

Statin Prescribing Patterns in Patient-Centered Medical Home Patients With NAFLD

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Nonalcoholic fatty liver disease (NAFLD) affects more than 30% of the US population, and its prevalence is anticipated to grow in the coming years.¹⁻³ NAFLD is a major contributor to the growing burden of chronic liver disease nationally and has emerged as a leading cause of cirrhosis, hepatocellular carcinoma, need for liver transplantation, and liver-related mortality.⁴⁻⁷ Despite NAFLD's immense contribution to severe liver outcomes, the leading cause of death among affected patients is cardiovascular disease (CVD).^{8,9} NAFLD is associated with other known CV risk factors including metabolic syndrome, type 2 diabetes, obesity, and hyperlipidemia, which may contribute to the relationship observed with CVD.¹⁰⁻¹³ However, a recent meta-analysis demonstrated an independent association between NAFLD and CVD risk (HR, 1.45; 95% CI, 1.31-1.61) when controlling for these aforementioned CVD risk factors.⁹ It is not well understood how NAFLD may be related to CVD, but it has been suggested that low-grade inflammation and oxidative stress may play a role.¹⁴⁻¹⁶

Statin therapy has become the standard of care for primary and secondary prevention of CV events such as stroke and myocardial infarction. Statins are currently indicated in those with elevated CVD risk defined by the presence of diabetes, obesity, hypertension, and hyperlipidemia.¹⁷ Despite the link between NAFLD and these drivers of CVD risk, a diagnosis of NAFLD is not yet an indication for statin prescribing. Thus, patients with NAFLD may not receive statin prescriptions despite their heightened risk for CVD.^{18,19} Additionally, NAFLD is among the leading causes of elevated aminotransferase (ie, aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) levels in primary care. Many patients with aminotransferase elevations have not historically received statin prescriptions due to the potential for hepatotoxicity, a safety concern that was allayed with an FDA safety announcement in 2012.²⁰⁻²² Multiple studies have continued to verify the safety of statins in patients with aminotransferase abnormalities, and some even demonstrate a decrease in aminotransferases in treated patients.²³⁻²⁵

Our goal was to investigate statin prescribing in primary care patients with NAFLD to determine if and how CVD risk is being addressed in this cohort of at-risk patients. We hypothesized that

ABSTRACT

OBJECTIVES: Cardiovascular disease is the leading cause of mortality in patients with nonalcoholic fatty liver disease (NAFLD), and statins play a pivotal role in the primary prevention of cardiovascular events. This study investigates statin prescribing in primary care patients with NAFLD to identify opportunities to address cardiovascular disease risk in this cohort.

STUDY DESIGN: Retrospective cohort study of primary care electronic health record data from 2012-2018.

METHODS: This cohort included 652 patients with radiographic evidence of hepatic steatosis and no evidence of competing chronic liver disease. A statin prescription identified at any time during the study period was the primary outcome. Univariate and multivariable analyses were performed to evaluate the association of clinical signals and comorbidities with statin prescribing.

RESULTS: Of the 652 patients in the NAFLD cohort, 56% received a statin prescription during the study period. Elevations in aminotransferases were not associated with statin prescribing [adjusted odds ratio [AOR], 1.17; 95% CI, 0.78-1.76], whereas older patients [AOR, 1.06; 95% CI, 1.05-1.08] and those with diabetes [AOR, 2.61; 95% CI, 1.73-3.92], hypertension [AOR, 2.76; 95% CI, 1.70-4.48], and a BMI greater than or equal to 30 kg/m² [AOR, 1.49; 95% CI, 1.01-2.22] had higher odds of having a statin prescribed. Of the 288 patients without a statin prescription, 49% had an indication for statin therapy by atherosclerotic cardiovascular disease risk. In total, 16% of included patients did not have lipid panel results during the study period.

CONCLUSIONS: This study showed no association between NAFLD and statin prescribing, and the findings highlight opportunities to improve primary prevention of cardiovascular disease in these at-risk patients.

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statins would be underutilized in patients with NAFLD, especially in those with abnormal aminotransferases.

METHODS

This retrospective cohort study of electronic health record (EHR) data from a patient-centered medical home (PCMH) evaluated statin prescribing for primary care patients with presumed NAFLD, identified by radiographic report of hepatic steatosis and the absence of competing liver diseases.²⁶ This primary care, internal medicine PCMH in Charleston, South Carolina, delivers highly coordinated, team-based care to more than 12,000 patients and includes physicians, nurses, case managers, and pharmacists in an urban setting.

