An Evidence-Based Review of Statin Use in Patients With Nonalcoholic Fatty Liver Disease

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ABSTRACT

BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) is a common complication in patients with metabolic syndrome. The role of statin therapy specifically for the treatment of NAFLD remains unknown. The aim of this review is to discuss outcomes of recent articles analyzing statin therapy in patients with NAFLD.

FINDINGS: A total of 12 trials met the inclusion criteria. Statins were not found to increase the prevalence of NAFLD once confounding variables were considered. Statins were also found to be beneficial in treating dyslipidemia and improving liver function. Pathological liver outcomes in patients with NAFLD were controversial. One trial found a reduction in the incidence of hepatocellular carcinoma associated with the use of statins.

CONCLUSIONS: Overall, therapy with statins appears to be safe for use in patients with NAFLD. Several trials have validated the use of statins for the treatment of dyslipidemia; however, it remains unknown as to whether statins should be used to specifically treat NAFLD.

KEYWORDS: Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, HMG-CoA reductase inhibitors, statins, safety

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Introduction

As defined by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association, nonalcoholic fatty liver disease (NAFLD) is the presence of ≥5% hepatic steatosis in the absence of secondary causes of fat accumulation, including heavy alcohol consumption, treatment with steatogenic medications, and genetic causes of hepatic fat deposition.¹ Nonalcoholic fatty liver disease is further histologically divided into nonalcoholic steatohepatitis (NASH) associated with inflammation, ballooning of hepatocytes, and fibrosis, or nonalcoholic fatty liver (NAFL), which is not associated with hepatocellular damage.²⁻⁵ Serum aminotransferases may be elevated or within the upper limit of normal (ULN).¹ The clinical implications of NAFLD include progression to cirrhosis, hepatocellular carcinoma (HCC), liver failure requiring liver transplantation, and increased risk of cardiovascular disease (CVD).¹ Global prevalence of NAFLD is estimated to be between 25% and 33%.¹,⁴,⁵ Of relevance in the United States, NASH is the only indication for liver transplant that has increased from 2001 to 2009, and this trend is expected to continue.⁶

Metabolic syndrome and NAFLD share common risk factors, including visceral obesity, impaired fasting glucose, and dyslipidemia.¹,⁷ Metabolic syndrome itself is an established risk factor for NAFLD, with estimations that approximately 43% of patients with NAFLD have metabolic syndrome, contributing to the theory that NAFLD is a hepatic manifestation of metabolic syndrome.¹,⁴,⁸ Physiologically, NAFLD is associated with increased accumulation of both hepatic triglycerides and free cholesterol, and elevated free cholesterol is closely associated with increased expression of HMG-CoA reductase.⁹ Furthermore, free cholesterol increases generation of reactive oxygen species and inflammatory processes via activation of Kupffer and stellate cells and induces dysfunction in mitochondria.¹⁰ These processes contribute to hypercoagulation and atherogenic dyslipidemia, factoring into the significant increased risk of CVD and cardiovascular-related death in patients with NAFLD.¹¹ It was recently demonstrated that among patients with type 2 diabetes mellitus, the subgroup with known NAFLD was at a 1.39 times higher risk of CVD-related mortality and 2.11 times higher risk of all-cause mortality as compared with the patients with diabetes without NAFLD.¹² The combination of risk factors leading to NAFLD and the presence of elevated cardiovascular risk concomitant with NAFLD may indicate a role for statins in this patient population.

Statin therapy originally required routine monitoring of liver function tests (LFTs) and was contraindicated in chronic liver disease due to an increase in LFTs as a class effect. After

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reviewing the available literature, the National Lipid Association (NLA) released statements indicating that statin-induced LFT elevations are not indicative of hepatocellular damage, and that frequent monitoring of LFTs is not likely to identify patients who may experience idiosyncratic reactions to statin therapy.13,14

Reviews by the Food and Drug Administration (FDA) of postmarketing data using the Adverse Event Reporting System also revealed exceedingly low rates of statin-associated liver injury, with no cases of severe injury being categorized as either highly likely to be associated or definitely associated with the use of statins.15 The NLA has further stated that the utilization of statin therapy in NAFLD, including NASH, is most likely safe; however, statin therapy as a viable treatment option for NAFLD would require further investigation.16

A 2011 comprehensive review of the safety and efficacy of statins in patients with chronic liver disease, including patients with NAFLD, was completed by Tzefos and Olin.17 There were 12 trials reviewed and the authors concluded that statins were safe for the management of dyslipidemia in patients with NAFLD, including NASH. No conclusions were made regarding histological outcomes in patients with NAFLD treated with statins.

