Original research

Long-term liver-related outcomes and liver stiffness progression of statin usage in steatotic liver disease

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ABSTRACT

Background Statins have multiple benefits in patients with metabolic-associated steatotic liver disease (MASLD).

Aim To explore the effects of statins on the long-term risk of all-cause mortality, liver-related clinical events (LREs) and liver stiffness progression in patients with MASLD.

Methods This cohort study collected data on patients with MASLD undergoing at least two vibration-controlled transient elastography examinations at 16 tertiary referral centres. Cox regression analysis was performed to examine the association between statin usage and long-term risk of all-cause mortality and LREs stratified by compensated advanced chronic liver disease (cACLD): baseline liver stiffness measurement (LSM) of ≥10 kPa. Liver stiffness progression was defined as an LSM increase of ≥20% for cACLD and from <10 kPa to ≥10 or LSM for non-cACLD. Liver stiffness regression was defined as LSM reduction from ≥10 kPa to <10 or LSM decrease of ≥20% for cACLD.

Results We followed up 7988 patients with baseline LSM 5.9 kPa (IQR 4.6–8.2) for a median of 4.6 years. At baseline, 40.5% of patients used statins, and cACLD was present in 17%. Statin usage was significantly associated with a lower risk of all-cause mortality (adjusted HR=0.233; 95% CI 0.127 to 0.426) and LREs (adjusted HR=0.380; 95% CI 0.268 to 0.539). Statin usage was also associated with lower liver stiffness progression rates in cACLD (HR=0.542; 95% CI 0.389 to 0.755) and non-cACLD (adjusted HR=0.450; 95% CI 0.342 to 0.592), but not with liver stiffness regression (adjusted HR=0.914; 95% CI 0.778 to 1.074).

Conclusions Statin usage was associated with a relatively lower long-term risk of all-cause mortality, LREs and liver stiffness progression in patients with MASLD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Statins have cardiovascular benefits and offer multiple benefits on metabolic-associated steatotic liver disease (MASLD), but their long-term effects on MASLD are not fully established.

WHAT THIS STUDY ADDS

⇒ This study provides long-term evidence demonstrating that statins were associated with a relatively lower long-term risk of all-cause mortality, liver-related clinical events, and liver stiffness progression in MASLD patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The findings encourage further research into the mechanisms by which statins affect liver stiffness and suggest that clinical practice and policies may increasingly incorporate statins in managing MASLD.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a significant health concern affecting up to 30% of people worldwide, which is mainly caused by the increasing global prevalence of obesity and metabolic disorders.[1 2] Despite major efforts to develop effective treatments, there has only been one drug (resmetirom) recently receiving conditional approval by the US Food and Drug Administration for treating patients with metabolic dysfunction-associated steatohepatitis (MASH) with moderate-to-advanced hepatic fibrosis.[3 4]

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Statins are widely recognised for their effectiveness in reducing the risk of cardiovascular disease (CVD) by lowering plasma low-density lipoprotein-cholesterol concentrations by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase.[5 6] Most patients with MASLD have indications for statins, including dyslipidaemia, pre-existing CVD or high risk of CVD.[7] Statins exert anti-inflammatory, antifibrotic, antithrombogenic and antioxidant effects, which may also aid in reducing the progression of liver fibrosis in MASLD.[8–10] This has generated increasing interest in the potential of statins to manage complications in people with MASLD, in which CVD represents the leading cause of death.[10–12] However, statins are still not widely used in patients with chronic liver disease, mainly due to concerns about possible statin-induced liver damage and muscle weakness.[13] Several studies have shed light on the efficacy of statin usage in patients with MASLD, without and with cirrhosis, and have also shown encouraging results in recent years.[14] Consequently, recent expert recommendations have strongly recommended the use of statin therapy for treating patients with MASLD who have pre-existing CVD or are at high risk of CVD.[15]

Statins have not been shown to improve MASH or liver fibrosis in histological studies. However, numerous observational studies have reported an association between statin use and a lower incidence of hepatocellular carcinoma (HCC).[16] If this protective effect is real, it is unclear whether it is mediated by preventing liver fibrosis progression.

Therefore, this observational multicentre cohort study aimed to explore the effects of statins on the long-term risk of all-cause mortality, liver-related clinical outcomes and liver stiffness progression in patients with MASLD.

