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Contents

Monthly Volume 14 Number 1 January 27, 2022

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

World Journal of Hepatology

Monthly Volume 14 Number 1 January 27, 2022

Contents

World Journal of Hepatology

Monthly Volume 14 Number 1 January 27, 2022

Contents

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REVIEW

Is there a role of lipid-lowering therapies in the management of fatty liver disease?

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Abstract

Atherogenic dyslipidemia is characterized by increased triglyceride-rich lipoproteins and low high-density lipoprotein cholesterol concentrations. It is highly prevalent in non-alcoholic fatty liver disease (NAFLD) and contributes to the increased cardiovascular risk associated with this condition. Alongside insulin resistance it plays an important pathogenetic role in NAFLD/non-alcoholic steatohepatitis (NASH) development and progression. It has been shown that cholesterol-lowering reduces cardiovascular risk more in NAFLD *vs* non-NAFLD high-risk individuals. This evidence highlights the importance of effective lipid modulation in NAFLD. In this narrative review the effects of the most commonly used lipid-lowering therapies on liver outcomes alongside their therapeutic implications in NAFLD/NASH are critically discussed. Preclinical and clinical evidence suggests that statins reduce hepatic steatosis, inflammation and fibrosis in patients with NAFLD/NASH. Most data are derived from observational and small prospective clinical studies using changes in liver enzyme activities, steatosis/fibrosis scores, and imaging evidence of steatosis as surrogates. Also, relevant histologic benefits were noted in small biopsy studies. Atorvastatin and rosuvastatin showed greater benefits, whereas data for other statins are scarce and sometimes conflicting. Similar studies to those of statins showed efficacy of ezetimibe against hepatic steatosis. However, no significant anti-inflammatory and anti-fibrotic actions of ezetimibe have been shown. Preclinical studies showed that fibrates through peroxisome proliferator-activated receptor (PPAR)α activation may have a role in NAFLD prevention and management. Nevertheless, no relevant benefits have been noted in human studies. Species-related differences in PPARα expression and its activation responsiveness may help explain this discrepancy. Omega-3 fatty acids reduced hepatic steatosis in numerous hetero-

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geneous studies, but their benefits on hepatic inflammation and fibrosis have not been established. Promising preliminary data for the highly purified eicosapentaenoic acid require further confirmation. Observational studies suggest that proprotein convertase subtilisin/kexin9 inhibitors may also have a role in the management of NAFLD, though this needs to be established by future prospective studies.

Key Words: Non-alcoholic fatty liver; Non-alcoholic steatohepatitis; Statin; Ezetimibe; Fibrates; ω-3 fatty acids; Bile acid resins

Core Tip: Statins may be beneficial against non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) in association with their cholesterol-lowering efficacy as well as their anti-inflammatory, antioxidant and anti-fibrotic actions. Elimination of hepatic steatosis, inflammation and fibrosis was noted with statin use in the clinical setting of NAFLD/NASH. Experimental evidence suggests that ezetimibe has similar benefits to statins against NAFLD/NASH. However, ezetimibe was beneficial only against hepatic steatosis, but not against inflammation or fibrosis in NAFLD patients. Despite their promising mechanistic potential against NAFLD/NASH through PPARα activation benefits of fibrates on liver outcomes have not been established in clinical studies. Ample heterogeneous evidence suggests benefits of ω-3 fatty acids against hepatic steatosis, but not inflammation or fibrosis.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become a pandemic with an estimated prevalence of 24%, 30% and 32% in Europe, America and Middle East respectively[1,2]. It has epidemiologic and pathophysiologic links with obesity, type 2 diabetes mellitus, dyslipidemia, unhealthy lifestyle patterns and the metabolic syndrome[3]. Its increasing prevalence is strongly associated with the corresponding rise in those conditions globally.

NAFLD histologic spectrum varies from steatosis alone to non-alcoholic steatohepatitis (NASH) that also encompasses various degrees of necroinflammation and fibrosis. Cirrhosis with or without portal hypertension leading to death or liver transplantation are the liver-specific endpoints of NAFLD[4-6]. Concerningly, NASH-associated liver transplantation cases increased by 170% from 2004 to 2013 in the United States[5].

NAFLD is typically asymptomatic or presents with non-specific symptoms particularly in more advanced forms. It is biochemically characterized by variable elevations in liver enzymes, mainly of elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyltransferase (γ-GT) activities. Of note, liver enzymes may not be sensitive for NAFLD diagnosis, hence many NAFLD cases may be undiagnosed *via* routine biochemical screening. It was estimated that up to 60% of patients with advanced NAFLD have normal liver enzymes[7,8]. Coagulopathy and abnormalities of albumin and bilirubin levels are typically encountered in more advance stages of the disease.

Liver imaging aims to reveal hepatic steatosis and determine whether NAFLD is accompanied by a degree of fibrosis. Liver ultrasound and magnetic resonance imaging (MRI) or computed tomography (CT) are the most frequently imaging modalities in this respect[9]. Vibration controlled transient elastography is used to grade the different levels of liver fibrosis[9]. Liver biopsy remains the 'gold standard' for the diagnosis and staging of NASH as well as for identifying cirrhosis[10].

Cirrhosis and hepatocellular carcinoma account for 4%-8% and 1%-5% of NAFLD-associated mortality respectively[1]. However, cardiovascular (CV) disease is the major mortality cause accounting for approximately 40% of all deaths[11]. NAFLD has been recognized as a risk factor for CV disease by various analyses[12]. However, it is difficult to dissociate this correlation from the high prevalence of concomitant abnormalities representing traditional CV risk factors in NAFLD. These include, but are not limited to obesity, type 2 diabetes, metabolic syndrome and atherogenic dyslipidemia. In fact, it was suggested that it is not the hepatic steatosis itself but the constellation of those metabolic abnormalities contributing to the increased CV risk in NAFLD[13].

To prevent from the progress and complications of NAFLD its early identification and management is crucial. Mainstay treatment involves lifestyle modifications, such as weight management, alcohol restriction, regular exercise and dietary intervention [14-17]. To date, there are no evidence-based drug therapies recommended for the management of NAFLD/NASH leaving a significant unmet clinical need[18]. Nevertheless, pharmacotherapy to address the increased CV risk through anti-obesity, anti-diabetic and lipid-lowering drugs is commonly used in clinical practice[19].

Dyslipidemia and NAFLD

Insulin resistance and the associated dyslipidemia play an important pathogenetic role in NAFLD. Insulin is a key player in lipid metabolism by promoting triglyceride (TG) storage into adipose tissue and by inhibiting hepatic production of the TG-rich very low-density lipoproteins (VLDL). Also, the catabolism of VLDL and their remnants *via* lipoprotein lipase is partly dependent on insulin action. In contrast, insulin resistance is associated with impaired fat storage in adipose tissue resulting in increased influx of non-esterified fatty acids (NEFAs) to the liver and subsequent hepatic fat accumulation. Besides, high cholesterol diet and increased cholesterol influx to the hepatocytes seems to promote *de novo* lipogenesis (through mechanisms that are explained further below) and hepatic steatosis. Free unesterified cholesterol further promotes pro-inflammatory and pro-fibrotic pathways which facilitate progression of NAFLD to NASH and/or cirrhosis[13].

Liver NEFAs further serve as substrate for increased VLDL hepatic production. This abnormality alongside an impaired catabolism of TG-rich lipoproteins results in increased concentrations of the atherogenic apolipoprotein(apo) B-rich lipoproteins in NAFLD. Subsequent lipolysis of these lipoproteins results in increased production of the atherogenic small dense LDL particles[13]. Furthermore, cholesteryl ester transfer protein (CETP) facilitates cholesteryl ester shift from high density lipoproteins (HDL) to TG-rich lipoproteins in exchange for TG. In insulin resistant states such as NAFLD, both TG-rich lipoprotein concentration and CETP activity are enhanced. These abnormalities result in TG-enriched HDL particles which are easily eliminated *via* the hepatic lipase. Also, in NAFLD there is reduced hepatic and intestinal production of the anti-atherogenic apoA1 (the main apolipoprotein of HDL) through decreased adiponectin levels. Through these mechanisms HDL cholesterol (HDL-C) levels are typically reduced in NAFLD. This profile is associated with impaired endothelial function and reverse cholesterol transport by HDL. Other antiatherogenic, including anti-inflammatory, antioxidant and anti-thrombotic effects of HDL are diminished too [20,21].

In summary, the serum lipid profile in NAFLD is similar to the atherogenic dyslipidemia encountered in other insulin resistant states, including the metabolic syndrome and type 2 diabetes. It is characterized by increased TG, non-HDL cholesterol and apoB levels together with low HDL-C and apoA1 Levels. Furthermore, a predominance of the small dense LDL particles further adds to atherogenicity. The same abnormalities seem to contribute to the maintenance and progression of NAFLD. All these considered, aggressive management of dyslipidemia is important to prevent CV disease, while it might be helpful in reducing liver-specific complications in NAFLD.

In this narrative review, a possible therapeutic role of the most commonly used lipid-lowering therapeutics against NAFLD/NASH is discussed.

Statins (3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors)

Statins are potent cholesterol-lowering agents and evidenced-based drugs to reduce CV outcomes. Their cholesterol-lowering efficacy is expected to be beneficial for NAFLD, which is characterized by aggregation of free cholesterol into hepatocytes[22,23]. Besides, statins have been suggested to exert variable lipid-independent pleiotropic benefits, including antioxidant, anti-thrombotic, anti-fibrotic and anti-inflammatory actions as well as endothelial function improvement. Except for their protective role against atherothrombosis these effects may play a role in the prevention

and management of NAFLD/NASH[22,24-26].

Mechanistic implications

Free unesterified cholesterol appears to be toxic to the hepatocytes by promoting liver inflammation and subsequent fibrosis. Namely, cholesterol crystals accumulation into hepatocytes results in inflammatory response *via* activated Kupffer cells surrounding the steatotic liver cells in crown-like structures. Besides, cholesterol crystals activate NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome within the Kupffer cells. Atorvastatin both alone or in combination with ezetimibe attenuated these effects in high-fat and high-cholesterol diet fed mice after 16 wk. These findings indicated a potential role of cholesterol lowering in NASH prevention[27].

Statins also inhibit the synthesis of isoprenoids, which are mevalonate pathway products. Prenylation/activation of the small guanosine triphosphate (GTP)ases through isoprenoids regulates the intracellular signaling of numerous receptors mediating liver inflammation and fibrosis. Statin-related inhibition of this isoprenoid-dependent process led to significant anti-inflammatory and anti-fibrotic effects in an experimental model of NAFLD[28].

Furthermore, statins may reduce the expression of pro-inflammatory and pro-fibrinogenic mediators. Namely, rosuvastatin significantly decreased the expression of tumor necrosis factor (TNF)α, interleukin(IL)-6, IL-1β, interferon (IFN)-γ and transforming growth factor (TGF)-β1 in a rodent model of hepatocellular carcinoma (HCC) fed with high-fat and high-cholesterol diet. These effects alongside a reduced expression of the vascular epidermal growth factor receptor (VEGFR), the epidermal growth factor receptor (EGFR) and the platelet-derived growth factor (PDGF) suggested a protective role of rosuvastatin against HCC associated with NAFLD/NASH[29].

Furthermore, antioxidant actions of statins may be beneficial against NAFLD/NASH. Peroxisomes play a key role in the maintenance of intracellular redox balance. Statins were suggested to increase the gene expression of peroxisome proliferator-activated receptor α (PPARα), a regulator of peroxisomal and mitochondrial fatty acid oxidation. Through this mechanism statin treatment limited hepatic steatosis and improved peroxisomal and mitochondrial function in an experimental rodent model [24]. Paraoxonase (PON)1 is another liver-derived enzyme, which is linked to HDL. It has a limiting role in oxidative stress and inflammation by hydrolysing peroxides and lactones associated with lipoproteins. Genetic studies have shown that reduced PON1 activity plays a significant pathogenetic role in NASH[30]. Atorvastatin 40 mg/d was associated with increased PON1 activity in 25 NAFLD patients after 8 mo. This effect was accompanied by significantly reduced serum malondialdehyde levels as a marker of lipid peroxidation, suggesting a promising role of this statin in NASH prevention [25].

Also, *in vitro* and *in vivo* experimental evidence suggested that the antioxidant and anti-inflammatory actions of statins can prevent hepatic stellate cells (HSCs) activation and subsequent fibrosis in NASH. This benefit may be mediated *via* reduced expression of pro-inflammatory genes as well as of reactive oxygen species (ROS), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase gp91 phox subunit, α-smooth muscle actin (α-SMA) and nuclear factor-κ (NF-κB) p65 nuclear translocation [31]. An inhibitory effect of statins on HSCs activation may also be mediated *via* increased endothelial NO synthase (eNOS) together with reduced inducible NO synthase (iNOS) expression[32].