In this review, we aim to present the most current evidence concerning statin use in patients with NAFLD. Evidence will be reviewed that has been published since the release of the most recent guidelines on management of NAFLD published in 2011.1 The impact of statins on the prevalence of NAFLD, lipid and liver enzyme concentrations in patients with NAFLD, fibrosis/NASH and HCC outcomes in patients with NAFLD, as well as future directions for research on statin use in patients with NAFLD will be explored.

Methods

Queries of trials were conducted in PubMed and Ovid/MEDLINE. The following search terms were used in various combinations: “non-alcoholic fatty liver disease,” “non-alcoholic steatohepatitis,” “Hydroxymethylglutaryl-CoA reductase Inhibitors,” “HMG-CoA reductase inhibitors,” “statins,” “atorvastatin,” “cerivastatin,” “fluvastatin,” “lovastatin,” “mevastatin,” “pitavastatin,” “pravastatin,” “rosuvastatin,” “simvastatin,” “therapeutic use,” and “safety.”

Only literature in the English language and published after 2011 were screened for inclusion. Prior studies were excluded in effort to focus on data published after the release of the latest NAFLD guidelines.3 Trials not conducted in humans were excluded. All bibliographies of the selected literature were reviewed for additional references. Outcomes of interest included the following: impact of statin use on NAFLD prevalence; biochemical analysis; hepatic histology, including HCC; mortality outcomes; and cardiovascular outcomes. The literature search was concluded on October 11, 2017; therefore, any trial published after this time was not included. All 3 authors searched for literature, whereas the first 2 authors selected the eligible articles.

Results

Out of more than 180 articles retrieved using the selected search terms, there were a total of 21 trials available for inclusion based on the above search criteria. Most of the trials excluded were dismissed based on title alone as they did not pertain to statin use in patients with NAFLD. Out of the 21 available studies, 3 were conducted in nonhuman models, and 5 did not specifically assess patients with NAFLD. One trial looked at a combination of ursodeoxycholic acid and atorvastatin, with no comparator group and was excluded because the results did not independently assess the impact of statin administration on the outcomes. The following is a review of the selected 12 articles (see Table 1 for a summary of these trials).

Impact of statins on prevalence of NAFLD

Three trials assessed the prevalence of NAFLD among statin users versus nonusers.18–20 In the study by de Keyser et al,18 35.3% of the cohort had hepatic steatosis. Statin users were more likely to have insulin resistance, type 2 diabetes mellitus, CVD, and metabolic syndrome compared with nonstatin users (P < .0001 for all). After adjusting for potential confounders, statin use was not associated with an increased prevalence of hepatic steatosis (P = .648); however, after adjusting for duration, the prevalence of hepatic steatosis was reduced if statins were administered for greater than 2 years (P = .040).

Oni et al19 desired to determine the prevalence of NAFLD and severity of liver fibrosis between users and nonusers of statins. Only patients without coronary heart disease were included. Several differences in baseline characteristics between the groups existed, including more patients in the statin cohort having metabolic risk factors (hyperglycemia, obesity, and hypertension; P < .001 for all components). Overall, prevalence of NAFLD was 36%, with 48% in the statin group and 35% in the nonstatin group (P < .001). Among patients with NAFLD, no statistically significant difference in the fatty liver index was found. The fatty liver index was calculated as a predictor of NAFLD severity, with lower scores representing less severe forms of NAFLD. Conversely, the statin group did have a higher fibrosis-4 (FIB-4) index compared with nonusers. The FIB-4 index is used as an aid in determining the degree of fibrosis. Yet, because both groups in this cohort had a score of less than 1.45, this suggests that neither group had severe fibrosis.