METHODS

Study design and participants

This cohort study (the VCTE-Prognosis study) was conducted on patients with MASLD who underwent vibration-controlled transient elastography (VCTE) examinations at 16 centres in the USA, Europe and Asia. Detailed information on the VCTE-Prognosis study has been presented in a previously published work.[17] This study retrospectively analysed patient encounters recorded in the electronic medical records. Patients aged ≥18 years with MASLD diagnosed by liver histology (steatosis in ≥5% of hepatocytes) or imaging methods (ultrasonography, CT, MRI or controlled attenuation parameter (CAP) ≥248 dB/m by VCTE) were eligible.[18 19] Patients with other liver diseases, such as chronic viral hepatitis, HIV infection, excessive alcohol consumption (>30 g/day in men and >20 g/day in women), drug-induced hepatic steatosis (eg, usage of systemic steroids) or a history of HCC, hepatic decompensation, liver resection, liver transplant, or other malignancies were excluded (figure 1).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Clinical, biochemical and VCTE assessments

During each visit to the clinic, the patient's medical history was recorded, and body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in metres. After at least 8 hours of fasting, a venous blood sample was taken to examine kidney and liver biochemistry and complete blood count. CAP and liver stiffness measurement (LSM) were performed on FibroScan devices (Echosens, Paris, France) by healthcare professionals who were trained as per the manufacturer's instructions. LSMs were considered valid and reliable if ten measurements were obtained with IQRs/medians of less than 30%. While using the probe (M or XL), the instructions given by the manufacturer were followed. The XL probe was only available from 2014 for study sites. To ensure accuracy, patients enrolled in the study were required to have at least 10 valid acquisitions. Compensated advanced chronic liver disease (cACLD) was defined as baseline LSM of ≥10 kPa.

Study outcomes

As no patient had a history of decompensating events, we classified cACLD based on Baveno VII criteria and divided patients into 'cACLD' (LSM≥10 kPa) and 'No cACLD' (LSM<10 kPa) at baseline.[20] The diagnosis of the events was based on prospective follow-up, medical record review, or validated registries with positive predictive values of at least 90%. The primary study outcome was a composite outcome inclusive of all-cause death and liver-related events (LREs), including the development of

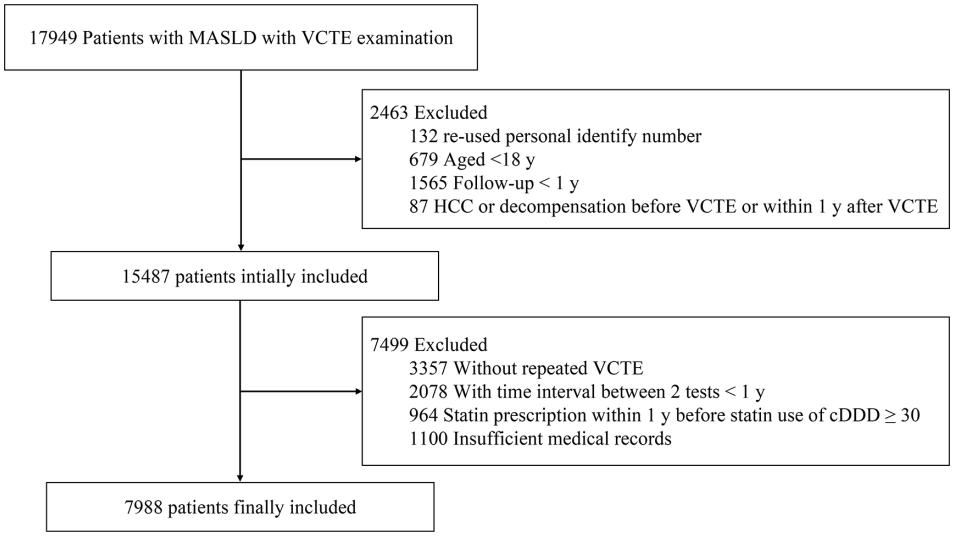

Figure 1 Study participant flow. cDDD, cumulative defined daily dose; HCC, hepatocellular carcinoma; MASLD, metabolic-associated steatotic liver disease; VCTE, vibration-controlled transient elastography.

cirrhosis (cirrhosis, decompensation or portal hypertension ICD codes), HCC or liver-related mortality (including liver transplantation). The secondary study outcome was the change in hepatic steatosis and liver stiffness (assessed by VCTE). For MASLD patients with cACLD at baseline (ie, those with baseline LSM≥10 kPa), a clinically relevant increase in LSM was defined as at least a 20% increase in LSM (ie, liver stiffness progression).[21] A clinically relevant decrease in LSM was defined as a follow-up LSM of less than 10 kPa or baseline LSM of less than 20 kPa with a decrease of at least 20% (liver stiffness regression).[21] For MASLD patients without cACLD at baseline (ie, those with baseline LSM<10 kPa), a clinically relevant LSM increased if the follow-up LSM was ≥10 kPa (liver stiffness progression).[21] The remaining patients were considered to be 'liver stiffness stable'.[21] For patients with multiple VCTE examinations, we selected the first and last examinations if they did not experience the event of interest, such as the VCTE for liver stiffness progression/regression. If the event of interest occurred, we included the first event and the first related VCTE examination.