Furthermore, statins may exert anti-fibrotic effects and reduce portal pressure *via* improving the nitric-oxide (NO)-dependent liver sinusoidal endothelial cells (LSECs) function. LSECs dysfunction in NASH is considered to precede portal hypertension and its subsequent fibrosis *via* activation of the HSCs[33].

Clinical evidence

Due to their evidence-based anti-atherothrombotic benefits statins have a key role in addressing the increased CV risk in NAFLD. Interestingly, it was suggested that the reduction of CV events by statin use is greater in high-risk patients with *vs* without NAFLD[34]. Also, long-term statin use was associated with reduced risk of cancer in NAFLD. This protection was greater with increasing the time of statin exposure, becoming significant after 1 year of treatment[35].

Unfortunately, real-life statin use in NAFLD is often limited by the abnormal pre-treatment liver enzymes and the possibility of their further treatment-induced elevations. This is relevant despite several clinical studies showing that statins may improve liver enzyme activities and limit hepatic steatosis in NAFLD/NASH. However, these benefits have not been reflected by relevant recommendations in the

treatment guidelines, possibly awaiting further confirmation by larger scale studies. Current evidence suggests that statin use is overall safe with appropriate liver function test monitoring except for Child-Pugh B and C cirrhosis, particularly when total bilirubin is > 3 mg/dl. In this context, the vast majority of patients with increased aminotransferase activities due to an established chronic liver disease, including NAFLD/NASH, should not be exempt from statin use[36-38].

To date, statin benefits on several markers and surrogates of NAFLD/NASH have been demonstrated in several large population studies as well as in smaller prospective clinical ones. A large-population study tested whether statin therapy can lower NAFLD incidence in healthy individuals or reduce progression to hepatic fibrosis among patients with established NAFLD. Overall, 11,539,409 individuals were recruited and were followed up for 6 years. Fatty liver index (FLI) and BARD score were used for the diagnosis of NAFLD and the assessment of hepatic fibrosis, respectively. Of all study participants 5,339,901 were NAFLD-free (FLI<30); of those, 164,856 subjects were diagnosed with NAFLD at the end of the follow-up. Statin treatment was associated with reduced incidence of NAFLD (assessed by FLI > 60; adjusted odds ratio (OR:) (0.66; 95% confidence interval [CI] 0.65-0.67). Statin treatment was also associated with reduced progression to hepatic fibrosis (BARD score > 2) among NAFLD patients (adjusted OR: 0.43; 95%CI: 0.42-0.44)[39].

In a multicenter cohort study liver biopsy was performed in 1,201 individuals considered to have NASH. In the biopsy-proven NASH cases statin use was associated with a significant dose-dependent protection against hepatic steatosis, NASH and hepatic fibrosis F2-F4 stage. In statin-treated patients with genetic mutations (PNPLA3 I148M risk alleles, TM6SF2 E167K variant), impaired fasting glucose, type 2 diabetes, increased age and elevated body mass index (BMI), statin use was associated with reduced risk of steatosis (OR: 0.09, 95%CI: 0.01-0.32; P = 0.004), steatohepatitis (OR: 0.25, 95%CI: 0.13-0.47; P < 0.001), and fibrosis F2-F4 stage (OR: 0.42, 95%CI: 0.20-0.80; P = 0.017)[40].

A randomized clinical trial included 5,400 military personnel who were screened through clinical and laboratory checkup. Of those individuals, 604 were diagnosed with NAFLD/NASH and were randomized by 1:1:1:1 to diet/exercise, rosuvastatin, atorvastatin or pitavastatin treatment. After 1 year, changes of 2 non-invasive scores [NAFLD Activity Score (NAS); Fibrosis-4 score (FIB-4)] were assessed. No significant changes in any of these scores were observed in the diet/exercise group. However, statin treatment was associated with significantly reduced NAS and FIB-4 scores at the end of follow up. This benefit was relevant for all statins used in this study[41].

A possible protective role of statin treatment against NAFLD progression to HCC was also demonstrated in observational studies. A case-control study included 102 NAFLD patients with *vs* without HCC (cases, n = 34 *vs* controls, n = 68 respectively). In multivariate analysis statin treatment was associated with lower risk of HCC (OR: 0.20, 95%CI: 0.07-0.60, P = 0.004)[42]. Another retrospective cohort study investigated the likelihood of progression to HCC in 18,080 non-cirrhotic NAFLD patients identified in Taiwan's National Health Insurance Research Database between 1998 and 2012. The median follow-up period was 6.32 years. The 10-year cumulative incidence of HCC was estimated to be 2.73% (95%CI: 1.69%-3.76%). In multivariate analysis statin use was associated with reduced risk of HCC progression (hazard ratio, HR 0.29, 95%CI: 0.12-0.68)[43]. However, all these studies should be interpreted with caution due to their retrospective character. More prospective longitudinal data may be required to establish a protective role of statin treatment against HCC development in NAFLD.

Atorvastatin

The Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study included 1,600 patients with established coronary artery disease, low density lipoprotein cholesterol (LDL-C) > 2.6 mmol/l (100 mg/dl) and TG < 4.5 mmol/l (400 mg/dl). These patients were randomized to atorvastatin 10-80 mg/d or usual care (including statins) to achieve LDL-C < 2.6 mmol/l (100 mg/dl). A *post hoc* analysis of this study included 437 patients with suspected NAFLD due to moderately abnormal liver function tests: 227 received atorvastatin at a mean dose of 24 mg/d and 210 received usual care. The primary outcome of this analysis was risk reduction by statin *vs* non-statin treatment for first recurrent CV event in patients with moderately abnormal liver tests (AST and ALT levels < 3 x the upper limit of normal). A relative risk reduction by 68% was noted in the atorvastatin-treated group compared with usual care. Interestingly, this benefit was significantly greater by 39% in the subgroup of patients with suspected NAFLD compared with patients exhibiting normal liver function tests at baseline. This finding suggested that CV benefits of atorvastatin is

more prominent among high-risk patients who have NAFLD compared with the corresponding patients who do not have NAFLD. Also, the use of atorvastatin was safe in NAFLD patients leading to rare treatment discontinuations due to liver enzyme abnormalities (7/880 patients)[34].

Small pilot prospective studies also suggested that atorvastatin monotherapy improves liver-specific outcomes in NAFLD/NASH. Namely, atorvastatin across dose range 10-80 mg/d was given in patients with dyslipidemia and NAFLD for 3-12 mo [44,45]. Treatment improved the lipid profile and was associated with significant reductions of the baseline elevated liver function tests. A large proportion of patients (*i.e.*, 36.3%) showed liver enzyme normalization after 6 mo of treatment with additional patients exhibiting similar benefits with continuation of treatment for up to 1 year. Radiographic regression of liver steatosis assessed by CT was noted too[44].

Atorvastatin was also beneficial when used in combination with other agents. 1005 individuals were randomized to atorvastatin 20 mg/d + vitamin C (1 g/d) + vitamin E (1000 IU/d) *vs* placebo for 4 years. The combination treatment was associated with a 71% reduced odds of hepatic steatosis development assessed by CT (liver-to-spleen ratio) compared with placebo[46]. Another prospective study included 186 non-diabetic patients with metabolic syndrome and ultrasonographic findings of NAFLD. These patients were randomized to atorvastatin 20 mg/d, (n = 63), fenofibrate 200 mg/d (n = 62) or their combination (n = 61). After 54 wk, liver enzymes and ultrasound findings of NAFLD normalized in 67% of the participants in the atorvastatin, 42% in the fenofibrate and 70% in the combination group[47].

In another phase 2 randomized placebo-controlled trial atorvastatin treatment blunted the increases in LDL-C levels and LDL particle concentration (LDL-pc) associated with obeticholic acid (OCA) in NASH patients. OCA is an agent with promising effects on liver histology and fibrosis, which adversely impacts on lipoprotein metabolism. The latter may be safely alleviated when it is used in combination with atorvastatin[48].

Rosuvastatin

Like atorvastatin, rosuvastatin effectively improved liver-specific endpoints of NAFLD in small pilot studies. Rosuvastatin 10 mg/d treatment was given in 6 non-diabetic non-hypertensive dyslipidemic patients with metabolic syndrome and biopsy-proven NASH. A second biopsy as well as liver ultrasound after 12 mo showed complete resolution of NASH characteristics (steatosis, necroinflammation and fibrosis) in 5/6 patients. Additionally, rosuvastatin was associated with significantly reduced ALT and AST activities by 76 and 61% respectively[49]. Similar were the findings of another small prospective study including 23 NAFLD patients with dyslipidemia who received rosuvastatin 10mg/d. After 8 mo liver enzymes normalized in all patients[50].

In another study rosuvastatin 10 mg/d was given in 20 patients with dyslipidemia, biopsy-proven NASH and metabolic syndrome for 12 mo. Significant improvement of the course of NASH and metabolic syndrome was confirmed through laboratory tests, repeated biopsies and ultrasound assessment at the end of follow-up. Furthermore, significant reductions in serum uric acid and fasting plasma glucose levels implied additional cardiometabolic benefits of rosuvastatin in these patients[51]. Another pilot study included 19 dyslipidemic patients with biopsy-proven NASH treated with rosuvastatin 2.5 mg/d. After 24 mo biopsies in 9 patients showed improved NAS and fibrotic stage in 33.3% patients[52].

Despite this promising evidence long-term (96 wk) rosuvastatin 10 mg/d failed to reduce hepatic steatosis assessed by the liver fat score *vs* placebo in 147 human immunodeficiency virus (HIV)-positive patients on antiretroviral treatment. Instead, hepatic steatosis progression was noted both in the rosuvastatin and placebo groups at the end of follow-up. Reassuringly, multivariate regression analysis suggested that this finding was associated with increased inflammatory biomarkers, but not with rosuvastatin treatment[53].

Simvastatin

Data on simvastatin are limited. A retrospective study evaluated the safety and efficacy of simvastatin alone or in combination with ezetimibe in 45 patients with NAFLD, metabolic syndrome, and increased CV risk[54]. Twenty-six patients received simvastatin monotherapy 20 mg/d and 19 simvastatin/ezetimibe 10/10 mg/d. After 6 mo AST and ALT activities were significantly reduced compared with pre-treatment values. Interestingly, simvastatin monotherapy was associated with significantly greater AST/ALT reductions compared with the combination therapy. This finding suggested a potential dose-dependent benefit of simvastatin in this respect[54].

In contrast, a pilot randomized study evaluating the effects of simvastatin 40 mg/d *vs* placebo in 16 patients with NASH and dyslipidemia did not show similar benefits [55]. Despite significant improvement of the serum lipid profile, liver biopsy performed after 1 year in 10 patients did not show any differences in hepatic steatosis or fibrosis stage between the simvastatin and the placebo group. No significant changes in serum aminotransferases in any of the groups were noted either[55].

Pravastatin

Limited clinical data suggest that pravastatin may be a safe and tolerable option in improving the serum lipid profile in NAFLD patients whilst improving NASH-related liver histology. A multicenter randomized clinical trial included 326 hypercholesterolemic patients with known chronic liver disease (64% with NAFLD) treated with high-dose pravastatin (80 mg/d) *vs* placebo. After 36 wk, pravastatin significantly improved the serum lipid profile. No statistically significant difference between the pravastatin and the placebo group was noted in ALT elevation events (defined as doubling from pre-treatment values): 8% *vs* 13%, respectively. These results suggest that pravastatin is a safe option to beneficially modify the lipid profile among NAFLD patients[56]. In another small study, pravastatin 20 mg/d was given in 5 participants with biopsy-proven NASH and abnormal liver enzyme activities. After 6 mo, hepatic enzymes normalized in all participants. Also, repeat biopsy in 4/5 participants showed that hepatic steatosis and inflammation were persistent only in 1 and 3 participants, respectively[57].

Pitavastatin

Pitavastatin effectively reduces LDL-C, while increasing HDL-C levels, especially in patients with pre-diabetes or diabetes[58]. Its favorable metabolic profile associated with improved insulin resistance and carbohydrate metabolism may be promising for the management and prevention of NAFLD/NASH[59]. It was suggested that these benefits are mediated through increased adiponectin levels and reduced oxidative stress[58].

