which might
confound the exact diagnosis and have important consequences on disease progression\textsuperscript{35,36}.

NAFLD is usually asymptomatic, but reduced exercise tolerance and fatigue might limit daily living activities in some, and lead to a poorer quality of life compared with healthier controls\textsuperscript{37}. The use of CV therapies that are commonly used for primary or secondary prevention, such as statins, is rarely reported in observational studies conducted in patients with NAFLD (Table 1). When reported, therapeutic use appears suboptimal with respect to CV risks faced by these patients.

The natural history of NAFLD and NASH is not fully elucidated. Current knowledge about the natural course of the disease is based on placebo arms of clinical trials and longitudinal cohorts with multiple liver biopsies performed. It has been previously suggested that disease progression follows a linear trajectory with one-stage progression every seven years for those with NASH\textsuperscript{38}. This is now known to be imprecise; it is more likely that the course of the disease is bi-directional with some patients showing regression whilst others progress\textsuperscript{18}. Disease activity, measured by the severity of lobular inflammation and hepatocellular ballooning, is a key determinant of fibrosis change\textsuperscript{39}. Weight gain\textsuperscript{40} and increasing AST and ALT have been associated with worsening disease activity\textsuperscript{18}. Conversely, weight loss has been linked to decreased disease activity\textsuperscript{41}. While a 10\% weight loss threshold has been suggested to identify those who experience fibrosis improvement\textsuperscript{42}, recent data indicate that fibrosis can change without changes in weight\textsuperscript{18}. The rate of fibrosis progression to cirrhosis depends on the baseline stage of fibrosis and ranges from less than 10\% in 10 years in those with stage 1 disease to 5-10\% annually for those with bridging fibrosis \textsuperscript{18,43}. 
From a clinical point of view, liver-related outcomes are almost entirely related to the development of cirrhosis; by then, many patients with NAFLD might have already suffered the clinical consequences of an overlapping cardio-metabolic disease (*Figure 1*).

**Liver-related endpoints in cardiovascular trials**

*Patient populations.*

From a hepatological perspective, the population to be selected should be linked to the mechanism of action of the intervention to be tested and the outcome to be measured. Thus, for metabolic agents that are primarily focused on reducing atherogenic risk, assessment of hepatic steatosis is often used in phase 2A trials to obtain proof of concept that the drug is potentially active. On the other hand, agents which may impact fibrogenic pathways or have complex effects on cardio-metabolic risk, may also improve NASH and hepatic fibrosis. In such cases, the entry criteria for the trial should include a measure of hepatic steatosis and liver stiffness. A transient elastography (CAP $>300$ db/m and liver stiffness measurement (LSM) $>8$ kp) or MRI-PDFF ($>5\%$ steatosis)/2D-MRE ($>2.8$ kp) are the best choices for this purpose. Depending on the objectives of a given study, these criteria could be used as inclusion or for stratification.

In trials specifically targeting those with established heart failure, there is a high probability of having underlying NASH with advanced fibrosis. In such studies, the presence of previously undiagnosed cirrhosis, but also the concomitant presence of renal and cardiac dysfunction, may alter the pharmacokinetics of drugs administered and it is prudent to obtain a measure of liver stiffness at baseline. If LSM is greater than 12.6 or 16 kp, the threshold values for 90%
sensitivity and specificity respectively for the diagnosis of cirrhosis, study sponsors will need to decide whether to include or exclude such patients. However, in HF, the use of transient elastography or MRI may be confounded by the effect of hepatic congestion on liver stiffness which can result in over-diagnosis of cirrhosis. A FIB-4 >3.2 also can be used to diagnose cirrhosis with high specificity but the sensitivity of this cut-off is poor. For drugs that target underlying lipotoxicity or with direct antifibrotic activity, patients with both significant cardiac dysfunction and NASH with advanced fibrosis (stages 3 and 4) could be treated with such agents to improve both cardiac and liver clinical outcomes.

New onset liver dysfunction in a trial including such patients could reflect either decompensation of underlying cirrhosis, drug induced liver injury, or might be secondary to development or worsening of heart failure. It might be recommended to measure liver enzymes and bilirubin about 4 weeks apart during the screening period of the trial, to evaluate their possible fluctuations prior to initiation of therapy. This might help to interpret their changes during the course of the trial.

