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Review Article

The efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease

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ABSTRACT

Non-alcoholic fatty liver disease is an emerging liver disease in Western countries and the most frequent cause of incidental elevation of serum liver enzymes.

Dyslipidaemia is frequently observed in patients with non-alcoholic fatty liver disease, and treatment of dyslipidaemia plays a critical role in the overall management of these patients. Moreover, coronary artery disease remains the most common cause of death. Statins are effective lipid-lowering agents, associated with a lowering the risk of cardiovascular events in several interventional randomized clinical trials.

However, statins are often underused in patients with non-alcoholic fatty liver disease and many physicians are concerned about the prescription of statins to patients with unexplained persistent elevation of liver enzymes or active liver disease.

Based on currently available data, statin therapy, at low-to-moderate doses, seems to be safe and has low liver toxicity. Treatment of dyslipidaemia in patients with non-alcoholic fatty liver disease is recommended and may also improve liver function tests. In these patients, the risks of not taking statins could outweigh the risks of taking the drug. Conversely, the usefulness of statins for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis is still a matter of debate and randomized clinical trials of adequate size and duration are required.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common and emerging liver disease in Western countries [1]. Fatty liver includes a wide spectrum of histological alterations ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), characterized by inflammation and fibrosis [2]. Therefore, NAFLD has been traditionally interpreted as a condition which may progress to liver-related complications such as cirrhosis, liver cancer, and liver mortality [3].

NAFLD is currently the most common cause of incidental abnormal liver tests and elevated serum liver enzyme activities in the developed world. NAFLD is regarded as the liver manifestation of the metabolic syndrome, as it is strongly associated with obesity, insulin resistance, hypertension, and dyslipidaemia [4], conditions associated with high cardiovascular risk. Patients with NAFLD have shown an increased risk for cardiovascular diseases, and coronary artery disease is the most common cause of death [5–7].

Statins are among the most-prescribed class of medications and increasing numbers of patients have received statins in recent decades in all developed countries. Over the last few years it has become possible to obtain simvastatin 10 mg over-the-counter in the United Kingdom and a potential increase in self-medication is predicted in other countries as well. Recently, the 2013 guidelines by the American College of Cardiology (ACC) and the American Heart Association (AHA) for the treatment of cholesterol expanded the indications for statin therapy for the prevention of cardiovascular disease [8]. As a consequence, it has been estimated that this would increase the number of adults who would be eligible for statin therapy by 12.8 million, with the increase seen mostly among older adults without cardiovascular disease [8].

Large scale, well-conducted, placebo-controlled, randomized clinical trials have established conclusive evidence that the

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Table 1
Statins and non-alcoholic fatty liver disease: highlights and open issues.

- Non-alcoholic fatty liver disease is the most common cause of incidental abnormal elevation of serum liver enzyme activities
- Non-alcoholic fatty liver disease is associated with dyslipidaemia and high risk for cardiovascular events
- Statins reduce the risk of major coronary and vascular events
- Statins are hepatically cleared and can cause elevations in liver biochemistries
- There is a concern that patients with underlying liver disease may be at increased risk for hepatotoxicity

long-term use of statins results in important reductions in the risk of experiencing major coronary and vascular events in patients with a wide range of lipid levels, both in primary and secondary prevention [9,10].

In primary prevention [10], statin treatment, compared with placebo, was associated with lower rates of all-cause mortality (relative risk [RR], 0.86), combined fatal and nonfatal cardiovascular disease (RR, 0.75), coronary heart disease events (RR, 0.73), and fatal and non-fatal stroke (RR, 0.78). Statins were also associated with reduced coronary revascularization (percutaneous coronary intervention and coronary bypass surgery) rates as compared to controls (RR, 0.62) [10].

This effect seems also to be dose-related as reported in a meta-analysis by Patti et al. [9] in which high-dose statin treatment significantly reduced periprocedural and 1-month cardiovascular events in patients undergoing percutaneous coronary intervention compared to no treatment/low-dose statin treatment (44% risk reduction).