Study Population

Patients seen in the Internal Medicine PCMH at the Medical University of South Carolina (MUSC) with at least 1 abdominal image (ultrasound, CT, or MRI) from 2012 through 2018 with evidence of hepatic steatosis were evaluated. Cohort inclusion required aminotransferase and platelet laboratory results at the time of, or within the 1 year prior to, the first abdominal imaging report with steatosis. Patients with a diagnosis, laboratory result, or exposure history (ie, alcohol use documentation) suggestive of a non-NAFLD chronic liver disease or severe liver disease outcome (eg, cirrhosis, hepatocellular carcinoma) were excluded (eAppendix [available at ajmc.com]).²⁶ The institutional review board at MUSC approved this study.

Outcome

Statin prescription recorded by the EHR on at least 1 occasion during the study period was the primary outcome of interest. The PCMH EHR electronic order entry feature was implemented across the institution enterprise in 2012. EHR prescription data included both printed and electronically transmitted prescriptions and incorporated data from the outpatient, emergency department (ED), and inpatient settings at this institution. Inpatient and ED prescriptions comprised those printed or transmitted to pharmacies and did not include statins provided during hospital or ED care episodes.

Covariates

Based on our hypothesis, aminotransferase abnormality served as the primary predictor variable. AST and ALT results needed to have occurred within 1 year preceding the image of hepatic steatosis. AST and ALT levels were categorized as elevated (AST > 34 U/L and ALT > 45 U/L) using the upper limit of normal thresholds within the institution's EHR in an effort to model the aminotransferase signal most likely used by primary care clinicians. AST and ALT were also analyzed as continuous variables.

TAKEAWAY POINTS

Patients with nonalcoholic fatty liver disease (NAFLD) are at heightened risk for cardiovascular disease. This study demonstrates opportunities to improve statin prescribing to mitigate cardiovascular risk in this population.

- ▶ This study showed no association of aminotransferase elevations or NAFLD diagnosis with receipt of statin therapy, and 16% of patients in this cohort had no lipid panel results during the study period.
- ▶ Statin prescriptions were more prevalent in those with hypertension, diabetes, and body mass index greater than or equal to 30 kg/m².
- ▶ It is imperative for providers to address cardiovascular disease in patients with NAFLD through modifiable risk factors, including hyperlipidemia.

Age, sex (male/female), body mass index (BMI), and race (Black, non-Black) variables were included. Laboratory variables within the EHR from 2011 to 2018 (to allow 1 year prior to steatosis for aminotransferases) comprised bilirubin, alkaline phosphatase, platelets, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. All laboratory variables were analyzed as continuous variables, and BMI was categorized as BMI of less than 30 kg/m² and BMI greater than or equal to 30 kg/m². Cholesterol levels came from the first lipid (LDL, HDL, and triglyceride) values identified during the study period and the proportion of patients with lipid results were calculated.

Clinical indications for statin prescribing and other comorbidities were identified using composites of *International Classification of Diseases, Ninth Revision (ICD-9)* and *Tenth Revision (ICD-10)* codes from Elixhauser coding algorithms.^{27,28} Comorbidities included CVD (coronary artery disease and cerebrovascular disease), diabetes, and hypertension. We also included known diagnosis of NAFLD (*ICD-9*: 571.8; *ICD-10*: K76.0, K75.8) as a covariate.²⁹ NAFLD severity was estimated using noninvasive advanced fibrosis risk scores. We calculated Fibrosis-4 Index (FIB-4) and NAFLD Fibrosis Scores (NFS) for each patient using the included covariates and categorized them as high risk (FIB-4 \geq 2.67; NFS \geq 0.676) or not based on each score.³⁰⁻³² The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on Assessment of Cardiovascular Risk was utilized to determine indication for statin use in our cohort patients with no statin prescription (statin indication being a 10-year atherosclerotic CVD [ASCVD] risk > 7.5%). This was calculated using the most recent lipid values in the study period.³³ We were unable to calculate ASCVD risk for those without lipid panels, and we categorized these patients as without an indication for statin therapy. Patient characteristics were compared by statin indication.