However, limited clinical evidence is conflicting and cannot firmly establish a beneficial role of this statin against NAFLD. Namely, a 12 wk pitavastatin 2-4 mg/d treatment significantly reduced liver enzyme activities in 97 patients with mildly-to-moderately elevated liver enzyme tests at baseline[44]. This benefit was accompanied by reduced severity of the CT-assessed hepatic steatosis among patients with this abnormality at baseline. Events of moderate to severe ALT elevations at > 100 and > 120 IU/L at 12 wk were rare in pitavastatin-treated patients: 5/97 and 1/97, respectively[60].

Similar were the results of a 12 mo pitavastatin 2 mg/d treatment in 20 NASH patients with dyslipidemia. However, NAS and fibrosis stage in biopsy were not significantly altered[61]. In accordance with this finding a 6-month pitavastatin 4 mg/d treatment did not significantly reduce Hydrogen-1 MRI-assessed hepatic fat compared with placebo in 50 adults with Body Mass Index (BMI) ≥ 27 kg/m^2 and waist circumference ≥ 102 cm who had not used statins for ≥1 year. In the same study pitavastatin did not favorably improve indices of carbohydrate metabolism, including endogenous glucose production, whole body insulin sensitivity or insulin-induced glucose uptake[62]. Therefore, more data are needed to clarify the effects of this statin on hepatic steatosis, inflammation and fibrosis as well as on the associated metabolic abnormalities.

Lovastatin

In one multicenter study 87 patients with NAFLD/NASH and dyslipidemia received lovastatin 10 mg/d for 4 mo. Significant reductions in transaminase and cholesterol levels were noted even within the first 2 mo of treatment. Also, a decreased the AST-to-platelet ratio index (APRI) as a marker of liver fibrosis was noted[63].

EZETIMIBE

Mechanistic implications

Ezetimibe exerts its mild-to-moderate LDL-C-lowering action *via* inhibiting intestinal cholesterol absorption through the Niemann-Pick C1-like 1 (NPC1L1) protein[64]. Its additive LDL-C lowering effects to statins were associated with further significant reductions in the risk of CV events in high-risk patients[65,66].

Experimental studies suggested that dietary cholesterol uptake is associated with hepatic steatosis and, hence high cholesterol-fed animals have been extensively used as experimental models of NAFLD/NASH. Increased cholesterol absorption and hepatocyte cholesterol content results in a cholesterol-dependent activation of the liver X receptor α (LXRα). The latter enhances the expression of several transcriptional factors that promote hepatic lipogenesis, including the sterol regulatory element binding protein (SREBP)-1c and the carbohydrate response element-binding protein (ChREBP). Reducing cholesterol absorption *via* ezetimibe can help reverse this deleterious process[67].

NPC1L1 is also expressed in the human liver and facilitates cholesterol reuptake from bile to hepatocytes[67]. Further experiments suggested that NPC1L1 may be associated with impaired VLDL-TG secretion and subsequent TG hepatic accumulation[68]. NPC1L1 inhibition by ezetimibe ameliorated hepatic steatosis in genetically engineered L1-Tg mice characterized by enhanced hepatic NPC1L1 expression[69,70].

Ezetimibe-related liver de-lipidation can be facilitated through other mechanisms too. Lipoprotein secretion and lipid removal from the liver is mediated by the microsomal TG transfer protein (MTP) whose degradation is inhibited by ezetimibe [71]. Ezetimibe may also enhance the expression of cholesterol efflux transporters like Abcg5/g8[72]. Furthermore, ezetimibe was associated with improved hepatic insulin sensitivity through an upregulation of the small heterodimer partner (SHP). This effect was accompanied by an upregulation of SREBP2 and downregulation of SREBP-1c expression[73]. Also, ezetimibe was associated with a decreased hepatic expression of *Cd36* gene. Cd36 is a multifunctional scavenger receptor facilitating fatty acid uptake and oxidation, and it has been associated with dysfunctional fatty metabolism and fatty liver[74].

Besides, according to experimental studies ezetimibe can confer significant protection against inflammation and oxidative stress associated with hepatic steatosis. A proposed mechanism is through activation of the nuclear factor erythroid 2-related factor 2 (Nrf2), a transcriptional factor whose target genes are antioxidant proteins and detoxification enzymes[67].

Further *in vitro* experimental data suggested that ezetimibe exerts anti-inflammatory benefits against NASH in human liver cells. In this context, ezetimibe may promote autophagy, which plays a key role in hepatic lipid catabolism (lipophagy) and prevents from hepatic steatosis[75]. This effect may be mediated by AMP-activated protein kinase (AMPK) activation and transcription factor EB (TFEB) nuclear translocation associated with the MAPK/ERK pathway. Ezetimibe may also reduce NLRP3 inflammasome activation in macrophages by modulating autophagy and a hepatocyte-driven exosome pathway[76]. Besides, it was shown to reduce hepatic fat content and prevent from the associated NFκB pathway-mediated liver inflammation by high-fat diet[77].

Last, ezetimibe was suggested to exert protective effects against angiogenesis associated with HCC development in NASH[78]. In this context, ezetimibe was also associated with downregulated expression of SKP2 which serves as an oncogene in HCC in a high-fat diet rodent model[74].

Clinical evidence

The effects of ezetimibe on liver-specific outcomes of NAFLD/NASH were mainly evaluated in small interventional studies with similar design to the statin ones. Namely, ezetimibe 10 mg/d was associated with significantly decreased ALT, AST and γ-GT activities in 70 individuals with dyslipidemia and NAFLD. Also, the ultrasonographic progress of steatosis was limited in 38.6% of these patients[79]. Another small study included 8 non-obese individuals with NAFLD who were treated with ezetimibe. Four patients had been receiving ursodeoxycholic acid which was subsequently switched to ezetimibe, while the remaining 4 patients had been previously treatment naive. After 12 mo, ALT activity was significantly reduced by 49.3% and normalized in 4 of 8 patients. Nevertheless, ezetimibe treatment was not associated with any significant ultrasonographic changes of hepatic steatosis[80].

Long-term effects of ezetimibe monotherapy on hepatic steatosis were evaluated in 45 biopsy-proven NAFLD patients. After 2 years of treatment histologically-assessed hepatic steatosis and NAFLD activity scores were significantly reduced. However, no improvement in the fibrosis state was observed[81].

A randomized double-blind placebo-controlled study assessed whether ezetimibe reduces hepatic steatosis in NASH. It included 50 biopsy-proven patients randomized to ezetimibe 10 mg/d or placebo. After 24 wk ezetimibe was associated with reduced liver steatosis assessed by magnetic resonance imaging-derived proton density-fat fraction (MRI-PDFF) compared with baseline. However, no significant difference

between the ezetimibe and the placebo group was noted[82]. Another study assessed the effects of a 6-month ezetimibe treatment in 10 patients with dyslipidemia and NASH. Significantly improved activities of AST, ALT, γ-GT as well as reduced LDL-C, CRP and type IV collagen 7 levels were observed. Histologically-assessed steatosis also improved in every patients, whilst significant benefits on fibrosis status was noted in 6/10 patients[83].

A further randomized controlled trial included 32 NAFLD patients of whom 17 received ezetimibe, while the rest were controls. After 6 mo ezetimibe significantly reduced total cholesterol levels by 9.5% compared with control group and ameliorated hepatic fibrosis. Namely, histologically-assessed staging and ballooning scores were significantly improved in the ezetimibe group compared with baseline. In contrast, the steatosis score, lobular inflammation and NAS did not significantly change in either group[84].

The efficacy and safety of ezetimibe 10 mg/d + simvastatin 20 mg/d combination was evaluated in 19 patients with type 2 diabetes and NAFLD[85]. After 6 mo, treatment was associated with significantly reduced ALT activity by 48.9%[85]. The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) included 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 ds and had LDL-C levels of 1.3-2.6 mmol/l (50-100 mg/dl) if they were receiving lipid-lowering therapy or 1.3-3.2 mmol/l (50-125 mg/dl) if they were not receiving lipid-lowering therapy. These patients were randomized to simvastatin 40 mg/d + placebo *vs* simvastatin 40/d + ezetimibe 10 mg/d. The primary endpoint was the composite of CV death, myocardial infarction, rehospitalization for unstable angina, coronary revascularization or stroke. After 7 years the simvastatin + ezetimibe combination significantly reduced the primary endpoint compared with simvastatin monotherapy (34.7 *vs* 32.7%, p = 0.016)[65]. In a sub-analysis, NAFLD fibrosis score (NFS) was prospectively applied to 14,819 IMPROVE-IT participants. NFS is a serum-based index, originally developed for the diagnosis of advanced hepatic fibrosis in patients with NAFLD and it was found to be associated with increased CV morbidity and mortality. Using validated NFS cutoffs the effect of treatment on the primary endpoint was assessed. In the IMPROVE-IT patients with high NFS score (> 0.67) had a 30% increased risk of major CV events compared with the low-risk group. Simvastatin+ezetimibe combination was associated with a 3.7% absolute reduction in the risk of recurrent CV events, compared with placebo + simvastatin (HR 0.85 [0.74–0.98]) translating to a number-needed-to-treat of 27. This additional CV benefit was not noted in the low-risk group based on NFS. This finding suggests that ezetimibe confers additional CV protection amongst NAFLD patients with higher fibrosis score[86].

A meta-analysis of 2 randomized controlled trials (RCTs) + 4 single-arm trials included 273 participants with NAFLD and NASH. Ezetimibe treatment was not associated with improved hepatic inflammation and fibrosis, although an improvement in transaminase levels was observed[87]. Similar were the results of a more recent meta-analysis of 5 lipid-lowering treatment studies (2 ezetimibe, 1 simvastatin, 1 atorvastatin and 1 any-statin) including 199 patients with NAFLD[88]. Ezetimibe was associated with decreased NAS, but not with reduced hepatic steatosis [88].

FIBRATES

Mechanistic implications

TG reduction is the main lipid-lowering action of fibrates accompanied by moderate increases in HDL-C and mild reductions in LDL-C levels. Despite these favorable effects their role in CV disease prevention remains controversial[89]. Nevertheless, several animal studies suggested a promising role of fibrates for the management of NAFLD. Specifically, fibrates ameliorated hepatic steatosis, necroinflammation and fibrosis induced by high-fat diet in several experimental studies[90-96].

PPARα activation is their main mechanism of action associated with multiple benefits on the lipid and glucose metabolism[97]. Through this effect fibrates upregulate lipoprotein lipase, a key enzyme for the TG-rich lipoprotein catabolism. This enzyme also plays a key pathogenetic role in hepatic steatosis when downregulated[98]. Also, PPARα activation through fibrates is expected to reduce hepatic steatosis mainly *via* enhanced expression of target genes. These include fatty acid transport and binding proteins, carnitine palmitoyltransferase II, as well as medium- and long-chain acyl-CoA dehydrogenase and acyl-CoA oxidase mediating

mitochondrial and peroxisomal FA β-oxidation[97,99,100]. In the same context, fibrate use has been associated with reduced hepatic insulin resistance mostly by enhanced fatty PPARα-related acid β-oxidation. Also, PPARα activation is associated with increased expression of FGF21, a hepatokine enhancing extra-hepatic tissue insulin sensitivity through glucose transporter 1 activation[99].

Additionally, fibrates downregulate the expression of pro-inflammatory cytokines genes, such as TNFα, monocyte chemoattractant protein (MCP)-1, intercellular adhesion molecule (ICAM)-1 and vascular adhesion molecule (VCAM)-1. This suggests a promising role against NASH[97,99]. Fibrates were also suggested to exert antioxidant actions, mainly through reducing fatty acid peroxidation and ROS production. The latter effects appear to be PPARα-dependent. Furthermore, fibrate treatment was associated with amelioration of high-fat diet-induced disturbances in hepatic microvasculature. This effect seems to improve the liver microvascular environment and oxygenation and may be protective against NAFLD in a PPARα-dependent manner[97].

Many of the abovementioned effects may be also mediated by a fibrate-associated increased production of adiponectin, an adipokine that exerts multiple benefits on lipid and glucose metabolism, mainly *via* reducing hepatic insulin resistance. This adipokine also exerts variable anti-inflammatory, antioxidant and anti-fibrotic actions in the liver being potentially protective against NASH. Besides, fibrate treatment seems to preserve the liver-specific adiponectin receptor (AdipoR2), which is protective against liver steatosis and inflammation[97].