Nevertheless, despite his proven efficacy, statin administration is sometimes limited by the concern about related side-effects, mostly due to muscle and liver injury.

Statins can cause elevations in liver biochemistries and there is a concern that patients with underlying liver disease may be at increased risk for hepatotoxicity (Table 1) [11]. All statins are cleared by the liver and their clearance depends on hydrophobicity (Fig. 1). The more hydrophilic compounds, as pravastatin, exhibit more pronounced active renal excretion, while the lipophilic compounds are mainly excreted by the liver (Table 2).

It has been also suggested that long term statin treatment may worsen hepatic histology in patients with NAFLD. Many physicians are concerned about the prescription of statins to patients with unexplained persistent elevation of liver enzymes or active liver disease, although the concern for monitoring liver function in patients taking statins is not shared by all. In fact, in a recent survey including 937 primary care physicians, only 50% would prescribe statins if the baseline liver alanine aminotransferase (ALT) values were 1.5 times the upper limit of normal (ULN) [12].

However, the majority of people who take statins tolerate them well and very few experience adverse effects. Occasionally, statin use could cause a mild rise in serum liver enzymes, which may rarely become severe and require treatment discontinuation. The exact mechanism by which statins cause ALT elevations is uncertain and liver damage is extremely rare. In fact, at currently recommended doses, an elevation of liver enzymes >3 times ULN, occurs in <1% of treated patients [13,14]. Moreover, it has also been highlighted that monitoring for hepatotoxicity is ineffective in predicting serious liver toxicity.

In this article we will review the available data from the international literature to summarize current evidence on the safety of the use of statins in patients with NAFLD.

2. Long-term statin treatment and liver toxicity

2.1. Liver toxicity of statins

Relevant statin-related liver toxicity is a rare but important adverse event occurring during statin treatment [15]. In fact, while asymptomatic elevations in serum ALT are relatively common in patients treated with statins [15], severe hepatic toxicity has been rarely described.

Data from the literature estimate an incidence of acute liver failure in patients exposed to statins similar to that of the general population (1:130,000 vs. 1:114,000) (Table 3) [16]. In a cohort of 270 patients undergoing liver transplantation for acute liver failure, only 3 of the liver recipients had acute liver failure attributed to a statin (2 to cerivastatin and 1 to simvastatin) over the 12-year study period [17].

During statin treatment, an asymptomatic elevation in ALT should not be considered a sign of ongoing liver disease or injury. The term of "transaminitis" has been proposed to describe the situation of liver enzyme leakage without hepatotoxic consequences [18]. Thus, "transaminitis" may explain many of the serum ALT elevations seen in patients treated with statins. There is general agreement that ALT is more useful than aspartate aminotransferase (AST) to reveal possible hepatotoxicity, as AST levels may increase either in muscle and liver injury. Moreover, ALT elevations should be confirmed in subsequent determinations, as a single ALT elevation is more suggestive for "transaminitis" than for liver damage. A possible effect of serum lipid lowering on the structure of cellular membranes has been hypothesized, allowing for more leakage of cellular enzymes [18].

Nevertheless, previous case reports reported that statin use may induce an autoimmune hepatitis [19–22]. In particular, Alla et al. [19] described three cases of autoimmune hepatitis after treatment with fluvastatin in two cases and atorvastatin in the third. Two similar cases were previously described by Pelli et al. [21] in a 65-year-old woman with primary hypercholesterolaemia treated with atorvastatin, and by Wolters et al. after rosuvastatin administration [22].

Table 2
Main pharmacokinetic characteristics of statins.

