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Statin Use and Risk of Hepatocellular Carcinoma and Liver Fibrosis in Chronic Liver Disease

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IMPORTANCE Statins may lower the risk of hepatocellular carcinoma (HCC) by mitigating liver fibrosis progression.

OBJECTIVE To evaluate the association between statin use and the risk of HCC and hepatic decompensation, with an emphasis on liver fibrosis progression, among adult patients with chronic liver disease (CLD).

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from the Research Patient Data Registry from 2000 to 2023 on patients 40 years or older with CLD and a baseline Fibrosis-4 (FIB-4) score of 1.3 or higher. Participants were grouped into statin users and nonusers. Data analysis was conducted from August 5, 2024, to January 3, 2025.

EXPOSURES Statin use.

MAIN OUTCOMES AND MEASURES Outcomes included 10-year cumulative incidence of HCC and hepatic decompensation as well as transitions in liver fibrosis risk categories based on FIB-4 scores. Statin use was defined as exposure to a cumulative defined daily dose (cDDD) of 30 or more. Fibrosis progression was assessed through FIB-4 group transitions (low, intermediate, and high) over time. Outcomes were analyzed using adjusted subhazard ratio (aSHR) and trends in serial FIB-4 scores.

RESULTS The analysis included 16 501 participants (mean [SD] age, 59.7 [11.0] years; 6750 females [40.9%] and 9751 males [59.1%]) with CLD, including 3610 statin users and 12 891 nonusers. Statin users exhibited a significantly lower 10-year cumulative incidence of HCC (3.8% vs 8.0.%; risk difference, −4.2%; 95% CI, −5.3 to −3.1%) and hepatic decompensation (10.6% vs 19.5%; risk difference, −9.0%; 95% CI, −10.6 to −7.3) compared with nonusers. The aSHR was 0.67 (95% CI, 0.59 to 0.76) for HCC and 0.78 (95% CI, 0.67 to 0.91) for hepatic decompensation. Exposure to lipophilic statins and duration of statin use (≥600 cDDDs) were associated with further reductions in HCC and hepatic decompensation risks. Among 7038 patients with serial FIB-4 data, patients with intermediate baseline FIB-4 scores, 14.7% (95% CI, 13.0% to 16.6%) of statin users transitioned to the high group compared with 20.0% (95% CI, 18.6% to 21.5%) of nonusers. For patients with high baseline FIB-4 scores, 31.8% (95% CI, 28.0% to 35.9%) of statin users transitioned to the intermediate group and 7.0% (95% CI, 5.2% to 9.6%) transitioned to the low-risk group, compared to 18.8% (95% CI, 17.2% to 20.6%) and 4.3% (95% CI, 3.5% to 5.2%) of nonusers, respectively ($P < .001$).

CONCLUSIONS AND RELEVANCE This cohort study found that statin use was associated with a reduced risk of HCC and hepatic decompensation in patients with CLD, as well as improved FIB-4 group transitions over time. These findings provide support for the potential role of statins in prevention of HCC and liver disease progression.

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Supplemental content

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The incidence of hepatocellular carcinoma (HCC) has been steadily increasing in the US and globally.[1] Traditionally, chronic viral hepatitis has been the primary cause of HCC. However, advancements in effective antiviral therapies during the past decade have reduced HCC cases associated with viral hepatitis. On the other hand, metabolic- and alcohol-related steatotic liver diseases have become more prevalent and have risen as the major cause of HCC.[1,2] This rising prevalence of HCC and mortality associated with it underscores an urgent need for effective HCC prevention strategies.

Experimental studies[3-5] suggest that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may prevent chronic liver disease (CLD) progression and hepatocarcinogenesis through mechanisms such as anti-inflammatory, antifibrotic, and antioxidant mechanisms. Observational studies[6-12] also associate statins with a reduced risk of liver disease progression and HCC. However, limitations of previous studies include their focus on specific CLD causes or the lack of exploration of the effects of statins on liver fibrosis progression over time.[6-12] Given that hepatocarcinogenesis is closely associated with chronic inflammation and fibrosis, serial tracking of changes in liver fibrosis among statin users is essential for understanding the role of statins in reducing HCC risk. Furthermore, because patients with minimal liver fibrosis exhibit very low HCC incidence, patients with intermediate or high fibrosis risk in the setting of CLD may represent key subset of patients who may benefit from HCC chemoprevention.

In this study, we investigated the association between statin use and the risk of incident HCC and hepatic decompensation. Additionally, we analyzed changes in liver fibrosis among patients with substantial fibrosis, leveraging data from a large-scale hospital registry database.

Key Points

Question What is the association between statin use and the risk of hepatocellular carcinoma (HCC), hepatic decompensation, and fibrosis progression in patients with chronic liver disease (CLD)?

Findings This cohort study including 16 501 patients who were 40 years or older and living with CLD, statin use was significantly associated with a lower 10-year cumulative incidence of HCC (3.8% vs 8.0%) and hepatic decompensation (10.6% vs 19.5%). Lipophilic statins and longer cumulative statin use (≥600 cumulative defined daily dose) were associated with further risk reductions, and statin users exhibited a reduced likelihood of remaining in or transitioning to high-risk Fibrosis-4 score groups.