Clinical evidence

The very promising experimental evidence suggesting a therapeutic role of fibrates in NAFLD has not been confirmed by clinical studies. This inconsistency might be explained by differences between animals and humans in PPARα tissue expression, being higher in the former[101]. Another important factor is the difference in PPARα responsiveness to treatment between rodents and humans. Namely, fibrate-related human PPARα activation is less prominent in humans than in rodents at equivalent doses[99,102]. Also, in experimental rodent studies the fibrate doses used were significantly higher than the human equivalent ones in clinical studies[102]. These factors may have obscured any benefits of fibrates in human studies[99,102].

Like statins and ezetimibe, clinical data for fibrates are mainly derived from small clinical studies, in which these drugs were used as monotherapy or in combination with other agents.

In a small study, fenofibrate 200 mg/d was given in 16 individuals with biopsy-proven NAFLD for 48 wk. Fenofibrate significantly reduced triglycerides and increased apolipoprotein A1 levels, while it improved the glycemic status. Significant reductions in liver enzyme activities, including ALT, AST, ALP and γ-GT were noted at the end of follow up. Minor improvements of liver histologic abnormalities were also noted in the fenofibrate-treated patients. Namely, a significantly reduced grade of hepatocellular ballooning degeneration was observed, while the grade of steatosis, lobular inflammation and fibrosis or NAS remained unchanged[103].

Another study included 90 patients with NAFLD who were randomized to fenofibrate 300 mg/d monotherapy or fenofibrate 300 mg/d + pentoxifylline 1200 mg 3 times daily for 24 wk. Pentoxifylline+fenofibrate combination were significantly more beneficial on liver enzyme activities than fenofibrate monotherapy. Namely, ALT/AST/γGT activity was reduced by 50.0/45.6/43.2% in the monotherapy *vs* 60.6/62.0/54.2% in the combination group. Of note, liver fibrosis assessed by indirect biochemical markers, a direct marker linked to matrix deposition (hyaluronic acid), a cytokine/growth factor linked to liver fibrosis (*i.e.*, TGF-β1), the inflammatory pathway, insulin resistance and liver stiffness (assessed by Fibroscan) were improved more in the combination treatment compared with the fenofibrate monotherapy group. This finding indicated that therapy with pentoxifylline + fenofibrate may have a therapeutic role against NAFLD and progression of NASH to cirrhosis[104].

Another randomized placebo-controlled trial assessed the effects of fenofibrate *vs* nicotinic acid on intrahepatic TG levels and CV risk in 27 obese patients with NAFLD. Study participants were randomized to fenofibrate 200 mg/d for 8 wk or nicotinic acid extended release 2000 mg/d for 16 wk, or placebo for 8 wk. Both fenofibrate and nicotinic acid significantly lowered circulating very low-density lipoprotein-TG (VLDL-TG) concentrations to a similar extent: by 48.9% and 40.2% respectively. Nevertheless, the hepatic triglyceride content remained unchanged in both treatment groups[105].

Fenofibrate effects on hepatic fat was also compared with free omega-3 carboxylic acid (OM-3CA) treatment in a trial including 78 obese patients with NAFLD. Those patients were randomized to OM-3CA 4 g/d (n = 25), fenofibrate 200 mg/d (n = 27) or placebo (n = 26). After 12 wk both fenofibrate and OM-3CA significantly reduced serum TG levels by 26% ($p = 0.02$) and 38% ($p < 0.001$) respectively compared with placebo. However, none of the treatments significantly altered hepatic fat. Interestingly, hepatic fat and volume increased in the fenofibrate compared with the OM-3CA group[106].

Another study included 90 overweight patients with NAFLD who were randomized by 1:1:1 to lifestyle intervention alone or in combination with fenofibrate 200 mg/d or pioglitazone 30/d. Improved ALT and AST activities as well as significant reductions in blood pressure and BMI were noted in all study groups. However, no significant differences between groups were noted in the median changes of ALT/AST activities or BMI[107].

Also, in an abovementioned study the effects of atorvastatin and fenofibrate monotherapies or in combination were assessed in patients with metabolic syndrome and NAFLD. Normalization in the liver biochemistry and ultrasound findings of NAFLD was noted 67, 42 and 70% of participants in the atorvastatin, fenofibrate and combination group respectively[47].

OTHER LIPID-LOWERING DRUGS

ω-3 fatty acids

α-Linolenic acid (ALA), Stearidonic acid (SDA), Eicosapentaenoic acid (EPA), Docosapentanoic acid (DPA) and Docosahexaenoic acid (DHA) are ω-3 Polyunsaturated Fatty Acids (PUFAs). It was suggested that ω-3 PUFAs exert multiple benefits on the CV and nervous system, maternal and child health, cancer progression and diabetes[108]. However, their efficacy to reduce CV mortality and morbidity as well as total mortality was not supported by meta-analyses of RCTs[109]. There is some variation between different ω-3 PUFAs in this regard, with the highly purified EPA, icosapent ethyl being more beneficial[110].

An association between ω-3 PUFAs and NAFLD has also been suggested. Specifically, NAFLD patients were shown to have reduced hepatic levels of ω-3 PUFAs. This observation may be relevant for the disease development and progression. Namely, adequate levels of PUFAs were suggested to reduce liver lipogenesis and hepatic inflammation in animal studies[111]. Interestingly, a cross-sectional analysis evaluated a potential prognostic role of ω-3 PUFAs in childhood NAFLD. The study included 223 children (aged 6-18 years) who were recruited from the "*Treatment of Nonalcoholic Fatty Liver Disease in Children*" trial. Their intake on fish and ω-3 PUFA was estimated based on the *Block Brief 2000 Food Frequency Questionnaire*. Inadequate consumption of fish and ω-3 PUFA was observed in NAFLD children, and it was linked to increased inflammation of the liver. This finding suggests a significant prognostic role of limited ω-3 fatty acids intake in the development and progression of the disease[112].

The hypothesis of whether ω-3 PUFA supplementation can be beneficial on liver endpoints in NAFLD was assessed in various clinical studies. In a recent meta-analysis including 1,366 NAFLD participants of 22 RCTs, ω-3 PUFA supplements were associated with reduced hepatic fat content compared with placebo (pooled risk ratio 1.52; 95%CI: 1.09-2.13). This benefit was attributed at least in part to favorable changes in BMI, but also to effective lipid modulation by reductions in TG and total cholesterol levels in ω-3 fatty acid-treated patients. However, the heterogeneity of the RCTs (diverse ethnicity and age groups) was considered a significant limitation of this analysis. Other limitations included the small sample size as well as paucity of data from follow up, and significant differences in the treatment plans (related to therapeutic dosages, duration and regimens) of the included trials[113].

A clinical trial included 48 patients with diabetes and NAFLD who were randomized to a combination of probiotics + ω-3 PUFAs *vs* placebo for 8 wk. Fatty Liver Index and Liver stiffness were determined through Shear Wave Elastography (SWE). Combination therapy ameliorated hepatic fat, improved the serum lipid profile and decreased systemic inflammation[114].

Another study investigated potential benefits of ω-3 PUFAs on NAFLD progression. Thirty NAFLD patients were separated into 2 groups depending on the severity of their disease (moderate *vs* severe). This distinction was based on biochemical and ultrasonographic characteristics, NAS and FLI. Participants in the severe NAFLD

group received ω-3 PUFA (2 g/d) for 6 mo. At the end of the study, patients displayed increased circulating levels of EPA/DHA and reduced hepatic steatosis[115]. Similar were the results of another study that assessed whether long-term (1-year) ω-3 PUFAs use is beneficial in 56 NAFLD patients: 42 received ω-3 PUFAs (1 g/d) and 14 were controls. ω-3 PUFAs were associated with significantly reduced ALT/AST activities as well as with decreased TGs levels. Ultrasonographically assessed hepatic steatosis also improved in the treatment group[116].

Promising clinical evidence suggested a potential therapeutic role of highly purified EPA against NAFLD/NASH. A pilot study included 23 biopsy-proven NASH patients who were treated with highly purified EPA 2,700 mg/d. After 12 mo, treatment was associated with significantly improved biomarkers or NAFLD and its associated oxidative stress. Those included improved ALT activity as well as reduced fatty acid, TNF receptors 1 and 2, serum ferritin and thioredoxil levels. Also, follow up biopsy after 12 mo showed reduced hepatic steatosis and hepatocyte ballooning as well as improved lobular inflammation and liver fibrosis in 6/7 patients[117]. These benefits were evident even in the absence of any significant changes in body weight, insulin resistance and adiponectin levels[117]. Several mechanisms were proposed to mediate potential benefits of highly purified EPA on NAFLD in a mouse model. These included reduced fatty acid hepatic uptake, increased intrahepatic TG hydrolysis as well as inhibition of the SREBP-1 maturation. All those actions were proven independent of PPARα activation[118].

Bile acid sequestrant resins

Bile acid sequestrants (BAS) are lipid-lowering drugs recommended for individuals with increased cholesterol levels, but normal TGs. Both as monotherapy or in combination with other lipid-lowering drugs they may decrease LDL-C by 20% and CV risk[119].

A study including 50 NASH patients assessed whether colesevelam can reduce hepatic fat. These patients were randomized to colesevelam 3.75 g/d or placebo. After 24 wk, colesevelam was associated with slightly worsened hepatic fat and inflammation than placebo. The hepatic outcomes were evaluated by MRI-PDFF and conventional MR spectroscopy (MRS). The clinical impact and the responsible mechanism explaining these findings have not been established and more clinical trials are needed to reach safer conclusions[120].

An ongoing Phase 2 randomized trial (NCT04235205) is testing whether combination therapy of elobixibat (EXB), an ileal bile acid transporter inhibitor and cholestyramine is efficient in the management of NAFLD. This study will include 100 NAFLD patients who will be randomized to 4 treatment groups: EXB 10 mg + cholestyramine 4g, EXB 10 mg monotherapy, cholestyramine 4g monotherapy or placebo. Changes in the course of NAFLD will be evaluated by means of biochemical parameters and liver imaging after 16 wk of treatment[121].

PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors

To date, there are 2 available fully human monoclonal antibodies (mAbs) inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9). These drugs are highly efficacious in reducing LDL-C levels by up 60% even when given on top of existing lipid lowering therapy[122]. RCTs showed that this additional LDL-C lowering was associated with additional CV outcome benefits in high-risk populations[123,124].

PCSK9 seems to play a role in the pathogenesis of NAFLD. Increased intrahepatic and circulating PCSK9 levels were associated with enhanced hepatic fatty acid and TG content along with lipid deposition in the muscle and adipose tissue[125]. Whether PCSK9 inhibition with the currently available mAbs, but also with the upcoming small interference RNA PCSK9 inhibitor (inclisiran) can beneficially alter the development and progression of NAFLD remains unknown. There are only 2 studies suggesting a promising role[126,127].

An observational study included 26 patients with Familial Hypercholesterolemia (FH) and NAFLD maintaining increased LDL-C levels despite statins + ezetimibe treatment. These patients were divided into 2 groups based on the TG/HDL median value as a surrogate of atherogenic dyslipidemia. All patients received PCSK9 inhibitors for 6 mo. PCSK9 inhibitors significantly improved hepatic steatosis biomarkers, including triglyceride-glucose index (TyG) and HIS (by -7.5% and -8.4% respectively), particularly in individuals with low TG/HDL. This finding suggests a possible role of PCSK9 inhibitors in the management of NAFLD especially in patients who lack features of atherogenic dyslipidemia[126]. The role of PCSK9 inhibitors in NAFLD was also assessed in a retrospective chart review-based study including 29 NAFLD patients. PCSK9 inhibitors were associated with full resolution of NAFLD

radiologic features in 8 of 11 individuals with liver steatosis. Moreover, transaminase levels improved in all participants[127].

CONCLUSION

Atherogenic dyslipidemia contributes significantly to an increased CV risk in NAFLD. It also plays a key role in NAFLD development and progression. Therefore, its aggressive management through effective lipid lowering drugs is crucial. This was highlighted by the results of a *post hoc* analysis of the GREACE study suggesting that statin-related CV benefits are more prominent in high-risk NAFLD *vs* non-NAFLD patients. However, the most commonly used lipid-lowering drug classes have been associated with adverse elevations of the liver enzymes (*e.g.*, statins, fibrates). Hence, clinicians cautiously use them in NAFLD. For this reason, it is important to clarify the safety and efficacy of lipid-lowering drugs in this clinical context.

The amount of evidence in this respect varies amongst different drug classes with more data being available for statins, ezetimibe and fibrates. There is considerable evidence from pre-clinical mechanistic studies suggesting that the lipid-lowering and pleiotropic effects of statins are beneficial for NAFLD/NASH. Besides, these effects may be protective against cirrhosis/HCC development in NAFLD. Also, promising were the results from observational studies about statin effects on liver outcomes. However, due to their retrospective character these results should be viewed with caution.