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Optimal time of dosing	Any time of day	Bed-time	With meals morning and evening	Bed-time	Any time of day	Evening
Absorption, %	30	98	31	37	50	65–85
t_{max}, h	2–4	0.5–1.5	2–4	0.9–16	3–4	1.3–2.4
$t_{1/2}$	11–30	0.5–2.3	2.5–3	0.8–3	20	1.9–3
Bioavaibility, %	12	10–35	<5	18	20	<5
Solubility	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Protein binding, %	>98	>98	96–98.5	43–54	88	>95
Primary metabolic pathway	CYP3A4	CYP2C9	CYP3A4	Glucuronidation – CYP3A4	CYP2C9–CYP2C19	CYP3A4
Hepatic excretion, %	>70	>68	>70	46–66	90	78–97
Renal excretion, %	2	6	30	60	10	13

Modified from Gazzerro et al. [11].

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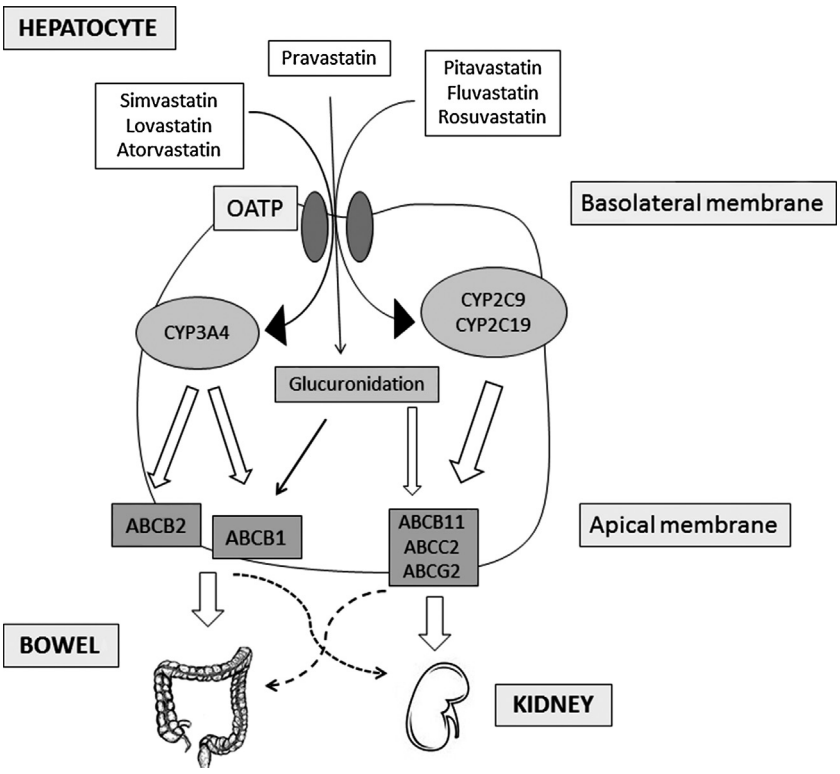

Fig. 1. Hepatic metabolism and clearance of statins. OATP: organic anion transporting polypeptides.

Atorvastatin use was also associated with hepatocellular and cholestatic injury [23–26].

Lovastatin administration, especially for higher dosage (80 mg per day), is associated with mild elevations in hepatic enzymes (ALT <3 times the upper limit of normal) in up to 5% of patients. A risk to develop centrilobular necrosis, cholestasis and fulminant liver failure (2/1,000,000 patients) has also been described [23].

For other statins, such as simvastatin, liver toxicity seems to be attributable to drug-drug interactions rather than to simvastatin itself [23].

2.2. Safety of statin treatment in clinical trials

Overwhelming data now exist that statins are safe in the primary and secondary prevention of coronary and vascular events in a wide variety of patients.

The Prospective Pravastatin Pooling (PPP) project [27] combined the experience from 3 major long-term, large, placebo-controlled trials of a single dose of pravastatin – the West of Scotland Coronary Prevention Study (WOSCOPS) [28], the Cholesterol And Recurrent Events (CARE) study [29], and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study [30] – to evaluate potential safety issues. This prospective analysis indicated that during prolonged exposure, 40 mg of pravastatin was well tolerated, with no excess of non-cardiovascular serious adverse events, including liver function abnormalities [31].

