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HEPATOLOGY

Statins Are Associated With a Decreased Risk of Severe Liver Disease in Individuals With Noncirrhotic Chronic Liver Disease

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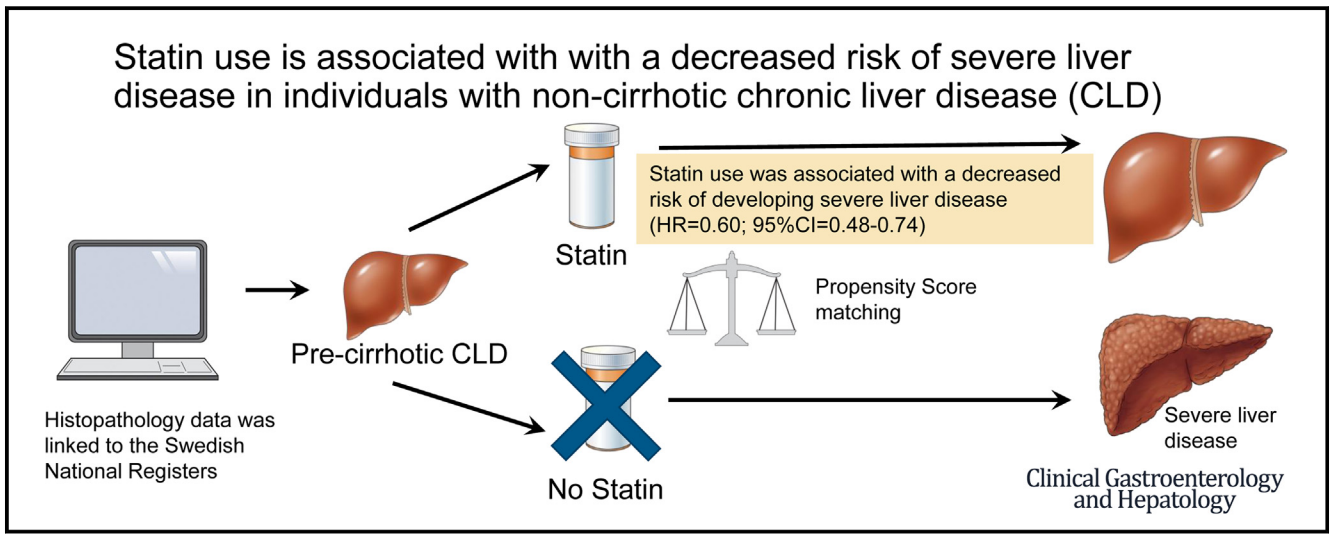

BACKGROUND & AIMS: **Little is known about the potential impact of statins on the progression of noncirrhotic chronic liver diseases (CLDs) to severe liver disease.**

METHODS: **Using liver histopathology data in a nationwide Swedish cohort, we identified 3862 noncirrhotic individuals with CLD and statin exposure, defined as a statin prescription filled for 30 or more cumulative defined daily doses. Statin users were matched to 3862 (statin) nonusers with CLD through direct 1:1 matching followed by propensity score matching. Cox regression was used to estimate hazard ratios (HRs) for the primary outcome of incident severe liver disease (a composite of cirrhosis, hepatocellular carcinoma, and liver transplantation/liver-related mortality).**

Abbreviations used in this paper: **AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; ATC, Anatomical Therapeutic Chemical classification system codes; cDDD, cumulative defined daily dose; CLD, chronic liver disease; ESPRESSO, Epidemiology Strengthened by histopathology Reports in Sweden cohort; HCC, hepatocellular carcinoma; HR, hazard ratio; ICD, International Classification of Diseases; NAFLD, nonalcoholic fatty liver disease; SNOMED, Systemized Nomenclature of Medicine.**

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RESULTS: **A total of 45.3% of CLD patients had nonalcoholic fatty liver disease, 21.9% had alcohol-related liver disease, 17.7% had viral hepatitis, and 15.1% had autoimmune hepatitis. During follow-up evaluation, 234 (6.1%) statin users vs 276 (7.1%) nonusers developed severe liver disease. Statin use was associated with a decreased risk of developing severe liver disease (HR, 0.60; 95% CI, 0.48–0.74). Statistically significantly lower rates of severe liver disease were seen in alcohol-related liver disease (HR, 0.30; 95% CI, 0.19–0.49) and in nonalcoholic fatty liver disease (HR, 0.68; 95% CI, 0.45–1.00), but not in viral hepatitis (HR, 0.76; 95% CI, 0.51–1.14) or autoimmune hepatitis (HR, 0.88; 95% CI, 0.48–1.58). Statin use had a protective association in both prefibrosis and fibrosis stages at diagnosis. Statin use was associated with lower rates of progression to cirrhosis (HR, 0.62; 95% CI, 0.49–0.78), hepatocellular carcinoma (HR, 0.44; 95% CI, 0.27–0.71), and liver-related mortality (HR, 0.55; 95% CI, 0.36–0.82).**

CONCLUSIONS: **Among individuals with noncirrhotic CLD, incident statin use was linked to lower rates of severe liver disease, suggesting a potential disease-modifying role.**

Keywords: Cirrhosis; Hepatocellular Carcinoma; Fibrosis.

See editorial on page 708.

Statins have been shown to inhibit inflammatory pathways, promote endothelial cell function, and reduce hepatic stellate cell activity, leading to the hypothesis that statins could attenuate the progression of liver fibrosis.[1] Prior clinical and epidemiologic studies of patients with noncirrhotic chronic liver disease (CLD) suggest that statins may have beneficial effects on the progression to cirrhosis, hepatocellular carcinoma (HCC), and mortality.[2–8] Although many of these are large studies, the majority include only viral hepatitis, and the identification of precirrhotic liver disease was based largely on fibrosis scores or International Classification of Diseases (ICDs) coding, leading to a risk of misclassification and considerable heterogeneity in results.

Therefore, we aimed to study the association between statins and liver disease progression to cirrhosis, HCC, and death in patients with noncirrhotic CLD using a nationwide cohort with liver histopathology data.[9]

Methods

Individuals With Chronic Liver Disease

Using prior algorithms applied to the Epidemiology Strengthened by histopathology Reports in Sweden (ESPRESSO) cohort, adults with CLD diagnosed at 18 years of age or older were identified by requiring the presence of an index liver biopsy between 1969 and 2017 and at least 1 ICD code for CLD. We included patients with viral hepatitis, including hepatitis C virus and hepatitis B virus,[10] alcohol-related liver disease (ALD),[11,12] autoimmune hepatitis (AIH),[13] and nonalcoholic fatty liver disease (NAFLD)[14] (see Supplementary Table 1 for codes). The diagnosis date for CLD was the latter of either index liver biopsy or CLD ICD code date, except for NAFLD, in which earlier validation has found that a relevant Systemized Nomenclature of Medicine (SNOMED) code is sufficient for the diagnosis.[14]

Specifically, the identification of individuals with NAFLD[14] and AIH[13] have been validated in the ESPRESSO cohort with positive predictive values of 92% and 95%, respectively. We used a combination of ICD codes to define alcohol-related liver disease determined by a consensus.[11] Finally, we used a hierarchy for the definition of CLD to further reduce misclassification (Supplementary Table 1) (also reported previously[15]).

Liver Histopathology Report Data

Histopathology report data were available for each individual in the ESPRESSO cohort at CLD diagnosis, and was linked to the Swedish National Registers.[9] Noncirrhotic fibrosis (includes stages F1–F3 fibrosis, inflammation without fibrosis, and no fibrosis or inflammation) were defined as mutually exclusive groups using SNOMED codes (Supplementary Table 2).[9] The ESPRESSO cohort was approved by the Stockholm Ethics Board (2014/1287-31/4) on August 27, 2014.

Exclusion Criteria

We excluded patients for the following reasons. Patients who had a SNOMED code for cirrhosis on the index liver biopsy, and those with an ICD code for cirrhosis before CLD diagnosis. ICD codes for cirrhosis included cirrhosis, decompensation, or portal hypertension, and were validated in a previous study with positive predictive values greater than 90%.[16] We also excluded patients who, before the index statin exposure date, acquired ICD codes for the following reasons: (1) cirrhosis, (2) HCC, (3) liver transplant, (4) had migrated within the 5 years before statin exposure, or (5) had a personal identity number that was re-used before the index statin exposure date (Figure 1, Supplementary Table 3 for ICD codes).

Exposure to Statins

The Prescribed Drug Register prospectively includes all prescribed dispensed drugs from pharmacies in

Sweden since July 1, 2005, and is nearly 100% complete.[17] Statins were defined using Anatomical Therapeutic Chemical (ATC) classification system codes (Supplementary Methods and Supplementary Table 4).

An individual was defined as being exposed to a statin if a statin prescription was filled for 30 or more cumulative defined daily doses (cDDDs) starting July 1, 2006, or later (consistent with prior studies of statins[4,6,7,10]). The index date for statin exposure was the date an individual first attained a cDDD of 30 or more for a statin, provided this occurred after a liver disease diagnosis. Using an intention-to-treat design, statin use as initially determined remained as such during the follow-up period. Individuals who had any statin prescription for a 365-day period or less before the first attainment of a cDDD of 30 or more were excluded to ensure that we captured incident statin use.

For each of the matched statin nonusers, the control who had a propensity score closest to that of the statin user and who had prescriptions (except drugs related to liver disease or HCC treatment) filled within ±3 months

What You Need to Know

Background

A small number of prior studies have examined the effects of statins in noncirrhotic chronic liver disease specifically, but there is considerable heterogeneity in results owing to misclassification.

Findings

Incident statin use is associated with decreased progression to severe liver disease in precirrhotic stages. The inverse association was significant in alcohol-related and nonalcoholic fatty liver disease, and was similar in both prefibrosis and fibrosis stages.

Implications for patient care

Statins may be beneficial in preventing the progression of liver fibrosis in early stages of chronic liver disease.

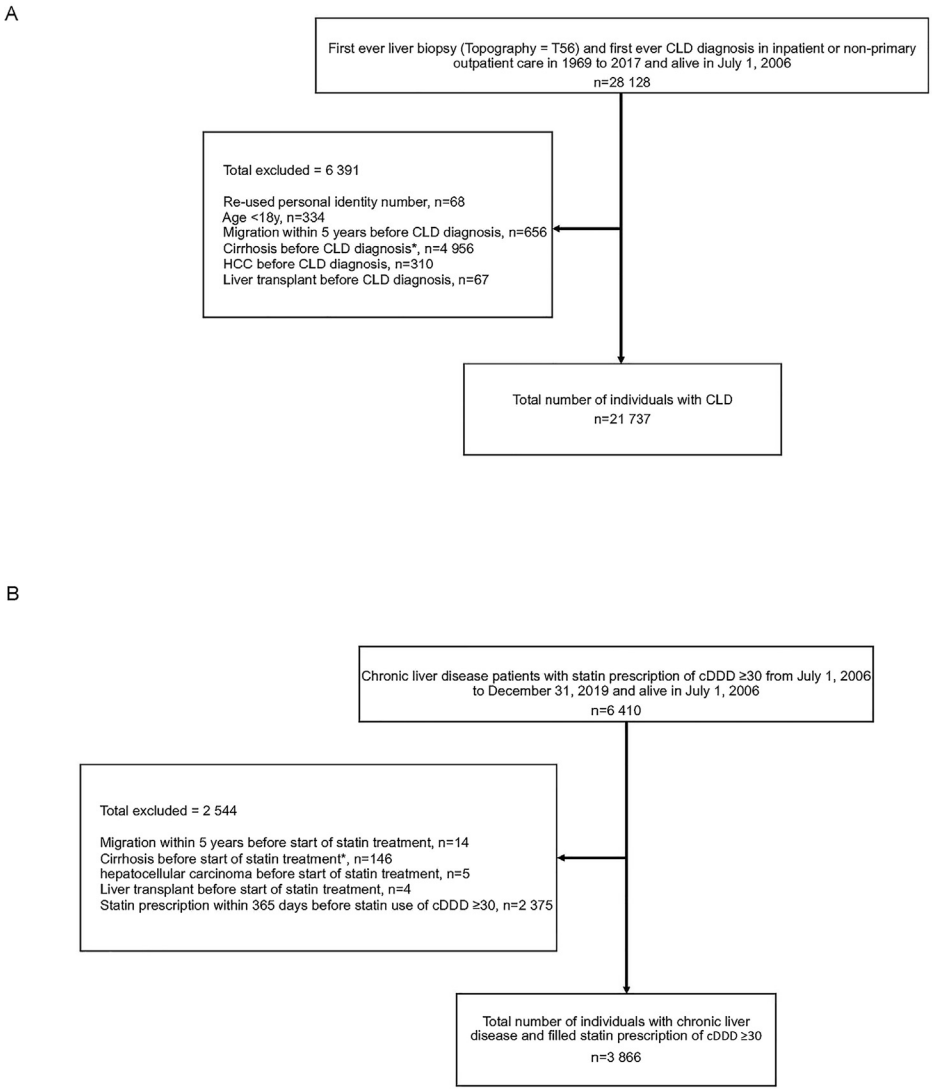

Figure 1. (*A*) Flowchart of patients with chronic liver disease (CLD). (*B*) Flowchart of patients with chronic liver disease and start of statin treatment with filled statin prescription of cumulative defined daily dose (cDDD) of 30 or more. HCC, hepatocellular carcinoma.