Smaller prospective studies showed beneficial effects of statins on NAFLD histology, clinical (steatosis and fibrosis) surrogate scores and biochemical biomarkers, especially with atorvastatin and rosuvastatin. Data are more limited and somehow conflicting with other statins. Besides, statin use amongst NAFLD/NASH patients appears to be overall safe. In fact, liver enzyme elevations with statins are limited to a small proportion of NAFLD patients and are not accompanied by any evidence of hepatic dysfunction.

Ezetimibe is associated with more infrequent liver enzyme elevations than statins, hence clinicians comfortably prescribe it in the NAFLD/NASH clinical setting. There is considerable pre-clinical evidence suggesting that ezetimibe is beneficial on hepatic steatosis mainly through its cholesterol lowering effects and its associated reduction of *de novo* hepatic lipogenesis. Besides, ezetimibe may facilitate liver delipidation by inhibiting MTP degradation and by enhancing the expression of cholesterol efflux transporters. Experimental data also suggest significant anti-inflammatory and antioxidant effects of ezetimibe on the liver tissue through various molecular pathways. Ezetimibe may be protective against HCC development in NAFLD too.

Clinical evidence suggesting benefits of ezetimibe on hepatic outcomes in NAFLD/NASH is limited to small prospective studies, few of which were randomized placebo-controlled. Most studies showed that ezetimibe monotherapy for few mo was associated with improvements of the liver enzyme activities as well as of histologically-assessed hepatic steatosis and relevant surrogate imaging endpoints. However, evidence suggesting benefits on hepatic inflammation and fibrosis is less robust. Given the milder lipid-lowering effects of ezetimibe and its less potent pleiotropy than this of statins it is uncertain whether more longitudinal data would better establish benefits on hepatic inflammation and fibrosis too.

Fibrates exert significant lipid modifying effects against atherogenic dyslipidemia which is very prevalent in NAFLD. Their effects are exhibited mainly through activation of PPARα, which play a key role in various metabolic pathways, especially in favorably modulating key lipid and glucose metabolic pathways involved in NAFLD pathogenesis. In this context, pre-clinical studies suggested that fibrates reduce hepatic steatosis *via* increasing hepatic insulin sensitivity and by accelerating the catabolism of the TG-rich lipoproteins and fatty acid oxidation. There is also promising preclinical evidence suggesting significant liver anti-inflammatory and antioxidant effects of fibrates.

Despite this promising mechanistic potential fibrate effects on liver steatosis, necroinflammation and fibrosis were poor in clinical studies. Liver enzyme improvement was the only established improved NAFLD surrogate associated with fibrate use, though this evidence should be cautiously interpreted in view of the variability of this biomarker. Fenofibrate combination with pentoxifylline is promising but its benefits require further confirmation by larger scale longitudinal studies with histological endpoints. It should be acknowledged though that the lack of fibrate efficacy in clinical studies as compared with the experimental ones may be explained

by inter-species variation in PPARα expression and responsiveness to drug-induced activation. Also, relatively reduced human equivalent fibrate doses were used in clinical studies compared with the experimental rodent ones.

Omega-3 fatty acids can beneficially modulate lipid abnormalities encountered in NAFLD. Also, low hepatic ω-3 fatty acid levels have been associated with the development of hepatic steatosis. There have been multiple studies to suggest that ω-3 fatty acid supplementation is associated with reduced hepatic steatosis, though these are characterised by significant heterogeneity in design, study populations, type of intervention and study end points. No robust evidence exists to suggest that ω-3 fatty acid reduce hepatic inflammation or fibrosis in NAFLD.

Bile acid sequestrants have not shown any benefits against NAFLD. Instead, deleterious effects of colesevelam on hepatic steatosis and inflammation were shown in one study. Cholestyramine is currently being evaluated alone or in combination with an ileal bile acid transporter inhibitor under development in NAFLD participants of a Phase 2 RCT. Both circulating and hepatic PCSK9 seems to play a pathogenetic role in hepatic steatosis and may represent an attractive therapeutic target in NAFLD. The currently available PCKS9 inhibitor mAbs have shown promising effects only in small observational studies, particularly among patients without atherogenic dyslipidemia. However, this benefit should be established by large scale longitudinal prospective clinical trials.

Limitations of the studies discussed in this review include their relatively small size and short follow up period. For example, benefits of certain drug classes could arise with their long-term continuation. Likewise, marginal benefits could be missed due to small sample sizes of the studies. NAFLD/NASH development has long natural history and any potential reversal/regression may require long-term treatment too. Designing large-scale liver outcome studies with liver biopsy, which remains the gold-standard method for assessment of hepatic steatosis, necroinflammation and fibrosis is also challenging. Furthermore, the heterogeneity of other liver endpoints assessed in most studies hampers the pooling of data that could help reach safer conclusions. Most studies have assessed the effects of lipid lowering agents on liver enzyme activities, a biomarker which has poor correlation with disease activity and broad variability. Importantly, the predictive value of liver enzyme activity lowering on histological endpoints of NAFLD/NASH *via* certain interventions has not been validated. Identifying well-validated and easy-to-use disease surrogates remains an ongoing challenge for the assessment of various therapeutic interventions, including lipid-lowering drugs, in NAFLD/NASH.

REFERENCES

1 **Younossi ZM**, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73-84 [PMID: 26707365 DOI: 10.1002/hep.28431]

2 **Vernon G**, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; **34**: 274-285 [PMID: 21623852 DOI: 10.1111/j.1365-2036.2011.04724.x]

3 **Rinella ME**. Nonalcoholic fatty liver disease: a systematic review. *JAMA* 2015; **313**: 2263-2273 [PMID: 26057287 DOI: 10.1001/jama.2015.5370]

4 **Neuschwander-Tetri BA**. Non-alcoholic fatty liver disease. *BMC Med* 2017; **15**: 45 [PMID: 28241825 DOI: 10.1186/s12916-017-0806-8]

5 **Wong RJ**, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, Ahmed A. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology* 2015; **148**: 547-555 [PMID: 25461851 DOI: 10.1053/j.gastro.2014.11.039]

6 **Goh GB**, McCullough AJ. Natural History of Nonalcoholic Fatty Liver Disease. *Dig Dis Sci* 2016; **61**: 1226-1233 [PMID: 27003142 DOI: 10.1007/s10620-016-4095-4]

7 **Dounis E**, Giamarellou H, Peppas T, Sfikakis P. Skull, patella and thigh cryptococcosis after a crashing injury of the temporal bone. *J Chemother* 1991; **3**: 130-133 [PMID: 1875233 DOI: 10.1080/1120009x.1991.11739079]

8 **Verma S**, Jensen D, Hart J, Mohanty SR. Predictive value of ALT levels for non-alcoholic steatohepatitis (NASH) and advanced fibrosis in non-alcoholic fatty liver disease (NAFLD). *Liver Int* 2013; **33**: 1398-1405 [PMID: 23763360 DOI: 10.1111/Liv.12226]

9 **Castera L**. Noninvasive Evaluation of Nonalcoholic Fatty Liver Disease. *Semin Liver Dis* 2015; **35**: 291-303 [PMID: 26378645 DOI: 10.1055/s-0035-1562948]

10 **Nalbantoglu IL**, Brunt EM. Role of liver biopsy in nonalcoholic fatty liver disease. *World J Gastroenterol* 2014; **20**: 9026-9037 [PMID: 25083076 DOI: 10.3748/wjg.v20.i27.9026]

11 **Sinn DH**, Kang D, Chang Y, Ryu S, Gu S, Kim H, Seong D, Cho SJ, Yi BK, Park HD, Paik SW, Song YB, Lazo M, Lima JA, Guallar E, Cho J, Gwak GY. Non-alcoholic fatty liver disease and progression of coronary artery calcium score: a retrospective cohort study. *Gut* 2017; **66**: 323-329 [PMID: 27599521 DOI: 10.1136/gutjnl-2016-311854]

12 **Kasper P**, Martin A, Lang S, Kütting F, Goeser T, Demir M, Steffen HM. NAFLD and cardiovascular diseases: a clinical review. *Clin Res Cardiol* 2021; **110**: 921-937 [PMID: 32696080 DOI: 10.1007/s00392-020-01709-7]

13 **Lonardo A**, Arab JP, Arrese M. Perspectives on Precision Medicine Approaches to NAFLD Diagnosis and Management. *Adv Ther* 2021; **38**: 2130-2158 [PMID: 33829368 DOI: 10.1007/s12325-021-01690-1]

14 **Vilar-Gomez E**, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, Friedman SL, Diago M, Romero-Gomez M. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. *Gastroenterology* 2015; **149**: 367-78.e5; quiz e14 [PMID: 25865049 DOI: 10.1053/j.gastro.2015.04.005]

15 **Zelber-Sagi S**, Godos J, Salomone F. Lifestyle changes for the treatment of nonalcoholic fatty liver disease: a review of observational studies and intervention trials. *Therap Adv Gastroenterol* 2016; **9**: 392-407 [PMID: 27134667 DOI: 10.1177/1756283X16638830]

16 **Orci LA**, Gariani K, Oldani G, Delaune V, Morel P, Toso C. Exercise-based Interventions for Nonalcoholic Fatty Liver Disease: A Meta-analysis and Meta-regression. *Clin Gastroenterol Hepatol* 2016; **14**: 1398-1411 [PMID: 27155553 DOI: 10.1016/j.cgh.2016.04.036]

17 **Hannah WN Jr**, Harrison SA. Lifestyle and Dietary Interventions in the Management of Nonalcoholic Fatty Liver Disease. *Dig Dis Sci* 2016; **61**: 1365-1374 [PMID: 27052013 DOI: 10.1007/s10620-016-4153-y]

18 **Sanyal AJ**, Friedman SL, McCullough AJ, Dimick-Santos L; American Association for the Study of Liver Diseases; United States Food and Drug Administration. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations from an American Association for the Study of Liver Diseases-U.S. Food and Drug Administration Joint Workshop. *Hepatology* 2015; **61**: 1392-1405 [PMID: 25557690 DOI: 10.1002/hep.27678]

19 **Carr RM**, Oranu A, Khungar V. Nonalcoholic Fatty Liver Disease: Pathophysiology and Management. *Gastroenterol Clin North Am* 2016; **45**: 639-652 [PMID: 27837778 DOI: 10.1016/j.gtc.2016.07.003]

20 **Florentin M**, Liberopoulos EN, Wierzbicki AS, Mikhailidis DP. Multiple actions of high-density lipoprotein. *Curr Opin Cardiol* 2008; **23**: 370-378 [PMID: 18520722 DOI: 10.1097/HCO.0b013e3283043806]

21 **Annema W**, von Eckardstein A. Dysfunctional high-density lipoproteins in coronary heart disease: implications for diagnostics and therapy. *Transl Res* 2016; **173**: 30-57 [PMID: 26972566 DOI: 10.1016/j.trsl.2016.02.008]

22 **Ahsan F**, Oliveri F, Goud HK, Mehkari Z, Mohammed L, Javed M, Althwanay A, Rutkofsky IH. Pleiotropic Effects of Statins in the Light of Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis. *Cureus* 2020; **12**: e10446 [PMID: 33072455 DOI: 10.7759/cureus.10446]

23 **Chan J**, Sharkey FE, Kushwaha RS, VandeBerg JF, VandeBerg JL. Steatohepatitis in laboratory opossums exhibiting a high lipemic response to dietary cholesterol and fat. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G12-G19 [PMID: 22556142 DOI: 10.1152/ajpgi.00415.2011]

24 **Park HS**, Jang JE, Ko MS, Woo SH, Kim BJ, Kim HS, Park HS, Park IS, Koh EH, Lee KU. Statins Increase Mitochondrial and Peroxisomal Fatty Acid Oxidation in the Liver and Prevent Non-Alcoholic Steatohepatitis in Mice. *Diabetes Metab J* 2016; **40**: 376-385 [PMID: 27098507 DOI: 10.4093/dmj.2016.40.5.376]

25 **Samy W**, Hassanian MA. Paraoxonase-1 activity, malondialdehyde and glutathione peroxidase in non-alcoholic fatty liver disease and the effect of atorvastatin. *Arab J Gastroenterol* 2011; **12**: 80-85 [PMID: 21684478 DOI: 10.1016/j.ajg.2011.04.008]

26 **Ding YH**, Ma Y, Qian LY, Xu Q, Wang LH, Huang DS, Zou H. Linking atrial fibrillation with non-alcoholic fatty liver disease: potential common therapeutic targets. *Oncotarget* 2017; **8**: 60673-60683 [PMID: 28948002 DOI: 10.18632/oncotarget.19522]