Statistical Analysis

Cohort characteristics were calculated for the overall sample and by aminotransferase elevation. Categorical variables were displayed as proportions and compared by χ^2 tests. Continuous variables (except for age) were presented as medians with IQRs and compared by Mann-Whitney U tests. Age is shown as a mean with SD and compared using a 2-sample *t* test. The proportion of cohort patients

TABLE 1. Cohort Characteristics Overall and by Aminotransferase Abnormality

Characteristics	Overall n = 652	Elevated AST or ALT level		P
		Yes n = 245	No n = 407	
Demographics				
Age in years, mean (SD)	54.7 (14.1)	52.5 (14.1)	56.0 (13.9)	.002 ^a
Sex, n (%)				.004 ^b
Male	234 (35.9%)	105 (42.9%)	129 (31.7%)	
Female	418 (64.1%)	140 (57.1%)	278 (68.3%)	
Race, n (%)				.012 ^b
Black	234 (35.9%)	73 (29.8%)	161 (39.6%)	
Non-Black	418 (64.1%)	172 (70.2%)	246 (60.4%)	
Clinical variables, median (IQR)				
BMI, kg/m ²	32.4 (27.7-37.6)	31.6 (27.3-37.1)	32.7 (27.8-38.5)	.096 ^c
Bilirubin, mg/dL	0.5 (0.4-0.8)	0.6 (0.4-0.95)	0.5 (0.4-0.7)	<.001 ^c
AST, U/L	26 (20-39)	48 (36-74)	22 (18-26)	<.001 ^c
ALT, U/L	28 (19-49)	60 (46-86)	22 (17-28)	<.001 ^c
ALP, U/L	82 (66-105)	89 (68-122)	79 (64-98)	<.001 ^c
Platelets, × 10 ³ /L	241 (200-293)	233 (185-290)	246 (207-294)	.058 ^c
Lipid variables				
Lipid results, n (%)	563 (86.4%)	209 (85.3%)	354 (87.0%)	.547 ^b
LDL, median (IQR)	100 (77-127)	102 (78-132)	99 (76-125)	.231 ^c
HDL, median (IQR)	44 (37-55)	45 (37-56)	44 (37-54)	.599 ^c
Triglycerides, median (IQR)	135 (92-203)	135.5 (90-213)	135 (93-197)	.839 ^c
Comorbidities, n (%)				
NAFLD (diagnosed)	164 (25.2%)	83 (33.9%)	81 (19.9%)	<.001 ^b
Cardiovascular disease	153 (23.5%)	55 (22.5%)	98 (24.1%)	.634 ^b
Diabetes	300 (46.0%)	103 (42.0%)	197 (48.4%)	.114 ^b
Hypertension	507 (77.8%)	189 (77.1%)	318 (78.1%)	.769 ^b
High-risk advanced fibrosis assessments, n (%)				
FIB-4 (≥2.67)	75 (11.5%)	59 (24.1%)	16 (3.9%)	<.001 ^b
NFS (≥0.676)	117 (17.9%)	46 (18.8%)	71 (17.4%)	.668 ^b

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 Index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD Fibrosis Score.

^aTwo-sample Student *t* test.

^bChi-square test.

^cMann-Whitney U test.

with a prescription for a statin was calculated, and covariates were compared by statin prescription. Logistic regression models for the outcome of a statin prescription were developed. The first model included the primary predictor variable of AST or ALT elevation and comorbidities, many of which play a role in determining an indication for statin therapy: CVD, diabetes, and hypertension. A known diagnosis of NAFLD was also included as a categorical covariate. The second model included all covariates from the first model plus age, sex, race, BMI, and FIB-4/NFS risk status. Model covariates were selected a priori. Multicollinearity was assessed. Model 2 initially included bilirubin, alkaline phosphatase, and platelets, but these were removed with little change to model fit. Sensitivity analyses were performed using elevated AST and ALT, elevated AST, and elevated ALT levels as

predictor variables. A sensitivity analysis with AST and ALT as continuous predictor variables was also performed. SAS 9.4 (SAS Institute) was used for all analyses.

RESULTS

The primary care NAFLD cohort included 652 patients with a mean (SD) age of 55 (14) years, median (IQR) BMI of 32.4 (27.7-37.6) kg/m², median (IQR) AST of 26 (20-39), and median (IQR) ALT of 28 (19-49) (Table 1). Of the cohort, 64% were female, 36% were Black, and 24%, 46%, and 78% had CVD, diabetes, and hypertension, respectively. Serologic advanced fibrosis scores were high risk in 12% (FIB-4) and 18% (NFS) of patients. One in 4 patients received a formal diagnosis of NAFLD; 16% of patients did not have lipid results during the study period.

Elevated AST or ALT values were identified in 38% (245) of the patient sample. Higher proportions of patients with elevated aminotransferases were younger, male, and non-Black and had a diagnosis of NAFLD compared with those with AST and ALT results in the normal range (Table 1).