Meaning These findings indicate that statin use, particularly lipophilic statin use, and longer duration of statin exposure may reduce the risks of HCC and hepatic decompensation in patients with CLD.

Methods

This study was reviewed and approved by the Institutional Review Board of Massachusetts General Hospital (No. 2023P003249). Informed consent was waived due to the retrospective nature of the study. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Design and Data Sources

This was a historical cohort study using the Research Patient Data Registry (RPDR), which aggregates clinical data from hospitals within Mass General Brigham (formerly Partners Healthcare System) health care system in Boston, Massachusetts. The RPDR covers approximately 4 million patients in state. *International Classification of Diseases, Ninth Revision* and *Tenth Revision* (*ICD-9/10*) codes were used to identify CLD cases and comorbidities of interest (eTable 1 in Supplement 1).

Study Population

Adults 40 years and older diagnosed with CLD from July 2000 to June 2023 were eligible for inclusion (n = 125 436). A new-user design was used, requiring statin users to have a 180-day entry period between their first CLD diagnosis and statin initiation date (index date). Nonusers were required to complete an equivalent 180-day entry period without any statin prescriptions. Exclusion criteria included prior HCC (n = 2334); history of hepatic decompensation (n = 5419); non-HCC malignant tumors (n = 48 180); HIV coinfection (n = 1116); prior liver transplant (LT; n = 227) or other solid organ transplant (n = 273); and statin use before the entry period (n = 11 769). During the entry period, patients with HCC (n = 741), decompensation (n = 1859), LT (n = 108), solid organ transplant (n = 120), statin use (n = 1789), or who had died or were otherwise lost to follow-up (n = 11 756) were excluded. Of the 39 745 remaining patients, those with a baseline Fibrosis-4 (FIB-4)[13] score of less than 1.3 (n = 12 948) or unavailable FIB-4 data (n = 10 296) were excluded (eFigure 1 in Supplement 1). Demographic characteristics, including race and ethnicity, were based on self-reported data.

Exposures

Seven statins were evaluated, including 5 lipophilic statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin) and 2 hydrophilic statins (rosuvastatin and pravastatin). Statin use was defined as a cumulative defined daily dose of 30 or higher, calculated by summing monthly defined daily dose, consistent with previous studies.[6,8,14,15] Cumulative statin exposure was categorized as less than 30 (reference), 30 to 599, and 600 cumulative defined daily dose (cDDD) or higher.

Outcomes

The primary outcome was incident HCC. The secondary outcome was hepatic decompensation, defined by the *ICD-9/10* codes for variceal bleeding, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome (eTable 1 in Supplement 1).

Assessment of Liver Fibrosis

Fibrosis was assessed using FIB-4 scores.[13] All patients had baseline FIB-4 scores of 1.3 or higher. Due to variability in testing frequency, not all patients had regular serial FIB-4 measurements throughout the study period. FIB-4 group transi-

tions were analyzed in a subset of 7038 patients (42.7% of the cohort) with FIB-4 measurements available at the 3-year follow-up or later. The proportion of patients transitioning between FIB-4 groups (low, intermediate, and high) was compared between statin users and nonusers for baseline high and intermediate FIB-4 groups at the 3-year follow-up.

Statistical Analysis

Baseline characteristics were balanced using inverse probability of treatment weighting (IPTW) based on propensity scores (PS). Each observation was weighted by the inverse probability of statin treatment, estimated using observed confounders at the index date, to yield population average treatment effect estimates with optimal balance between groups.

The primary analyses assessed the association between statin use and the risks of incident HCC and hepatic decompensation. Follow-up began at the index date and continued until HCC diagnosis, competing events, or April 30, 2024, whichever occurred first. Competing events included death and LT. IPTW-adjusted Cox proportional hazards regression models were used to estimate cumulative incidence, absolute risk differences, and adjusted subhazard ratios (aSHR). These models accounted for covariate effects on the cumulative incidence function while considering competing risks. Associations between statin types (lipophilic vs hydrophilic statin) and outcomes were also evaluated. Subgroup analyses were conducted for cirrhosis, dyslipidemia, metabolic dysfunction-associated steatotic liver disease (MASLD), and comedications (eg, aspirin and metformin) to evaluate potential association.

To verify the robustness of the findings, 4 sensitivity analyses were conducted: analysis without IPTW; exclusion of competing risks; application of a 1:1 PS-matched design (additional details on the development of PS-matched pairs and diagnostic of PS are available in the eMethods and eTable 2 in Supplement 1); and evaluation of negative control outcomes (incident lung cancer and bladder cancer). All statistical tests were 2-tailed, with $P < .05$ considered statistically significant. Analyses were conducted using R, version 4.2.1 (The R Foundation for Statistical Computing), from August 5, 2024, to January 3, 2025.

Results

Study Population

This study analysis included 16 501 adults (mean [SD] age, 59.7 [11.0] years; 6750 females [40.9%] and 9751 males [59.1%]; 646 Asian [3.9%], 1067 Black [6.5%], 13 023 White [78.9%], and 1765 individuals of other race and ethnicity [10.7%]) comprising 3160 statin users and 12 891 nonusers (**Table 1**). Statin users were significantly older and had higher rates of comorbidities, including diabetes, hypertension, coronary artery disease, and dyslipidemia. After IPTW adjustment, covariates were well balanced. The median (IQR) follow-up period was 2.8 (1.0-6.3) years for nonusers and 4.6 (2.0-7.9) years for statin users. Overall, 755 incident cases of HCC and 2011 cases of hepatic decompensation were observed.

