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Prevalence and factors associated with statin use among patients with non-alcoholic fatty liver disease in TARGET-NASH

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Keywords

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Introduction

Patients with nonalcoholic fatty liver disease (NAFLD) are at an increased risk of cardiovascular disease. Hydoxy-3-Methyglutaryl-coenzyme reductase inhibitors, “statins”, reduce the risk of cardiovascular events.[1] Studies have shown statins are safe among patients with liver disease, including those with compensated cirrhosis,[2] and their use is associated with lower mortality, hepatic decompensation, and possibly hepatocellular carcinoma.[3,4] Despite these data, statins are under prescribed among patients with liver disease due to concerns about hepatotoxicity.[5] This study aimed to assess prevalence and patient factors associated with indicated statin use in patients with NAFLD in a real-world cohort.

Methods

Adults with NAFLD enrolled in TARGET-NASH, across 60 sites in the U.S., with an indication for statin therapy were included. Statin indication was based on the 2013 American College of Cardiology guidelines for primary and secondary prevention of cardiovascular disease: 1) atherosclerotic cardiovascular disease (ASCVD), 2) low density lipoprotein (LDL-C) ≥190 mg/dL, 3) history of diabetes and age 40–75 years, or 4) 10-year ASCVD risk score ≥7.5%.[6]

Medical records available within 3 years prior to enrollment were reviewed for co-morbidities and liver disease severity; statin use within six months of enrollment was determined (Supplemental materials). Patients were classified as having nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), or compensated or decompensated NAFLD cirrhosis according to clinical assessments previously described.[7] Unadjusted and adjusted logistic regression models were fit to assess the association between patient demographic and clinical characteristics with statin use.

Results

This analysis included 2,214 patients with at least one statin indication. Median age was 62 years, 80.2% were white, and 61.1% female. At enrollment, 26.2% had compensated and 20.1% had decompensated cirrhosis, 73.2% had hypertension, 83.2% type 2 diabetes, and

62.6% dyslipidemia. Diabetes plus age 40–75 years was the most common indication for statin use (81.4%) (Table S1).

Overall, 55.8% of patients with at least one indication used a statin, with the highest use among patients with clinical ASCVD (63.0%) (Figure 1a). Patients on an indicated statin were older (63 vs 61 years old; p<0.0001), with more cardiovascular comorbidities, and were less often female (58.9% vs 63.8%; p<0.019) (Table S1). The proportions of patients who received an indicated statin were lower in patients with more advanced liver disease: 60.8%, 61.6%, 55.1%, and 42.2%, respectively in patients with NAFL, NASH, compensated cirrhosis, and decompensated cirrhosis (Figure S1).

In a multivariable analysis adjusting for demographics, liver disease severity, and other clinical characteristics, age ≥65 (OR 1.44, 95%CI 1.11–1.88), no cirrhosis versus decompensated cirrhosis (OR 1.88,95% CI 1.34–2.65), compensated versus decompensated cirrhosis (OR 1.44, 95%CI 1.04–1.99), history of hypertension (OR 1.32, 95%CI 1.03–1.69), type 2 diabetes (OR 1.96, 95%CI 1.44–2.67), dyslipidemia (OR 5.42, 95%CI 4.34–6.77), and clinical ASCVD (OR 1.49, 95%CI 1.16–1.92) were independently associated with higher odds of statin use (Figure 1b). There was a non-significant trend towards higher statin use in patients without cirrhosis compared to those with compensated cirrhosis (OR 1.31, 95%CI 1.00–1.72). Female sex (OR 0.70, 95%CI 0.56–0.88) and platelet count <100,000/μL (OR 0.7, 95%CI 0.50–0.97) were associated with lower odds of statin use.

Discussion

In this study, only 56% of patients with NAFLD were taking guideline-recommended statin therapy. Older patients as well as those with dyslipidemia or hypertension were more likely to be on a statin. Statin use decreased as NAFLD became more advanced, likely reflecting safety concerns in patients with decompensated cirrhosis.[8] Women were less likely to be on an indicated statin compared to men, even after adjusting for cardiovascular risk factors and liver disease severity.

There were several limitations to this study. The majority of patients were seen in academic gastroenterology or hepatology practices, statin use may be lower in other settings. Clinical information was extracted from clinic notes, which depends on accurate and complete documentation. The pragmatic NAFLD diagnoses utilized may be inaccurate in classifying disease severity; however, this reflects real world practice where biopsies are uncommonly done. Finally, follow-up was not long enough to determine the effect on cardiovascular or hepatic outcomes.