In a recent study by Nascimbeni et al,20 patients treated with statins or antidiabetic medications were assessed for the prevalence of NASH and significant fibrosis. Significant fibrosis defined as ≥F2 per Kleiner criteria (higher scores representing more severe fibrosis). Scores in these categories are significant for perisinusoidal and portal or periportal fibrosis. Significant characteristics differentiating the statin from the nonstatin cohort included older age, male sex, higher blood pressure, greater antidiabetic medication use, metabolic syndrome,
| TRIAL          | STUDY DESIGN                                                                 | INTERVENTIONS                                      | OUTCOMES ASSESSED                                                                 | RESULTS                                                                                                                                                     |
|---------------|-------------------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| de Keyser et al18 | Cross-sectional single-center trial; prospectively underwent liver ultrasound for outcome | N=2578 Current statin use, n=631 Past statin use, n=359 No statin use, n=1588                      | Prevalence of NAFLD among current/past statin users versus nonusers                                                                      | Overall NAFLD prevalence (adjusted for confounders): OR: 1.06, 95% CI: 0.82-1.73 Current statin use, greater than 2 y: OR: 0.43, 95% CI: 0.19-0.96 No difference found with other variables, including past statin use |
| Oni et al19    | Cross-sectional, single-center trial; prospectively underwent laboratory screenings and abdominal ultrasound | N=6385 Statin use, n=553 No statin use, n=5833                      | Prevalence of NAFLD and severity of liver fibrosis among statin users versus nonusers                                                     | Statin cohort versus nonusers: Fatty liver index in patients with NAFLD: 71±18 versus 69±23; P=.18 FIB-4 index: 1.20 versus 1.02; P<.001 Metabolic syndrome stratification: OR: 1.08; 95% CI: 0.88-1.32 Severe fibrosis: OR: 0.88, 95% CI: 0.60-1.29 |
| Nascimbeni et al20 | Cross-sectional, 2-center trial; biopsy-proven patients with NAFLD prospectively underwent liver biopsies | N=346 Statin use, n=154 Low-to-moderate: Simvastatin, n=23 Pravastatin, n=10 Fluvastatin, n=3 Moderate-to-high: Atorvastatin, n=82 Rosuvastatin, n=24 Statin with ezetimibe, n=10 | Association of statin OR: antidiabetic medications on NASH and significant fibrosis (medication classes assessed separately) | Statin users versus nonusers: Prevalence of NASH: 57% versus 56%, respectively (P=.868) Prevalence of NASH in multivariable analysis: OR: 0.57, 95% CI: 0.32-1.01 Prevalence of NASH assessing moderate-to-high intensity statins: OR: 0.54, 95% CI: 0.29-0.99 Prevalence of significant fibrosis: 48% versus 48%, respectively (P=.943) Prevalence of significant fibrosis in multivariable analysis: OR: 0.47, 95% CI: 0.26-0.84 Prevalence of significant fibrosis assessing moderate-to-high intensity statins: OR: 0.40, 95% CI: 0.21-0.76 |
| Dongiovanni et al21 | Retrospective, multicenter, cross-sectional trial, with a nested case-control | N=1059 Statin use, n=107 No statin use, n=952 Data collected over 14-y duration | Association of statin use and presence of steatosis, NASH, and fibrosis stage F2-F4 | Statin users versus nonstatin users: Hepatic steatosis: OR: 0.43, 95% CI: 0.23-0.80 NASH: OR: 0.63, 95% CI: 0.40-0.97 Fibrosis stage F2-F4: OR: 0.62, 95% CI: 0.33-1.00 Matched analysis of statin users to nonstatin users: Hepatic steatosis: OR: 0.10, 95% CI: 0.02-0.3 NASH: OR: 0.26, 95% CI: 0.14-0.48 Fibrosis stage F2-F4: OR: 0.48, 95% CI: 0.26-0.88 |
| Maroni et al22 | Retrospective trial                                                             | N=43 Atorvastatin, n=19 Simvastatin, n=11 Rosuvastatin, n=10 Fluvastatin, n=2 Lovastatin, n=1 Retrospective data collected for 12 mo | Impact of statins on lipid panel and on serum liver enzyme concentrations               | Change from baseline: Total cholesterol: −97.5 mg/dL; P<.001 LDL-C: −83.5 mg/dL; P<.001 Triglycerides: −65.8 mg/dL; P<.001 HDL-C: −1.74 mg/dL; P=.35 AST: +7.85 IU/L; P=.06 ALT: +7.1 IU/L; P=.10 GGT: +10.11 IU/L; P=.30 |

(Continued)
### Table 1. (Continued)