Hepatocellular Carcinoma

The 10-year cumulative incidence of HCC was 3.8% (95% CI, 3.2-4.6) for statin users and 8.0% (95% CI, 7.4-8.6) for nonusers, with a risk difference (RD) of −4.2% (95% CI, −5.3 to −3.1; $P < .001$; **Figure 1**A and **Table 2**). Multivariable adjustment indicated that statin users had a 33% lower risk of HCC compared with nonusers (aSHR, 0.67; 95% CI, 0.59-0.76). This inverse association was consistent across all prespecified subgroups (eFigure 2 in Supplement 1). The complete list of factors associated with HCC from the multivariable model is presented in eTable 3 in Supplement 1.

Hepatic Decompensation

The 10-year cumulative incidence of hepatic decompensation was 19.5% (95% CI, 18.7-20.4) for nonusers and 10.6% (95% CI, 9.4-11.9) for statin users, with an RD of −9.0% (95% CI, −10.6 to −7.3; $P < .001$) (Figure 1B; Table 2). Multivariable adjustment showed a 22% lower risk of hepatic decompensation among statin users (aSHR, 0.78; 95% CI, 0.67-0.91). Ascites was the most common decompensation event, comprising 64.3% of these events in statin users and 58.2% in nonusers.

Statin Use and Type

The cumulative incidence, RDs, and aSHRs for HCC differed by statin type. Hydrophilic statin users had a 10-year cumulative incidence of HCC of 4.1% compared with 8.0% among nonusers, yielding an absolute RD of −3.9% (95% CI, −6.2 to −1.6; **Figure 2**A) and an aSHR of 0.79 (95% CI, 0.63-0.99) after adjustment. Lipophilic statin users demonstrated an even lower 10-year cumulative incidence of HCC (3.7%), with an RD of −4.3% (95% CI, −5.5 to −3.1; Figure 2A) and a 36% reduced risk after adjustment (aSHR, 0.64; 95% CI, 0.55-0.73).

For hepatic decompensation, hydrophilic statin users showed a 10-year cumulative incidence of 7.9% compared with 19.5% among nonusers, with an RD of −11.6% (95% CI, −14.4 to −8.9; Figure 2B). After adjustment, hydrophilic statins were associated with a 42% reduced risk (aSHR, 0.58; 95% CI, 0.42-0.88). Lipophilic statin users also demonstrated a significantly lower 10-year cumulative incidence of hepatic decompensation (11.2%), with an RD of −8.4% (95% CI, −10.1 to −6.6; Figure 2B) and a 18% reduced risk after adjustment (aSHR, 0.82; 95% CI, 0.69-0.97).

Statin Use Duration

When stratified by statin use duration, patients with 600 or higher cDDD had the lowest 10-year cumulative incidence of HCC (3.5%), compared with 8.0% among nonusers (RD, −4.5%; 95% CI, −5.6 to −3.2; Figure 2C). The aSHR for this group was 0.60 (95% CI, 0.52-0.70). Those with 30 to 599 cDDD had a cumulative incidence of 3.8% (RD, −4.2%; 95% CI, −6.2 to −2.2) and an aSHR of 0.79 (95% CI, 0.67-0.93).

For hepatic decompensation, patients with 600 or higher cDDD exhibited the greatest reduction, with a 10-year cumulative incidence of 9.1% vs 19.5% in nonusers (RD, −10.4%; 95% CI, −12.2 to −8.7) and an aSHR of 0.64 (95% CI, 0.51-0.80). Those with 30 to 599 cDDD had a cumulative incidence of 12.3% (RD, −7.2%; 95% CI, −10.9 to −3.5) and an aSHR of 0.87 (95% CI, 0.75-1.01).

Table 1. Characteristics of Pooled Study Population of 16 501 Patients, by Statin Use Status[a,b]