of statin exposure in the statin user was selected. Start of follow-up evaluation was at the time of statin exposure in statin users and corresponded to drug prescription in nonusers that fit the earlier-described criteria, and all individuals had to be event-free between CLD diagnosis and start of follow-up evaluation.

Propensity Score and Matching

We used a propensity score–matched cohort design to account for differences in health-related factors that would affect the likelihood of receiving a statin prescription. Matching was performed in a 2-step fashion. First, statin users and nonusers were matched directly by sex, age, year of CLD diagnosis, type of CLD, and liver histology findings at diagnosis. Second, statin users and nonusers subsequently were propensity score matched. Our propensity score included a priori–selected parameters including age, CLD duration, number of inpatient/outpatient health care visits, country of birth, level of education, and the presence of ischemic heart disease, cerebrovascular disease, congestive heart failure, arrhythmias, peripheral vascular disease or other vascular disorders, arrhythmias, obesity, myositis, diabetes including diabetes medications, chronic obstructive pulmonary disease (proxy for heavy smoking), end-stage renal disease, obstructive sleep apnea, non–hepatocellular carcinoma cancers, aspirin, nonaspirin antiplatelet medications, nonstatin lipid-lowering medications, anticoagulation, hepatitis C virus medications, AIH medications, and hepatitis B virus medications. For more details on the propensity score, see the Supplementary Methods and Supplementary Tables 5 and 6.

Outcomes

Our main outcome was a composite outcome to represent progression to severe liver disease including the development of cirrhosis (includes cirrhosis, decompensation, or portal hypertension ICD codes), HCC, or liver-related mortality (includes liver transplantation) (Supplementary Table 3).

Statistical Analyses

Main analyses. Follow-up time accrued from statin exposure in statin users or a corresponding nonstatin drug prescription in matched statin nonusers and ended with the first record of cirrhosis, HCC, death or liver transplantation, emigration, or end of follow-up evaluation on December 31, 2019. Nonstatin users additionally were censored on the date of first statin exposure, if it occurred. Incidence rates of the main composite outcome and secondary outcomes were reported with a 95% CI. We also reported hazard ratios (HRs) for developing each secondary outcome separately: cirrhosis, HCC, and liver-related death (includes liver transplantation).

Kaplan–Meier failure curves were plotted. In main analyses and subanalyses, we performed Cox regression conditioned on the matching set. We then adjusted for potential confounders that remained unbalanced despite propensity score matching (ischemic heart disease, nonaspirin antiplatelet medications, and AIH medications), and these HRs are presented in the Results section.

Subanalyses. We reported HRs for the main composite outcome of incident severe liver disease by prespecified key subgroups based on clinical relevance listed in the Supplementary Methods. To determine whether differences in the extent of statin exposure affect outcomes, we reported HRs for the main outcome by predefined categories of statin exposure (30 to $<$300, 300 to $<$600, and $\geq$600 cDDDs). To test for statistical evidence of heterogeneity between subgroups, we performed interaction tests.[18]

Sensitivity Analyses

We performed several sensitivity analyses to test the robustness of our results. We determined the risk of the main outcome and secondary outcomes by including statin treatment as a time-dependent exposure with follow-up evaluation beginning at the latest of either CLD diagnosis or January 1, 2006. Given that this analysis was not propensity score matched, we first adjusted for age, sex, year of CLD, type of liver disease, and liver histopathology (model I). We then subsequently adjusted for disease duration, number of inpatient or outpatient health care visits, country of birth, level of education, Charlson Comorbidity Index,[19] aspirin use, nonaspirin antiplatelet medications, nonstatin lipid-lowering medications, and anticoagulants (model II).

In a landmark sensitivity analysis, we restricted study participants to those who were event-free 1 year after CLD diagnosis, and started follow-up evaluation at that date. We applied similar adjustments in this analysis as for the time-dependent analysis because this analysis also could not be propensity score matched. This sensitivity analysis helps address potential differences in the proportion of those excluded from the main analysis owing to experiencing an outcome between CLD diagnosis and prescription start.

Given that cDDD can introduce short immortal time after start of follow-up evaluation, we performed a sensitivity analysis in which we removed individuals with fewer than 30 cDDDs of statin exposure, who may be at risk for immortal time.

Finally, we reported cumulative incidence curves and performed competing risk regression (subdistribution HRs reported) for the main composite outcome as well as secondary outcomes separately with non–liver-related death as the competing event.

Table 1. Baseline Characteristics of CLD Patients With and Without Statin Treatment After Matching

Characteristic	Statin users (n = 3862)	Nonstatin users (n = 3862)	Standardized difference
Sex, n (%)			
Women	1515 (39.2)	1515 (39.2)	0
Men	2347 (60.8)	2347 (60.8)	0
Age, *y*			
Mean (SD)	62.2 (11.2)	61.6 (12.7)	0.052
Median (IQR)	62.6 (14.6)	61.9 (16.1)	
Range, minimum–maximum	18.8–95.0	18.8–96.9	
Categories, n (%)			
18 to <40 y	121 (3.1)	207 (5.4)	-0.111
40 to <50 y	425 (11.0)	339 (8.8)	0.075
50 to <60 y	1009 (26.1)	1157 (30.0)	-0.085
≥60 y	2307 (59.7)	2159 (55.9)	0.078
18 to <50 y	546 (14.1)	546 (14.1)	0
≥50 y	3316 (85.9)	3316 (85.9)	0
Country of birth, n (%)			
Nordic country	3402 (88.1)	3396 (87.9)	0.005
Other European country	213 (5.5)	199 (5.2)	0.016
Other non-European country	247 (6.4)	267 (6.9)	-0.021
Level of education, n (%)			
≤9 y	1143 (29.6)	1180 (30.6)	-0.021
10–12 y	1859 (48.1)	1833 (47.5)	0.013
>12 y	850 (22.0)	839 (21.7)	0.007
Missing	10 (0.3)	10 (0.3)	0
Start year of follow-up evaluation, n (%)			
2006–2010	1315 (34.0)	1313 (34.0)	0.001
2011–2015	1359 (35.2)	1357 (35.1)	0.001
2016–2019	1188 (30.8)	1192 (30.9)	-0.002
Chronic liver disease diagnosis, n (%)			
1969–1980	28 (0.7)	28 (0.7)	0
1981–1990	503 (13.0)	503 (13.0)	0
1991–2000	1379 (35.7)	1379 (35.7)	0
2001–2010	1449 (37.5)	1449 (37.5)	0
2011–2017	503 (13.0)	503 (13.0)	0
Liver disease diagnosis, n (%)			
Viral hepatitis (B or C)	683 (17.7)	683 (17.7)	0
Alcohol-related liver disease	846 (21.9)	846 (21.9)	0
Autoimmune hepatitis	583 (15.1)	583 (15.1)	0
Nonalcoholic fatty liver disease	1750 (45.3)	1750 (45.3)	0
Duration of chronic liver disease (chronic liver disease diagnosis to index date), *y*			
Mean (SD)	12.5 (8.2)	12.4 (8.3)	0.010
Median (IQR)	12.0 (13.0)	11.8 (13.0)	
Range, minimum–maximum	0.0–42.6	0.0–41.4	
Time between liver biopsy and index date, *y*			0.037
Median (SD)	13.8 (8.2)	13.5 (8.2)	
Median (IQR)	13.6 (12.8)	13.2 (12.5)	
Range, minimum–maximum	0.0–46.1	0.0–41.6	
Categories, n (%)			
<1 y	261 (6.8)	220 (5.7)	0.044
1 to <5 y	623 (16.1)	708 (18.3)	-0.058
5 to <10 y	753 (19.5)	753 (19.5)	0.000
≥10 y	2225 (57.6)	2181 (56.5)	0.023
Inpatient/outpatient health care visits between 2 years and 6 months before start of follow-up evaluation, n			
Mean (SD)	5.3 (9.3)	5.5 (7.8)	-0.021
Median (IQR)	3 (6)	3 (6)	
Range, minimum–maximum	0–243	0–262	

Table 1. Continued

Characteristic	Statin users (n = 3862)	Nonstatin users (n = 3862)	Standardized difference
Categories, n (%)			
0	762 (19.7)	651 (16.9)	0.074
1	539 (14.0)	528 (13.7)	0.008
2–3	815 (21.1)	785 (20.3)	0.019
≥4	1746 (45.2)	1898 (49.1)	-0.079
Charlson comorbidity score from inpatient/outpatient health care visits within 5 years before start of follow-up/index date			
Mean (SD)	2.1 (2.4)	2.3 (2.7)	-0.074
Median (IQR)	1 (3)	2 (3)	
Range, minimum–maximum	0–18	0–19	
Categories, n (%)			
0	1385 (35.9)	1430 (37.0)	-0.024
1	583 (15.1)	426 (11.0)	0.121
2	409 (10.6)	359 (9.3)	0.043
3	611 (15.8)	734 (19.0)	-0.084
≥4	874 (22.6)	913 (23.6)	-0.024
Comorbidities within 5 years before start of follow-up evaluation, n (%)			
Ischemic heart disease	762 (19.7)	558 (14.4)	0.141
Cerebrovascular disease	432 (11.2)	352 (9.1)	0.069
Congestive heart failure	216 (5.6)	183 (4.7)	0.039
Arrhythmia (including antiarrhythmic medications)	374 (9.7)	357 (9.2)	0.015
Peripheral vascular disease and other vascular disorders	212 (5.5)	198 (5.1)	0.016
Obesity	512 (13.3)	478 (12.4)	0.026
Myositis	4 (0.1)	5 (0.1)	-0.008
Diabetes (including antidiabetic medications)	1570 (40.7)	1639 (42.4)	-0.036
Chronic obstructive pulmonary disease	195 (5.0)	213 (5.5)	-0.021
End-stage renal disease	32 (0.8)	39 (1.0)	-0.019
Obstructive sleep apnea	158 (4.1)	140 (3.6)	0.024
Nonhepatocellular carcinoma cancer	351 (9.1)	387 (10.0)	-0.032
Medications			
Aspirin	1670 (43.2)	1600 (41.4)	0.037
Nonaspirin antiplatelet medications	680 (17.6)	341 (8.8)	0.261
Hepatitis C virus medications	276 (7.1)	277 (7.2)	-0.001
Nonstatin lipid-lowering medications	140 (3.6)	134 (3.5)	0.008
Anticoagulation	311 (8.1)	306 (7.9)	0.005
Autoimmune hepatitis medications	881 (22.8)	1076 (27.9)	-0.116
Hepatitis B virus medications	38 (1.0)	37 (1.0)	0.003
Liver histopathology, n (%)			
No fibrosis no inflammation	2069 (53.6)	2069 (53.6)	0
Inflammation without fibrosis	729 (18.9)	729 (18.9)	0
Fibrosis (F1–F3)	1064 (27.6)	1064 (27.6)	0
Type of statin drug at treatment start, n (%)			
Simvastatin	2336 (60.5)		
Atorvastatin	1448 (37.5)		
Other statins	78 (2.0)		
Follow-up time (main outcome), *y*			
Mean (SD)	5.8 (3.8)	3.9 (3.5)	
Median (IQR)	5.3 (6.4)	2.9 (5.1)	
Range, minimum–maximum	0.0–13.5	0.0–13.5	
Categories, n (%)			
<1 y	412 (10.7)	953 (24.7)	
1 to <5 y	1456 (37.7)	1686 (43.7)	
5 to <10 y	1296 (33.6)	892 (23.1)	
≥10 y	698 (18.1)	331 (8.6)	
Reason for end of follow-up evaluation (main outcome)			
Outcome event	234 (6.1)	276 (7.1)	
Statin prescription	0	1151 (29.8)	
Non–liver-related death	596 (15.4)	558 (14.4)	
Emigration	16 (0.4)	21 (0.5)	
End of data (December 31, 2019)	3016 (78.1)	1856 (48.1)	