A further meta-analysis of randomized, placebo-controlled trials of statins used for the treatment of hyperlipidaemia or for primary or secondary prevention of cardiovascular disease was performed on a total of 49,275 patients from 13 trials [32]. The results supported previous observations that pravastatin, lovastatin, and simvastatin, at low-to-moderate doses, are not associated with a significant risk of liver function test (LFT) abnormalities and that LFT monitoring, other than prior to starting therapy, is not warranted in patients taking a low-to-moderate dose (40 mg/day) [32].

The relationship between statin use, hepatic triglyceride content (HTGC), and serum ALT levels was also examined in 2,264 Dallas Heart Study participants who were using no lipid lowering agent ($n = 2124$) or using only a statin for lipid management ($n = 140$) [33]. Statin use was not associated with a higher frequency of serum ALT abnormalities, even among those with hepatic steatosis [33].

Recently, a more aggressive statin therapy was suggest based on the results of randomized controlled trials (RCTs) showing a dramatically decrease of cardiovascular events in secondary prevention (TNT [34], A to Z [35], Prove-IT [36]). In the last year, this approach was extended by new ACC guidelines also to patients at high CV risk in primary prevention, such as those with type 2 diabetes (ATP-IV) [8].

Two meta-analyses addressed the issue of the impact of using higher vs. lower intensity statin therapy on liver toxicity [37,38]. In the first, performed in 23 statin treatment arms with 309,506 person-years of follow-up, raise of liver enzymes increased significantly with higher statin dose while there was no significant relationship between LDL-C reduction and hepatotoxicity [37]. The Authors concluded that the risk of statin associated liver enzyme elevation is not related to the magnitude of LDL lowering but is more likely determined by drug- and dose-specific effects [37]. Similar results were obtained in a second meta-analysis of RTCs comparing higher vs. lower intensity therapy [38]. However, when hydrophilic (pravastatin and atorvastatin) and lipophilic (simvastatin and lovastatin) statins were evaluated separately, high intensity hydrophilic statin therapy increased the risk for transaminases elevation, but higher intensity lipophilic therapy did not [38].

Based on the above data, we may conclude that treatment with low-moderate intensity statins is safe. By contrast, high-intensity statin treatment may induce liver toxicity, particularly hydrophilic statin use.

ESC/EAS guidelines for the management of dyslipidaemia [39] suggest what to do if liver enzymes became raised in a person taking

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statins. If ALT < 3xULN, therapy may be continued and liver enzymes checked annually; if values rise ≥ 3xULN, statin treatment should be discontinued or reduced in dose and liver enzymes checked within 4–6 weeks [39].

By contrast, a Liver Expert Panel providing advice to the US National Lipid Association's (NLA) Safety Task Force [13] discouraged routine liver biochemistry, since severe liver injury with statins is rare and unpredictable in individual patients, and monitoring individuals with asymptomatic liver enzymes elevation could lead to inappropriate therapy discontinuation [13]. This recommendation is based on the 2012 safety label changes to cholesterol-lowering statin drugs made by FDA that removed the need for routine periodic monitoring of liver enzymes in patients taking statins [40].

3. Safety and efficacy of long-term statin treatment in patients with abnormal liver tests

One common challenge in everyday clinical practice is the presence of baseline elevations of serum liver enzymes, not infrequently seen in patients at risk of or with established CHD. This abnormality is frequently secondary to associated comorbid conditions, such as obesity, dyslipidaemia, pre-diabetes, and diabetes mellitus, which share features of NAFLD.

The issue of a possible liver-related adverse effects of statin treatment in patients with coronary heart disease and liver enzyme elevation was addressed in a post hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study [41]. The frequency of liver-related adverse effects was low (1.1%) and did not differ from rates reported in patients not treated with statins (0.4%; $p = 0.2$). Additionally, 227 patients with abnormal rises in AST or ALT concentrations of up to three times the upper limit of normal at entry in the trial, who were given a statin had a substantial improvement in liver tests during 3-year follow-up, whereas 210 not treated had a further increase of transaminases. Finally, the statin-related relative risk reduction was greater in patients with abnormal liver tests than in those with normal liver tests. The Authors conclude that statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in patients with mild-to-moderately abnormal liver tests that are potentially attributable to non-alcoholic fatty liver disease.