Overall, 56% of patients received a prescription for statin therapy. A similar proportion of patients receiving a statin prescription and those not receiving a statin prescription had AST and ALT abnormalities, and the groups had similar AST and ALT values (Table 2). Patients with a statin ordered were older, had higher BMIs (median, 33.2 vs 31.5; *P* = .025), and had higher proportions of CVD (30% vs 16%; *P* < .001), diabetes (59% vs 30%; *P* < .001), and hypertension (90% vs 62%; *P* < .001) than patients without statins prescribed. The proportion of patients with an ICD-9 or ICD-10 diagnosis

of NAFLD did not differ by statin prescription. The proportion of patients with high-risk FIB-4 scores were similar by statin group, and a higher proportion of patients prescribed a statin had a high-risk NFS compared with those not receiving a statin.

Higher proportions of patients with multiple components of metabolic syndrome, including hypertension, diabetes, hyperlipidemia, and NAFLD, received statin therapies compared with those with only a single component (Table 2). Of the 15 patients with NAFLD and no diagnosis of hypertension, diabetes, or hyperlipidemia, none had a statin prescribed (*P* < .001) (Table 2).

The first logistic regression model (model 1) demonstrated no significant association between elevated AST or ALT values and a statin prescription outcome (AOR, 0.88; 95% CI, 0.62-1.25) when

adjusting for medical comorbidities (Table 3). CVD (AOR, 1.52; 95% CI, 1.00-2.32), diabetes (AOR, 2.29; 95% CI, 1.61-3.26), and hypertension (AOR, 4.20; 95% CI, 2.71-6.53) were associated with higher odds of receiving a statin prescription. No significant association was observed between diagnosed NAFLD (AOR, 1.18; 95% CI, 0.79-1.75) and the statin outcome.

Model 2 incorporated demographic, clinical, and high-risk fibrosis assessment variables (Table 3). Again, AST or ALT elevations were not significantly associated with statin prescribing (AOR, 1.17; 95% CI, 0.78-1.76). CVD (AOR, 1.72; 95% CI, 1.09-2.71), diabetes (AOR, 2.61; 95% CI, 1.73-3.92), hypertension (AOR, 2.76; 95% CI, 1.70-4.48), advancing age (AOR, 1.06; 95% CI, 1.05-1.08), and BMI greater than or equal to 30 kg/m² (AOR, 1.49; 95% CI, 1.02-2.22) were associated with higher odds of receiving a statin. Diagnoses of NAFLD (AOR, 1.29; 95% CI, 0.84-1.98) and high-risk fibrosis assessments (FIB-4: AOR, 0.87; 95% CI, 0.45-1.68; NFS: AOR, 0.59; 95% CI, 0.34-1.04) were not significantly associated with statin prescription outcomes.

Of the 288 patients with no statin prescription, 49% (n = 141) had an indication for a statin using the ASCVD risk calculator and patients' most recent lipid test results as inputs (Table 4). The proportion of patients with an indication for a statin who had a formal diagnosis of NAFLD was similar to that of patients without a statin indication (24.1% vs 21.8%; P = .636). Higher proportions of patients with an indication for a statin had diabetes (50.4% vs 10.2%; P < .001), hypertension (77.3% vs 46.9%; P < .001), and hyperlipidemia (41.8% vs 20.4%; P < .001) compared with patients with no indication for statin therapy.

DISCUSSION

Overall, 56% of this primary care NAFLD cohort received a prescription for a statin during the study period, but statin prescribing did not differ by aminotransferase abnormalities or NAFLD diagnosis. Although NAFLD's association with CVD is not fully understood, numerous studies have demonstrated an association between the 2 diseases and therefore many patients with NAFLD would surely benefit from statin therapy, if not based on a diagnosis of NAFLD alone then perhaps due to their other comorbidities.^{14,23,33}

Many barriers exist to increasing statin prescriptions in those with NAFLD. One of the most significant barriers is that many patients in the early stages of NAFLD are asymptomatic, resulting in significant underdiagnosis.³⁴ It is also possible that many providers are unaware that CVD is the leading cause of mortality in patients with NAFLD, and thus they do not always make the association between NAFLD and risk of CVD events. Our data show that 16% of patients included in this study had no lipid panel completed throughout the study period (2012-2018). The association between NAFLD and metabolic syndrome has now been shown in numerous studies, and therefore investigating lipids in patients with NAFLD is warranted. No national guideline or recommendation to treat isolated NAFLD with statin therapy for primary or secondary prevention of ASCVD existed during the study period, nor does one currently exist. The