CLD, chronic liver disease; IQR, interquartile range.

Table 2. Risk of Main Composite Outcome in Chronic Liver Disease Patients With and Without Statin Treatment

Outcome	N (%)		Events, N (%)		Incidence rate (95% CI) per 1000 PY		HR[a] (95% CI)	HR[b] (95% CI)	*P* value for interaction
	Statin users	Nonstatin users	Statin users	Nonstatin users	Statin users	Nonstatin users			
Overall	3862 (100)	3862 (100)	234 (6.1%)	276 (7.1%)	10.5 (9.1–11.8)	18.1 (16.0–20.3)	0.59 (0.48–0.72)	0.60 (0.48–0.74)	
Follow-up time, *y*									
<1	3862 (100)	3862 (100)	35 (0.9%)	73 (1.9%)	9.6 (6.4–12.7)	22.1 (17.1–27.2)	0.42 (0.28–0.65)	0.40 (0.25–0.65)	.70
1 to <5	3450 (89.3)	2909 (75.3)	114 (3.3%)	146 (5.0%)	10.5 (8.6–12.5)	18.8 (15.7–21.8)	0.60 (0.46–0.80)	0.63 (0.47–0.84)	
5 to <10	1994 (51.6)	1223 (31.7)	70 (3.5%)	52 (4.3%)	10.5 (8.0–12.9)	14.3 (10.4–18.2)	0.77 (0.49–1.21)	0.72 (0.44–1.16)	
≥10	698 (18.1)	331 (8.6)	15 (2.1%)	5 (1.5%)	12.9 (6.4–19.4)	9.6 (1.2–17.9)	1.00 (0.20–4.95)	3.00 (0.31–28.84)	
Sex									
Women	1515 (39.2)	1515 (39.2)	76 (5.0%)	101 (6.7%)	8.7 (6.8–10.7)	16.3 (13.1–19.4)	0.57 (0.40–0.80)	0.55 (0.38–0.79)	.72
Men	2347 (60.8)	2347 (60.8)	158 (6.7%)	175 (7.5%)	11.6 (9.8–13.4)	19.4 (16.5–22.3)	0.60 (0.46–0.77)	0.62 (0.48–0.81)	
Age, *y*									
18 to <50	546 (14.1)	546 (14.1)	25 (4.6%)	29 (5.3%)	6.6 (4.0–9.2)	9.7 (6.2–13.2)	0.91 (0.51–1.65)	0.89 (0.47–1.69)	.13
≥50	3316 (85.9)	3316 (85.9)	209 (6.3%)	247 (7.4%)	11.3 (9.7–12.8)	20.2 (17.7–22.7)	0.55 (0.44–0.69)	0.56 (0.45–0.71)	
Start year of follow-up evaluation									
2006–2010	1315 (34.0)	1313 (34.0)	113 (8.6%)	121 (9.2%)	9.3 (7.6–11.0)	15.7 (12.9–18.5)	0.57 (0.42–0.79)	0.60 (0.43–0.84)	.44
2011–2015	1359 (35.2)	1357 (35.1)	94 (6.9%)	123 (9.1%)	12.0 (9.6–14.4)	22.0 (18.1–25.9)	0.51 (0.37–0.70)	0.49 (0.35–0.69)	
2016–2019	1188 (30.8)	1192 (30.9)	27 (2.3%)	32 (2.7%)	11.6 (7.3–16.0)	16.5 (10.8–22.3)	0.76 (0.44–1.32)	0.75 (0.42–1.35)	
Chronic liver disease diagnosis, n (%)									
1969–1980	28 (0.7)	28 (0.7)	2 (7.1%)	2 (7.1%)	10.6 (0.0–25.4)	20.7 (0.0–49.4)	–	–	.55
1981–1990	503 (13.0)	503 (13.0)	21 (4.2%)	27 (5.4%)	6.3 (3.6–9.0)	13.7 (8.5–18.8)	0.54 (0.28–1.06)	0.46 (0.21–1.05)	
1991–2000	1379 (35.7)	1379 (35.7)	84 (6.1%)	94 (6.8%)	9.3 (7.3–11.3)	15.8 (12.6–19.0)	0.58 (0.41–0.83)	0.60 (0.41–0.86)	
2001–2010	1449 (37.5)	1449 (37.5)	109 (7.5%)	116 (8.0%)	13.4 (10.9–15.9)	19.6 (16.1–23.2)	0.69 (0.51–0.93)	0.71 (0.52–0.97)	
2011–2017	503 (13.0)	503 (13.0)	18 (3.6%)	37 (7.4%)	11.0 (5.9–16.1)	28.8 (19.6–38.1)	0.35 (0.18–0.68)	0.28 (0.12–0.64)	
Liver disease diagnosis									
Viral hepatitis (B or C)	683 (17.7)	683 (17.7)	61 (8.9%)	74 (10.8%)	17.7 (13.2–22.1)	27.8 (21.5–34.1)	0.70 (0.48–1.02)	0.76 (0.51–1.14)	.02
Alcohol-related liver disease	846 (21.9)	846 (21.9)	59 (7.0%)	95 (11.2%)	13.4 (10.0–16.8)	31.8 (25.4–38.2)	0.35 (0.23–0.54)	0.30 (0.19–0.49)	
Autoimmune hepatitis	583 (15.1)	583 (15.1)	38 (6.5%)	32 (5.5%)	12.0 (8.2–15.9)	13.5 (8.8–18.2)	0.96 (0.56–1.65)	0.88 (0.48–1.58)	
Nonalcoholic fatty liver disease	1750 (45.3)	1750 (45.3)	76 (4.3%)	75 (4.3%)	6.7 (5.2–8.2)	10.4 (8.1–12.8)	0.62 (0.43–0.91)	0.68 (0.45–1.00)	
Liver histopathology									
No fibrosis no inflammation	2069 (53.6)	2069 (53.6)	87 (4.2%)	112 (5.4%)	6.7 (5.3–8.1)	13.5 (11.0–16.1)	0.54 (0.39–0.76)	0.57 (0.41–0.79)	.34
Inflammation without fibrosis	729 (18.9)	729 (18.9)	52 (7.1%)	60 (8.2%)	13.1 (9.5–16.6)	21.6 (16.1–27.0)	0.48 (0.30–0.77)	0.36 (0.20–0.63)	
Fibrosis (F1–F3)	1064 (27.6)	1064 (27.6)	95 (8.9%)	104 (9.8%)	17.6 (14.1–21.2)	24.9 (20.2–29.7)	0.70 (0.51–0.96)	0.72 (0.51–1.02)	
Type of statin drug at treatment start									
Simvastatin	2336 (60.5)	2336 (60.5)	181 (7.7%)	212 (9.1%)	10.5 (9.0–12.0)	18.4 (16.0–20.9)	0.55 (0.44–0.70)	0.57 (0.45–0.73)	.30
Atorvastatin	1448 (37.5)	1448 (37.5)	49 (3.4%)	61 (4.2%)	10.6 (7.7–13.6)	18.0 (13.5–22.6)	0.65 (0.42–0.99)	0.61 (0.38–0.99)	
Other statins	78 (2.0)	78 (2.0)	4 (5.1%)	3 (3.8%)	8.7 (0.2–17.3)	8.9 (0.0–18.9)	2.00 (0.37–10.92)	1.50 (0.25–8.98)	

HR, hazard ratio; PY, person-year.
[a]Conditioned on matching set.
[b]Conditioned on matching set and further adjusted for ischemic heart disease, autoimmune hepatitis medications, and nonaspirin antiplatelet medications.

Results

Background Data

Our final cohort consisted of 3862 statin users matched to 3862 statin nonusers with noncirrhotic CLD (Figure 1, Table 1, Supplementary Table 7). After propensity score matching, all standardized mean differences for variables included in the matching algorithm were between -0.1 and 0.1, except ischemic heart disease, nonaspirin antiplatelet medications, and AIH medications (Table 1). These variables therefore additionally were adjusted for in the final regression models. Clinical characteristics of statin and nonstatin users are described in Table 1.

Main Results

Overall, there were 234 (6.1%) total events of the main composite outcome, incident severe liver disease, in statin users with noncirrhotic CLD, with an incidence rate of 10.5 per 1000 person-years (95% CI, 9.1–11.8) and 276 events in statin nonusers (7.1%) with an incidence rate of 18.1 per 1000 person-years (95% CI, 16.0–20.3) (Table 2). This corresponded to an HR of 0.60 (95% CI, 0.48–0.74). The Kaplan–Meier curve showed a sustained decreased risk of incident severe liver disease in statin users compared with nonusers (Figure 2).

In subanalyses, compared with nonuse, statin use was associated with a statistically significant lower risk of incident severe liver disease in noncirrhotic CLD individuals with ALD (7.0% vs 11.2%; HR, 0.30; 95% CI, 0.19–0.49) and NAFLD (4.3% vs 4.3%; HR, 0.68; 95% CI, 0.45–1.00), but not for individuals with AIH (6.5% vs 5.5%; HR, 0.88; 95% CI, 0.48–1.58) or viral hepatitis (8.9% vs 10.8%; HR, 0.76; 95% CI, 0.51–1.14) (Table 2, subgroup interaction $P = .02$). On liver biopsy at CLD diagnosis, CIs overlapped between all 3 histopathology groups and the interaction test was not significant ($P = .34$). We also did not see differences between different cDDD groups of statin exposure (Supplementary Table 8, subgroup interaction $P = .76$). Finally, there were no statistically significant differences by type of statin (Table 2, subgroup interaction $P = .30$).

Statin use also was associated inversely with secondary outcomes: cirrhosis, HCC, and liver-related death (including liver transplantation) (Table 3, Figure 2).

Sensitivity Analyses

With statin treatment as a time-dependent exposure, the risk of incident severe liver disease remained lower in statin users compared with statin nonusers (HR, 0.87; 95% CI, 0.75–1.00) (Supplementary Table 9).