Characteristic	Patients, No. (%)		SMD	
	No statin use (n = 12 891)	Statin use (n = 3610)	Before IPTW	After IPTW
Participants	12 891 (78.1)	3610 (21.9)		
Age, mean (SD), y	58.5 (11.0)	63.7 (10.1)	0.49	0.082
Sex				
Female	5335 (41.4)	1415 (39.2)	0.02	0.075
Male	7556 (58.6)	2195 (60.8)		
Race and ethnicity, self-reported				
Asian	472 (3.7)	174 (4.8)	0.01	0.001
Black	784 (6.1)	283 (7.8)	0.02	−0.001
White	10 235 (79.3)	2788 (77.3)	−0.02	−0.001
Other[c]	1400 (10.9)	365 (10.1)	−0.01	0.001
BMI score				
<25	1570 (12.2)	477 (13.2)	0.01	0.006
≥25 to <30	2080 (16.1)	938 (26.0)	0.10	0.008
≥30	2770 (21.5)	1425 (39.5)	0.18	0.016
Not available	6471 (50.2)	770 (21.3)	−0.29	−0.030
Comorbidities[b]				
Causes of chronic liver disease				
HBV infection	562 (4.4)	209 (5.8)	0.01	−0.013
HCV infection	2422 (18.8)	756 (20.9)	0.02	−0.043
Autoimmune hepatitis	301 (2.3)	43 (1.2)	−0.01	0.002
Primary biliary cholangitis	419 (3.3)	147 (4.1)	0.01	−0.003
Alcoholic hepatitis	2681 (20.7)	500 (13.9)	−0.07	−0.012
MASLD	4004 (31.1)	1100 (30.5)	−0.01	0.054
Cryptogenic cirrhosis	1337 (10.4)	205 (5.7)	−0.05	0.014
Other	1165 (9.0)	650 (17.9)	0.09	0.001
Cirrhosis	5476 (42.5)	1258 (34.8)	−0.08	−0.046
Diabetes	2185 (16.9)	1532 (42.4)	0.25	0.045
Hypertension	5599 (43.4)	2868 (79.4)	0.36	0.038
Coronary artery disease	1875 (14.5)	1462 (40.5)	0.26	0.028
Peripheral vascular disease	693 (5.4)	503 (13.9)	0.09	0.018
Dyslipidemia	3122 (24.2)	2624 (72.7)	0.48	0.035
Chronic kidney disease	729 (5.7)	459 (12.7)	0.07	0.028
Cerebrovascular accident	907 (7.0)	625 (17.3)	0.10	0.014
Median FIB-4 score[d]	2.3 (1.6 to 4.2)	1.9 (1.5 to 2.8)	−0.20	−0.030
FIB-4 score group				
Intermediate (1.30 to ≤2.67)	7470 (57.9)	2627 (72.8)	0.14	−0.016
High (>2.67)	5421 (42.1)	983 (27.2)	−0.15	−0.002
Medication use				
Metformin	810 (6.3)	861 (23.9)	0.18	0.020
Aspirin	2593 (20.1)	2045 (56.6)	0.37	0.056
Fibrate	188 (1.5)	170 (4.7)	0.03	0.008
Nicotinic acid	57 (0.4)	55 (1.5)	0.01	0.001
Bile acid sequestrants	172 (1.3)	66 (1.8)	0.01	0.001
SGLT-2 inhibitor	49 (0.4)	46 (1.3)	0.01	0.001
Interferon	58 (0.4)	88 (2.4)	0.02	0.003
Oral antiviral therapy				
Anti-HBV	145/562 (25.8)	74/209 (35.4)	0.01	−0.002
Anti-HCV	143/2422 (5.9)	190/756 (25.1)	0.04	0.004
Laboratory parameters, median (IQR)				
Platelet count, $\times 10^3/\mu L$	181 (128 to 228)	197 (158 to 237)	0.21	0.040
AST, U/L	42 (28 to 74)	32 (23 to 49)	−0.12	−0.019
ALT, U/L	35 (21 to 64)	29 (19 to 48)	−0.11	0.06
Albumin, g/dL[e]	4.0 (3.5 to 4.4)	4.2 (3.8 to 4.5)	0.32	−0.072
Total bilirubin, mg/dL[e]	0.8 (0.4 to 1.1)	0.5 (0.4 to 0.8)	−0.25	−0.016

(continued)

Table 1. Characteristics of Pooled Study Population of 16 501 Patients, by Statin Use Status[a,b] (continued)

Characteristic	Patients, No. (%)		SMD	
	No statin use (n = 12 891)	Statin use (n = 3610)	Before IPTW	After IPTW
Abdominal imaging examinations/y				
<1	3764 (29.2)	1298 (36.0)	0.07	0.015
1-2	1463 (11.3)	446 (12.4)	0.01	−0.010
>2	2669 (20.7)	629 (17.4)	−0.03	0.036
Not identified	4995 (38.7)	1237 (34.3)	−0.04	−0.011

Abbreviations: ALT, alanine aminotransferase (to convert to U/mL, multiply by 0.001); AST, aspartate aminotransferase (to convert to U/mL, multiply by 0.001); BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FIB-4, Fibrosis-4; HBV, hepatitis B virus; HCV, hepatitis C virus; IPTW, inverse probability treatment weighting; MASLD, metabolic dysfunction-associated steatotic liver disease; SGLT-2, sodium-glucose cotransporter-2; SMD, standardized mean difference.

[a] Statin use was defined as use of statin for 30 or more consecutive cumulative defined doses after the index date (first recorded date of a filled prescription for a statin after 180-day statin-naive period).

