Non-alcoholic fatty liver disease and cardiovascular risk: an update

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Non-alcoholic fatty liver disease and cardiovascular risk: an update

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Editorial:

The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing worldwide, reflecting the current epidemics of obesity, insulin resistance and type 2 diabetes mellitus (DM), and metabolic syndrome (MetS) [1]. Currently, NAFLD affects about 15-30% of the general population, and its prevalence increases to 60-70% in people with obesity and type 2 DM [2]. NAFLD encompasses a wide spectrum of liver disease including non-alcoholic steatohepatitis (NASH), a variable degree of fibrosis up to cirrhosis, and hepatocellular carcinoma [1]. Cardiovascular disease (CVD) is the leading cause of mortality in this group [3] (with men being at higher risk of both clinical and subclinical CVD compared to women [4,5]), followed by non-liver cancer and liver-related complications [1]. As such, a thorough CV risk assessment is mandatory in all patients with NAFLD and should be repeated each 1-2 years, regardless of the presence of traditional risks factors [2].

The etiology of increased CV risk in NAFLD appears to be multifactorial and at least partly explained by the association with MetS risk factors. In particular, it is still unclear whether NAFLD represents an additional CV risk factor *per se* [6]. However, NAFLD is associated with an adverse lipid profile [7] and with Abnormal Peri-Organ or Intra-organ Fat (APIFat) Depositions [8] in other organs, which have been previously associated with adverse CV outcomes. Specifically, enhanced insulin-induced hepatic lipogenesis characterises NAFLD, which seems to be responsible for the increased serum concentrations of very low density lipoprotein (VLDL), low density lipoprotein (LDL) and ApoB found in non-cirrhotic NAFLD patients [9]. Moreover, patients with NAFLD show features of endothelial dysfunction independently of age, sex, BMI and other MetS components [10].

At present, CV risk is assessed using traditional scores (e.g. Framingham score, Q-RISK2 score), which were not derived from a NAFLD population. As such, it is unclear whether these scores might underestimate CV prediction in this high-risk population. Furthermore, there is a major interest in finding disease-specific risk factors for CVD in NAFLD. In particular, the association between histological features and CV events has been investigated, as histology represents the gold standard in diagnosing and staging NASH [2]. The presence of advanced fibrosis (F3-F4) is a strong independent predictive factor for CVD, while there is

still no conclusive evidence regarding the consequences for CVD risk of the presence of NASH or steatosis [11].

Given the burden of the disease and the limitations of performing a liver biopsy, several non-invasive markers of fibrosis and steatosis have been developed and used in clinical practice [2]. In particular, the NAFLD Fibrosis score (NFS) has been investigated for the prediction of CV events, CV mortality and overall mortality in the general and in the NAFLD population. A recently published sub-study from the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (which primarily investigated the rate of further CV events after administration of ezetimibe/simvastatin *vs* simvastatin alone in patients with ACS) [12] reported that 14.2% of the patients were at high CV risk based on NFS score >0.67. This group showed a 30% increased risk of recurrent major CV events compared with the group with low NFS score. The relationship between NFS categories and recurrent CV events was also confirmed in another cohort, using participants from the Stabilization of Plaque Using Darapladib-Thrombolysis in Myocardial Infarction 52 (SOLID-TIMI 52) trial [12,13]. Therefore, the NFS may prove to be a useful CV risk predictor in NAFLD. Of note, however, IMPROVE-IT was not designed specifically to assess the link between NAFLD and vascular risk. This is one of a number of limitations of this recent *post-hoc* analysis, with others including the assumptions made in the use of the NFS as a proxy for NAFLD severity, together with the changes in liver enzymes that occur in patients with ACS [12,14]. However, it is of particular interest that a similar link was found when using the fatty liver index (FLI) [15].

Primary and secondary prevention of CVD events in patients with NAFLD should focus on multifactorial risk reduction and CV protection. Old trials hinted at a greater benefit from statin treatment in CVD in patients with NAFLD while also improving transaminase activity [16,17]. However, these were *post hoc* analyses based on relatively small numbers of patients and without a biopsy-confirmed diagnosis of NAFLD [17]. Since then, there has been evidence from studies involving patients with biopsy-confirmed NAFLD that statins improve several aspects of NAFLD/NASH-related liver histology [1,18].

The use of a combined therapy with simvastatin + ezetimibe may be particularly useful in patients with Acute Coronary Syndrome (ACS) and NAFLD. In the IMPROVE-IT Study, when the groups simvastatin/ezetimibe *vs* simvastatin/placebo were compared, the benefit of using a combined therapy was greater in the group with high NFS than in the group with low NFS (hazard ratio 0.85 [0.74-0.98] compared with 1.01 [0.91-1.12]). Combined therapy was also associated with significantly lower number of cases with AST (aspartate transaminase)/ALT ratio elevation and lower gamma-glutamyl transpeptidase activity [12]. There were no safety concerns when comparing both treatment options. However, the use of statins, though considered safe by guidelines [19], has very limited use in clinical practice.

There is ongoing research into treatment options for NAFLD/NASH; these options include drugs used to treat type 2 DM (e.g. pioglitazone, glucagon-like peptide-1 receptor agonists), antifibrotic agents (e.g. cenicriviroc, obeticholic acid) and bariatric surgery [20,21]. However, currently there is no definitive treatment for NASH other than weight loss following the implementation of lifestyle measures [1].

It is important to perceive the overall clinical relevance of NAFLD/NASH. Moreover, any diagnostic tools and treatment may prove cost effective because of the increased prevalence of NAFLD/NASH and its hepatic and extra-hepatic complications that are likely to require costly treatment (e.g. liver transplantation and coronary interventions). Furthermore, the extra-hepatic consequences of NAFLD/NASH include an increased risk of type 2 DM, cerebrovascular disease, chronic kidney disease and non-liver cancer which were not considered in this brief editorial [1,8,22].

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Papers of special note have been highlighted as:

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