Statin exposure

All patients who were prescribed statin medications during the study observation period were identified. The clinical follow-up period was between the first VCTE and the final clinical follow-up or death or LRE, whichever came first. Statin prescriptions included simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin and pitavastatin. The cumulative defined daily dose (cDDD) is the total sum of all defined daily doses of a specific drug used during the follow-up period. The usage of statins was defined as the consistent use of statins on most days for more than 1 month within a year, with an average dose of at least 30 cDDDs per year, consistent with prior studies.[22–24]

Statistical analysis

All statistical analyses were performed using the IBM SPSS software, V.23.0 for Windows. Continuous variables were expressed as means±SD or medians (IQR), and categorical variables as percentages. Statistical comparisons between the study groups were carried out using the unpaired Student's t-test (for normally distributed continuous variables), the Mann-Whitney U test (for non-normally distributed continuous variables) and the χ^2 test (for categorical variables). During the follow-up, we performed unadjusted and adjusted Cox proportional hazards models to examine the association between statin usage and the risk of long-term clinical outcomes (all-cause death and LREs) and LSM changes, using HRs and 95% CIs. We conducted a graphical assessment and confirmed that the proportional hazards assumption was satisfied by plotting Schoenfeld residuals against ranks of time, and no violation was found. Adjustments were undertaken for clinically important covariates, including age, sex, BMI (continuous), diabetes, hypertension, baseline LSM and CAP. Kaplan-Meier survival analysis was performed, and the log-rank test was used to determine any significant differences between the curves. A p value <0.05 was considered statistically significant.

We conducted multiple sensitivity analyses to assess the reliability of our findings. First, to minimise the effect of immortal time bias (people with more prolonged survival might have a greater possibility for events), we left-truncated the follow-up period at 3 years and conducted time-to-event analyses again. Second, to test if the LSM cut-off used to define liver stiffness regression and progression may impact the results, we have also provided HRs for the primary outcome by increasing the LSM cut-off to 30%. This was done to alleviate any concerns regarding the presence of enough signal to ensure that a genuine LSM change is being measured. Third, we also conducted competing risk regression analysis using Fine and Grey's model to estimate subdistribution HR (SHR) for non-outcome death. Fourth, we conducted an analysis using propensity score matching (PSM) to confirm our findings. We performed PSM to balance the baseline characteristics between patients with and without statins. We used one-to-one PSM to select similar groups of individuals prescribed statins and those not, based on age, sex, BMI, hypertension, diabetes, LSM and CAP at baseline. The adjustment was made following the calibration of the calliper width to 0.1 of the SD found in the logit-transformed propensity scores. The balance of potentially associated factors between the two-propensity score-matched groups was evaluated using standardised mean differences. Adjusted Cox proportional hazards models were also applied, with robust SEs accounting for the clustering of matched pairs.

RESULTS

Participants characteristics

Between February 2004 and January 2023, we found 17 949 patients who underwent one or more VCTE examinations. After screening for inclusion and exclusion criteria, we excluded 9961 patients, leaving 7988 patients with MASLD in the final analysis, as shown in figure 1. Compared with non-statin users, patients with statin usage were older (56.3±12.0 vs 50.5±14.3 years, p<0.001) and more likely to have hypertension (48.8% vs 29.0%, p<0.001) and type 2 diabetes mellitus (51.2% vs 24.1%, p<0.001). Despite being older, patients taking statins had a lower prevalence of cACLD (11.8% vs 20.9%, p<0.001), whereas no significant differences were found in the prevalence of liver steatosis (CAP: 299 (IQR: 273–330) dB/m vs 303 (IQR 273–335) dB/m, p=0.062). Detailed clinical features of the population, stratified by statin usage, are shown in table 1.