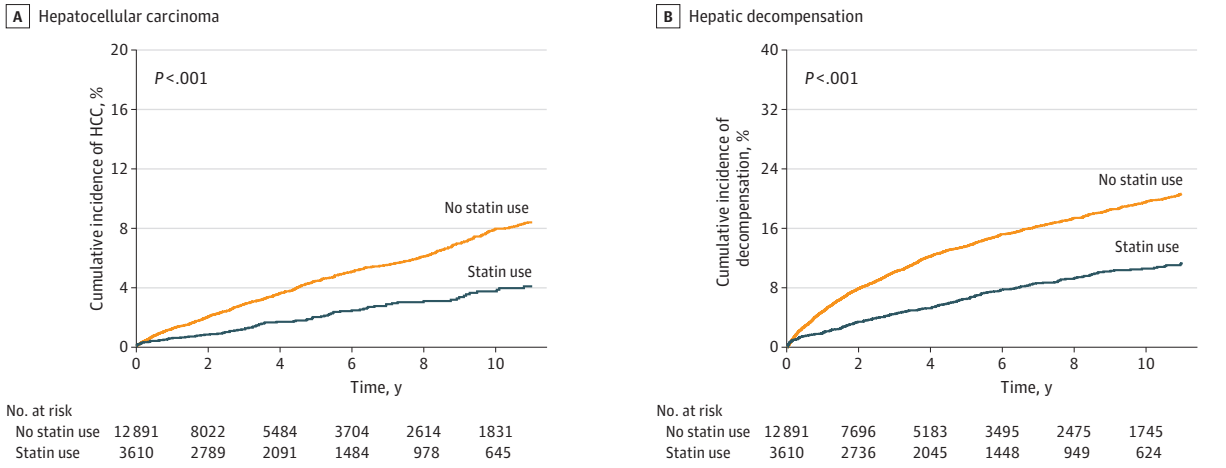
[b] Per the *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision* or *Tenth Revision* coding system (eTable 1 in Supplement 1).

[c] Included American Indian, Alaska Native, Native Hawaiian, Pacific Islander, other, unknown, and declined to respond.

[d] Fibrosis-4 score is a noninvasive marker of liver fibrosis in patients with chronic liver disease, including age and 3 parameters (ie, alanine aminotransferase, aspartate aminotransferase, and platelet count).[13]

[e] Not available in 60 patients for albumin (to convert to g/dL, multiply by 10), and 74 patients for total bilirubin (to convert to μmol/L, multiply by 17.104).

Figure 1. Cumulative Incidence of Hepatocellular Carcinoma (HCC) and Hepatic Decompensation Among Statin Users and Nonusers



Statin use was associated with lower cumulative incidence of hepatocellular carcinoma and hepatic decompensation. Statin use was defined as at least 30 cDDD; no statin use was defined as less than 30 cDDD or neverd used. *P* values were calculated using Gray test for equality of cumulative incidence of functions between groups after inverse probability of treatment weighting, accounting for competing risks of death and liver transplant. cDDD indicates cumulative defined daily dose.

Subgroup Analysis

Statin use was consistently associated with reduced risks of HCC and hepatic decompensation across cirrhosis subgroups. Among patients with cirrhosis (n = 6734), statin users had a lower 10-year incidence of both HCC (6.3% vs 10.2%; aSHR, 0.82; 95% CI, 0.69-0.98) and hepatic decompensation (17.7% vs 29.3%; aSHR, 0.80; 95% CI, 0.65-0.98). When the same analysis was applied to patients without cirrhosis (n = 9767), statin use was associated with a reduced risk of HCC (2.4% vs 6.2%; aSHR, 0.62; 95% CI, 0.51-0.75) and hepatic decompensation (6.8% vs 12.0%; aSHR, 0.76; 95% CI, 0.59-0.98; eTable 4, eFigure 3 in Supplement 1). In subgroup analyses stratified by dyslipidemia status, statin use was consistently associated with reduced risks of HCC and hepatic decompensation. Among patients with dyslipidemia (n = 5746), statin use was associated with a 57% lower risk of HCC (aSHR, 0.43; 95% CI, 0.33-0.56). In patients without dyslipidemia (n = 10 755), the risk reduction was 24% (aSHR, 0.76; 95% CI, 0.65-0.90; eTable 5, eFigure 4 in Supplement 1).

In subgroup analyses stratified by MASLD, statin use was associated with reduced risks of HCC in both MASLD and non-MASLD groups. Statin use was associated with a 28% reduction in HCC risk among patients with MASLD (n = 5104; aSHR 0.72; 95% CI, 0.56-0.93). Similar reductions in patients with other causes of CLD were observed (aSHR, 0.68; 95% CI, 0.60-0.78; eTable 6 and eFigure 5 in Supplement 1). Exploratory analysis further revealed statistically significant interactions between statin use and both aspirin and metformin use. Among aspirin users, statin use was associated with a greater reduction in HCC risk (HR, 0.46; 95% CI, 0.36-0.58) compared to non-users (HR, 0.68; 95% CI, 0.58-0.80; *P* for interaction = .006). Similarly, among metformin users, statin use was associated with a greater reduction in HCC risk (HR, 0.47; 95% CI, 0.32-

Table 2. Association of Statin Use and Risk of Incident HCC and Hepatic Decompensation