**Endpoints.**

**Hepatic steatosis:** changes in hepatic steatosis alone are not very meaningful clinically. Decrease in steatosis has not been shown to impact how a patient feels, functions or survives and thus does not meet criteria for a reasonably accepted surrogate primary endpoint.
Normalization of liver enzymes: In phase 2A trials of NASH, a reduction or normalization of ALT is the most reliable indicator for drug benefit and the likelihood that larger histology-based trials will be positive. However, by themselves, normalization of liver enzymes has not been linked to clinical outcome improvement and also does not meet criteria for therapeutic efficacy in advanced phase trials.

Fibrosis regression: The clinical relevance of fibrosis regression depends on the clinical context in which it occurs. If a drug improves hepatic fibrosis by treating the root cause of NASH (i.e. the underlying metabolic disturbance causing steatosis in the first place), it is likely to reflect improvement in the overall disease state. On the other hand, regression of fibrosis with a pure anti-fibrotic agent which does not address hepatic steatosis, tissue injury and inflammation may or may not result in overall improvement in the health status of the patient. Reduced fibrosis, measured by transient elastography, may be considered as a secondary endpoint in cardiovascular trials. MR elastography can also be used for this purpose especially if cardiac MRI is being performed as part of the trial.

Reduced progression to cirrhosis: The onset of cirrhosis is associated with an annual 3-4% risk of clinical decompensation and an increase in all-cause mortality and liver related mortality in those with NAFLD. Reduced progression to cirrhosis is expected to translate into reduced liver related outcomes and mortality, and it is generally accepted as a surrogate endpoint in clinical trials for NASH. For cardiovascular trials targeting underlying metabolic/inflammatory/fibrotic pathways, reduced progression to cirrhosis (diagnosed by a high specificity test such as MRE or transient elastography) would
provide evidence of improvement in liver status above and beyond the cardiovascular benefits of the agent.

**Reduced progression to MELD score of 15:** The model for end-stage liver disease (MELD) score is widely accepted and validated as a marker for three-month mortality risk in those with cirrhosis regardless of etiology. It is currently used to determine organ allocation for liver transplantation. A MELD score of 15 or higher identifies those where long term outcomes with liver transplant are superior to medical therapy\(^51\). In trials which might include patients with cirrhosis (i.e. heart failure trials), this may be included in a composite endpoint for long-term outcomes. An increase in MELD score from 12 or less to 15 or higher is considered an acceptable surrogate endpoint in trials of NASH with cirrhosis\(^49,50\).

**Reduced liver outcomes:** It is unlikely that cardiovascular trials will include patients with advanced liver disease at risk of liver outcomes within a 1-2-year time frame.

**Cardio-metabolic endpoints in trials for NAFLD**

There are a growing number of clinical trials for NAFLD or NASH (*Table 2*). While cardio-vascular outcomes are considered to be mainly safety measures in such trials, it is reasonable to consider these as part of the efficacy of treatments specifically for those agents that address underlying root causes for both the underlying cardiometabolic risk and liver disease. The baseline cardio-metabolic measures that should be considered are noted below.
**Atherogenic risk profile:** Multiple studies have shown that the development of NAFLD and particularly NASH is associated with increasing small dense LDL-C, which are particularly atherogenic.\(^{52,53}\) There is also increased hyperinsulinemia and elevated apolipoprotein-B in patients with NASH\(^{52}\). It is also noteworthy that insulin resistance is both a cause and effect of NAFLD and NASH and the association of NAFLD with metabolic syndrome is mutual and bi-directional \(^{54,55}\). With progression to cirrhosis, both the hypertriglyceridemia and hypercholesterolemia improve reflecting a decrease in de novo lipogenesis \(^{52}\). In pre-cirrhotic populations in clinical trials, it is recommended that detailed lipid profiling be performed in phase 2A or 2B trials to determine if these are reasonable surrogates to be included in phase 3 trials.