Baseline liver enzymes tests are recommended before initiating statin therapy, even though the quality of evidence and grade of strength are low. In case of elevated liver enzymes at baseline, it is recommended to repeat liver blood testing in a timely manner to confirm elevation [13]. Moreover, NLA Safety Task Force established the safety of statin in chronic liver disease, NAFLD, NASH and compensated cirrhosis. Decompensated cirrhosis and acute liver failure are contraindications for statin therapy [13].

4. Statins for the treatment of dyslipidaemia in patients with non-alcoholic fatty liver disease

Hyperlipidaemia is frequently associated with NAFLD. Most patients with moderately elevated ALT levels have 'atherogenic dyslipidaemia', which is characterized by increased serum triglycerides, low HDL cholesterol and the presence of small, dense LDL particles, a common finding also in insulin resistance and metabolic syndrome. "Atherogenic dyslipidaemia" is frequently associated with other features of metabolic syndrome such as obesity, diabetes mellitus, and hypertension.

Aggressive treatment of dyslipidaemia plays a critical role in the overall management of patients with NAFLD. Statins are the mainstay of lipid-lowering drug therapy in patients with hyperlipidaemia. All statins appear to be effective in lowering cholesterol levels in patients with NAFLD although there is more experience with atorvastatin which is the only statin to show a reduction in the incidence of cardiovascular events in these patients [41].

However, there is concern that patients with NAFLD or NASH and hyperlipidaemia who are treated with statins could develop serum ALT elevation or a further increase of already elevated enzymes. Therefore, in clinical practice, management of dyslipidaemia in patients with NAFLD has been often a matter of concern and under-treatment with statin therapy because of potential liver damage. Safety of statin treatment of dyslipidaemia in patients with NAFLD has been addressed in numerous studies.

High-dose pravastatin (80 mg/day) administered to hypercholesterolemic subjects with chronic liver disease significantly lowered LDL-C, TC, and TGs in comparison with the placebo and was safe and well tolerated [42]. ALT elevations were numerically more likely to occur in the placebo group thus supporting the recommendation that hypercholesterolemic patients with compensated chronic active liver disease should not be denied access to statin treatment.

In a retrospective study of 71 subjects with NAFLD and dyslipidaemia, only 15.4% of patients taking statins experienced a rise in serum ALT ≥ 40 U/L, and in each case the rise was transient, returning near baseline or below without discontinuation of statin treatment [43].

In some studies the reduction and/or normalization of serum liver enzymes has been also observed [44–47]. In a prospective-randomized study, performed in patients with hypercholesterolemia and elevated ALT concentration, pitavastatin and atorvastatin equally reduced LDL cholesterol and significantly reduced ALT (−8.4% and −8.9% respectively, $p < 0.05$, analysis of variance) [44]. In a further prospective study performed in 25 dyslipidemic and NAFLD patients with elevated baseline liver enzymes, 36.3% of patients after 6 months and 20% after 12 months of treatment with atorvastatin presented normal ALT levels [45].

Similar findings were obtained in a small prospective study on the treatment of 23 hyperlipidaemic patients with biochemical and ecographic evidence of NAFLD, where rosuvastatin 10 mg/day for 8 months normalized liver function tests in all patients (mean ALT from 90.9 to 29.8 U/L, $p < 0.001$ and mean AST from 91 to 30.5 U/L, $p < 0.001$) [46].