Outcome	Events/ total patients	10-y Cumulative incidence, %	Absolute risk difference (95% CI)	Hazard ratio (95% CI)	
				Unadjusted	Adjusted[a]
Primary outcome					
Incident HCC					
No statin use	653/12 891	8.0	NA	1 [Reference]	1 [Reference]
Statin use	102/3610	3.8	−4.2 (−5.3 to −3.1)	0.52 (0.47 to 0.59)	0.67 (0.59 to 0.76)
Incident HCC according to statin type					
No statin use	653/12 891	8.0	NA	1 [Reference]	1 [Reference]
Hydrophilic statin use	18/680	4.1	−3.9 (−6.2 to −1.6)	0.75 (0.60 to 0.93)	0.79 (0.63 to 0.99)
Lipophilic statin use	84/2930	3.7	−4.3 (−5.5 to −3.1)	0.48 (0.42 to 0.55)	0.64 (0.55 to 0.73)
Incident HCC by statin use duration					
No statin use	653/12 891	8.0	NA	1 [Reference]	1 [Reference]
30-599 cDDD	27/1518	3.8	−4.2 (−6.2 to −2.2)	0.69 (0.58 to 0.81)	0.79 (0.67 to 0.93)
≥600 cDDD	75/2092	3.5	−4.5 (−5.6 to −3.2)	0.45 (0.39 to 0.52)	0.60 (0.52 to 0.70)
Secondary outcome					
Hepatic decompensation					
No statin use	1731/12 891	19.5	NA	1 [Reference]	1 [Reference]
Statin use	280/3610	10.6	−9.0 (−10.6 to −7.3)	0.49 (0.44 to 0.56)	0.78 (0.67 to 0.91)
Hepatic decompensation by statin type					
No statin use	1731/12 891	19.5	NA	1 [Reference]	1 [Reference]
Hydrophilic	41/680	7.9	−11.6 (−14.4 to −8.9)	0.49 (0.39 to 0.64)	0.58 (0.42 to 0.88)
Lipophilic	239/2930	11.2	−8.4 (−10.1 to −6.6)	0.52 (0.45 to 0.59)	0.82 (0.69 to 0.97)
Hepatic decompensation, by statin use duration					
No statin use	1731/12 891	19.5	NA	1 [Reference]	1 [Reference]
30 to 599 cDDD	110/1518	12.3	−7.2 (−10.9 to −3.5)	0.73 (0.59 to 0.88)	0.87 (0.75 to 1.01)
≥600 cDDD	170/2092	9.1	−10.4 (−12.2 to −8.7)	0.41 (0.35 to 0.48)	0.64 (0.51 to 0.80)

Abbreviations: cDDD, cumulative defined daily dose; HCC, hepatocellular carcinoma; NA, not applicable.

[a] The multivariable adjusted model included 21 prespecified prognostic covariates, including age, sex, race and ethnicity, causes of chronic liver disease, body mass index; presence of cirrhosis, diabetes, hypertension, coronary artery disease, peripheral vascular disease, dyslipidemia, chronic kidney disease, or cerebrovascular accident; Fibrosis-4 score[13]; and of metformin, aspirin, fibrate, nicotinic acid, bile acid sequestrant, sodium-glucose cotransporter-2 inhibitor, oral antiviral therapy, and interferon.

0.70) compared to nonusers (HR, 0.69; 95% CI, 0.60-0.79; *P* for interaction = .01).

FIB-4 Group Transitions per Baseline Categories and Statin Use

Among patients with baseline intermediate FIB-4 scores, 14.7% (95% CI, 13.0% to 16.6%) of statin users transitioned to the high group after 3 years compared with 20.0% (95% CI, 18.6% to 21.5%) of nonusers (*P* < .001; **Figure 3**A). Among patients in the baseline high FIB-4 group, 31.8% (95% CI, 28.0% to 35.9%) of statin users transitioned to the intermediate group and 7.0% (95% CI, 5.2% to 9.6%) transitioned to the low group compared with 18.8% (95% CI, 17.2% to 20.6%) and 4.3% (95% CI, 3.5% to 5.2%) of nonusers, respectively (*P* < .001). Among the PS-matched cohort, 13.7% (95% CI, 11.7% to 16.0%) of statin users with baseline intermediate FIB-4 scores transitioned to the high group after 3 years compared with 18.2% of nonusers (95% CI, 15.5% to 21.2%; *P* < .001). Additionally, among patients in the baseline high FIB-4 scores group, 32.1% (95% CI, 27.7% to 36.8%) of statin users transitioned to the intermediate group and 7.5% (95% CI, 5.3% to 10.5%) transitioned to lower group compared with 22.7% (95% CI, 18.1% to 28.0%) and 4.0% (95% CI, 2.3% to 7.1%) of nonusers, respectively (*P* < .001; Figure 3B).

Furthermore, among patients with HCC, 88.8% remained in the high FIB-4 group after 3 years compared to 71.8% of those without HCC (eFigure 6 in Supplement 1). Similarly, patients with HCC transitioned from the intermediate to the high FIB-4 group more frequently (37.4%) than those without HCC (17.3%).