| TRIAL                  | STUDY DESIGN                        | INTERVENTIONS                        | OUTCOMES ASSESSED | RESULTS                                                                 |
|------------------------|--------------------------------------|---------------------------------------|-------------------|--------------------------------------------------------------------------|
| Hyogo et al<sup>23</sup> | Prospective, observational trial    | N = 42; atorvastatin 10 mg daily for 12 mo | Association of anthropometric, metabolic, and inflammatory variables in patients with NASH treated with atorvastatin | Results: Baseline versus ending values: Mean AST: 48.0 ± 26.7 IU/L and 33.0 ± 18.4 IU/L; \( P < .01 \)  |
|                        |                                      |                                       |                   | Mean ALT: 89.0 ± 61.9 IU/L and 56.8 ± 52.3 IU/L; \( P < .01 \)  |
|                        |                                      |                                       |                   | Mean GGT: 90.4 ± 89.9 IU/L and 65.1 ± 49.9 IU/L; \( P < .01 \)  |
|                        |                                      |                                       |                   | NAS: 3.9 ± 1.0 and 3.0 ± 0.9; \( P < .01 \)  |
|                        |                                      |                                       |                   | TNF-\( \alpha \): 17.1 ± 5.8 pg/mL and 11.7 ± 7.8 pg/mL; \( P < .01 \) \( L/S \) ratio: 0.5 ± 0.3 and 0.9 ± 0.2; \( P < .01 \) |
| Han et al<sup>24</sup>  | Prospective, randomized, open-label, active control trial | N = 189; Pitavastatin 2-4 mg daily for 12 wk, n = 97; Atorvastatin 10-20 mg daily for 12 wk, n = 92 | Proportion of patients which developed ALT concentrations greater than 100 IU/L (ie, >2.5 times ULN) at week 12. Secondary end points, change from baseline in ALT, AST, GGT, LDL-C, TC, TG, and HDL-C. Outcomes in subset include change in amount of fat in liver on computed tomographic imaging | Results: 5.2% and 4.3% of pitavastatin and atorvastatin, respectively, had ALT >100 IU/L (ie, >2.5 times ULN). Baseline versus ending values: Mean GGT in pitavastatin group: 75.7 ± 52.8 IU/L to 68.8 ± 52.6 IU/L; \( P = .034 \)  |
|                        |                                      |                                       |                   | Mean GGT in atorvastatin group: 79.9 ± 65.9 IU/L to 68.8 ± 52.6 IU/L; \( P = .040 \)  |
|                        |                                      |                                       |                   | Mean AST in pitavastatin group: 39.5 ± 13.0 IU/L to 39.0 ± 17.0 IU/L; \( P = .859 \)  |
|                        |                                      |                                       |                   | Mean AST in atorvastatin group: 44.5 ± 19.6 IU/L to 41.5 ± 21.4 IU/L; \( P = .541 \)  |
|                        |                                      |                                       |                   | Mean ALT in pitavastatin group: 56.4 ± 19.7 IU/L to 51.3 to 29.7 IU/L; \( P = .047 \)  |
|                        |                                      |                                       |                   | Mean ALT in atorvastatin group: 58.7 ± 22.5 IU/L to 53.3 ± 54.5 IU/L; \( P = .254 \)  |
| Rana et al<sup>25</sup> | Randomized, with a nested control trial | N = 98; Metformin, n = 31; Rosuvastatin, n = 34; Pioglitazone, n = 33 | Compared efficacy of insulin sensitizers with statins in patients with liver ultrasonography-proven NAFLD. Assessed weight, BMI, LFTs, lipid profile, and USG scores | Results: Mean change from baseline: Weight change in metformin group: −4.8 ± 1.5 kg; \( P < .001 \)  |
|                        |                                      |                                       |                   | Weight change in rosvastatin group: −4.3 ± 1.2 kg; \( P < .001 \)  |
|                        |                                      |                                       |                   | Weight change in pioglitazone group: 0.0 ± 1.1 kg; \( P = .875 \)  |
|                        |                                      |                                       |                   | Weight change across groups: \( P = .089 \)  |
|                        |                                      |                                       |                   | ALT change in metformin group: −14.1 ± 16.5; \( P < .001 \)  |
|                        |                                      |                                       |                   | ALT change in rosvastatin group: 8.4 ± 25.7; \( P = .067 \)  |
|                        |                                      |                                       |                   | ALT change in pioglitazone group: −23.7 ± 19.6; \( P < .001 \)  |
|                        |                                      |                                       |                   | Mean ALT change across groups: \( P = .012 \)  |
|                        |                                      |                                       |                   | AST change in metformin group: −15.5 ± 23.9; \( P < .001 \)  |
|                        |                                      |                                       |                   | AST change in rosvastatin group: 8.1 ± 24.5; \( P = .064 \)  |
|                        |                                      |                                       |                   | AST change in pioglitazone group: 24.7 ± 23.0; \( P < .001 \)  |
|                        |                                      |                                       |                   | Mean AST change across groups: \( P = .085 \)  |
|                        |                                      |                                       |                   | Total cholesterol difference across groups: \( P < .001 \)  |