TABLE 2. Patient Characteristics by Statin Prescription

Characteristic	Statin prescription		P
	Yes n = 364	No n = 288	
Aminotransferase variables			
Elevated AST or ALT, n (%)	131 (36.0%)	114 (39.6%)	.347 ^a
Elevated AST, n (%)	117 (32.1%)	91 (31.6%)	.882 ^a
Elevated ALT, n (%)	98 (26.9%)	89 (30.9%)	.265 ^a
AST, median (IQR)	26 (20-40)	26.3 (20-39)	.748 ^b
ALT, median (IQR)	28 (19-48)	29.8 (20-49)	.498 ^b
Demographics			
Age in years, mean (SD)	59.5 (11.8)	48.6 (14.5)	<.001 ^c
Sex, n (%)			.575 ^a
Male	146 (35.1%)	88 (37.3%)	
Female	270 (64.9%)	148 (62.7%)	
Race, n (%)			.191 ^a
Black	157 (37.7%)	77 (32.6%)	
Non-Black	259 (62.3%)	159 (67.4%)	
Clinical variables, median (IQR)			
BMI, kg/m ²	33.2 (28.6-37.6)	31.5 (26.9-37.6)	.025 ^b
Bilirubin, mg/dL	0.5 (0.4-0.8)	0.6 (0.4-0.9)	.331 ^b
ALP, U/L	82 (66-102)	82.5 (66-107)	.688 ^b
Platelets, × 10 ⁹ /L	238 (200-290)	245 (204-304)	.253 ^b
Comorbidities, n (%)			
NAFLD, diagnosed	98 (26.9%)	66 (22.9%)	.242 ^a
Cardiovascular disease	108 (29.7%)	45 (15.6%)	<.001 ^a
DM	214 (58.8%)	86 (29.9%)	<.001 ^a
HTN	329 (90.4%)	178 (61.8%)	<.001 ^a
HPL	353 (97.0%)	89 (30.9%)	<.001 ^a
NAFLD, DM, HTN, and HPL	63 (17.3%)	8 (2.8%)	<.001 ^a
3 of NAFLD, DM, HTN, and HPL	167 (45.9%)	42 (14.6%)	<.001 ^a
2 of NAFLD, DM, HTN, and HPL	256 (70.3%)	207 (71.9%)	.666
NAFLD only	0 (0.0%)	15 (5.2%)	<.001 ^a
No NAFLD, DM, HTN, or HPL	1 (0.3%)	58 (20.1%)	<.001 ^a
High-risk advanced fibrosis assessments, n (%)			
FIB-4 (≥ 2.67)	45 (12.4%)	30 (10.4%)	.439 ^a
NFS (≥ 0.676)	78 (21.4%)	39 (13.5%)	.009 ^a
Lipid variables			
Lipid results, n (%)	354 (97.3%)	209 (72.6%)	<.001 ^a
LDL, median (IQR)	99 (75-130)	102 (79-125)	.998 ^b
HDL, median (IQR)	43 (37-54)	46 (37-56)	.289 ^b
Triglycerides, median (IQR)	140 (97-212)	133 (88-194)	.203 ^b

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus; FIB-4, Fibrosis-4 Index; HDL, high-density lipoprotein; HPL, hyperlipidemia; HTN, hypertension; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD Fibrosis Score.

^aChi-square test.

^bMann-Whitney U test.

^cTwo-sample Student *t* test.

CLINICAL

TABLE 3. Estimated ORs for Multivariable Logistic Regression Models for the Outcome of Receiving a Statin Prescription

Characteristic	Model 1		Model 2 ^a	
	OR	95% CI	OR	95% CI
Aminotransferase variable				
Elevated AST or ALT	0.88	0.62-1.25	1.17	0.78-1.76
Comorbidities				
NAFLD, diagnosed	1.18	0.79-1.75	1.29	0.84-1.98
Cardiovascular disease	1.52	1.00-2.32	1.72	1.09-2.71
Diabetes	2.29	1.61-3.26	2.61	1.73-3.92
Hypertension	4.20	2.71-6.53	2.76	1.70-4.48
Demographics				
Age in years			1.06	1.05-1.08
Male (reference: female)			0.77	0.52-1.13
Black (reference: non-Black)			1.04	0.68-1.58
Clinical variables, median (IQR)				
BMI ≥ 30 kg/m ²			1.49	1.01-2.22
High-risk advanced fibrosis assessments				
FIB-4 (≥ 2.67)			0.87	0.45-1.68
NFS (≥ 0.676)			0.59	0.34-1.04

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 Index; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD Fibrosis Score; OR, odds ratio.