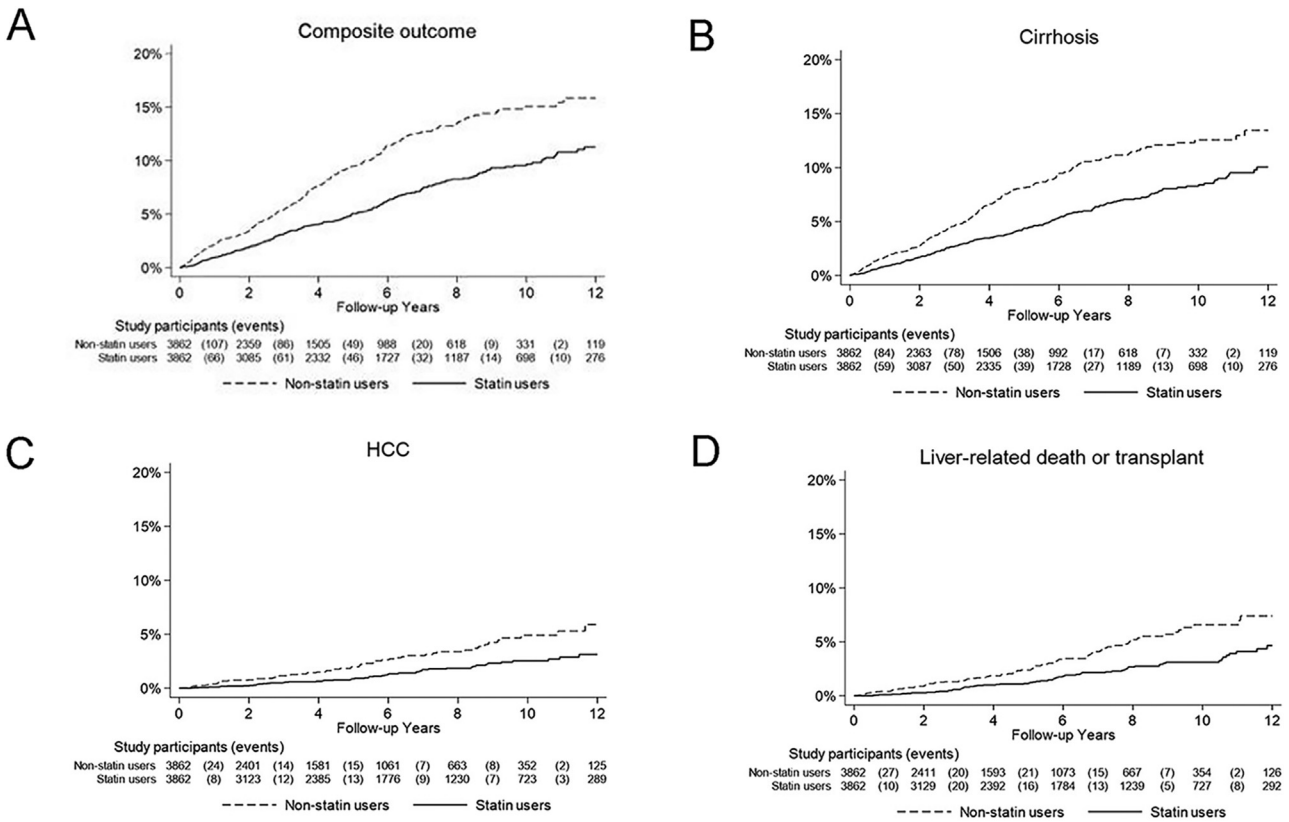

Figure 2. Kaplan–Meier failure curves of time to main composite outcome of severe liver disease and secondary outcomes in chronic liver disease patients with and without statin treatment: (*A*) severe liver disease, (*B*) cirrhosis, (*C*) hepatocellular carcinoma (HCC), and (*D*) liver-related death or transplant.

Table 3. Risk of Secondary Outcomes in Chronic Liver Disease Patients With and Without Statin Treatment

Outcome	Events, N		Incidence rate (95% CI) per 1000 PY			
	Statin users	Nonstatin users	Statin users	Nonstatin users	HR[a] (95% CI)	HR[b] (95% CI)
Main composite outcome	234 (6.1%)	276 (7.1%)	10.5 (9.1–11.8)	18.1 (16.0–20.3)	0.59 (0.48–0.72)	0.60 (0.48–0.74)
Cirrhosis	202 (5.2%)	228 (5.9%)	9.0 (7.8–10.3)	15.0 (13.0–16.9)	0.61 (0.49–0.77)	0.62 (0.49–0.78)
Hepatocellular carcinoma	53 (1.4%)	71 (1.8%)	2.3 (1.7–3.0)	4.5 (3.5–5.5)	0.45 (0.29–0.70)	0.44 (0.27–0.71)
Liver-related mortality or liver transplantation	76 (2.0%)	93 (2.4%)	3.3 (2.6–4.1)	5.9 (4.7–7.1)	0.56 (0.39–0.81)	0.55 (0.36–0.82)

HR, hazard ratio; PY, person-year.
[a]Conditioned on matching set.
[b]Conditioned on matching set and further adjusted for ischemic heart disease, autoimmune hepatitis medications, and nonaspirin antiplatelet medications.

We restricted our data to individuals who were event free for at least 1 year after CLD diagnosis in a landmark analysis. Baseline characteristics are presented in Supplementary Table 10, and statin use was associated with a lower risk of incident severe liver disease (HR, 0.81; 95% CI, 0.68–0.95) (Supplementary Table 11).

When excluding individuals at risk for immortal time less than 30 days, there was no change in the HR (0.58; 95% CI, 0.47–0.72).

When performing competing risk regression with nonliver death as the competing risk, the HRs were similar to our main analyses for our main and secondary outcomes (Supplementary Tables 12 and 13). Corresponding cumulative incidence curves also showed a decreased risk of our main and secondary outcomes in statin users compared with nonusers (Supplementary Figures 1 and 2).

Discussion

In this nationwide population-based study, we show that incident statin use in noncirrhotic individuals with CLD was associated with a lower rate of progression to severe liver disease compared with those who did not use statins. The inverse association for statin use was statistically significant in those with ALD and NAFLD, but not viral hepatitis and AIH, and similar in both prefibrosis and fibrosis stages of liver disease

We show an inverse association between statin use and progression to severe liver disease, and our overall HR of 0.60 is consistent with prior studies that included histology or surrogate measures of fibrosis.[3–5] Few prior studies have included noncirrhotic CLD individuals and were limited by lack of liver histopathology data and validated ICD codes, leading to potential misclassification of fibrosis, CLD diagnosis, and liver-related outcomes.[2–8] In addition, our study had stricter matching criteria and better balanced exposure groups, reducing confounding by indication. Time-varying sensitivity analysis for statin exposure and landmark sensitivity analysis also supported an inverse relationship between statin exposure and risk of severe liver disease. However, the 95% CI (0.75–1.00) in time-varying analyses does not overlap with main analyses (0.48–0.74), likely because careful propensity score matching to address confounding was not possible in this sensitivity analysis and the sample size was smaller.

Because of the presence of liver histopathology data at CLD diagnosis, we were able to exclude patients with cirrhosis and examine the effects of statins by different histopathology groups. We saw no difference between histopathology subgroups, indicating that statins likely are beneficial in both the prefibrosis and fibrosis stages. It is possible that hypothesized anti-inflammatory, vascular, and tissue healing benefits of statins could play a role in the prevention of fibrosis progression, but mechanistic studies are needed.[1]

Statin use was associated inversely with disease progression in ALD and NAFLD, but did not reach statistical significance in viral hepatitis and AIH. Surprisingly, very few studies have examined statins in NAFLD.[20,21] We show a protective association after controlling for metabolic syndrome and related medications. Thus far, there are no studies on statins in noncirrhotic ALD individuals, and conflicting evidence in cirrhotic patients with ALD.[22] We see a strong inverse association between statin use and the progression to severe liver disease in noncirrhotic ALD individuals, but our conclusions are limited by a lack of data on alcohol cessation after ALD diagnosis. The majority of prior studies have examined statins in noncirrhotic viral hepatitis,[3,4,6–8,10] but many lacked a propensity score, biopsy data, and were not population-based. Our results for viral hepatitis did not reach statistical significance, but the HR of 0.76 is close to our main HR of 0.60. We did not see an association between statin use and a reduction in progression to severe liver disease in noncirrhotic AIH individuals after adjusting for AIH medications. One explanation may be that AIH has disease-modifying therapies that are very effective[23] and therefore the risk of incident severe liver disease on AIH therapy already is low, and, therefore, the addition of statin therapy is not as

impactful. Another explanation is that we lacked enough power to detect an association in this subgroup. Larger studies are needed to make further conclusions.

This was a large study comprising approximately 3800 individuals exposed to statins with liver histopathology data for each individual allowing for more accurate CLD diagnoses, staging of liver disease, and exclusion of cirrhotic patients at CLD diagnosis. To address changes in medical care and the ability to diagnose liver diseases over time, we saw no difference in HRs between start year of follow-up evaluation or year of CLD diagnoses. In addition, we importantly performed key subanalyses by liver histopathology at CLD diagnosis and also by CLD type. The Swedish Patient Registers and Drug Register prospectively collect data and have nearly complete follow-up evaluation data, allowing for accurate representation of outcomes and medication prescriptions, respectively. To reduce confounding by indication, we carefully matched individuals on demographic factors, factors associated with being prescribed a statin, and factors that are known to affect CLD progression, adjusting for unbalanced variables. Competing risk regression also resulted in similar effect sizes to our main analyses. Finally, a time-varying analysis as well as a landmark sensitivity analysis confirmed our main findings.

This study had some limitations. First, we could not rule out unmeasured confounding. We did not have access to laboratory data, medication indications, or clinical notes to be able to track disease progression, response to treatments, or alcohol cessation. There were very few repeat liver biopsies in this cohort, and, therefore, we could not analyze changes in fibrosis over time according to statin use. We recognize that liver disease may have progressed between the CLD diagnosis and index date; however, we have taken several measures to balance risk factors for fibrosis progression by matching directly by age, year of CLD diagnosis, type of CLD, histopathology at CLD diagnosis, and including duration of CLD and CLD medications in the propensity score. We also excluded individuals who developed cirrhosis before the index date. We could not rule out a healthy user effect in that statin users are more likely to exercise, lose weight, and stop drinking, which is difficult to measure in the national patient registers. In addition, SNOMED codes available for liver histopathology reports cannot distinguish between F1, F2, and F3 fibrosis, but we reliably are able to distinguish lack of fibrosis from fibrosis and the presence of inflammation. The Swedish National Registers also do not have reliable data on smoking, obesity, race, or ethnicity. We used an intention-to-treat design for statin use and therefore could not account for patient adherence to statins or discontinuation of statins later in follow-up evaluation. To address this, we performed analyses with time-varying statin exposure, which confirmed an inverse relationship between statin use and risk of incident severe liver disease. In addition, we could not evaluate statin use before July 1, 2005, when the Swedish Prescription Drug Register started. However, our exposure was first receipt of 30 cDDDs or more to ensure new users. Furthermore, we excluded individuals with any statin prescription before that receipt. Censoring nonstatin users at the first use of any statin could decrease the risk of events in nonstatin users over time, resulting in HRs that approach 1.0. However, the HRs we report are quite consistent over different follow-up times (Table 2). We could not rule out selection bias because we required that all CLD individuals had a liver biopsy and therefore we may have missed individuals who were too sick or with contraindications to liver biopsy. In addition, we selected individuals with CLD who survived long enough to receive a statin prescription; however, we did not introduce immortal time bias given that we required that nonstatin users also survive long enough to receive a nonliver prescription within 3 months of statin prescription in matched statin users, and we included CLD duration in the propensity score. In addition, our landmark sensitivity analysis confirmed our main results. The use of cDDDs can introduce a very short immortal time after start of follow-up evaluation in a few individuals who initially are exposed to fewer than 30 cDDDs and then acquire 30 cDDDs within a maximum possible time of 30 days. When removing such patients from the main analyses in a sensitivity analysis, there was no change in the HR. Finally, we cannot rule out the risk of chance differences between subgroups; however, we have restricted our subgroup analyses to a select number of subgroups determined a priori and based on clinical relevance.