Similar to other studies of statin use in the general population and in NAFLD patients, this analysis of a large national real-world sample showed that guideline-recommended statins continue to be underutilized and were not prescribed in 40% of NAFLD patients with clear indications. Ongoing studies on the potential benefit of statins in preventing cirrhosis complications may broaden statin indications beyond cardiovascular disease in the future. Further steps are needed to educate providers and patients on statin safety and its benefits in preventing cardiovascular disease in at-risk NAFLD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
ALT	alanine aminotransferase
BMI	body mass index
IQR	interquartile range
LDL-C	low density lipoproteins
HCC	hepatocellular carcinoma
HDL-C	high density lipoproteins
NAFLD	nonalcoholic fatty liver disease
NAFL	nonalcoholic fatty liver
NASH	nonalcoholic steatohepatitis

REFERENCES

1. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013:CD004816. [PubMed: 23440795]
2. Lewis JH, Mortensen ME, Zweig S, et al. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Hepatology 2007;46:1453–63. [PubMed: 17668878]
3. Kaplan DE, Serper MA, Mehta R, et al. Effects of Hypercholesterolemia and Statin Exposure on Survival in a Large National Cohort of Patients With Cirrhosis. Gastroenterology 2019;156:1693–1706 e12. [PubMed: 30660733]
4. Kim RG, Loomba R, Prokop LJ, et al. Statin use and risk of cirrhosis and related complications in patients with chronic liver diseases: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology 2017;15:1521–1530. e8. [PubMed: 28479502]
5. Del Ben M, Baratta F, Polimeni L, et al. Under-prescription of statins in patients with non-alcoholic fatty liver disease. Nutr Metab Cardiovasc Dis 2017;27:161–167. [PubMed: 27914698]

6. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–934. [PubMed: 24239923]
7. Barritt ASt, Gitlin N, Klein S, et al. Design and rationale for a real-world observational cohort of patients with nonalcoholic fatty liver disease: The TARGET-NASH study. Contemp Clin Trials 2017;61:33–38. [PubMed: 28735109]
8. Kaplan DE. The Use of Statins in Patients With Cirrhosis. Gastroenterol Hepatol (N Y) 2018;14:485–487. [PubMed: 30302064]