**Myocardial function:** left ventricular hypertrophy and diastolic dysfunction are commonly described in those with NAFLD and are associated with the severity of hepatic fibrosis\(^{45,46}\). When the mechanism of action of a drug suggests that there could be beneficial effects on both the heart and the liver, MRI or echocardiographic assessment of ventricular structure and function might be performed. Electrocardiography studies should be included in all NASH trials to ensure that any agent is not causing QTc prolongation or rhythm abnormalities.

**Serum markers:** Elevated natriuretic peptides levels reflect increased myocardial wall stress, and are powerful predictors of future CV events in cardiovascular medicine. However, an inverse association exists between natriuretic peptides levels with obesity, liver enzymes and the amount of liver fat in patients with NAFLD\(^{56,57}\). Therefore, the
potential of natriuretic peptides as diagnostic tool for identifying early, subclinical cardiac dysfunction in patients with NAFLD might be questionable, as well as their use as surrogate endpoint in this setting. Elevated troponin levels, reflecting myocardial injury, are directly associated with liver enzymes, and could improve prognostic stratification in patients with NAFLD\textsuperscript{58}. Markers of fibrosis, which may be involved in the transition to both liver and heart failure, could be also considered but perhaps lack specificity.

**Renal outcomes:** Currently, based on regulatory advice, most trials for NAFLD exclude individuals with chronic kidney disease (CKD). However, the prevalence of CKD increases with NAFLD progression especially in those with cirrhosis\textsuperscript{59}. In trials targeting NAFLD subpopulations with a high prevalence of CKD, renal impairment studies to establish the pharmacokinetic-pharmacodynamics of novel first-in-class agents should be performed early in the course of development and appropriate renal safety strategies integrated into trial design to mitigate risk and still perform the trial in the relevant “intended use” population.

**MACE events:** These events are routinely measured in current phase 2B and 3 clinical trials for NASH and outcomes adjudicated by independent adjudication committees using current best practices for this purpose.

**Hospitalization from heart failure:** The reported incidence of hospitalization from heart failure is low to non-existent in populations currently being enrolled in trials for
NASH. This is surprising, considering the high number of CV risk factors and comorbidities, therefore the high risk of developing heart failure, of patients with NAFLD. Overall, these findings suggest a low awareness of heart failure amongst hepatologists, and lack of standardised and robust criteria to diagnose heart failure, particularly in the presence of a normal left ventricular systolic function at imaging.

**Candidate cardiovascular therapies for NAFLD**

It might be possible that treatments targeting an overt cardio-metabolic dysfunction could resolve some of the pathophysiological mechanisms that promote a progression from NAFLD to fibrosis and development of liver-related complications, and perhaps improve outcomes.

Elevated levels of aldosterone are common amongst patients with NAFLD and cirrhosis, as well as in those with CV risk factors and CVD, and promote endothelial dysfunction, fibrosis and inflammation. Hyperaldosteronism is a valid target of treatment in those with cardiac dysfunction and perhaps in those with NAFLD. In a single centre, open label, randomised trial conducted in 31 adults with biopsy-proven NAFLD, treatment for 52 weeks with spironolactone 25 mg/day combined to vitamin E vs vitamin E monotherapy, led to a decreased NAFLD liver fat score, an index of steatosis\(^60\).

Expert review of current evidence suggests that statins might prevent development of hepatic complications \(^61\). For those in whom statins cannot be used or are poorly tolerated, ezetimibe or PCSK9-inhibitors might be considered to improve hepatic steatosis and reduce liver enzymes \(^62,63\).
Sodium-glucose cotransporter type-2 (SGLT2) inhibitors improve glycemic control, decrease blood pressure and body weight, and lead to important beneficial effects on CV morbidity and mortality in patients with T2DM and heart failure\textsuperscript{64}. A series of small studies suggest that SGLT2-inhibitors are a promising class of drugs even for liver protection in NAFLD\textsuperscript{65}.