|                        |                                      |                                       |                   | Triglyceride difference across groups: \( P < .001 \)  |
|                        |                                      |                                       |                   | LDL-C change across groups: \( P < .001 \)  |
|                        |                                      |                                       |                   | HDL-C change across groups: \( P = .228 \)  |
|                        |                                      |                                       |                   | USG change in metformin group: 0.07 ± 0.7; \( P = .6 \)  |
|                        |                                      |                                       |                   | USG change in rosvastatin group: −1.3 ± 0.9; \( P < .01 \)  |
|                        |                                      |                                       |                   | USG change in pioglitazone group: −0.7 ± 0.8; \( P < .001 \)  |
|                        |                                      |                                       |                   | USG score across groups: \( P < .001 \)  |
| TRIAL            | STUDY DESIGN            | INTERVENTIONS                      | OUTCOMES ASSESSED                                                                 | RESULTS                                                                 |
|------------------|-------------------------|------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Hyogo et al.     | Open-label pilot trial  | N=20                               | Efficacy of pitavastatin in patients with NASH and dyslipidemia                  | Change from baseline: Mean ALT: 102.1 ± 60.1 iU/L to 68.2 ± 48.3 iU/L  |
|                  |                         | Pitavastin 2 mg daily for 12 mo     |                                                                                  | Mean GGT: -94.5 ± 82.7 iU/L to 59.6 ± 21.1                               |
|                  |                         |                                    |                                                                                  | No changes in steatosis, inflammation, fibrosis, or NAS                |
| Nakahara et al.  | Open-label pilot study  | N=19                               | Efficacy of rosuvastatin in patients with NASH and dyslipidemia                  | Change from baseline: Mean AST: 40.1 ± 22.8 iU/L to 33.8 ± 15.2 iU/L  |
|                  |                         | Rosuvastin 2.5 mg daily for 24 mo   |                                                                                  | Mean ALT: 68.7 ± 52.5 iU/L to 50.3 ± 27.8 iU/L                           |
|                  |                         |                                    |                                                                                  | No changes in fibrosis or NAS                                          |
| Kargiotis et al. | Prospective, randomized| N=20                               | Primary end point: degree of resolution of NASH on repeat biopsy compared with   | Liver biopsy and ultrasonography confirmed resolution of NASH in 19     |
|                  | open-label trial        |                                    | baseline                                                                       | patients                                                                 |
|                  |                         | Rosuvastin 10 mg/d for 12 mo        | Secondary end point: changes in liver enzymes, lipid values, and liver           | Mean baseline and ending:                                            |
|                  |                         |                                    | ultrasonography                                                                | Total cholesterol: 251 ± 22 to 179 ± 9; P < .001                       |
|                  |                         |                                    |                                                                                  | Triglycerides: 187 ± 19 to 117 ± 18; P < .001                           |
|                  |                         |                                    |                                                                                  | HDL-C: 38 ± 5 to 44 ± 5; P < .001                                     |
|                  |                         |                                    |                                                                                  | LDL-C: 180 ± 23 to 110 ± 11; P < .001                                 |
|                  |                         |                                    |                                                                                  | hsCRP: 4.2 ± 1.3 to 1.6 ± 0.5; P < .001                                |
|                  |                         |                                    |                                                                                  | Uric acid: 5.5 ± 1.1 to 4.8 ± 0.9; P = .016                             |
|                  |                         |                                    |                                                                                  | HbA\(_1c\): 5.3 ± 0.4 to 4.8 ± 0.3; P < .001                           |
|                  |                         |                                    |                                                                                  | Metabolic syndrome (n): 20 to 0; P < .001                              |
| Lee et al.       | Retrospective,          | N=18 080                           | Assessed various patient characteristics for the risk of HCC, including statin   | Statin use associated with incidence of HCC: 0.12% (HR: 0.29, CI:      |
|                  | observational trial     | Statin use: n=6382 (35.3%)         | use                                                                             | 0.12-0.88)                                                             |