27 **Ioannou GN**, Van Rooyen DM, Savard C, Haigh WG, Yeh MM, Teoh NC, Farrell GC. Cholesterol-lowering drugs cause dissolution of cholesterol crystals and disperse Kupffer cell crown-like structures during resolution of NASH. *J Lipid Res* 2015; **56**: 277-285 [PMID: 25520429 DOI: 10.1194/jlr.M053785]

28 **Schierwagen R**, Maybüchen L, Hittatiya K, Klein S, Uschner FE, Braga TT, Franklin BS, Nickenig G, Strassburg CP, Plat J, Sauerbruch T, Latz E, Lütjohann D, Zimmer S, Trebicka J. Statins improve NASH *via* inhibition of RhoA and Ras. *Am J Physiol Gastrointest Liver Physiol* 2016; **311**: G724-G733 [PMID: 27634010 DOI: 10.1152/ajpgi.00063.2016]

29 **Yokohama K**, Fukunishi S, Ii M, Nakamura K, Ohama H, Tsuchimoto Y, Asai A, Tsuda Y, Higuchi K. Rosuvastatin as a potential preventive drug for the development of hepatocellular carcinoma associated with non-alcoholic fatty liver disease in mice. *Int J Mol Med* 2016; **38**: 1499-1506 [PMID: 28025996 DOI: 10.3892/ijmm.2016.2766]

30 **Milaciu MV**, Vesa ȘC, Bocșan IC, Ciumărnean L, Sâmpelean D, Negrean V, Pop RM, Matei DM, Pașca S, Răchișan AL, Buzoianu AD, Acalovschi M. Paraoxonase-1 Serum Concentration and *PON1* Gene Polymorphisms: Relationship with Non-Alcoholic Fatty Liver Disease. *J Clin Med* 2019; **8** [PMID: 31847187 DOI: 10.3390/jcm8122200]

31 **Chong LW**, Hsu YC, Lee TF, Lin Y, Chiu YT, Yang KC, Wu JC, Huang YT. Fluvastatin attenuates hepatic steatosis-induced fibrogenesis in rats through inhibiting paracrine effect of hepatocyte on hepatic stellate cells. *BMC Gastroenterol* 2015; **15**: 22 [PMID: 25886887 DOI: 10.1186/s12876-015-0248-8]

32 **Wang W**, Zhao C, Zhou J, Zhen Z, Wang Y, Shen C. Simvastatin ameliorates liver fibrosis *via* mediating nitric oxide synthase in rats with non-alcoholic steatohepatitis-related liver fibrosis. *PLoS One* 2013; **8**: e76538 [PMID: 24098525]

33 **Bravo M**, Raurell I, Hide D, Fernández-Iglesias A, Gil M, Barberá A, Salcedo MT, Augustin S, Genescà J, Martell M. Restoration of liver sinusoidal cell phenotypes by statins improves portal hypertension and histology in rats with NASH. *Sci Rep* 2019; **9**: 20183 [PMID: 31882668 DOI: 10.1038/s41598-019-56366-2]

34 **Athyros VG**, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, Pagourelias ED, Theocharidou E, Karagiannis A, Mikhailidis DP; GREACE Study Collaborative Group. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *Lancet* 2010; **376**: 1916-1922 [PMID: 21109302 DOI: 10.1016/S0140-6736(10)61272-X]

35 **Hajifathalian K**, Tafesh Z, Rosenblatt R, Kumar S, Homan EA, Sharaiha RZ, Cohen DE, Brown RS Jr, Fortune BE. Effect of Statin Use on Cancer-related Mortality in Nonalcoholic Fatty Liver Disease: A Prospective United States Cohort Study. *J Clin Gastroenterol* 2021 [PMID: 33606428 DOI: 10.1097/MCG.0000000000001503]

36 **Calderon RM**, Cubeddu LX, Goldberg RB, Schiff ER. Statins in the treatment of dyslipidemia in the presence of elevated liver aminotransferase levels: a therapeutic dilemma. *Mayo Clin Proc* 2010; **85**: 349-356 [PMID: 20360293 DOI: 10.4065/mcp.2009.0365]

37 **Onofrei MD**, Butler KL, Fuke DC, Miller HB. Safety of statin therapy in patients with preexisting liver disease. *Pharmacotherapy* 2008; **28**: 522-529 [PMID: 18363535 DOI: 10.1592/phco.28.4.522]

38 **Bader T**. Liver tests are irrelevant when prescribing statins. *Lancet* 2010; **376**: 1882-1883 [PMID: 21109303 DOI: 10.1016/S0140-6736(10)62142-3]

39 **Lee JI**, Lee HW, Lee KS, Lee HS, Park JY. Effects of Statin Use on the Development and Progression of Nonalcoholic Fatty Liver Disease: A Nationwide Nested Case-Control Study. *Am J Gastroenterol* 2021; **116**: 116-124 [PMID: 33027082 DOI: 10.14309/ajg.0000000000000845]

40 **Dongiovanni P**, Petta S, Mannisto V, Mancina RM, Pipitone R, Karja V, Maggioni M, Kakela P, Wiklund O, Mozzi E, Grimaudo S, Kaminska D, Rametta R, Craxi A, Fargion S, Nobili V, Romeo S, Pihlajamaki J, Valenti L. Statin use and non-alcoholic steatohepatitis in at risk individuals. *J Hepatol* 2015; **63**: 705-712 [PMID: 25980762 DOI: 10.1016/j.jhep.2015.05.006]

41 **Sfikas G**, Psallas M, Koumaras C, Imprialos K, Perdikakis E, Doumas M, Giouleme O, Karagiannis A, Athyros VG. Prevalence, diagnosis and treatment with 3 different statins of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis in military personnel. Do genetics play a role? *Curr Vasc Pharmacol* 2020 [PMID: 33059580 DOI: 10.2174/1570161118666201015152921]

42 **German MN**, Lutz MK, Pickhardt PJ, Bruce RJ, Said A. Statin Use is Protective Against Hepatocellular Carcinoma in Patients With Nonalcoholic Fatty Liver Disease: A Case-control Study. *J Clin Gastroenterol* 2020; **54**: 733-740 [PMID: 31567625 DOI: 10.1097/MCG.0000000000001260]

43 **Lee TY**, Wu JC, Yu SH, Lin JT, Wu MS, Wu CY. The occurrence of hepatocellular carcinoma in different risk stratifications of clinically noncirrhotic nonalcoholic fatty liver disease. *Int J Cancer* 2017; **141**: 1307-1314 [PMID: 28509327 DOI: 10.1002/ijc.30784]

44 **Han KH**, Rha SW, Kang HJ, Bae JW, Choi BJ, Choi SY, Gwon HC, Bae JH, Hong BK, Choi DH, Han KR. Evaluation of short-term safety and efficacy of HMG-CoA reductase inhibitors in hypercholesterolemic patients with elevated serum alanine transaminase concentrations: PITCH study (PITavastatin *vs* atorvastatin to evaluate the effect on patients with hypercholesterolemia and mild to moderate hepatic damage). *J Clin Lipidol* 2012; **6**: 340-351 [PMID: 22836071 DOI: 10.1016/j.jacl.2012.01.009]

45 **Gómez-Domínguez E**, Gisbert JP, Moreno-Monteagudo JA, García-Buey L, Moreno-Otero R. A pilot study of atorvastatin treatment in dyslipemid, non-alcoholic fatty liver patients. *Aliment Pharmacol Ther* 2006; **23**: 1643-1647 [PMID: 16696815 DOI: 10.1111/j.1365-2036.2006.02926.x]

46 **Foster T**, Budoff MJ, Saab S, Ahmadi N, Gordon C, Guerci AD. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. *Am J Gastroenterol* 2011; **106**: 71-77 [PMID: 20842109 DOI: 10.1038/ajg.2010.299]

47 **Athyros VG**, Mikhailidis DP, Didangelos TP, Giouleme OI, Liberopoulos EN, Karagiannis A, Kakafika AI, Tziomalos K, Burroughs AK, Elisaf MS. Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study. *Curr Med Res Opin* 2006; **22**: 873-883 [PMID: 16709309 DOI: 10.1185/030079906X104696]

48 **Pockros PJ**, Fuchs M, Freilich B, Schiff E, Kohli A, Lawitz EJ, Hellstern PA, Owens-Grillo J, Van Biene C, Shringarpure R, MacConell L, Shapiro D, Cohen DE. CONTROL: A randomized phase 2 study of obeticholic acid and atorvastatin on lipoproteins in nonalcoholic steatohepatitis patients. *Liver Int* 2019; **39**: 2082-2093 [PMID: 31402538 DOI: 10.1111/Liv.14209]

49 **Kargiotis K**, Katsiki N, Athyros VG, Giouleme O, Patsiaoura K, Katsiki E, Mikhailidis DP, Karagiannis A. Effect of rosuvastatin on non-alcoholic steatohepatitis in patients with metabolic syndrome and hypercholesterolaemia: a preliminary report. *Curr Vasc Pharmacol* 2014; **12**: 505-

511 [PMID: 24805248 DOI: 10.2174/1570161113119990009]
50 **Antonopoulos S**, Mikros S, Mylonopoulou M, Kokkoris S, Giannoulis G. Rosuvastatin as a novel treatment of non-alcoholic fatty liver disease in hyperlipidemic patients. *Atherosclerosis* 2006; **184**: 233-234 [PMID: 16168995 DOI: 10.1016/j.atherosclerosis.2005.08.021]
51 **Kargiotis K**, Athyros VG, Giouleme O, Katsiki N, Katsiki E, Anagnostis P, Boutari C, Doumas M, Karagiannis A, Mikhailidis DP. Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome. *World J Gastroenterol* 2015; **21**: 7860-7868 [PMID: 26167086 DOI: 10.3748/wjg.v21.i25.7860]
52 **Nakahara T**, Hyogo H, Kimura Y, Ishitobi T, Arihiro K, Aikata H, Takahashi S, Chayama K. Efficacy of rosuvastatin for the treatment of non-alcoholic steatohepatitis with dyslipidemia: An open-label, pilot study. *Hepatol Res* 2012; **42**: 1065-1072 [PMID: 22583925 DOI: 10.1111/j.1872-034X.2012.01034.x]
53 **El Kamari V**, Hileman CO, Gholam PM, Kulkarni M, Funderburg N, McComsey GA. Statin Therapy Does Not Reduce Liver Fat Scores in Patients Receiving Antiretroviral Therapy for HIV Infection. *Clin Gastroenterol Hepatol* 2019; **17**: 536-542.e1 [PMID: 29908359 DOI: 10.1016/j.cgh.2018.05.058]
54 **Abel T**, Fehér J, Dinya E, Eldin MG, Kovács A. Safety and efficacy of combined ezetimibe/simvastatin treatment and simvastatin monotherapy in patients with non-alcoholic fatty liver disease. *Med Sci Monit* 2009; **15**: MS6-M11 [PMID: 19946244]
55 **Nelson A**, Torres DM, Morgan AE, Fincke C, Harrison SA. A pilot study using simvastatin in the treatment of nonalcoholic steatohepatitis: A randomized placebo-controlled trial. *J Clin Gastroenterol* 2009; **43**: 990-994 [PMID: 19448566 DOI: 10.1097/MCG.0b013e31819c392e]
56 **Lewis JH**, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R; Pravastatin in Chronic Liver Disease Study Investigators. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. *Hepatology* 2007; **46**: 1453-1463 [PMID: 17668878 DOI: 10.1002/hep.21848]
57 **Rallidis LS**, Drakoulis CK, Parasi AS. Pravastatin in patients with nonalcoholic steatohepatitis: results of a pilot study. *Atherosclerosis* 2004; **174**: 193-196 [PMID: 15135271 DOI: 10.1016/j.atherosclerosis.2004.01.008]
58 **Filippatos TD**, Elisaf MS. Pitavastatin and carbohydrate metabolism: what is the evidence? *Expert Rev Clin Pharmacol* 2016; **9**: 955-960 [PMID: 26967972 DOI: 10.1586/17512433.2016.1165607]
59 **Kostapanos MS**, Liamis GL, Milionis HJ, Elisaf MS. Do statins beneficially or adversely affect glucose homeostasis? *Curr Vasc Pharmacol* 2010; **8**: 612-631 [PMID: 20507274 DOI: 10.2174/157016110792006879]
60 **Berkelhammer C**, Lerma EV. Statin treatment in patients with elevated liver enzymes: pitch to proceed. *J Clin Lipidol* 2012; **6**: 310-311 [PMID: 22836066 DOI: 10.1016/j.jacl.2012.05.001]
61 **Hyogo H**, Ikegami T, Tokushige K, Hashimoto E, Inui K, Matsuzaki Y, Tokumo H, Hino F, Tazuma S. Efficacy of pitavastatin for the treatment of non-alcoholic steatohepatitis with dyslipidemia: An open-label, pilot study. *Hepatol Res* 2011; **41**: 1057-1065 [PMID: 21951922 DOI: 10.1111/j.1872-034X.2011.00849.x]
62 **Braun LR**, Feldpausch MN, Czerwonka N, Weiss J, Branch K, Lee H, Martinez-Salazar EL, Torriani M, Sponseller CA, Grinspoon SK, Stanley TL. Effects of Pitavastatin on Insulin Sensitivity and Liver Fat: A Randomized Clinical Trial. *J Clin Endocrinol Metab* 2018; **103**: 4176-4186 [PMID: 30239757 DOI: 10.1210/jc.2018-01446]
63 **Mihaila RG**, Nedelcu L, Fratila O, Rezi EC, Domnariu C, Deac M. Effects of lovastatin and pentoxyphyllin in nonalcoholic steatohepatitis. *Hepatogastroenterology* 2009; **56**: 1117-1121 [PMID: 19760953]
64 **Trinh MN**, Brown MS, Seemann J, Goldstein JL, Lu F. Lysosomal cholesterol export reconstituted from fragments of Niemann-Pick C1. *Elife* 2018; **7** [PMID: 30047864 DOI: 10.7554/eLife.38564]
65 **Cannon CP**, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015; **372**: 2387-2397 [PMID: 26039521 DOI: 10.1056/NEJMoa1410489]
66 **Filippatos TD**, Elisaf MS. Are lower levels of LDL-cholesterol really better? *Hellenic J Cardiol* 2015; **56**: 7-9 [PMID: 25701966]
67 **Yamanashi Y**, Takada T, Suzuki H. Associations between Lifestyle-Related Diseases and Transporters Involved in Intestinal Absorption and Biliary Excretion of Cholesterol. *Biol Pharm Bull* 2018; **41**: 1-10 [PMID: 29311470 DOI: 10.1248/bpb.b17-00690]
68 **Toyoda Y**, Takada T, Yamanashi Y, Suzuki H. Pathophysiological importance of bile cholesterol reabsorption: hepatic NPC1L1-exacerbated steatosis and decreasing VLDL-TG secretion in mice fed a high-fat diet. *Lipids Health Dis* 2019; **18**: 234 [PMID: 31883528 DOI: 10.1186/s12944-019-1179-0]
69 **Yamagishi S**, Nakamura K, Matsui T, Sato T, Takeuchi M. Inhibition of intestinal cholesterol absorption by ezetimibe is a novel therapeutic target for fatty liver. *Med Hypotheses* 2006; **66**: 844-846 [PMID: 16188393 DOI: 10.1016/j.mehy.2005.08.022]
70 **Toyoda Y**, Takada T, Umezawa M, Tomura F, Yamanashi Y, Takeda K, Suzuki H. Identification of hepatic NPC1L1 as an NAFLD risk factor evidenced by ezetimibe-mediated steatosis prevention and