Glucagon-like peptide-1 receptor agonists (GLP-1RA) promote satiety and reduce food intake, leading to weight loss, and prevent atherosclerotic and renal events in patients with T2DM, which makes them attractive therapies for patients with NAFLD\textsuperscript{66}. In a multi-center, double-blind, randomized, placebo-controlled phase-2 trial in NASH, treatment with liraglutide for 48 weeks led to a greater rate of histological resolution of disease, and slower progression to fibrosis, compared with placebo\textsuperscript{67}. A recently completed 72-week multi-center, randomized, double-blind placebo-controlled trial suggested that another GLP-1RA, semaglutide, also reduced histological features of NASH, compared with placebo\textsuperscript{68}. To date, no mechanistic link is established between liver protection and reduced cardiovascular events associated with use of SGLT2i or GLP-1RA.

**The unmet need for CV risk reduction in NAFLD: future perspectives**

Placing too much emphasis only on liver-related surrogate endpoints might delay discovery, or repurposing of potentially effective treatments, lead to waste of significant amount of resources and, more importantly, increase patients’ risk of developing side effects associated with use of therapies that are subsequently found to be clinically meaningless. Some of these concerns are also contemplated in the guidance for companies developing therapies for patients with NASH recently issued by U.S. Food and Drug Administration, in which it is recommended that sponsors
should consider trial endpoints that reflect robust clinical benefits (ie: histological resolution of NASH, reduced progression to, or reversal of fibrosis, need for a liver transplant), including improved survival, to support an accelerated approval process.

Targeting comorbidities and CV risk factors might be important for preventing CV complications and cancer in patients with NAFLD. However, the annual rate of these events might be low, and trials would require large sample size and long follow-up to produce convincing evidence. It is also unknown whether spontaneous resolution of less severe forms of NAFLD or NASH, as observed in >1/3 of patients randomised to placebo in clinical trials, might decrease future risk, further limiting trial feasibility and power.\textsuperscript{69} To increase event rates, many CV outcome trials use composite endpoints: a similar strategy might be applied to trials conducted in patients with NAFLD. Development of CV, but also cancer, kidney- or liver–related complications are all clinically relevant endpoints that have a significant impact on people health and well-being in people with NAFLD, and will ultimately lead to disability and death. Considering recurrent non-fatal and fatal events would further increase power. Alternative statistical methods that prioritize the more important clinical event (for instance, death over changes in liver function tests) between matched pairs of patients exposed to treatment and controls might be useful in these scenarios.\textsuperscript{70}

Testing multiple doses of the same treatment, or various treatments simultaneously within this very heterogeneous population\textsuperscript{71} using innovative trial designs would perhaps speed up discovery and avoid exposure of patients with NAFLD to futile therapies for long periods. Flexible, adaptive trial designs would initially identify safety issues and signs of efficacy on key
metabolic targets (i.e., reduction in liver fat content by imaging or normalization of liver enzymes) to screen treatments and doses that should progress further, allowing a direct transition between a phase 2 to a phase 3 trial, maximizing time and resources. These trials might identify which medicines work best for which patients and whether some patients require higher doses, or several medicines, to reduce risk to target levels. Important biological and behavioral differences exist between men and women that might be relevant to explain the epidemiology of many diseases, including NAFLD, and influence response to treatment. Considering these often neglected issues in future trial design, analysis, and interpretation will potentially advance personalized approaches to the management of NAFLD. Matching a particular patient profile to a specific treatment could help tailor treatment to the individual patient’s needs and fulfil aims of precision medicine.

Conclusions

There is a strong rationale for considering cardiovascular endpoints in the context of NAFLD trials. A detailed characterization of the baseline cardio-metabolic profile and a careful collection and adjudication of adverse events will improve understanding of safety and efficacy of interventions in patients with NAFLD, and clarify its natural history. To achieve all of this, a closer collaboration between cardiologists, endocrinologists and hepatologists is desirable.

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Central Illustration/Figure 1. Unmet Need for Cardiovascular Risk Reduction in Non-alcoholic Fatty Liver Disease (NAFLD). NAFLD is a very heterogeneous condition, often asymptomatic. While patients with NAFLD develop liver complications only in the presence of significant liver fibrosis, NAFLD has been linked with excess metabolic and cardiovascular complications, and non-liver related cancers. Therefore, there is a rationale for considering CV endpoints in the context of NAFLD trials, and vice versa, to consider the concomitant presence of NAFLD in drug development for cardiometabolic disorders.