Finally, in a study performed in 45 patients with NAFLD, type 2 diabetes and elevated LDL-C, a significant reduction was observed after 6 months of combined ezetimibe/simvastatin treatment (mean ALT 63.78 vs. 32.57 U/L, $p < 0.0001$ and mean AST 50.79 vs. 23.68 U/L, $p < 0.0001$) and simvastatin mono-therapy (mean ALT 66.58 vs. 29.46 U/L, $p < 0.0001$ and mean AST 59.61 vs. 24.00 U/L, $p < 0.0001$). Simvastatin monotherapy reduced ALT to a significantly larger extent compared to combined ezetimibe/simvastatin therapy ($p < 0.0112$ for ALT, $p < 0.0001$ for AST) [47].

All the above data provide evidence that statins can be used safely to treat hyperlipidaemia in patients with NAFLD. The risk for serious liver injury from statins is quite rare and patients with NAFLD and hyperlipidaemia are not at increased risk for statin hepatotoxicity. Therefore, the presence of NAFLD or NASH should not deter physicians from using statins in patients with hyperlipidaemia.

5. Statins for the treatment of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

Statins have anti-inflammatory, anti-oxidant and anti-thrombotic effects that are independent of their lipid-lowering activity [48,49]. Therefore, they have been proposed for the treatment of NAFLD and NASH, since in these conditions both inflammation and oxidative stress play an important pathogenetic

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role [50]. In particular, in a recent work by our group, we found an increased NOX2-related oxidative stress in patients with NAFLD, that was associated with the severity of liver steatosis [50].

No drug is currently indicated for the treatment of NAFLD/NASH, since there is insufficient evidence to support the use of drugs improving insulin resistance in these patients [51]. Actually, the only therapeutic approach is based on antioxidant treatment with vitamin E for biopsy-proven NASH [52]. So far, very little data about the effects of statins in NAFLD exists.

In a recent study of Wang et al. [53], simvastatin treatment improved the prognosis of NASH-related fibrosis in rat models of steatosis, by increasing the expression of endothelial nitric oxide synthase (eNOS), decreasing the expression of inducible nitric oxide synthase (iNOS), and inhibiting the activation of hepatic stellate cells (HSC) [53].

In a case report recently described by Riche et al. [54], short-term elevations in aminotransferases induced discontinuation of rosuvastatin in an obese dyslipidemic patient with severe NAFLD. After 9 months of combined treatment with rosuvastatin 20 mg daily and pioglitazone 15 mg daily, the patient's ALT and AST serum concentrations normalized and an improvement in steatosis grading at ultrasound was found. The authors conclude that this case represents a potential solution for initiating or maintaining statin therapy in patients with NAFLD who are at high cardiovascular risk [54].

In a recent Cochrane meta-analysis on the effect of statins for NAFLD and NASH based on two trials with high risk of bias and a small numbers of participants, statins were found to improve serum aminotransferase levels as well as ultrasound findings [55]. However, none of the trials reported on possible histological changes, liver-related morbidity or mortality.

An open-label, pilot study evaluated the efficacy of pitavastatin for the treatment of non-alcoholic steatohepatitis with dyslipidaemia. After 12 months, follow-up biopsies available for 13 NASH patients showed a slight, non-significant reduction of NASH activity score (NAS), while fibrosis stage did not change significantly [56]. In one more open-label study by the same Authors in patients with NASH and hyperlipidaemia [57], follow up biopsies were performed after 24 months of treatment with atorvastatin 10 mg. After treatment, liver macrovescicular steatosis and NAS score were significantly improved in both studies, whereas some patients had increased fibrosis stage. All patients showed a significant reduction of serum liver enzymes. The Authors suggest that atorvastatin may improve disease activity of NASH partly via its tumour necrosis factor-alpha lowering property [57]. In a study performed in Sweden, follow up biopsies were obtained 13.8 years after the first liver biopsy in 68 patients with NAFLD. Patients on statins significantly reduced fatty liver infiltration over time, as opposed to those who were not, while liver related biochemical parameters did not differ significantly between the two cohorts after statin treatment [58].