In conclusion, this large prospective, nationwide population-based study with liver histopathology data shows an inverse association between statin use in noncirrhotic individuals with CLD and the development of severe liver disease. Although this study provides robust estimates, prospective randomized controlled trials are necessary to recommend statin use in clinical practice.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.04.017.

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Conflicts of interest
These authors disclose the following: Jonas F. Ludvigsson has coordinated a study on behalf of the Swedish IBD quality register, which received funding from the Janssen corporation; Rajani Sharma is a consultant for Takeda and Volv; Hannes Hagström's institution has received research funding from Pfizer, MSD, EchoSens, Intercept, Astra Zeneca, and Gilead, and he previously served as a scientific board advisor for BMS and Gilead; Elizabeth C. Verna receives grant support to her institution from Salix; Paul Lochhead is an employee of GlaxoSmithKline PLC, however, GlaxoSmithKline had no role in the funding or conduct of the study; and Tracey G. Simon's reports grants to the institution from Amgen, and has previously served as a consultant to Aetion. The remaining authors disclose no conflicts.

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Data Availability
Data, analytic methods, and study materials will not be made available to other researchers.

Supplementary Methods

Statin Exposure

The DDD was established by the World Health Organization as a standardized measurement of drug consumption defined as the average maintenance dose per day of a drug consumed for its main indication in adults (DDD is equivalent to 30 mg simvastatin, 20 mg atorvastatin, 30 mg pravastatin, 10 mg rosuvastatin). The cDDD often is used to measure total drug exposure.

Propensity Score Matching

Matching was performed by sampling 1:1 without replacement in 2 steps: (1) direct matching and (2) propensity score matching. After the first direct match step, an index date in potential control patients with chronic liver disease were assigned using any prescription date from the Prescribed Drug Register (except drugs related to liver disease or hepatocellular carcinoma treatment) ±3 months in relation to start date of statin treatment in the matched statin-exposed patient with chronic liver disease.

First, statin users and nonusers were matched directly on sex, age (<50 y, ≥50 y), year of CLD diagnosis (1969–1980, 1981–1990, 1991–2000, 2001–2010, 2011–2017), type of CLD (viral hepatitis, ALD, AIH, NAFLD), and liver histology findings at diagnosis (no fibrosis or inflammation, inflammation without fibrosis, and noncirrhotic fibrosis [F1–F3]).

Second, statin users and nonusers subsequently were propensity score matched using a nearest-neighbor algorithm without replacement.[1] Of the statin nonusers who fulfilled direct matching criteria in step one, we looked for individuals who had filled any drug prescription within 3 months before or after the statin exposure date in the matched case that was unrelated to liver disease or HCC treatment (Supplementary Table 5 for ATC codes). The propensity score for the probability of a statin prescription was calculated using a logistic regression model in the full sample.

Our propensity score included a priori–selected sociodemographic parameters, exposure to health care, and comorbidities or medications known to affect the likelihood of statin prescription, as listed later (see Supplementary Table 6 for ICD and ATC codes). Covariates and medications used in the propensity score were identified within 5 years before the statin exposure or index date. The number of inpatient and outpatient health care visits was determined within 2 years to 6 months of the index date. We included CLD duration in the propensity score to ensure that statin users and nonstatin users had a similar disease duration, and matched on year of CLD diagnosis to ensure that individuals were subject to similar practice patterns. A standardized difference between -0.10 and 0.10 was considered to indicate the balance of parameters included in the propensity score between stain users and statin nonusers. In our analyses, we additionally adjusted for parameters that were not in balance after the propensity score matching.

Direct match. Sex (women/men); age (<50 y/≥50 y); year of chronic liver disease diagnosis (1969–1980, 1981–1990, 1991–2000, 2001–2010, 2011–2017); liver disease diagnosis (viral hepatitis, alcohol-related liver disease, autoimmune hepatitis, nonalcoholic fatty liver disease); liver histopathology (no fibrosis no inflammation, inflammation without fibrosis/fibrosis).

Propensity score match: nearest-neighbor algorithm. Age (continuous); chronic liver disease duration (continuous); number of inpatient/outpatient health care visits (continuous); country of birth (Nordic/non-Nordic); level of education (≤9 y, 10–12 y, >12 y, missing); comorbidities/drugs (ischemic heart disease, cerebrovascular disease, congestive heart failure, arrhythmias, peripheral vascular disease and other vascular disorders, arrhythmias, obesity, myositis, diabetes including diabetes medications, chronic obstructive pulmonary disease (proxy for heavy smoking), end-stage renal disease, obstructive sleep apnea, nonhepatocellular carcinoma cancers, aspirin, nonaspirin antiplatelet medications, nonstatin lipid-lowering medications, anticoagulation, hepatitis C virus medications, autoimmune hepatitis medications, hepatitis B virus medications) (see Supplementary Table 6 for ICD and ATC codes).

Standardized Difference

A standardized difference between -0.10 and 0.10 is considered to indicate a balance between stain users and statin nonusers. Hence, a standardized difference of ≤-0.10 or ≥0.10 indicates an imbalance between the groups

Subanalyses

Prespecified subgroup analyses included the following: follow-up time (<1, 1 to <5, 5 to <10, ≥ 10 y), sex (men, women), age group (≥50, <50 y), start year of follow-up evaluation (2006–2010, 2011–2015, 2016–2019), year of CLD diagnosis (1969–1980, 1981–1990, 1991–2000, 2001–2010, 2011–2017), CLD type (viral hepatitis, ALD, AIH, NAFLD), liver histopathology at CLD diagnosis (no fibrosis or inflammation, inflammation without fibrosis, fibrosis [F1–F3]), and type of statin drug at treatment start (simvastatin, atorvastatin, other statins).

Supplementary Reference

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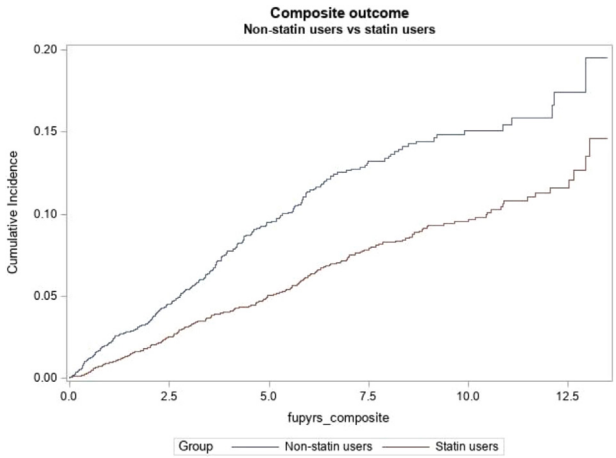
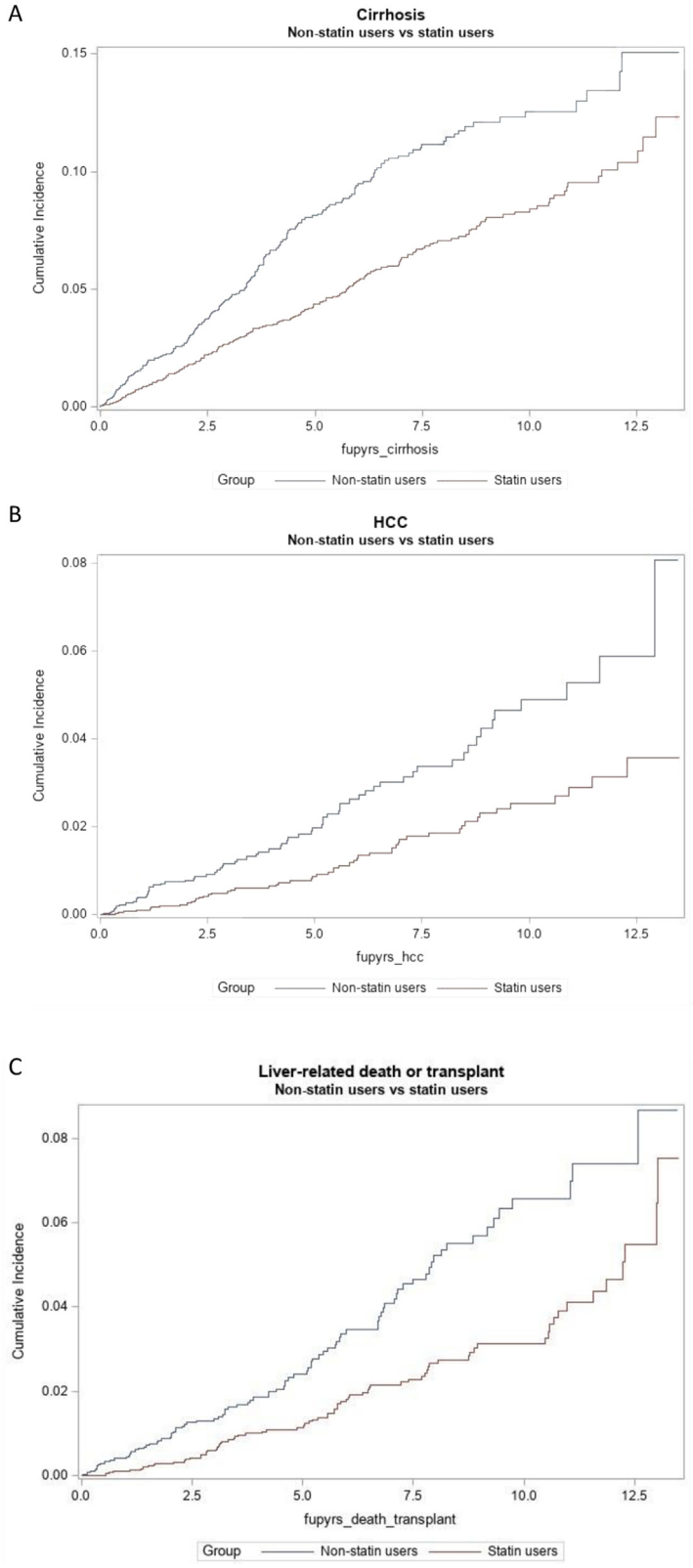


Supplementary Figure 1. Cumulative incidence curves of time to main composite outcome in chronic liver disease patients with and without statin treatment.



Supplementary Figure 2. Cumulative incidence curves of time to secondary outcomes in CLD patients with and without statin treatment: (*A*) cirrhosis, (*B*) hepatocellular carcinoma (HCC), and (*C*) liver-related death or transplant. fupyrs, years of follow-up evaluation.

Supplementary Table 1. Definitions of Chronic Liver Disease Using SNOMED and ICD Codes

	Histopathology		ICD codes			
Disease/condition	Topographic code	SNOMED codes	ICD, 8th revision	ICD, 9th revision	ICD, 10th revision	Exclusion criteria
All liver disease included in this study (viral hepatitis, ALD, AIH, nonalcoholic fatty liver disease)			All codes below	All codes below	All codes below	
Viral hepatitis including hepatitis C virus and hepatitis B virus	T56	D052	070; 999,20	070	B15, B16, B17, B18, B19, B008, B251	
ALD	T56		261,00, 262,00, 291, 303, 571,00, 571,01, 980,00, 980,01, 980,99	571A, 571B, 571C, 571D, 291, 303, 357F, 425F, 535D, 790D, 977D, 980A, 980X, V79B	K70, F10, E24.4, G31.2, G62.1, G72.1, I42.6, K29.2, K85.2, K86.0, O35.4, T51.0, T51.9, R78.0, X65, Y57.3, Y90, Y91, Z50.2, Z71.4, Z72.1	Exclude: viral hepatitis
AIH	T56		573,0; 571,9	571E, 573D	K75.4	Exclude: viral hepatitis, ALD
Nonalcoholic fatty liver disease	T56	M5008, M5520				Exclude: viral hepatitis, ALD, AIH

NOTE. ICD codes included both inpatient and outpatient diagnosis for chronic liver disease. We did not include primary biliary cholangitis and primary sclerosing cholangitis due to low numbers that limited matching.
AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; ICD, International Classification of Diseases; SNOMED, Systemized Nomenclature of Medicine.