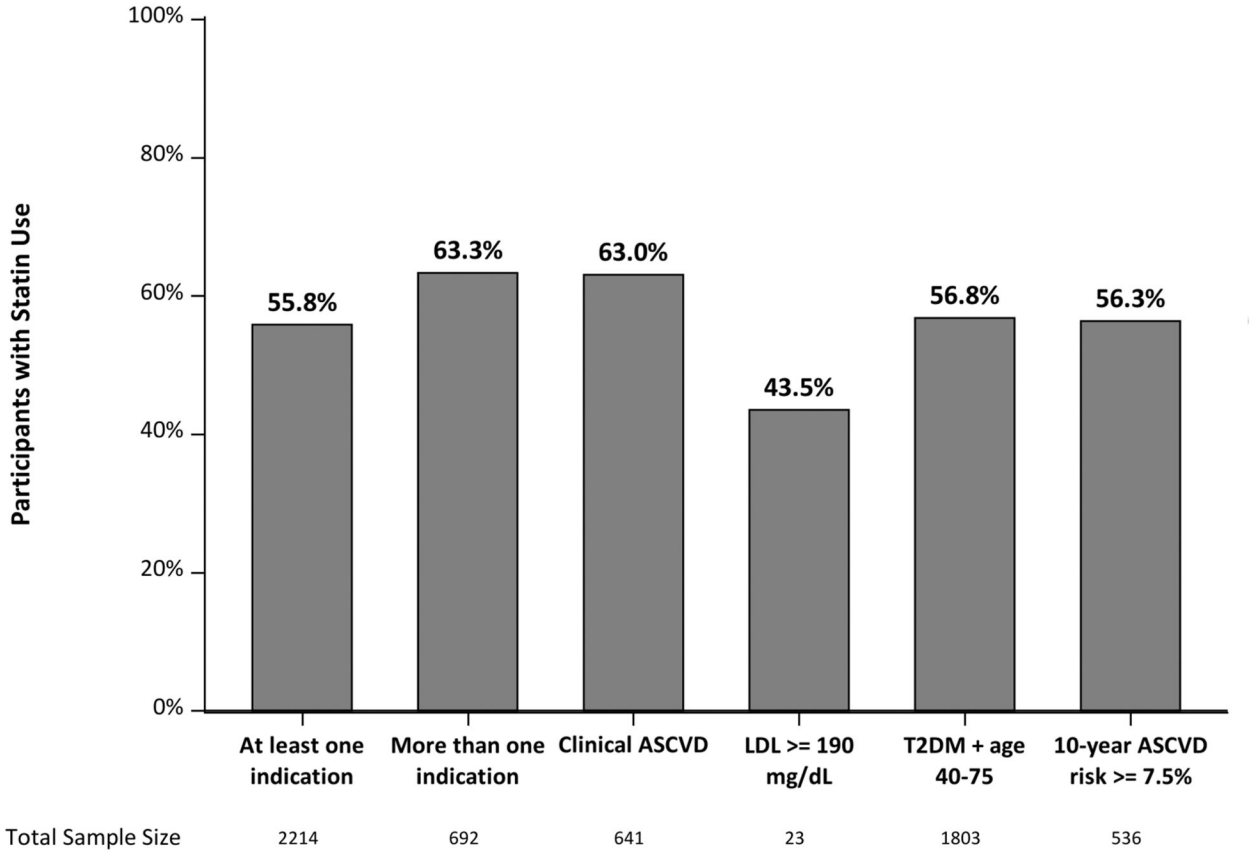

Figure 1a.

Percentage of patients in TARGET-NASH prescribed statin by statin indications.

Abbreviations: atherosclerotic cardiovascular disease (ASCVD), body mass index (BMI), history (Hx), lower and upper confidence limits (LCL and UCL), milligrams per deciliter (mg/dL), type 2 diabetes mellitus (T2DM)

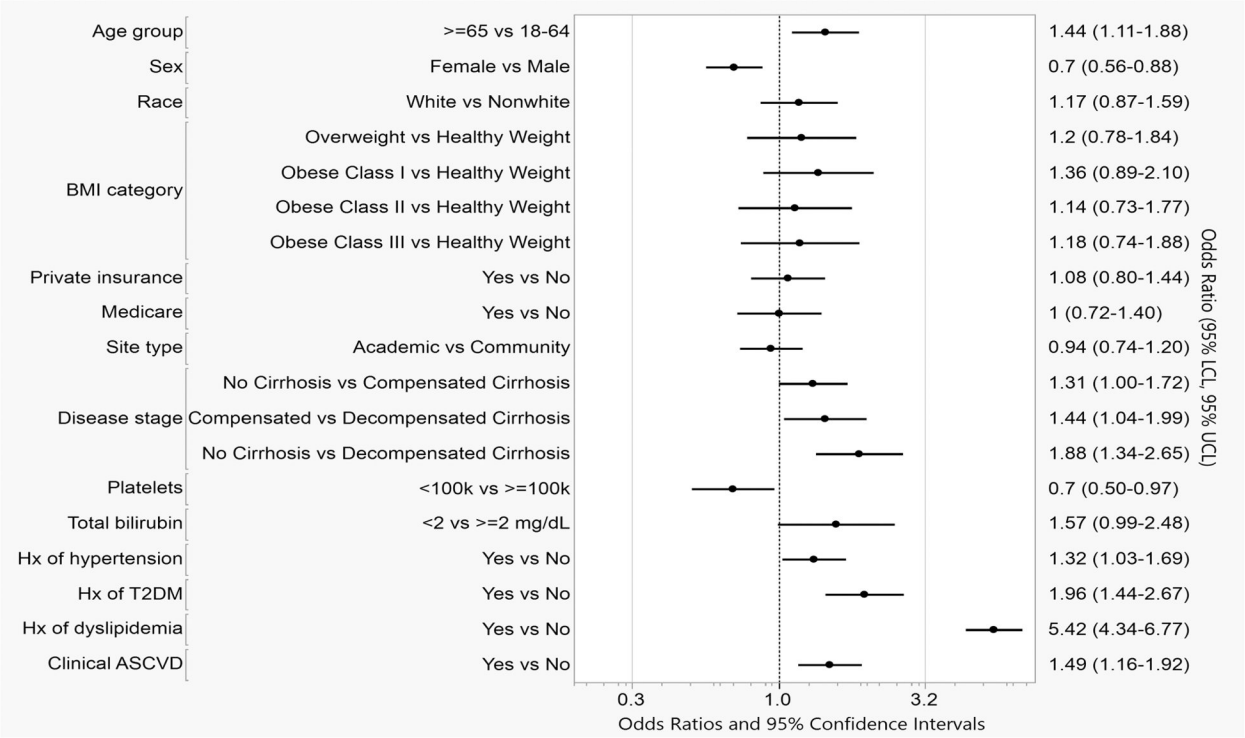

Figure 1b.

Multivariate model showing odds of statin use in TARGET-NASH patients with indications for statin therapy.

Effect estimates are adjusted for all other variables in the model.

Abbreviations: atherosclerotic cardiovascular disease (ASCVD), body mass index (BMI), history (Hx), lower and upper confidence limits (LCL and UCL), milligrams per deciliter (mg/dL), type 2 diabetes mellitus (T2DM)