recovery. *FASEB Bioadv* 2019; **1**: 283-295 [PMID: 32123832 DOI: 10.1096/fba.2018-00044]

71 **Wang X**, Sugimoto K, Fujisawa T, Shindo N, Minato S, Kamada Y, Hamano M, Ohishi M, Ikegami H, Rakugi H. Novel effect of ezetimibe to inhibit the development of non-alcoholic fatty liver disease in Fatty Liver Shionogi mouse. *Hepatol Res* 2014; **44**: 102-113 [PMID: 23510093 DOI: 10.1111/hepr.12092]

72 **Tanaka Y**, Ikeda T, Ogawa H, Kamisako T. Ezetimibe Markedly Reduces Hepatic Triglycerides and Cholesterol in Rats Fed on Fish Oil by Increasing the Expression of Cholesterol Efflux Transporters. *J Pharmacol Exp Ther* 2020; **374**: 175-183 [PMID: 32366600 DOI: 10.1124/jpet.120.265660]

73 **Muraoka T**, Aoki K, Iwasaki T, Shinoda K, Nakamura A, Aburatani H, Mori S, Tokuyama K, Kubota N, Kadowaki T, Terauchi Y. Ezetimibe decreases SREBP-1c expression in liver and reverses hepatic insulin resistance in mice fed a high-fat diet. *Metabolism* 2011; **60**: 617-628 [PMID: 20673929 DOI: 10.1016/j.metabol.2010.06.008]

74 **Wang X**, Ren Q, Wu T, Guo Y, Liang Y, Liu S. Ezetimibe prevents the development of nonalcoholic fatty liver disease induced by highfat diet in C57BL/6J mice. *Mol Med Rep* 2014; **10**: 2917-2923 [PMID: 25310357 DOI: 10.3892/mmr.2014.2623]

75 **Chang E**, Kim L, Park SE, Rhee EJ, Lee WY, Oh KW, Park SW, Park CY. Ezetimibe improves hepatic steatosis in relation to autophagy in obese and diabetic rats. *World J Gastroenterol* 2015; **21**: 7754-7763 [PMID: 26167075 DOI: 10.3748/wjg.v21.i25.7754]

76 **Kim SH**, Kim G, Han DH, Lee M, Kim I, Kim B, Kim KH, Song YM, Yoo JE, Wang HJ, Bae SH, Lee YH, Lee BW, Kang ES, Cha BS, Lee MS. Ezetimibe ameliorates steatohepatitis *via* AMP activated protein kinase-TFEB-mediated activation of autophagy and NLRP3 inflammasome inhibition. *Autophagy* 2017; **13**: 1767-1781 [PMID: 28933629 DOI: 10.1080/15548627.2017.1356977]

77 **Fraunberger P**, Gröne E, Gröne HJ, Drexel H, Walli AK. Ezetimibe reduces cholesterol content and NF-kappaB activation in liver but not in intestinal tissue in guinea pigs. *J Inflamm (Lond)* 2017; **14**: 3 [PMID: 28167864 DOI: 10.1186/s12950-017-0150-y]

78 **Miura K**, Ohnishi H, Morimoto N, Minami S, Ishioka M, Watanabe S, Tsukui M, Takaoka Y, Nomoto H, Isoda N, Yamamoto H. Ezetimibe suppresses development of liver tumors by inhibiting angiogenesis in mice fed a high-fat diet. *Cancer Sci* 2019; **110**: 771-783 [PMID: 30520543 DOI: 10.1111/cas.13902]

79 **Shiwa T**, Kawanami Y, Yokoyama T, Moritani A, Hashimoto M, Gotoh T. The efficacy of ezetimibe on nonalcoholic fatty liver disease (NAFLD). *Nihon Shokakibyo Gakkai Zasshi* 2011; **108**: 1383-1392 [PMID: 21817841]

80 **Enjoji M**, Machida K, Kohjima M, Kato M, Kotoh K, Matsunaga K, Nakashima M, Nakamuta M. NPC1L1 inhibitor ezetimibe is a reliable therapeutic agent for non-obese patients with nonalcoholic fatty liver disease. *Lipids Health Dis* 2010; **9**: 29 [PMID: 20222991 DOI: 10.1186/1476-511X-9-29]

81 **Park H**, Shima T, Yamaguchi K, Mitsuyoshi H, Minami M, Yasui K, Itoh Y, Yoshikawa T, Fukui M, Hasegawa G, Nakamura N, Ohta M, Obayashi H, Okanoue T. Efficacy of long-term ezetimibe therapy in patients with nonalcoholic fatty liver disease. *J Gastroenterol* 2011; **46**: 101-107 [PMID: 20658156 DOI: 10.1007/s00535-010-0291-8]

82 **Loomba R**, Sirlin CB, Ang B, Bettencourt R, Jain R, Salotti J, Soaft L, Hooker J, Kono Y, Bhatt A, Hernandez L, Nguyen P, Noureddin M, Haufe W, Hooker C, Yin M, Ehman R, Lin GY, Valasek MA, Brenner DA, Richards L; San Diego Integrated NAFLD Research Consortium (SINC). Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART trial). *Hepatology* 2015; **61**: 1239-1250 [PMID: 25482832 DOI: 10.1002/hep.27647]

83 **Yoneda M**, Fujita K, Nozaki Y, Endo H, Takahashi H, Hosono K, Suzuki K, Mawatari H, Kirikoshi H, Inamori M, Saito S, Iwasaki T, Terauchi Y, Kubota K, Maeyama S, Nakajima A. Efficacy of ezetimibe for the treatment of non-alcoholic steatohepatitis: An open-label, pilot study. *Hepatol Res* 2010; **40**: 566-573 [PMID: 20412324 DOI: 10.1111/j.1872-034X.2010.00644.x]

84 **Takeshita Y**, Takamura T, Honda M, Kita Y, Zen Y, Kato K, Misu H, Ota T, Nakamura M, Yamada K, Sunagozaka H, Arai K, Yamashita T, Mizukoshi E, Kaneko S. The effects of ezetimibe on non-alcoholic fatty liver disease and glucose metabolism: a randomised controlled trial. *Diabetologia* 2014; **57**: 878-890 [PMID: 24407920 DOI: 10.1007/s00125-013-3149-9]

85 **Abel T**, Fehér J, Dinya E, Gamal Eldin M, Kovács A. [Efficacy and safety of ezetimibe/simvastatin combination therapy in patients with type 2 diabetes and nonalcoholic fatty liver disease]. *Orv Hetil* 2009; **150**: 989-993 [PMID: 19443308 DOI: 10.1556/OH.2009.28624]

86 **Simon TG**, Corey KE, Cannon CP, Blazing M, Park JG, O'Donoghue ML, Chung RT, Giugliano RP. The nonalcoholic fatty liver disease (NAFLD) fibrosis score, cardiovascular risk stratification and a strategy for secondary prevention with ezetimibe. *Int J Cardiol* 2018; **270**: 245-252 [PMID: 29903515 DOI: 10.1016/j.ijcard.2018.05.087]

87 **Nakade Y**, Murotani K, Inoue T, Kobayashi Y, Yamamoto T, Ishii N, Ohashi T, Ito K, Fukuzawa Y, Yoneda M. Ezetimibe for the treatment of non-alcoholic fatty liver disease: A meta-analysis. *Hepatol Res* 2017; **47**: 1417-1428 [PMID: 28257594 DOI: 10.1111/hepr.12887]

88 **Lee HY**, Jun DW, Kim HJ, Oh H, Saeed WK, Ahn H, Cheung RC, Nguyen MH. Ezetimibe decreased nonalcoholic fatty liver disease activity score but not hepatic steatosis. *Korean J Intern Med* 2019; **34**: 296-304 [PMID: 29551054 DOI: 10.3904/kjim.2017.194]

89 **Kim NH**, Kim SG. Fibrates Revisited: Potential Role in Cardiovascular Risk Reduction. *Diabetes Metab J* 2020; **44**: 213-221 [PMID: 32347023 DOI: 10.4093/dmj.2020.0001]

90 **Shiri-Sverdlov R**, Wouters K, van Gorp PJ, Gijbels MJ, Noel B, Buffat L, Staels B, Maeda N, van Bilsen M, Hofker MH. Early diet-induced non-alcoholic steatohepatitis in APOE2 knock-in mice and its prevention by fibrates. *J Hepatol* 2006; **44**: 732-741 [PMID: 16466828 DOI: 10.1016/j.jhep.2005.10.033]

91 **Zhang N**, Lu Y, Shen X, Bao Y, Cheng J, Chen L, Li B, Zhang Q. Fenofibrate treatment attenuated chronic endoplasmic reticulum stress in the liver of nonalcoholic fatty liver disease mice. *Pharmacology* 2015; **95**: 173-180 [PMID: 25896720 DOI: 10.1159/000380952]

92 **Nakano S**, Nagasawa T, Ijiro T, Inada Y, Tamura T, Maruyama K, Kuroda J, Yamazaki Y, Kusama H, Shibata N. Bezafibrate prevents hepatic stellate cell activation and fibrogenesis in a murine steatohepatitis model, and suppresses fibrogenic response induced by transforming growth factor-beta1 in a cultured stellate cell line. *Hepatol Res* 2008; **38**: 1026-1039 [PMID: 18513333 DOI: 10.1111/j.1872-034X.2008.00363.x]