Supplementary Table 2. SNOMED Codes for Liver Histopathology

Histopathology category	SNOMED code
Fibrosis	M4500x (inflammation with fibrosis), M4900xx (includes all stages of fibrosis and multifocal fibrosis of the liver)
Inflammation without fibrosis	M4, exclude codes for fibrosis (M4500x) and cirrhosis (M4950x)
No fibrosis or inflammation	M001xx (normal liver), other histopathology codes, exclude all M4 codes

SNOMED, Systemized Nomenclature of Medicine.

Supplementary Table 3. SNOMED and ICD codes for outcomes

Disease/condition	Topographic code	SNOMED codes	ICD codes				Source
			ICD, 7th revision	ICD, 8th revision	ICD, 9th revision	ICD, 10th revision	
Cirrhosis (includes compensated and decompensated cirrhosis/portal hypertension)	T56	M4950x		571.9 (cirrhosis) 456 (esophageal varices) 785.3 (ascites) 571.00 (liver cirrhosis with alcoholism)	572F (cirrhosis) 572D (portal hypertension) 456A, 456B, 456C (esophageal varices) 789F (ascites) 572E (hepatorenal syndrome) 571C (liver cirrhosis with alcoholism)	K74.6 (cirrhosis) K76.6 (portal hypertension) I85.0, I85.9 (esophageal varices) R18.9 (ascites) K76.7 (hepatorenal syndrome) ICD10: B18.1G/E, B18-2G/E (viral hepatitis B/C with cirrhosis) K70.3 (liver cirrhosis with alcoholism)	National Patient Register
HCC			155.0 (used for Cancer Register)	155,0 (used for Patient Register)	155A used for Patient Register)	C22.0 (used for Patient Register)	Because of concerns that HCC may be under-reported in the Cancer Register alone, HCC codes were derived from both the National Patient Register and Cancer Register
Liver transplantation				5200–5299 (surgery code)	5200–5299 (surgery code)	Z94.4 JJC (surgery code)	
Liver failure				570, 573	570, 572W	K72.x	

NOTE. Liver-related death included liver transplantation and death resulting from cirrhosis, liver failure, or HCC as primary or contributing etiologies derived from the Patient Register (codes listed in table) and from the Cause of Death Register.

HCC, hepatocellular carcinoma; ICD, International Classification of Diseases; ; SNOMED, SNOMED, Systemized Nomenclature of Medicine.

Supplementary Table 4. ATC Codes for Statins

Statin	ATC code
Simvastatin	C10AA01
Lovastatin	C10AA02
Pravastatin	C10AA03 or C10BA03
Fluvastatin	C10AA04
Atorvastatin	C10AA05
Cerivastatin	C10AA06
Rosuvastatin	C10AA07 or C10BA07
Pitavastatin	C10AA08

Supplementary Table 5. ATC Codes for Liver Disease and Hepatocellular Carcinoma Related Treatment That Were Not Included in Any Prescription for Nonusers to Determine Index Date

Medication	ATC codes
Autoimmune hepatitis treatments	
Azathioprine	L04AX01
6MP	L01BB02
Tacrolimus	L04AD02
Cyclosporine	L04AD01
Mycophenolate	L04AA06
Prednisolone (oral)	H02AB06
Prednisone (oral)	H02AB07
Budesonide (oral)	A07EA06
Methylprednisolone (systemic)	H02AB04
Hepatitis B virus treatments (including entecavir, tenofovirs, lamivudine, and other nucleos(t)ide reverse transcriptase inhibitors)	J05AF
Hepatitis C virus treatments (including DAA and interferons)	J05AP L03AB10 L03AB60 L03AB61
Nonalcoholic fatty liver treatments	
Vitamin E (tocopherol)	A11HA03
Pioglitazone	A10BG03
Systemic hepatocellular carcinoma treatments	
Sorafenib	L01EX02
Bevacizumab	L01FG01
Atezolizumab	L01FF05
Lenvatinib	L01EX08
Nivolumab	L01FF01
Pembrolizumab	L01FF02
Regorafenib	L01EX05
Cabozantinib	L01EX07
Ipilimumab	L01FX04

ATC, anatomic therapeutic chemical; DAA, direct-acting antiviral; 6MP, 6-mercaptopurine.

Supplementary Table 6. Covariates and Medications Used in the Propensity Score

Covariate/medication	ICD, 10th revision code	ATC code	Procedure codes
Age (continuous), *y*			
Chronic liver disease duration (continuous), *y*			
Number of inpatient and outpatient health care visits (continuous)			
Country of birth (Nordic vs non-Nordic)			
Level of education (≤9 y; 10–12 y; >12 y; missing)			
Ischemic heart disease	I20–I25		
Cerebrovascular disease	I60–I69		
Peripheral vascular disease (includes atheroemboli and excludes septic emboli and capillary disorders such as telangiectasias)	I70–I75, I77, I79		
Congestive heart failure	I50, I42		
Arrythmias and anti-arrythmia medications	I44–I49	C01BA, C01BB, C01BC, C01BD, C01BG	
Aspirin		B01AC06	
Nonaspirin antiplatelet medications		B01AC excluding aspirin (B01AC06)	
Anticoagulation medications		B01AA, B01AE, B01AF, B01AX	
Nonstatin lipid-lowering medications		C10AB, C10AC, C10AD, C10AX01-14	
Obesity	E78, E65, E66		
Myositis (no adequate codes present for rhabdomyolysis)	M60		
Diabetes	E10–E14, O24	A10 (includes oral medications and insulin)	
Chronic obstructive pulmonary disease (only if patient diagnosed at age ≥40 y)	J41–J44		

Supplementary Table 6. Continued

Covariate/medication	ICD, 10th revision code	ATC code	Procedure codes
End-stage renal disease	N18.0, N18.5, Z49, Z99.2, Z94.0		9200, V9200, 9212, V9212, 9314, V9531, DR012, DR013, DR016, DR024, QF006; 9211, V9211, 9213, V9213, V9532, DR015, DR023, DR055, DV056, 9219, V9219, 9223, V9223, DR017, DR020, DR055, DR056, 6070, KAS10, KAS20
Obstructive sleep apnea	G47.3		
Cancers except HCC, nonmelanoma skin cancer	C00–C97 excluding C44 (nonmelanoma skin cancer) and C22 (HCC)		
Hepatitis C virus treatment (including DAA and peg-interferons)		J05AP, L03AB10, L03AB60, L03AB61	
Hepatitis B virus treatment (including entecavir, tenofovirs, lamivudine, and other nucleos(t)ide reverse-transcriptase inhibitors)		J05AF	
Autoimmune hepatitis treatment		L04AX01 (azathioprine) L01BB02 (6-MP) L04AD02 (tacrolimus) L04AD01 (cyclosporine) L04AA06 (mycophenolate) H02AB06 (prednisolone, oral) H02AB07 (prednisone, oral) A07EA06 (budesonide, oral) H02AB04 (methylprednisolone, systemic	

ATC, antatomical therapeutic chemical; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; ICD, International Classification of Diseases; 6-MP, 6-mercaptoprurine.

Supplementary Table 7. Baseline Characteristics of All Included Chronic Liver Disease Patients and Chronic Liver Disease Patients Exposed to Statins Before Matching

Characteristic	Statin users (n = 3866)	All CLD patients (n = 21,737)
Sex, n (%)		
Women	1517 (39.2)	9532 (43.9)
Men	2349 (60.8)	12,205 (56.1)
Age, *y*		
Mean (SD)	62.2 (11.2)	54.2 (14.3)
Median (IQR)	62.6 (14.6)	54.3 (19.7)
Range, minimum–maximum	18.8–95.0	18.0–96.3
Categories, n (%)		
18 to <40 y	121 (3.1)	3530 (16.2)
40 to <50 y	426 (11.0)	4762 (21.9)
50 to <60 y	1010 (26.1)	5683 (26.1)
≥60 y	2309 (59.7)	7762 (35.7)
Country of birth, n (%)		
Nordic country	3406 (88.1)	19,180 (88.2)
Other European country	213 (5.5)	1102 (5.1)
Other non-European country	247 (6.4)	1455 (6.7)
Level of education, n (%)		
≤9 y	1143 (29.6)	6318 (29.1)
10–12 y	1862 (48.2)	10,681 (49.1)
>12 y	851 (22.0)	4656 (21.4)
Missing	10 (0.3)	82 (0.4)
Start year of follow-up evaluation/index date, n (%)		
2006–2010	1316 (34.0)	17,133 (78.8)
2011–2017	1981 (51.2)	4604 (21.2)
2018–2019	569 (14.7)	0
CLD diagnosis, n (%)		
1969–1980	31 (0.8)	117 (0.5)
1981–1990	504 (13.0)	1968 (9.1)
1991–2000	1379 (35.7)	6174 (28.4)
2001–2010	1449 (37.5)	8874 (40.8)
2011–2017	503 (13.0)	4604 (21.2)
Liver disease diagnosis, n (%)		
Viral hepatitis (B or C)	684 (17.7)	5281 (24.3)
Alcohol-related liver disease	847 (21.9)	6066 (27.9)
Autoimmune hepatitis	583 (15.1)	3755 (17.3)
Nonalcoholic fatty liver disease	1752 (45.3)	6635 (30.5)
Duration of CLD to start of follow-up evaluation/index date, y		
Mean (SD)	12.5 (8.3)	5.4 (6.6)
Median (IQR)	12.0 (13.0)	2.3 (9.7)
Range, minimum–maximum	0.0–47.2	0.0–36.5
Categories, n (%)		
<1 y	261 (6.8)	9749 (44.8)
1 to <5 y	623 (16.1)	3248 (14.9)
5 to <10 y	753 (19.5)	3491 (16.1)
≥10 y	2229 (57.7)	5249 (24.1)
Time from index date to start of follow-up evaluation (years)		
Mean (SD)	5.5 (3.9)	
Median (IQR)	4.8 (6.8)	
Range, minimum–maximum	0.0–13.5	
Categories, n (%)		
<1 y	564 (14.6)	
1 to <5 y	1439 (37.2)	
5 to <10 y	1181 (30.5)	
≥10 y	682 (17.6)	