In the St Francis Heart Study Randomized Clinical Trial, atorvastatin 20 mg combined with vitamins C and E was effective in reducing the odds of having hepatic steatosis by 71% (based on liver to spleen ratio on CT scans) in healthy individuals with NAFLD at baseline after 4 years of active therapy [59]. Improvement of liver steatosis was obtained both in NAFLD patients with dyslipidaemia and in those without, raising the possibility that, on the basis of the PIVENS Study [52], vitamin E alone may have had this effect.

The effect of multifactorial treatment including lifestyle and drug treatment for risk factors in subjects with biochemical and ultrasonographic evidence of NAFLD was assessed in a randomized study performed in Greece. After 54 weeks of treatment, 67% in the atorvastatin, 42% in the fenofibrate and 70% in the combination treatment groups no longer had any surrogate evidence of NAFLD, as established by normalization of serum ALT plus normal liver echopattern [60].

Conversely, negative findings were obtained in a RCT where patients with NASH were randomized to simvastatin 40 mg daily or

Table 3
Meta-analyses on long-term statin treatment and liver toxicity.

Meta-analysis	Number of studies	Total of subjects	Age (years)	Exposure to study medication	Treatment type and dosage (mg/day)	Liver function tests abnormalities	Conclusions
PPP Project [11]	3	19.768	21–75	>5 years	Pravastatin 40	Pravastatin: 0.9% Placebo: 1.0%	Pravastatin was well tolerated, with no excess of liver function abnormalities
de Denus S [16]	13	49.275	55–75	From 48 weeks to 6.1 years	Pravastatin 40 Lovastatin 30–45 Simvastatin 27–30 Fluvastatin 40–80	Statins 1.14% Placebo 1.05%	Only fluvastatin was associated with a significant increase in the odds of having liver function tests abnormalities (1.13% vs. 0.29%)
Alsheikh-Ali AA [21]	23 treatment arms	75.317	55–75	From 0.9 to 6.1 years	Lovastatin 20–80 Simvastatin 20–80 Atorvastatin 10–80 Pravastatin 40 Fluvastatin 80	High-dose: 271; Intermediate: 195; Low-dose: 114 (per 100,000 person-years for each 10% reduction in LDL-C)	Drug- and dose-specific effects are more important determinants of liver toxicity than magnitude of LDL-C lowering
Dale KM [22]	9	21.765	48–64	From 1 to 5 years	High dose: Atorvastatin 80 Simvastatin 40–80 Lovastatin 76 Low dose: Simvastatin 20–40 Pravastatin 40 Atorvastatin 10 Lovastatin 4	High-dose statin: 1.5% Low-dose statin: 0.4%	Higher intensity statin therapy significantly increases the incidence of transaminase elevation in higher intensity hydrophilic statins group

LDL-C: low-density lipoprotein cholesterol.

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Table 4
Summary of the recommendations for statin treatment in patients with non-alcoholic fatty liver disease.

Long-term statin treatment and liver toxicity	■ Treatment with low-moderate intensity statins is safe. By contrast, high intensity statin treatment may induce liver toxicity. ■ Discourage routine liver biochemistry monitoring in asymptomatic individuals. ■ If ALT < 3xULN, continue therapy and re-check liver enzymes annually. ■ If values rise ≥ 3xULN, stop statin or reduce dose and re-check within 4–6 weeks.
Safety and efficacy of long-term statin treatment in patients with abnormal liver tests	■ Hepatologists are often consulted to advise referring physicians about the safety of prescribing statins in patients with elevated serum transaminases. ■ This abnormality is frequently secondary to associated comorbid conditions. ■ Statin treatment is safe and can improve liver tests.
Statins for the treatment of dyslipidaemia in patients with non-alcoholic fatty liver disease	■ Atherogenic hyperlipidaemia is frequently associated with NAFLD. ■ Treatment of dyslipidaemia plays a critical role in the overall management of NAFLD. ■ The risk for serious liver injury from statins is quite rare and patients with NAFLD and hyperlipidaemia are not at increased risk for statin hepatotoxicity. ■ Previous recommendations advising against the use of statins in patients with dyslipidaemia and NAFLD are not evidence-based and should be reviewed.
Statins for the treatment of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis	■ Preliminary studies have shown that statins may possibly improve hepatic histology in patients with underlying NAFLD. ■ No convincing histological data are available. ■ At present, treatment with statins to cure liver disease in patients with NAFLD is not recommended. ■ New RCTs of adequate size and duration are required to assess efficacy of statins for the treatment of NAFLD.