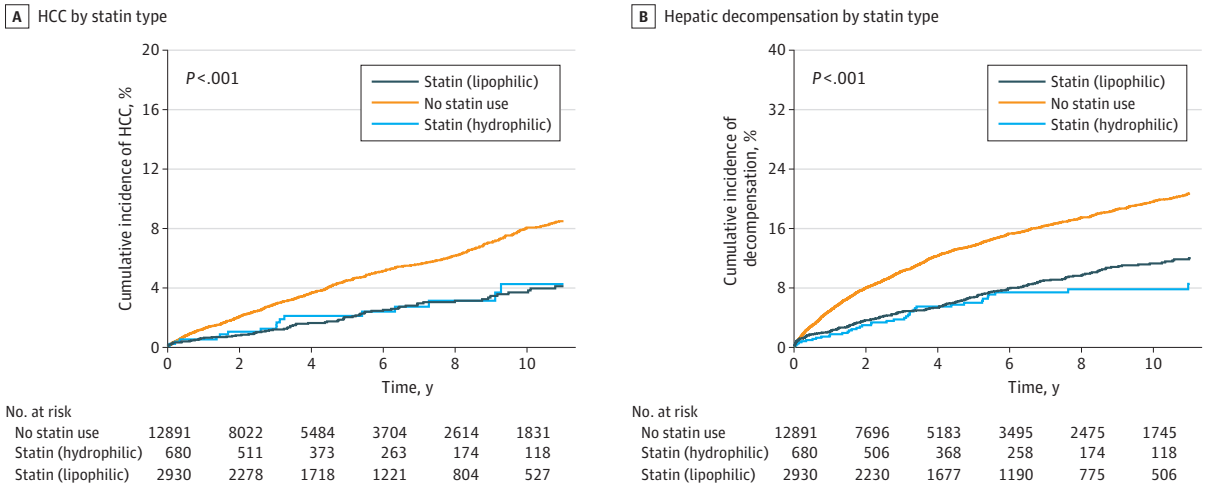
Sensitivity Analysis

In a sensitivity analysis of 2561 PS-matched pairs (eTables 7 and 8 in Supplement 1), statin users had a significantly lower 10-year cumulative incidence of HCC (2.9% vs 7.1%; RD, −4.2%; 95% CI, −6.0 to −2.4; eFigure 7 in Supplement 1) compared with nonusers, even after adjustment (aSHR, 0.69; 95% CI, 0.51-0.92; eTable 8 in Supplement 1). Consistent results were observed across all sensitivity analyses, including without IPTW (aSHR, 0.58; 95% CI, 0.44-0.76), without competing risks (aSHR, 0.63; 95% CI, 0.55-0.71; eTable 9 in Supplement 1), and using negative control outcomes (eTable 10; eFigure 8 in Supplement 1).

Discussion

In this hospital-based cohort study of patients with CLD, statin use was significantly associated with a reduced risk of incident HCC and hepatic decompensation compared with nonuse. Longer duration of statin exposure (≥600 cDDDs) was

Figure 2. Cumulative Incidence of Hepatocellular Carcinoma (HCC) and Hepatic Decompensation, by Statin Type and Duration



No. at risk

No statin use	12891	8022	5484	3704	2614	1831
Statin (hydrophilic)	680	511	373	263	174	118
Statin (lipophilic)	2930	2278	1718	1221	804	527

No. at risk

No statin use	12891	7696	5183	3495	2475	1745
Statin (hydrophilic)	680	506	368	258	174	118
Statin (lipophilic)	2930	2230	1677	1190	775	506

No. at risk

No statin use (<30 cDDD)	12 891	8022	5484	3704	2614	1831
cDDD 30–599	1518	709	235	119	67	28
cDDD ≥600	2092	2080	1856	1365	911	617

No. at risk

No statin use (<30 cDDD)	12891	7696	5183	3495	2475	1745
cDDD 30–599	1518	676	223	118	65	27
cDDD ≥600	2092	2060	1822	1330	884	597

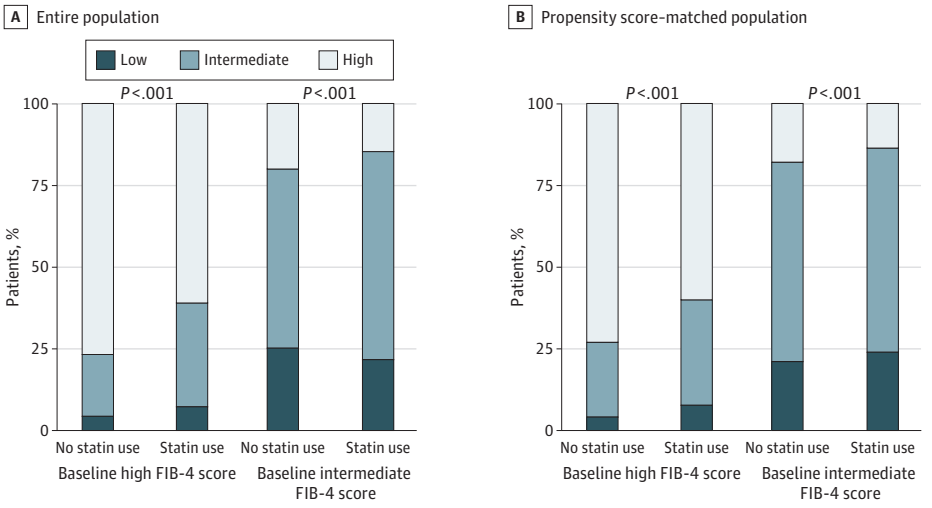
Statin use was associated with reduced cumulative incidence of HCC and hepatic decompensation across both statin type and duration categories. Statin use was defined as at least 30 cDDD; no statin use was defined as less than 30 cDDD or never used. *P* values were calculated using Gray test for equality of cumulative incidence of functions between groups after inverse probability of treatment weighting, accounting for competing risks of death and liver transplant. Lipophilic statins included atorvastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin; hydrophilic statins included rosuvastatin and pravastatin. cDDD indicates cumulative defined daily dose.

associated with even greater reductions in HCC and hepatic decompensation risk. Additionally, statin users were more likely to transition from high to intermediate or low FIB-4 score groups and less likely to remain in the high group than nonusers, as revealed by FIB-4 group transition analysis.