^aBilirubin, alkaline phosphatase, and platelet count were originally included in the model, but were not significant and removal did not affect overall model fit ($C=0.794$). Sensitivity analyses with elevated AST and ALT, elevated AST, elevated ALT, AST (continuous), and ALT (continuous) were performed with no significant change in results.

results of this study demonstrate an opportunity for providers to address CVD risk by acquiring lipid panels and calculating ASCVD risk scores in patients with NAFLD.

Current guidelines for the use of statins in primary prevention of CVD likely also preclude more prescribing among patients with NAFLD. The 2013 ACC/AHA document used in our analysis recommended statins for primary prevention in patients aged 40 to 75 years with a 10-year risk of CV events greater than or equal to 7.5%. Currently, the US Preventive Services Task Force (USPSTF) recommends statin prescriptions in patients with 1 or more CVD risk factors and a calculated 10-year risk of CV events 10% of higher.^{35,36} The CVD risk factors listed in the USPSTF recommendation include dyslipidemia, diabetes, hypertension, and smoking, whereas the ASCVD scoring system accounts for diabetes, sex, smoking history, hyperlipidemia, and hypertension diagnoses.^{11,36} The absence of NAFLD in the USPSTF and ASCVD risk assessments could explain why diabetes and hypertension had statistically significant associations with statin prescribing throughout our study whereas NAFLD did not have any association at all. Although neither the USPSTF nor ASCVD risk scoring has historically accounted for NAFLD as a CVD risk factor, the AHA recently released new guidance highlighting NAFLD as a risk-enhancer for ASCVD.³⁷ In our NAFLD cohort, 51% would not have met criteria for statin therapy based on 2013 guidelines. Additionally, a portion of those classified as

TABLE 4. Cohort Patients Without a Statin Prescription by ASCVD Risk Indication for Statin Therapy

Characteristic	Overall n = 288	ASCVD risk indication		P
		Yes n = 141	No n = 147	
Demographics				
Age in years, mean (SD)	48.6 (14.5)	53.6 (14.2)	43.9 (13.0)	<.001 ^a
Sex, n (%)				.048 ^b
Male	114 (39.6%)	64 (45.4%)	50 (34.0%)	
Female	174 (60.4%)	77 (54.6%)	97 (66.0%)	
Race, n (%)				.260 ^b
Black	93 (32.3%)	50 (35.5%)	43 (29.3%)	
Non-Black	195 (67.7%)	91 (64.5%)	104 (70.8%)	
Clinical variables, n (%)				
BMI ≥ 30 kg/m ²	162 (56.3%)	76 (53.9%)	86 (58.5%)	.431 ^b
Comorbidities, n (%)				
NAFLD (diagnosed)	66 (22.9%)	34 (24.1%)	32 (21.8%)	.636 ^b
Diabetes	86 (29.9%)	71 (50.4%)	15 (10.2%)	<.001 ^b
Hypertension	178 (61.8%)	109 (77.3%)	69 (46.9%)	<.001 ^b
Hyperlipidemia	89 (30.9%)	59 (41.8%)	30 (20.4%)	<.001 ^b

ASCVD, atherosclerotic cardiovascular disease, as calculated by 2013 American College of Cardiology/American Heart Association Guideline on the Assessment of Cardiovascular Risk; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease.

^aTwo-sample Student *t* test.

^bChi-square test.

“no ASCVD risk indication” for statin therapy were categorized this way due to an absence of lipid panel results, which likely results in a conservative underestimation of the scale of unmet care need in this patient sample. As providers, we do not typically consider risk factors outside of what is recommended in the current guidelines, and thus NAFLD is not routinely accounted for in these situations.

Even if patients meet criteria for statin use based on current guidelines for primary CVD prevention, statins are unfortunately still heavily underutilized.¹⁹ In our cohort, 49% of patients without statin prescriptions had an indication for statin therapy based on the 2013 ASCVD risk ACC/AHA guidelines. There are many reasons for this underprescribing, which ultimately contributes to the significant gap in CV risk reduction in NAFLD cohort patients.

We had hypothesized that abnormal liver function tests may play a role in preventing statin prescribing in those with NAFLD given the historically well-known hepatotoxicity of statins, as many patients with NAFLD present with abnormal aminotransferases. Contrarily, our data showed that proportions of patients with abnormal aminotransferases (36% vs 40%; $P=.35$) were similar in patients with and without statin prescriptions, suggesting that LFT abnormalities did not heavily influence prescription practices. Other studies have shown that in recent years, statin use has increased among patients with liver disease (NAFLD included) and abnormal aminotransferase levels.