placebo [61]. In fact, in 10 subjects who underwent 1-year repeat liver biopsy, there was no statistically significant improvement in serum ALT, hepatic steatosis, necroinflammatory activity or stage of fibrosis in the simvastatin group. In this pilot study, monotherapy with simvastatin did not seem to be an effective treatment for NASH, although the small number of subjects under study and the low severity of NASH at entry could have been a major limitation in the interpretation of these negative results [61].

Very recently, data from the population-based Rotterdam Study, including 2578 subjects who underwent liver ultrasonography, reported a lower prevalence of liver steatosis in patients treated with statins for more than 2 years [62].

6. Future research perspectives

Hepatic effect and metabolism of statin consists of several co-transporters and enzymes, which are able to regulate both efficacy and tolerance to statin treatment. In particular, some polymorphisms in genes affecting statin pharmacodynamics and pharmacokinetics have been described [63]. Among membrane and cellular drug transporters, two families of plasma membrane proteins play a major role in the intra and inter-cellular networking of statins: the ATP-binding cassette (ABC) and solute carriers (SLC) (Fig. 1). In the ABC superfamily, the transport of drugs, including statins, is mainly associated to the P-glycoprotein (Pg-P/ABCB1), breast cancer resistance protein (BCRP/ABCG2), and multidrug resistance-associated proteins (ABCC1 and ABCC2) [63]. Their main function is to regulate the diffusion of these agents to other tissues, and to eliminate drugs via bile. The alterations of these systems have been described to influence the metabolism of statins.

In the particular context of NAFLD, some polymorphisms responsible for alterations in the progression of fatty liver disease and lipid metabolism have been described. For example, an increased expression of cytochrome P450-2E1 has been found in patients with NAFLD [64,65] and polymorphisms in peroxisome proliferator-activated receptors (PPAR) alpha and gamma2 have been suggested to be linked to the risk of NAFLD [66].

As mentioned above, the family of cytochrome P450 is highly involved in the metabolism of statins, thus it would be of great interest to understand if the coexistence, in NAFLD patients, of multiple gene variants in the intracellular co-transporters of ABC family and enzymes of the family of cytochrome P450 or PPAR may further contribute to influence statin metabolism and safety.

7. Conclusions

A summary of the efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease in different clinical settings is reported in Table 4.

A large body of data deriving from the large RCTs performed with statins clearly suggest that statin therapy, at low to moderate doses, is safe and has very low liver toxicity. Clinically important liver toxicity is an extremely rare side effect in primary and in secondary prevention.

Management of "atherogenic dyslipidaemia" associated with NAFLD plays a pivotal role in the prevention of cardiovascular events both in primary and secondary prevention.

As far, statins seem to be effective and safe for the treatment of hypercholesterolemia and/or atherogenic dyslipidaemia in patients with elevated serum liver enzymes, without inducing a further elevation of liver enzymes in treated patients [58]. Therefore, an effective treatment of dyslipidaemia should be achieved even in the presence of chronic liver disease. In fact, statin treatment will reduce cardiovascular events and mortality in these patients and the risks of not taking statins will likely outweigh the risks of taking the drug.

Conversely, the usefulness of statins for the treatment of NAFLD/NASH is still a matter of debate. Few data suggest normalization of serum liver enzymes. However, no convincing histological data are available, and the effect of statin treatment on steatosis, inflammation and fibrosis are statistically non-significant. Therefore, at present, treatment with statins to cure liver disease in patients with NAFLD is not recommended. Further RCTs of adequate size and duration are required to assess efficacy of statins for the treatment of NAFLD.

Conflict of interest
None declared.

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