Supplementary Table 7. Continued

Characteristic	Statin users (n = 3866)	All CLD patients (n = 21,737)
Number of inpatient/outpatient health care visits between 2 years and 6 months before start of follow-up evaluation/index date		
Mean (SD)	5.3 (9.3)	5.0 (9.7)
Median (IQR)	3 (6)	3 (5)
Range, minimum–maximum	0–243	0–246
Categories, n (%)		
0	763 (19.7)	4517 (20.8)
1	540 (14.0)	3219 (14.8)
2–3	816 (21.1)	4691 (21.6)
≥4	1747 (45.2)	9310 (42.8)
Charlson comorbidity score from inpatient/outpatient health care visits within 5 years before start of follow-up evaluation/index date		
Mean (SD)	2.1 (2.4)	2.2 (2.5)
Median (IQR)	1 (3)	2 (3)
Range, minimum–maximum	0–18	0–23
Categories, n (%)		
0	1385 (35.8)	8272 (38.1)
1	585 (15.1)	1529 (7.0)
2	409 (10.6)	1404 (6.5)
3	611 (15.8)	6973 (32.1)
≥4	876 (22.7)	3559 (16.4)
Comorbidities within 5 years before start of follow-up evaluation/index date, n (%)		
Ischemic heart disease	762 (19.7)	1292 (5.9)
Cerebrovascular disease	433 (11.2)	652 (3.0)
Congestive heart failure	216 (5.6)	659 (3.0)
Arrhythmia (including antiarrhythmic medications)	375 (9.7)	1103 (5.1)
Peripheral vascular disease and other vascular disorders	212 (5.5)	418 (1.9)
Obesity	513 (13.3)	1405 (6.5)
Myositis	4 (0.1)	42 (0.2)
Diabetes (including antidiabetic medications)	1573 (40.7)	3289 (15.1)
Chronic obstructive pulmonary disease	197 (5.1)	691 (3.2)
End-stage renal disease	32 (0.8)	152 (0.7)
Obstructive sleep apnea	158 (4.1)	399 (1.8)
Non–hepatocellular carcinoma cancer	352 (9.1)	2453 (11.3)
Medications		
Aspirin	1671 (43.2)	2995 (13.8)
Nonaspirin antiplatelet medications	681 (17.6)	535 (2.5)
Hepatitis C virus medications	276 (7.1)	582 (2.7)
Nonstatin lipid-lowering medications	140 (3.6)	548 (2.5)
Anticoagulation	311 (8.0)	671 (3.1)
Autoimmune hepatitis medications	882 (22.8)	3855 (17.7)
Hepatitis B virus medications	38 (1.0)	122 (0.6)
Liver histopathology, n (%)		
No fibrosis no inflammation	2069 (53.5)	10,504 (48.3)
Inflammation without fibrosis	731 (18.9)	4720 (21.7)
Fibrosis (F1–F3)	1066 (27.6)	6513 (30.0)
Type of statin drug at treatment start, n (%)		
Simvastatin	2338 (60.5)	
Atorvastatin	1450 (37.5)	
Rosuvastatin	49 (1.3)	
Pravastatin	23 (0.6)	
Other statins	6 (0.2)	
Follow-up period (main outcome), *y*		
Mean (SD)	5.8 (3.8)	
Median (IQR)	5.3 (6.4)	
Range, minimum–maximum	0.0–13.5	

Supplementary Table 7. Continued

Characteristic	Statin users (n = 3866)	All CLD patients (n = 21,737)
Categories, n (%)		
<1 y	414 (10.7)	
1 to <5 y	1457 (37.7)	
5 to <10 y	1296 (33.5)	
≥10 y	699 (18.1)	

CLD, chronic liver disease; IQR, interquartile range.

Supplementary Table 8. Risk of Main Composite Outcome in Chronic Liver Disease Patients With and Without Statin Treatment by cDDD

Outcome	Patients, N	Events, N	Incidence rate (95% CI) per 1000 PY	HR[a] (95% CI)	HR[b] (95% CI)	sHR[c] (95% CI)	*P* value for interaction
None (reference)	2727	197 (7.2%)	17.4 (14.9–19.8)	1.00	1.00	1.00	
30 to <300 cDDDs	1984	119 (6.0%)	10.0 (8.2–11.8)	0.66 (0.50–0.87)	0.66 (0.50–0.87)	0.70 (0.58–0.85)	.76
300 to <600 cDDDs	135	7 (5.2%)	12.5 (3.2–21.8)	0.45 (0.16–1.31)	0.49 (0.17–1.43)	0.58 (0.27–1.24)	
≥600 cDDDs	608	28 (4.6%)	11.0 (6.9–15.1)	0.54 (0.31–0.93)	0.55 (0.31–0.99)	0.56 (0.37–0.84)	

cDDD, cumulative defined daily dose; HR, hazard ratio; PY, person-year; sHR, subdistribution hazard ratio.
[a]Conditioned on matching set.
[b]Conditioned on matching set and adjusted further for ischemic heart disease, autoimmune hepatitis medications, and nonaspirin antiplatelet medications.
[c]Competing risk regression using non–liver-related death as competing event. Conditioned on matching set and further adjusted for ischemic heart disease, autoimmune hepatitis medications, and nonaspirin antiplatelet medications.

Supplementary Table 9. Risk of Main and Secondary Outcomes Including Statin Treatment as Time-Dependent Exposure From the Latest of Chronic Liver Disease Diagnosis and January 1, 2006

Outcome	HR[a] (95% CI)	HR[b] (95% CI)	HR[c] (95% CI)	sHR[d] (95% CI)
Main composite outcome	0.90 (0.78–1.03)	0.87 (0.76–1.00)	0.87 (0.75–1.00)	1.11 (0.96–1.27)
Cirrhosis	0.91 (0.79–1.06)	0.93 (0.80–1.08)	0.93 (0.80–1.08)	1.16 (1.00–1.34)
Hepatocellular carcinoma	0.88 (0.67–1.16)	0.74 (0.56–0.98)	0.72 (0.55–0.96)	0.95 (0.72–1.25)
Liver-related mortality or liver transplantation	0.83 (0.66–1.04)	0.72 (0.57–0.90)	0.72 (0.57–0.90)	0.95 (0.76–1.19)

HR, hazard ratio; sHR, subdistribution hazard ratio.
[a]Unadjusted.
[b]Model I: adjusted for age, sex, year of chronic liver disease, type of liver disease, and liver histopathology.
[c]Model II: Model I and further adjusted for disease duration, number of inpatient/outpatient health care visits, country of birth, level of education, Charlson Comorbidity Index, aspirin use, nonaspirin antiplatelet medications, nonstatin lipid-lowering medications, and anticoagulants.
[d]Competing risk regression using non–liver-related death as competing event. Adjusted for the same covariates as in Model II.

Supplemental Table 10. Landmark Analysis: Baseline Characteristics of Chronic Liver Disease Patients With and Without Statin Treatment 1Year After Chronic Liver Disease Diagnosis or July 1, 2007

Characteristic	Statin users (n = 2621)	Nonstatin users (n = 17,495)
Sex, n (%)		
Women	1112 (42.4)	7824 (44.7)
Men	1509 (57.6)	9671 (55.3)
Age, *y*		
Mean (SD)	63.1 (10.8)	53.0 (14.1)
Median (IQR)	63.8 (56.2–70.4)	53.0 (43.5–62.6)
Range, minimum–maximum	19.8–91.3	19.0–95.2
Categories, n (%)		
18 to <40 y	71 (2.7)	3059 (17.5)
40 to <50 y	225 (8.6)	4208 (24.1)
50 to <60 y	652 (24.9)	4804 (27.5)
≥60 y	1673 (63.8)	5424 (31.0)
18 to <50 y	296 (11.3)	7267 (41.5)
≥50 y	2325 (88.7)	10,228 (58.5)
Country of birth, n (%)		
Nordic country	2351 (89.7)	15,311 (87.5)
Other European country	136 (5.2)	913 (5.2)
Other non-European country	134 (5.1)	1271 (7.3)
Level of education, n (%)		
≤9 y	911 (34.8)	4721 (27.0)
10–12 y	1220 (46.5)	8740 (50.0)
>12 y	483 (18.4)	3971 (22.7)
Missing	7 (0.3)	63 (0.4)
Start year of follow-up evaluation, n (%)		
2006–2010	1998 (76.2)	13,331 (76.2)
2011–2015	435 (16.6)	3206 (18.3)
2016–2019	188 (7.2)	958 (5.5)
Chronic liver disease diagnosis, n (%)		
1969–1980	33 (1.3)	79 (0.5)
1981–1990	420 (16.0)	1472 (8.4)
1991–2000	874 (33.3)	5112 (29.2)
2001–2010	749 (28.6)	7459 (42.6)
2011–2019	545 (20.8)	3373 (19.3)
Liver disease diagnosis, n (%)		
Viral hepatitis (B or C)	211 (8.1)	4955 (28.3)
Alcohol-related liver disease	600 (22.9)	4360 (24.9)
Autoimmune hepatitis	421 (16.1)	3163 (18.1)
Nonalcoholic fatty liver disease	1389 (53.0)	5017 (28.7)
Duration of chronic liver disease, y		
Mean (SD)	8.4 (7.6)	6.3 (6.4)
Median (IQR)	6.7 (1.0–14.1)	3.6 (1.0–10.6)
Range, minimum–maximum	1.0–35.4	1.0–37.5
Categories, n (%)		
<1 y	659 (25.1)	4985 (28.5)
1 to <5 y	496 (18.9)	4691 (26.8)
5 to <10 y	448 (17.1)	3096 (17.7)
≥10 y	1018 (38.8)	4723 (27.0)
Inpatient/outpatient health care visits between 2 years and 6 months before start of follow-up evaluation, n		
Mean (SD)	7.6 (15.8)	6.0 (9.3)
Median (IQR)	4 (2–9)	4 (1–8)

Supplemental Table 10. Continued

Characteristic	Statin users (n = 2621)	Nonstatin users (n = 17,495)
Range, minimum–maximum	0–286	0–244
Categories, n (%)		
0	348 (13.3)	2710 (15.5)
1	279 (10.6)	1841 (10.5)
2–3	488 (18.6)	3689 (21.1)
≥4	1506 (57.5)	9255 (52.9)
Charlson comorbidity score from inpatient/outpatient health care visits within 5 years before start of follow-up evaluation/index date		
Mean (SD)	2.3 (2.7)	2.3 (2.3)
Median (IQR)	2 (0–3)	3 (0–3)
Range, minimum–maximum	0–18	0–18
Categories, n (%)		
0	946 (36.1)	6255 (35.8)
1	332 (12.7)	1018 (5.8)
2	340 (13.0)	816 (4.7)
3	352 (13.4)	6677 (38.2)
≥4	651 (24.8)	2729 (15.6)
Comorbidities within 5 years before start of follow-up evaluation, n (%)		
Ischemic heart disease	728 (27.8)	448 (2.6)
Cerebrovascular disease	263 (10.0)	370 (2.1)
Congestive heart failure	225 (8.6)	326 (1.9)
Arrhythmia (including antiarrhythmic medications)	286 (10.9)	726 (4.1)
Peripheral vascular disease and other vascular disorders	161 (6.1)	196 (1.1)
Obesity	707 (27.0)	702 (4.0)
Myositis	6 (0.2)	33 (0.2)
Diabetes (including antidiabetic medications)	1237 (47.2)	1941 (11.1)
Chronic obstructive pulmonary disease	125 (4.8)	433 (2.5)
End-stage renal disease	51 (1.9)	79 (0.5)
Obstructive sleep apnea	119 (4.5)	311 (1.8)
Non–hepatocellular carcinoma cancer	332 (12.7)	1393 (8.0)
Medications		
Aspirin	1370 (52.3)	1560 (8.9)
Nonaspirin antiplatelet medications	394 (15.0)	165 (0.9)
Hepatitis C virus medications	41 (1.6)	1 310 (7.5)
Nonstatin lipid-lowering medications	203 (7.7)	389 (2.2)
Anticoagulation	208 (7.9)	466 (2.7)
Autoimmune hepatitis medications	533 (20.3)	3675 (21.0)
Hepatitis B virus medications	6 (0.2)	198 (1.1)
Liver histopathology, n (%)		
No fibrosis no inflammation	1557 (59.4)	7731 (44.2)
Inflammation without fibrosis	457 (17.4)	4020 (23.0)
Fibrosis (F1–F3)	607 (23.2)	5744 (32.8)
Type of statin drug at treatment start, n (%)		
Simvastatin	1948 (74.3)	
Atorvastatin	507 (19.3)	
Other statins	166 (6.3)	
Follow-up time (main outcome), *y*		
Mean (SD)	8.4 (4.2)	7.8 (4.3)
Median (IQR)	9.5 (4.6–12.5)	8.3 (3.9–12.5)
Range, minimum–maximum	0.0–12.5	0.0–12.5
Categories, n (%)		
<1 y	134 (5.1)	1124 (6.4)
1 to <5 y	578 (22.1)	4363 (24.9)
5 to <10 y	664 (25.3)	4871 (27.8)
≥10 y	1245 (47.5)	7137 (40.8)

Supplemental Table 10. Continued

Characteristic	Statin users (n = 2621)	Nonstatin users (n = 17,495)
Reason for end of follow-up evaluation (main outcome)		
Outcome event	224 (8.5)	1622 (9.3)
Statin prescription	0	3607 (20.6)
Non–liver-related death	770 (29.4)	2275 (13.0)
Emigration	12 (0.5)	235 (1.3)
End of data (December 31, 2019)	1615 (61.6)	9756 (55.8)

NOTE. Baseline characteristics of chronic liver disease patients with and without statin treatment 1 year after chronic liver disease diagnosis or July 1, 2007.
IQR, interquartile range.