**Table 1.** (Continued)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, γ-glutamyl transferase; Hb\(_{A1c}\), hemoglobin A\(_{1c}\); HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; L/S, liver-to-spleen ratio; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; OR, odds ratio; Statin, HMG-CoA reductase inhibitor; TNF-α, tumor necrosis factor α; USG, ultrasonography.
poorer glycemic control, and better total cholesterol. The prevalence of NASH and significant fibrosis was similar between the groups ($P = .868$ and $P = .943$, respectively). In a multivariate analysis, statin use was independently and negatively associated with NASH and significant fibrosis ($P = .055$ and $P = .011$, respectively). When assessing intensities of statins, only moderate-to-high intensity was significant for a negative association with NASH and significant fibrosis ($P = .047$ and $P = .005$, respectively).

In a 2015 publication by Dongiovanni et al., statin use and genetic risk factors were assessed for potential relationships with liver damage in patients at risk for NASH. Liver biopsies were performed to assess NASH and stage of fibrosis. Fibrosis stage ranged from F0 to F4, with higher numbers representing more severe fibrosis. Nonstatin users were matched to statin users in a nested case-control to account for the risk profile of statin users. In addition, the authors stratified patients according to their genetic profile, including patients with the I148M allele of the $PNPLA3$ (patatin-like phospholipase domain-containing-3) gene, which is a known genetic determinant of NASH. Of the patients on statins, excluding 142 pediatric patients, statin use was associated with a reduced risk for hepatic steatosis and NASH ($P = .009$ and $P = .035$, respectively); however, there was no difference regarding fibrosis stage F2-F4 ($P = .05$). In a matched analysis of 100 statin patients and 100 nonstatin patients, use of statins was associated with a reduced risk of steatosis, NASH, and fibrosis stage F2-F4 ($P < .001$, $P < .001$, and $P = .018$, respectively). When patients were stratified according to I148M $PNPLA3$ genotype, those with a positive I148M allele had no difference in NASH outcomes ($P = .15$). This study was a small retrospective multicenter analysis, limiting the utility of the outcomes due to the design of the trial. The authors were able to match users to nonusers in 2 separate analyses, which did help reduce bias of confounding by indication. In addition, this is one of the few trials which incorporated patients’ genetic risk profile to further assess whether or not statins were beneficial in a high-risk group for the development of NASH.

Impact of statins on lipid concentrations and liver function

In a retrospective study conducted by Maroni et al., patients with a clinical diagnosis of NAFLD and dyslipidemia were evaluated for statin effects on the lipid profile and changes in liver enzyme concentrations. After 5.4±5.4 months of therapy, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides significantly improved compared with baseline ($P < .0001$ for all parameters). There were no significant changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and $\gamma$-glutamyl transferase (GGT) concentrations ($P = .06$, $P = .10$, and $P = .30$, respectively). Adverse events related to statins were not reported. This retrospective analysis demonstrated that statins still have a positive impact on the lipid panel without adversely affecting liver enzymes in patients with NAFLD. It remains unknown as to whether there is a significant difference between statin intensities in this patient population regarding lipid and liver function parameters.

In a study by Hyogo et al., anthropometric, metabolic, and inflammatory variables were assessed for improvement relating to amelioration of NASH in patients treated with atorvastatin 10mg daily. At the end of the study, significant reductions from baseline were observed for AST, ALT, and GGT ($P < .01$, $P < .01$, and $P < .05$, respectively). The NAFLD Activity Score (NAS), which incorporates steatosis, inflammation, and ballooning of hepatocytes, as well as tumor necrosis factor $\alpha$ (TNF-$\alpha$), a marker of inflammation, was also significantly reduced ($P < .01$ for both). The average liver to spleen (L/S) density ratio, an estimate of liver fat content assessed by computed tomography (CT) with higher numbers corresponding to lower hepatic fat content, was increased at the end of the trial ($P < .01$). The L/S density ratio was found to be inversely associated with AST, ALT, total cholesterol, LDL-C, NAS, and TNF-$\alpha$. Furthermore, GGT and TNF-$\alpha$ were positively correlated with NAS. This was a small study, lacking a comparator group. As all patients had biopsy-proven NASH, having a comparator would have helped to determine whether or not atorvastatin could assist in slowing the progression of NASH.

Han et al. studied the safety and efficacy of atorvastatin and pitavastatin in patients receiving care in lipid clinics with mild-to-moderately increased ALT concentrations ($\geq1.25$ times to $\leq2.5$ times the ULN, with the ULN defined as 40IU/L). Only a subgroup of the participants underwent CT screening at baseline and follow-up. Doses of the statins were increased according to the recommendations of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) Guideline. At week 4, 3.7% had ALT concentrations $>2.5$ times ULN, and 1 patient in each treatment arm was withdrawn from the study due to ALT concentrations $>3$ times ULN. At week 12, only 1 patient in the atorvastatin group had persistent ALT elevations and 4 others had ALT reductions to $<2.5$ times ULN without needing to discontinue treatment. However, at week 12, 4.8% of the cohort had serum ALT $>2.5$ times ULN ($P = .86$). In both cohorts, GGT was significantly reduced from baseline, whereas AST was not significantly changed for either group. In addition, ALT concentrations were significantly reduced in the pitavastatin group and unchanged in the atorvastatin group. Out of 38 patients who underwent CT scanning, pitavastatin significantly reduced fat accumulation according to the L/S density ratio ($P = .008$), whereas there was no difference in the atorvastatin group ($P = .158$). There were 56 reported adverse events, all being classified as mild, and all but 2 subjects reported spontaneous resolution of the adverse event. One patient reported experiencing myalgias. In addition, 3 patients had an elevation in their creatinine kinase (CK) concentrations; however, it is unknown whether these elevations were clinically significant.
Although this trial assessed 2 specific statins, the analysis did not compare the two. In addition, the biochemical markers studied may not be the most reliable indicators for liver impairment.