Limitations

Data were extracted from a single center, which may threaten the generalizability of the findings. However, the primary care focus and the characteristics of the cohort are representative of many US primary care practices. Additionally, no causation can be elicited from this retrospective cohort study. Our study included only those patients with abdominal imaging results, which likely excluded many other patients with NAFLD in this primary care setting. We were unable to see when statin prescriptions were started, and the cohort did not include those with multiple liver disease etiologies.

CONCLUSIONS

Our study demonstrates ample opportunity to increase CV risk assessment and statin prescribing in primary care patients with NAFLD. CV events are the leading cause of death in those with NAFLD, and the beneficial effects of statins in CVD are well established. Evidence points toward the opinion that the majority of patients with NAFLD would also benefit from statin therapy as primary prevention of CVD. This study presents an opportunity to improve primary prevention in this population at risk for CVD, although further studies are indicated to determine the best way of doing so. It is imperative to shift our practices toward focusing on reducing CV risk in these patients, including increasing statin use in this growing population. ■

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REFERENCES

1. Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J Hepatol*. 2018;69(4):896-904. doi:10.1016/j.jhep.2018.05.036
2. Harrison SA, Gawrieh S, Roberts K, et al. Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort. *J Hepatol*. 2021;75(2):284-291. doi:10.1016/j.jhep.2021.02.034
3. Zhang X, Heredia NI, Balakrishnan M, Thrift AP. Prevalence and factors associated with NAFLD detected by vibration controlled transient elastography among US adults: results from NHANES 2017-2018. *PLoS One*. 2021;16(6):e0252164. doi:10.1371/journal.pone.0252164
4. Moon AM, Singal AG, Tapper EB. Contemporary epidemiology of chronic liver disease and cirrhosis. *Clin Gastroenterol Hepatol*. 2020;18(12):2650-2666. doi:10.1016/j.cgh.2019.07.060
5. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020;5(3):245-266. doi:10.1016/S2468-1253(19)30349-8