93 **Montagner A**, Polizzi A, Fouché E, Ducheix S, Lippi Y, Lasserre F, Barquissau V, Régnier M, Lukowicz C, Benhamed F, Iroz A, Bertrand-Michel J, Al Saati T, Cano P, Mselli-Lakhal L, Mithieux G, Rajas F, Lagarrigue S, Pineau T, Loiseau N, Postic C, Langin D, Wahli W, Guillou H. Liver PPARα is crucial for whole-body fatty acid homeostasis and is protective against NAFLD. *Gut* 2016; **65**: 1202-1214 [PMID: 26838599 DOI: 10.1136/gutjnl-2015-310798]

94 **Honda Y**, Kessoku T, Ogawa Y, Tomeno W, Imajo K, Fujita K, Yoneda M, Takizawa T, Saito S, Nagashima Y, Nakajima A. Pemafibrate, a novel selective peroxisome proliferator-activated receptor alpha modulator, improves the pathogenesis in a rodent model of nonalcoholic steatohepatitis. *Sci Rep* 2017; **7**: 42477 [PMID: 28195199 DOI: 10.1038/srep42477]

95 **Yan F**, Wang Q, Xu C, Cao M, Zhou X, Wang T, Yu C, Jing F, Chen W, Gao L, Zhao J. Peroxisome proliferator-activated receptor α activation induces hepatic steatosis, suggesting an adverse effect. *PLoS One* 2014; **9**: e99245 [PMID: 24926685 DOI: 10.1371/journal.pone.0099245]

96 **Hong XZ**, Li LD, Wu LM. Effects of fenofibrate and xuezhikang on high-fat diet-induced non-alcoholic fatty liver disease. *Clin Exp Pharmacol Physiol* 2007; **34**: 27-35 [PMID: 17201732 DOI: 10.1111/j.1440-1681.2007.04547.x]

97 **Kostapanos MS**, Kei A, Elisaf MS. Current role of fenofibrate in the prevention and management of non-alcoholic fatty liver disease. *World J Hepatol* 2013; **5**: 470-478 [PMID: 24073298 DOI: 10.4254/wjh.v5.i9.470]

98 **Staels B**, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation* 1998; **98**: 2088-2093 [PMID: 9808609 DOI: 10.1161/01.cir.98.19.2088]

99 **Tanaka N**, Aoyama T, Kimura S, Gonzalez FJ. Targeting nuclear receptors for the treatment of fatty liver disease. *Pharmacol Ther* 2017; **179**: 142-157 [PMID: 28546081 DOI: 10.1016/j.pharmthera.2017.05.011]

100 **Tanaka N**, Kimura T, Fujimori N, Nagaya T, Komatsu M, Tanaka E. Current status, problems, and perspectives of non-alcoholic fatty liver disease research. *World J Gastroenterol* 2019; **25**: 163-177 [PMID: 30670907 DOI: 10.3748/wjg.v25.i2.163]

101 **Rakhshandehroo M**, Hooiveld G, Müller M, Kersten S. Comparative analysis of gene regulation by the transcription factor PPARalpha between mouse and human. *PLoS One* 2009; **4**: e6796 [PMID: 19710929 DOI: 10.1371/journal.pone.0006796]

102 **Nakajima T**, Tanaka N, Kanbe H, Hara A, Kamijo Y, Zhang X, Gonzalez FJ, Aoyama T. Bezafibrate at clinically relevant doses decreases serum/Liver triglycerides *via* down-regulation of sterol regulatory element-binding protein-1c in mice: a novel peroxisome proliferator-activated receptor alpha-independent mechanism. *Mol Pharmacol* 2009; **75**: 782-792 [PMID: 19124612 DOI: 10.1124/mol.108.052928]

103 **Fernández-Miranda C**, Pérez-Carreras M, Colina F, López-Alonso G, Vargas C, Solís-Herruzo JA. A pilot trial of fenofibrate for the treatment of non-alcoholic fatty liver disease. *Dig Liver Dis* 2008; **40**: 200-205 [PMID: 18261709 DOI: 10.1016/j.dld.2007.10.002]

104 **El-Haggar SM**, Mostafa TM. Comparative clinical study between the effect of fenofibrate alone and its combination with pentoxifylline on biochemical parameters and liver stiffness in patients with non-alcoholic fatty liver disease. *Hepatol Int* 2015; **9**: 471-479 [PMID: 25956613 DOI: 10.1007/s12072-015-9633-1]

105 **Fabbrini E**, Mohammed BS, Korenblat KM, Magkos F, McCrea J, Patterson BW, Klein S. Effect of fenofibrate and niacin on intrahepatic triglyceride content, very low-density lipoprotein kinetics, and insulin action in obese subjects with nonalcoholic fatty liver disease. *J Clin Endocrinol Metab* 2010; **95**: 2727-2735 [PMID: 20371660 DOI: 10.1210/jc.2009-2622]

106 **Oscarsson J**, Önnerhag K, Risérus U, Sundén M, Johansson L, Jansson PA, Moris L, Nilsson PM, Eriksson JW, Lind L. Effects of free omega-3 carboxylic acids and fenofibrate on liver fat content in patients with hypertriglyceridemia and non-alcoholic fatty liver disease: A double-blind, randomized, placebo-controlled study. *J Clin Lipidol* 2018; **12**: 1390-1403.e4 [PMID: 30197273 DOI: 10.1016/j.jacl.2018.08.003]

107 **Yaghoubi M**, Jafari S, Sajedi B, Gohari S, Akbarieh S, Heydari AH, Jameshoorani M. Comparison of fenofibrate and pioglitazone effects on patients with nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol* 2017; **29**: 1385-1388 [PMID: 29023319 DOI: 10.1097/MEG.0000000000000981]

108 **Shahidi F**, Ambigaipalan P. Omega-3 Polyunsaturated Fatty Acids and Their Health Benefits. *Annu Rev Food Sci Technol* 2018; **9**: 345-381 [PMID: 29350557 DOI:

10.1146/annurev-food-111317-095850]
109 **Rizos EC**, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA* 2012; **308**: 1024-1033 [PMID: 22968891 DOI: 10.1001/2012.jama.11374]
110 **Bhatt DL**, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM; REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med* 2019; **380**: 11-22 [PMID: 30415628 DOI: 10.1056/NEJMoa1812792]
111 **Spadaro L**, Magliocco O, Spampinato D, Piro S, Oliveri C, Alagona C, Papa G, Rabuazzo AM, Purrello F. Effects of n-3 polyunsaturated fatty acids in subjects with nonalcoholic fatty liver disease. *Dig Liver Dis* 2008; **40**: 194-199 [PMID: 18054848 DOI: 10.1016/j.dld.2007.10.003]
112 **St-Jules DE**, Watters CA, Brunt EM, Wilkens LR, Novotny R, Belt P, Lavine JE; Nonalcoholic Steatohepatitis Clinical Research Network. Estimation of fish and ω-3 fatty acid intake in pediatric nonalcoholic fatty liver disease. *J Pediatr Gastroenterol Nutr* 2013; **57**: 627-633 [PMID: 24177784 DOI: 10.1097/MPG.0b013e3182a1df77]
113 **Lee CH**, Fu Y, Yang SJ, Chi CC. Effects of Omega-3 Polyunsaturated Fatty Acid Supplementation on Non-Alcoholic Fatty Liver: A Systematic Review and Meta-Analysis. *Nutrients* 2020; **12** [PMID: 32932796 DOI: 10.3390/nu12092769]
114 **Kobyliak N**, Abenavoli L, Falalyeyeva T, Mykhalchyshyn G, Boccuto L, Kononenko L, Kyriienko D, Komisarenko I, Dynnyk O. Beneficial effects of probiotic combination with omega-3 fatty acids in NAFLD: a randomized clinical study. *Minerva Med* 2018; **109**: 418-428 [PMID: 30221912 DOI: 10.23736/S0026-4806.18.05845-7]
115 **Spahis S**, Alvarez F, Ahmed N, Dubois J, Jalbout R, Paganelli M, Grzywacz K, Delvin E, Peretti N, Levy E. Non-alcoholic fatty liver disease severity and metabolic complications in obese children: impact of omega-3 fatty acids. *J Nutr Biochem* 2018; **58**: 28-36 [PMID: 29864682 DOI: 10.1016/j.jnutbio.2018.03.025]
116 **Capanni M**, Calella F, Biagini MR, Genise S, Raimondi L, Bedogni G, Svegliati-Baroni G, Sofi F, Milani S, Abbate R, Surrenti C, Casini A. Prolonged n-3 polyunsaturated fatty acid supplementation ameliorates hepatic steatosis in patients with non-alcoholic fatty liver disease: a pilot study. *Aliment Pharmacol Ther* 2006; **23**: 1143-1151 [PMID: 16611275 DOI: 10.1111/j.1365-2036.2006.02885.x]
117 **Tanaka N**, Sano K, Horiuchi A, Tanaka E, Kiyosawa K, Aoyama T. Highly purified eicosapentaenoic acid treatment improves nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2008; **42**: 413-418 [PMID: 18277895 DOI: 10.1097/MCG.0b013e31815591aa]
118 **Tanaka N**, Zhang X, Sugiyama E, Kono H, Horiuchi A, Nakajima T, Kanbe H, Tanaka E, Gonzalez FJ, Aoyama T. Eicosapentaenoic acid improves hepatic steatosis independent of PPARα activation through inhibition of SREBP-1 maturation in mice. *Biochem Pharmacol* 2010; **80**: 1601-1612 [PMID: 20691165 DOI: 10.1016/j.bcp.2010.07.031]
119 **Lent-Schochet D**, Jialal I. Antilipemic Agent Bile Acid Sequestrants. 2020 Sep 21. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2021 [PMID: 31751096]
120 **Le TA**, Chen J, Changchien C, Peterson MR, Kono Y, Patton H, Cohen BL, Brenner D, Sirlin C, Loomba R; San Diego Integrated NAFLD Research Consortium (SINC). Effect of colesevelam on liver fat quantified by magnetic resonance in nonalcoholic steatohepatitis: a randomized controlled trial. *Hepatology* 2012; **56**: 922-932 [PMID: 22431131 DOI: 10.1002/hep.25731]
121 **Kessoku T**, Kobayashi T, Ozaki A, Iwaki M, Honda Y, Ogawa Y, Imajo K, Saigusa Y, Yamamoto K, Yamanaka T, Usuda H, Wada K, Yoneda M, Saito S, Nakajima A. Rationale and design of a randomised, double-blind, placebo-controlled, parallel-group, investigator-initiated phase 2a study to investigate the efficacy and safety of elobixibat in combination with cholestyramine for non-alcoholic fatty liver disease. *BMJ Open* 2020; **10**: e037961 [PMID: 32907904 DOI: 10.1136/bmjopen-2020-037961]
122 **Sabatine MS**. PCSK9 inhibitors: clinical evidence and implementation. *Nat Rev Cardiol* 2019; **16**: 155-165 [PMID: 30420622 DOI: 10.1038/s41569-018-0107-8]
123 **Sabatine MS**, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017; **376**: 1713-1722 [PMID: 28304224 DOI: 10.1056/NEJMoa1615664]
124 **Schwartz GG**, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018; **379**: 2097-2107 [PMID: 30403574 DOI: 10.1056/NEJMoa1801174]
125 **Theocharidou E**, Papademetriou M, Reklou A, Sachinidis A, Boutari C, Giouleme O. The Role of PCSK9 in the Pathogenesis of Non-alcoholic Fatty Liver Disease and the Effect of PCSK9 Inhibitors. *Curr Pharm Des* 2018; **24**: 3654-3657 [PMID: 30317984 DOI: 10.2174/1381612824666181010123127]
126 **Scicali R**, Di Pino A, Urbano F, Ferrara V, Marchisello S, Di Mauro S, Scamporrino A, Filippello A, Rabuazzo AM, Purrello F, Piro S. Analysis of steatosis biomarkers and inflammatory profile after adding on PCSK9 inhibitor treatment in familial hypercholesterolemia subjects with nonalcoholic fatty liver disease: A single lipid center real-world experience. *Nutr Metab Cardiovasc Dis* 2021;

31: 869-879 [PMID: 33549441 DOI: 10.1016/j.numecd.2020.11.009]

127 **Shafiq M**, Walmann T, Nutalapati V, Gibson C, Zafar Y. Effects of proprotein convertase subtilisin/kexin type-9 inhibitors on fatty liver. *World J Hepatol* 2020; **12**: 1258-1266 [PMID: 33442452 DOI: 10.4254/wjh.v12.i12.1258]

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