In another study by Rana et al., statins were compared with insulin sensitizers in patients with NAFLD. No baseline characteristics were reported. No difference was noted for changes in weight between the groups at 24 weeks. At the end of 24 weeks, there was a significant difference between the groups for ALT, but not for AST. Cholesterol parameters were significantly reduced compared with baseline values in all groups. Rosuvastatin and pioglitazone had a significant reduction in ultrasonography (USG) scores at 24 weeks (both scores fell below 2; \( P < .001 \) for both), whereas metformin showed no difference compared with baseline. The USG score was used to grade hepatic steatosis, with a score of 2 or more representing fatty liver. This study is unique in that it used active comparators to assess efficacy.

**Impact of statins on fibrosis/NASH outcomes**

The efficacy of pitavastatin and rosuvastatin was assessed in 2 open-label pilot studies in patients with NASH and dyslipidemia.\(^{26,27}\) All patients had biopsy-proven NASH. Steatosis was graded as 1-3; necroinflammation was graded as 0-3; fibrosis was graded as 0-4; and ballooning was graded as 0-2, with higher numbers representing increased severity in all aforementioned parameters. The studies also analyzed the NAS. None of the patients in either study had cirrhosis. After 12 months on pitavastatin, mean ALT and GGT concentrations decreased (\( P < .01 \) and \( P < .05 \), respectively).\(^{26}\) Out of 13 patients who had a follow-up liver biopsy, there were no changes in steatosis, inflammation, or fibrosis (no \( P \) values reported). There were 54% of patients who had improvement in NAS, 15% with no change, and 31% with deterioration. The authors did not disclose whether there were any similar patient characteristics within the group which deteriorated while on statin therapy. The methodology of the study by Nakahara et al.\(^{25}\) was identical to the previous, with the exception of rosuvastatin instead of pitavastatin being studied. Mean changes in AST and ALT were not statistically significant compared with baseline (specific \( P \) values not reported). At the end of the study, 9 patients had follow-up biopsies, and there were no changes in the NAS or fibrosis stage. No adverse effects, including elevated CK concentrations, were observed in either study. Only a small sample of the study population underwent a final biopsy making external validity an issue.

In a recent study by Kargiotis et al., patients with biopsy-proven NASH were given rosuvastatin to determine whether there would be any resolution of the disease. Liver biopsy and USG showed resolution of NASH in 19 out of 20 patients. Serum ALT, AST, and GGT were normalized by the third treatment month (\( P < .001 \)), and alkaline phosphatase was normalized by the sixth treatment month (\( P = .01 \)). This was a very small study in a population with a relatively low cardiovascular risk, as overt CVD and type 2 diabetes mellitus were part of the exclusion criteria. There were no placebo or active treatment groups for comparison with determine the efficacy of rosuvastatin. However, the liver histology findings regarding the resolution of NASH are pertinent and promising.

**Impact of statin use on HCC outcomes**

Only 1 trial was found which assessed the incidence of HCC in statin versus nonstatin users. In a study by Lee et al., various patient characteristics were assessed to determine the risk of HCC in patients with noncirrhotic NAFLD. Between 1998 and 2012, patients in Taiwan’s National Health Insurance Research Database were screened for NAFLD and HCC. Out of 18 080 patients with NAFLD, the 10-year cumulative incidence of HCC was 2.73%. Statins were used in 35% of the patients with NAFLD. Compared with the patients not on statin therapy, statin use was associated with a reduced risk of HCC incidence (\( P = .005 \)). This study did not assess a specific statin and was limited to only patients available in the insurance database. However, this is one of the first studies which shows a potential protective effect of statins on the development of HCC. As the patients were limited to only noncirrhotic patients, it remains unknown whether the same benefit exists in patients with cirrhosis.