6. Zhai M, Liu Z, Long J, et al. The incidence trends of liver cirrhosis caused by nonalcoholic steatohepatitis via the GBD study 2017. *Sci Rep*. 2021;11(1):5195. doi:10.1038/s41598-021-84577-z
7. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. *BMJ*. 2018;362:k2817. doi:10.1136/bmj.k2817
8. 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(1):73-84. doi:10.1002/hep.28431
9. Mantovani A, Cserrmely A, Petracca G, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2021;6(11):903-913. doi:10.1016/S2468-1253(21)00308-3
10. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328-357. doi:10.1002/hep.29367
11. Bibbins-Domingo K, Grossman DC, Curry SJ, et al; US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;316(19):1997-2007. doi:10.1001/jama.2016.15450
12. Mantovani A, Scortetti E, Mosca A, Alisi A, Byrne CD, Targher G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. *Metabolism*. 2020;111S:154170. doi:10.1016/j.metabol.2020.154170
13. Powell EE, Wong WWS, Rinella M. Non-alcoholic fatty liver disease. *Lancet*. 2021;397(10290):2212-2224. doi:10.1016/S0140-6736(20)32511-3
14. Targher G, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. *Gut*. 2020;69(9):1691-1705. doi:10.1136/gutjnl-2020-320622
15. Polimeni L, Del Ben M, Baratta F, et al. Oxidative stress: new insights on the association of non-alcoholic fatty liver disease and atherosclerosis. *World J Hepatol*. 2015;7(10):1325-1336. doi:10.4254/wjh.v7.i10.1325
16. Ferro D, Baratta F, Pastori D, et al. New insights into the pathogenesis of non-alcoholic fatty liver disease: gut-derived lipopolysaccharides and oxidative stress. *Nutrients*. 2020;12(9):2762. doi:10.3390/nu12092762
17. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;74(10):1376-1414. doi:10.1016/j.jacc.2019.03.009
18. Labenz C, Prochaska JH, Huber Y, et al. Cardiovascular risk categories in patients with nonalcoholic fatty liver disease and the role of low-density lipoprotein cholesterol. *Hepatal Commun*. 2019;3(11):1472-1481. doi:10.1002/hep4.1428
19. Henson JB, Patel YA, Muir AJ. Trends in statin utilisation in US adults with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2021;54(11-12):1481-1489. doi:10.1111/apt.16646
20. FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. FDA. February 28, 2012. Updated January 19, 2016. Accessed November 20, 2022. <https://bit.ly/3DpUaAY>
21. Mercado C, DeSimone AK, Odom E, Gillespie C, Ayala C, Loustalot F. Prevalence of cholesterol treatment eligibility and medication use among adults—United States, 2005-2012. *MMWR Morb Mortal Wkly Rep*. 2015;64(47):1305-1311. doi:10.15585/mmwr.mm6447a1
22. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. *Am J Gastroenterol*. 2017;112(1):18-35. doi:10.1038/ajg.2016.517
23. Thomson MJ, Serper M, Khunger V, et al. Prevalence and factors associated with statin use among patients with nonalcoholic fatty liver disease in the TARGET-NASH study. *Clin Gastroenterol Hepatol*. 2022;20(2):458-460.e4. doi:10.1016/j.cgh.2021.03.031
24. Athyros VG, Tziomalos K, Gossios TD, et al; 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(9756):1916-1922. doi:10.1016/S0140-6736(10)61272-X
25. Jose J. Statins and its hepatic effects: newer data, implications, and changing recommendations. *J Pharm Biomed Sci*. 2016;8(1):23-28. doi:10.4103/0975-7406.171699
26. Nielsen EM, Anderson KP, Marsden J, Zhang J, Schreiner AD. Nonalcoholic fatty liver disease underdiagnosis in primary care: what are we missing? *J Gen Intern Med*. 2022;37(10):2587-2590. doi:10.1007/s11606-021-07197-3
27. Quan H, Li B, Saunders LD, et al; IMECCHI Investigators. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Serv Res*. 2008;43(4):1424-1441. doi:10.1111/j.1475-6773.2007.00822.x
28. Quan H, Sundararajan V, Halton P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83
29. Hagström H, Adams LA, Allen AM, et al. Administrative coding in electronic health care record-based research of NAFLD: an expert panel consensus statement. *Hepatology*. 2021;74(11):474-482. doi:10.1002/hep.31726
30. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology*. 2007;45(4):846-854. doi:10.1002/hep.21496
31. Shah AG, Lydecker A, Murray K, et al. Comparison of noninvasive markers of fibrosis in patients with non-alcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2009;7(10):1104-1112. doi:10.1016/j.cgh.2009.05.033
32. Sterling RK, Lissen E, Clumeck N, et al; APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43(6):1317-1325. doi:10.1002/hep.21178
33. Browning JD. Statins and hepatic steatosis: perspectives from the Dallas Heart Study. *Hepatology*. 2006;44(2):466-471. doi:10.1002/hep.21248
34. Che Z, Fendrick AM, Tapper EB. Baffled by NAFLD: the horse might be out of the barn but should not take us for a ride. *Am J Manag Care*. 2021;27(9):364-365. doi:10.37765/ajmc.2021.88671
35. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation*. 2014;129(25 suppl 2):S49-S73. doi:10.1161/01.cir.0000437741.48606.98
36. US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2022;328(8):746-753. doi:10.1001/jama.2022.13044
37. Arnett DK, Khera A, Blumenthal RS. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: part 1, lifestyle and behavioral factors. *JAMA Cardiol*. 2019;4(10):1043-1044. doi:10.1001/jamacardio.2019.2604

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eAppendix. ICD-9/10 codes for severe liver disease outcomes and chronic liver disease diagnoses

Severe liver disease outcomes	ICD-10	ICD-9
Cirrhosis	K65.2, K70.11, K70.30, K70.31, K72.10, K72.11, K74.4-K74.5, K74.60, K74.69, K76.7, I85.00, I85.01, I85.10, I85.11, I86.4, R18.8	456.0, 456.1, 456.2, 456.21, 567.23, 571.2, 571.5, 572.2-572.4
Hepatocellular carcinoma	C22.0	155.0
History of liver transplantation	Z94.4	V42.7
Chronic liver disease diagnoses		
Viral hepatitis B	B16.0, B16.1, B18.0, B18.1	070.20 - 070.23, 070.30 - 070.33
Viral hepatitis C	B17.10, B17.11, B18.2, B19.20, B19.21	070.41, 070.44, 070.51, 070.54, 070.70, 070.71
Alcohol-related liver disease (and alcohol use disorder)	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1	265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.x, V11.3
Autoimmune hepatitis	K75.4	571.42
Primary biliary cholangitis	K74.3	571.6
Hemochromatosis	E83.110, E83.111, E83.118, E83.119	275.01-275.03, 238.72
Wilson's disease	E83.01	275.1
α -1 anti-trypsin deficiency	E88.01	273.4