Supplementary Table 11. Landmark Analysis: Risk of Main- and Secondary Outcomes in Chronic Liver Disease Patients With and Without Statin Treatment After a Landmark Time of 1 Year

	Events, N		Incidence rate (95% CI) per 1000 PY				
Outcome	Statin users	Nonstatin users	Statin users	Nonstatin users	HR[a] (95% CI)	HR[b] (95% CI)	sHR[c] (95% CI)
Main composite outcome	224 (8.5%)	1622 (9.3%)	10.2 (8.8–11.5)	11.9 (11.3–12.4)	0.85 (0.73–0.98)	0.81 (0.68–0.95)	0.89 (0.76–1.05)
Cirrhosis	182 (6.9%)	1385 (7.9%)	8.3 (7.1–9.5)	10.1 (9.6–10.7)	0.87 (0.74–1.02)	0.84 (0.71–1.01)	0.93 (0.78–1.11)
Hepatocellular carcinoma	57 (2.2%)	337 (1.9%)	2.5 (1.9–3.2)	2.4 (2.1–2.6)	0.87 (0.65–1.17)	0.77 (0.55–1.08)	0.90 (0.65–1.24)
Liver-related mortality or liver transplantation	78 (3.0%)	563 (3.2%)	3.5 (2.7–4.2)	4.0 (3.7–4.3)	0.72 (0.56–0.93)	0.66 (0.50–0.87)	0.75 (0.57–0.98)

HR, hazard ratio; PY, person-year; sHR, subdistribution hazard ratio.

[a]Model I: Adjusted for age, sex, year of chronic liver disease, type of liver disease, and liver histopathology.

[b]Model II: Model I and further adjusted for disease duration, number of inpatient/outpatient health care visits, country of birth, level of education, Charlson Comorbidity Index, aspirin use, nonaspirin antiplatelet medications, nonstatin lipid-lowering medications, and anticoagulants.

[c]Competing risk regression using non–liver-related death as competing event. Adjusted for the same covariates as in Model II.

Supplemental Table 12. Competing Risk Regression of Main Composite Outcome in Chronic Liver Disease Patients With and Without Statin Treatment

Outcome	N (%)		Events, n		Incidence rate (95% CI) per 1000 PY		HR[a] (95% CI)	sHR[b] (95% CI)
	Statin users	Nonstatin users	Statin users	Nonstatin users	Statin users	Nonstatin users		
Overall	3862 (100)	3862 (100)	234 (6.1%)	276 (7.1%)	10.5 (9.1–11.8)	18.1 (16.0–20.3)	0.59 (0.48–0.72)	0.66 (0.57–0.77)
Follow-up time, *y*								
<1	3862 (100)	3862 (100)	35 (0.9%)	73 (1.9%)	9.6 (6.4–12.7)	22.1 (17.1–27.2)	0.42 (0.28–0.65)	0.75 (0.66–0.86)
1 to <5	3450 (89.3)	2909 (75.3)	114 (3.3%)	146 (5.0%)	10.5 (8.6–12.5)	18.8 (15.7–21.8)	0.60 (0.46–0.80)	0.75 (0.64–0.88)
5 to <10	1994 (51.6)	1223 (31.7)	70 (3.5%)	52 (4.3%)	10.5 (8.0–12.9)	14.3 (10.4–18.2)	0.77 (0.49–1.21)	0.81 (0.59–1.11)
≥10	698 (18.1)	331 (8.6)	15 (2.1%)	5 (1.5%)	12.9 (6.4–19.4)	9.6 (1.2–17.9)	1.00 (0.20–4.95)	4.00 (0.66–24.37)
Sex								
Women	1515 (39.2)	1515 (39.2)	76 (5.0%)	101 (6.7%)	8.7 (6.8–10.7)	16.3 (13.1–19.4)	0.57 (0.40–0.80)	0.65 (0.51–0.83)
Men	2347 (60.8)	2347 (60.8)	158 (6.7%)	175 (7.5%)	11.6 (9.8–13.4)	19.4 (16.5–22.3)	0.60 (0.46–0.77)	0.67 (0.56–0.80)
Age, *y*								
18 to <50	546 (14.1)	546 (14.1)	25 (4.6%)	29 (5.3%)	6.6 (4.0–9.2)	9.7 (6.2–13.2)	0.91 (0.51–1.65)	0.83 (0.52–1.30)
≥50	3316 (85.9)	3316 (85.9)	209 (6.3%)	247 (7.4%)	11.3 (9.7–12.8)	20.2 (17.7–22.7)	0.55 (0.44–0.69)	0.65 (0.55–0.76)
Start year of follow-up evaluation								
2006–2010	1315 (34.0)	1313 (34.0)	113 (8.6%)	121 (9.2%)	9.3 (7.6–11.0)	15.7 (12.9–18.5)	0.57 (0.42–0.79)	0.72 (0.57–0.89)
2011–2015	1359 (35.2)	1357 (35.1)	94 (6.9%)	123 (9.1%)	12.0 (9.6–14.4)	22.0 (18.1–25.9)	0.51 (0.37–0.70)	0.51 (0.40–0.66)
2016–2019	1188 (30.8)	1192 (30.9)	27 (2.3%)	32 (2.7%)	11.6 (7.3–16.0)	16.5 (10.8–22.3)	0.76 (0.44–1.32)	0.74 (0.48–1.15)
Chronic liver disease diagnosis, n (%)								
1969–1980	28 (0.7)	28 (0.7)	2 (7.1)	2 (7.1)	10.6 (0.0–25.4)	20.7 (0.0–49.4)	–	–
1981–1990	503 (13.0)	503 (13.0)	21 (4.2)	27 (5.4)	6.3 (3.6–9.0)	13.7 (8.5–18.8)	0.54 (0.28–1.06)	0.50 (0.29–0.88)
1991–2000	1379 (35.7)	1379 (35.7)	84 (6.1)	94 (6.8)	9.3 (7.3–11.3)	15.8 (12.6–19.0)	0.58 (0.41–0.83)	0.67 (0.52–0.86)
2001–2010	1449 (37.5)	1449 (37.5)	109 (7.5)	116 (8.0)	13.4 (10.9–15.9)	19.6 (16.1–23.2)	0.69 (0.51–0.93)	0.78 (0.63–0.97)
2011–2017	503 (13.0)	503 (13.0)	18 (3.6)	37 (7.4)	11.0 (5.9–16.1)	28.8 (19.6–38.1)	0.35 (0.18–0.68)	0.28 (0.14–0.57)
Liver disease diagnosis								
Viral hepatitis (B or C)	683 (17.7)	683 (17.7)	61 (8.9%)	74 (10.8%)	17.7 (13.2–22.1)	27.8 (21.5–34.1)	0.70 (0.48–1.02)	0.78 (0.59–1.03)
Alcohol-related liver disease	846 (21.9)	846 (21.9)	59 (7.0%)	95 (11.2%)	13.4 (10.0–16.8)	31.8 (25.4–38.2)	0.35 (0.23–0.54)	0.38 (0.28–0.53)
Autoimmune hepatitis	583 (15.1)	583 (15.1)	38 (6.5%)	32 (5.5%)	12.0 (8.2–15.9)	13.5 (8.8–18.2)	0.96 (0.56–1.65)	0.96 (0.65–1.42)
Nonalcoholic fatty liver disease	1750 (45.3)	1750 (45.3)	76 (4.3%)	75 (4.3%)	6.7 (5.2–8.2)	10.4 (8.1–12.8)	0.62 (0.43–0.91)	0.77 (0.59–1.01)
Liver histopathology								
No fibrosis no inflammation	2069 (53.6)	2069 (53.6)	87 (4.2%)	112 (5.4%)	6.7 (5.3–8.1)	13.5 (11.0–16.1)	0.54 (0.39–0.76)	0.65 (0.51–0.82)
Inflammation without fibrosis	729 (18.9)	729 (18.9)	52 (7.1%)	60 (8.2%)	13.1 (9.5–16.6)	21.6 (16.1–27.0)	0.48 (0.30–0.77)	0.45 (0.30–0.66)
Fibrosis (F1–F3)	1064 (27.6)	1064 (27.6)	95 (8.9%)	104 (9.8%)	17.6 (14.1–21.2)	24.9 (20.2–29.7)	0.70 (0.51–0.96)	0.78 (0.61–0.99)
Type of statin drug at treatment start								
Simvastatin	2336 (60.5)	2336 (60.5)	181 (7.7%)	212 (9.1%)	10.5 (9.0–12.0)	18.4 (16.0–20.9)	0.55 (0.44–0.70)	0.64 (0.54–0.76)
Atorvastatin	1448 (37.5)	1448 (37.5)	49 (3.4%)	61 (4.2%)	10.6 (7.7–13.6)	18.0 (13.5–22.6)	0.65 (0.42–0.99)	0.67 (0.48–0.93)
Other statins	78 (2.0)	78 (2.0)	4 (5.1%)	3 (3.8%)	8.7 (0.2–17.3)	8.9 (0.0–18.9)	2.00 (0.37–10.92)	1.50 (0.41–5.45)

HR, hazard ratio; PY, person-year; sHR, subdistribution hazard ratio.

[a]Conditioned on matching set.

[b]Competing risk regression using non–liver-related death as competing event. Conditioned on matching set and further adjusted for ischemic heart disease, autoimmune hepatitis medications, and nonaspirin antiplatelet medications.

Supplemental Table 13. Competing Risk Regression of Secondary Outcomes in Chronic Liver Disease Patients With and Without Statin Treatment

Outcome	Events, N		Incidence rate (95% CI) per 1000 PY			
	Statin users	Nonstatin users	Statin users	Nonstatin users	HR[a] (95% CI)	sHR[b] (95% CI)
Main composite outcome	234 (6.1%)	276 (7.1%)	10.5 (9.1–11.8)	18.1 (16.0–20.3)	0.59 (0.48–0.72)	0.66 (0.57–0.77)
Cirrhosis	202 (5.2%)	228 (5.9%)	9.0 (7.8–10.3)	15.0 (13.0–16.9)	0.61 (0.49–0.77)	0.68 (0.58–0.80)
Hepatocellular carcinoma	53 (1.4%)	71 (1.8%)	2.3 (1.7–3.0)	4.5 (3.5–5.5)	0.45 (0.29–0.70)	0.45 (0.32–0.65)
Liver-related mortality or liver transplantation	76 (2.0%)	93 (2.4%)	3.3 (2.6–4.1)	5.9 (4.7–7.1)	0.56 (0.39–0.81)	0.63 (0.48–0.82)

HR, hazard ratio; PY, person-year; sHR, subdistribution hazard ratio.
[a]Conditioned on matching set.
[b]Competing risk regression using non–liver-related death as competing event. Conditioned on matching set and further adjusted for ischemic heart disease, autoimmune hepatitis medications, and nonaspirin antiplatelet medications.