**Discussion**

In the 12 trials reviewed, statin use demonstrated overall mixed results for several surrogate markers of inflammation and liver damage. Most studies, but not all, showed a reduction in liver enzymes, however, none reported worsening. Individual studies showed either a reduction in or no change to fibrosis staging and NAS. One study demonstrated a higher FIB-4 index, whereas 2 others saw positive benefits in L/S density ratio. In one study, statins were linked to a decrease in TNF-\( \alpha \), whereas another study demonstrated a correlation between statin use and reduced USG scores as well as weight. Although there were histological outcome studies, several trials lacked a comparator group, had a small sample size, and were short in duration. Unfortunately, although NASH can progress to cirrhosis, none of the trials assessed this complication as an outcome, and there also remain limited data on patients with HCC. All of the trials did appropriately exclude patients with other causes of fatty liver and those taking medications which may have affected the outcomes. Because most of the above trials were published before the release of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) lipid guidelines,\(^{30}\) it is not known whether the intensity of the statin correlates with hepatocellular improvement.

Other limitations from specific trials include patient populations being restricted to certain geographic regions. The types and doses of statins were not reported in all trials, so it remains unknown whether a particular statin might have skewed the
results. The largest limitation to studies by de Keyser, Oni, and Nascimbeni is the potential for confounding by indication. In these patient populations, statin users tended to have more risk factors for the development of NAFLD, which is also more likely to be seen in the general population of statin users.

For patients with NAFLD with dyslipidemia, guidelines recommend statins as part of the armamentarium for treatment due to these patients typically having an atherogenic dyslipidemic profile (increased triglycerides, low high-density lipoprotein cholesterol, and increased small, dense, LDL-C particles), along with the proven benefits for statins to decrease CVD risks.1,3,31 A post hoc analysis published in 2010 of the prospective Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study focused on patients with coronary heart disease and abnormal LFTs (presumed to be due to NAFLD) who were treated with a statin or usual care.32 Patients with elevated enzymes who received statin therapy compared with those who had no fewer cardiovascular events (10% versus 30%, 68% radiological response rate; P < .001). In patients receiving statins, AST, ALT, and GGT concentrations were decreased (P < .001 for all) compared with baseline, whereas those not receiving statins had an increase in liver enzymes (P < .01 for all) at the end of the study. This trial demonstrated potential safety with statins in patients with moderately abnormal liver tests in patients with NAFLD and demonstrated cardiovascular protection in this patient population. There are also several small studies showing improvement in patients’ lipid panels, decreased liver enzymes, and a lack of evidence for hepatotoxicity associated with the use of statins.3,13,16,31

Besides the positive lipid-lowering effects of statins, the pleiotropic benefits may include decreasing progression of hepatic inflammation and fibrosis via anti-inflammatory, antiapoptotic, antiatherogenic, and antioxidant effects.33 Pleiotropic effects of statins have also been shown to decrease stress-activated c-Jun N-terminal kinase (JNK), reduce hepatic transforming growth factor β and connective tissue growth factor, increase peroxisomal β-oxidation; upregulate the expression of endothelial nitric oxide synthase (NOS) and downregulate the expression of inducible NOS; and prevent activation of hepatic stellate cells.33

A search through the US National Institutes of Health Clinical Trials database (clinicaltrials.gov) revealed 6 studies researching NAFLD/NASH treatment using statin therapy, with 5 of the studies focusing on atorvastatin.34–38 These trials compare atorvastatin with an active treatment: obeticholic acid, vitamin E, t-carnitine, metformin, or lifestyle counseling. The other agent currently being studied is pitavastatin, which is being compared with placebo.39 Outcomes for these trials vary, but all include some primary or secondary nonlipid outcomes focusing on hepatic clinical biochemical and/or ultrasound markers, which will help to add to the literature regarding the potential safety and efficacy of statins in the treatment of NAFLD.

Overall, recommendations from this update on the use of statins in patients with NAFLD are limited to currently available published literature and guidelines. The use of statins has been demonstrated to lower surrogate cholesterol markers for CVD prevention, and concurrent treatment of dyslipidemia is supported by the guidelines. Statin use for treatment of NAFLD is still controversial and off-label, but positive results have been shown for reductions in LFTs. In addition, pleiotropic effects may help provide anti-inflammatory and antioxidant effects, but consistent histological data are still pending. Statin use is likely safe in patients with LFTs < 3 times the ULN, as hepatic adverse events are rarely seen, which is supported by updated labeling which limits the need for routine monitoring. Given that CVD is the most common cause of death among patients with NAFLD, the use of statins for prevention and treatment of CVD seems to outweigh the risk for further adverse effects. Continued research into the role of statins and hepatic outcomes in patients with NAFLD are warranted.

Author Contributions
MAS: Responsible for design, data queries, analysis, and manuscript development, and final review of manuscript. LC: Responsible for data queries, manuscript development, and manuscript updates. KLE: Responsible for data queries, manuscript development, and manuscript updates.

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