These findings, robust across multiple sensitivity analyses, build on previous research[6-8,12,14] demonstrating the chemopreventive association of statins with HCC. Many prior studies[16-18] have been limited by focusing on specific CLD causes or relying on administrative databases that, despite large sample sizes, lack granular clinical data such as laboratory results or imaging findings. Conversely, hospital-based studies often are limited by smaller sample sizes and less generalizability. Our study addressed these limitations by using a large-scale hospital registry encompassing data from 10 hospitals, reflecting evidence from routine clinical practice. This diverse cohort included patients with various CLD causes and detailed baseline data, enabling FIB-4-based liver fibrosis assessment. Additionally, the availability of a large serial FIB-4 cohort allowed us to evaluate changes in FIB-4 group dynamics over time and explore potential associations with statin use. Importantly, we also accounted for the use of other chemopreventive agents, such as aspirin,[19,20] which was associated with a reduced HCC risk in our analysis (aSHR, 0.72; 95% CI, 0.61-0.85), consistent with previous studies.[19]

Fibrosis is a critical precursor to hepatocarcinogenesis, but the mechanisms through which statins influence fibrosis progression remain underexplored. Experimental studies[21,22] have shown that statins, particularly atorvastatin, exert antifibrotic effects by reducing the expression of profibrotic cytokines (eg, *TGFβ1*, *CTGF*, *PDGF*β-receptor mRNA), improving liver microcirculation and decreasing levels of procollagen I

Figure 3. Fibrosis-4 (FIB-4) Score Group Transitions at 3 Years by Statin Use Among Patients With Baseline High and Intermediate FIB-4 Scores



Statin use was associated with improved FIB-4 group transitions, with users less likely to progress to higher groups and more likely to transition to lower groups compared to nonusers. Analyses adjusted for baseline differences using propensity score matching.

and αsmooth muscle actin. Data from the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial[11] also suggested that statin users had a significantly lower risk of fibrosis progression than nonusers (10% vs 29%), although the sample size was small (n = 29). In our study, statin users maintained stable FIB-4 group distributions over time, whereas nonusers were more likely to transition to the high group over time. These associations were particularly evident among patients with high baseline FIB-4 scores, indicating a potential role of statins in mitigating the risk of worsening liver fibrosis in advanced disease stages. Recent randomized trials[23] support this hypothesis, showing that statins combined with other therapies (eg, carvedilol) can further reduce portal pressure in patients with cirrhosis by improving endothelial function and reducing proinflammatory cytokines.

Our findings also highlight important differences between statin types. Both lipophilic and hydrophilic statins were significantly associated with a reduced HCC risk; however, the association was stronger with lipophilic statins. Although the association between lipophilic statins and reduced HCC risk is well-established,[8,12,16] the association for hydrophilic statins remains controversial. Lipophilic statins appear more effective at preventing viral replication, potentiating antiviral therapy, and stimulating antitumor immunity, according to experimental evidence.[24] Differences in hepatocyte absorption mechanisms may also partially explain the stronger association observed with lipophilic statins.[25] However, the greater association of lipophilic statins with reduced HCC risk highlights their broader potential benefits in HCC prevention, warranting further investigation into their mechanisms of action and clinical applications. The stronger association observed with 600 or higher cDDD in this study supports a duration-response relationship, highlighting the potential importance of prolonged statin use in reducing the risks of HCC and hepatic decompensation. This observation supports previous studies[8,14,20,26] suggesting that the chemopreventive effects of statins and similar agents may require prolonged exposure to influence outcomes. The association that we observed between statin use and reduced hepatic decompensation risk was weaker than that seen in previous studies.[26,27] This finding likely reflected the broader population with CLD population, which included a lower proportion of cirrhosis cases, and our exclusion of patients with prior decompensation. This produced a lower baseline incidence of hepatic decompensation.

Limitations

There are several limitations to our study. First, despite our efforts to adjust for a wide range of confounders, unmeasured factors (eg, socioeconomic status, health care access, and health literacy) may have influenced the observed associations. Although randomized clinical trials to evaluate statins in HCC prevention are ideal, they would require large-scale enrollment and long-term follow-up, making them difficult to conduct. Well-designed historical cohort studies such as ours provide valuable insights into the intermediate pathways through which statins reduce HCC risk and fibrosis progression. Second, we could not account for potential postindex treatments that may influence outcomes, although patients were assumed to have received standard-of-care treatments based on CLD type. Third, to ensure adequate statistical power given the smaller cohort and fewer outcomes compared with larger studies, statin users were grouped into categories of 30 to 599 and 600 or higher cDDD. Future research could explore finer groupings to better elucidate the relationship between duration and response. Lastly, although we used FIB-4 score as a surrogate marker for liver fibrosis, it is not a direct measure, such as liver biopsy, which is the standard criterion. However, given the invasive nature of biopsy procedures, the FIB-4 score has been extensively validated and is widely recommended as a noninvasive fibrosis assessment tool.

Conclusions

This cohort study found that statin use, particularly lipophilic statin use and longer duration of therapy, was associated with reduced HCC risk and slower fibrosis progression in patients with CLD and intermediate to high fibrosis risk. Statin users with high baseline FIB-4 scores exhibited stable fibrosis trends and lower progression rates compared with nonusers. These findings underscore the potential of statins as chemopreventive agents against HCC through their role in mitigating fibrosis progression.

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