Association of statin usage and long-term adverse clinical outcomes

During a median follow-up of 4.6 years (IQR: 3.0–6.4 years), 87 deaths and 208 LREs occurred in the whole cohort of participants (table 2). In particular, 68 deaths and 156 LREs occurred in non-statin users with an incidence rate of 2.9 and 6.7 per 1000 person-years, while 19 deaths and 52 LREs occurred in statin users with an incidence event rate of 1.1 and 3.0 per 1000 person-years, respectively (table 3). Compared with non-statin users, patients treated with statins had a significantly lower incidence of all-cause death and LREs (both p<0.001). After adjusting for potential confounding factors, the Cox regression models indicated that statin usage was significantly associated with a lower risk of all-cause mortality (HR=0.233; 95% CI 0.127 to 0.426, p<0.001) and LREs (HR=0.380; 95% CI 0.268 to 0.539, p<0.001). Subgroup analysis also demonstrated that this association persisted in both non-cACLD and cACLD groups (all p<0.001). The Kaplan-Meier survival analysis showed a sustained decrease in the cumulative incidence rates of all-cause mortality and LRE in statin users compared with non-users (figure 2).

Association between statin usage and LSM changes

Patients with liver stiffness progression were more likely to develop clinical outcomes, including all-cause mortality and LRE, compared with those with stable liver stiffness, in both cACLD and non-cACLD groups (online supplemental figure

Table 1 Clinical characteristics of the whole cohort stratified by statin usage

Characteristics	All (N=7988)	No statin use (N=4755)	Statin use (N=3233)	P value
Age (years)	53.0±13.7	50.5±14.3	56.3±12.0	<0.001
Female sex, n (%)	4649 (58.2%)	2786 (58.6%)	1863 (57.6%)	0.390
BMI (kg/m^2)	27.6±4.7	28.0±5.1	27.0±4.0	<0.001
Diabetes, n (%)	2804 (35.1%)	1148 (24.1%)	1656 (51.2%)	<0.001
Hypertension, n (%)	2959 (37.0%)	1380 (29.0%)	1579 (48.8%)	<0.001
ALT (IU/L)	36 (23, 61)	39 (24, 67)	32 (21, 52)	<0.001
AST (IU/L)	30 (22, 46)	32 (23, 48)	28 (21, 42)	<0.001
GGT (IU/L)	43 (26, 76)	45 (28, 82)	39 (24, 69)	<0.001
Albumin (g/L)	44.7±3.5	44.8±3.6	44.5±3.3	<0.001
Total bilirubin (μmol/L)	13.7±7.5	13.9±8.1	13.5±6.6	0.040
Platelet count (×10^9/L)	241±67	240±70	242±64	0.191
Creatinine (μmol/L)	71 (59, 82)	71 (60, 81)	71 (59, 83)	0.745
Fasting glucose (mmol/L)	6.3±1.8	5.9±1.6	6.7±2.0	<0.001
TC (mmol/L)	4.9±1.1	4.9±1.0	4.7±1.2	<0.001
HDL (mmol/L)	1.2±0.3	1.3±0.4	1.2±0.3	<0.001
LDL (mmol/L)	2.9±1.0	3.0±0.9	2.8±1.1	<0.001
Triglycerides (mmol/L)	1.8±1.3	1.8±1.2	1.9±1.3	<0.001
cACLD, n (%)	1375 (17.2%)	994 (20.9%)	381 (11.8%)	<0.001
LSM, kPa (IQR)	5.9 (4.6, 8.2)	6.1 (4.6, 8.9)	5.5 (4.4, 7.3)	<0.001
CAP, dB/m (IQR)	301 (273, 333)	303 (273, 335)	299 (273, 330)	0.062

AST, aspartate aminotransferase; AST, alanine aminotransferase; BMI, body mass index; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, Low-density lipoprotein; LREs, liver-related events; LSM, liver stiffness measurement; TC, total cholesterol.

1 and online supplemental table 1). In the non-cACLD group, we found a ~3.8-fold risk of all-cause mortality (HR=3.797; 95% CI 1.522 to 9.474, p<0.001) and a ~7.5-fold risk of developing incident LREs (HR=7.548; 95% CI 3.844 to 14.823, p<0.001) in patients with liver stiffness progression compared with those with stable liver stiffness. In the cACLD group, the adjusted HRs were 5.576 with a 95% CI of 2.598 to 11.968 (p<0.001) for all-cause death and 21.338 with a 95% CI of 13.061 to 34.858 (p<0.001) for incident LREs in patients with liver stiffness progression compared with those with stable liver stiffness.

We also assessed the association between statin usage and changes in LSMs (figure 3 and online supplemental table 2). During a median VCTE follow-up of 3.0 (IQR: 1.9–4.5) years, compared with non-statin users, statin users had a 55% lower risk of liver stiffness progression in the non-cACLD group and a 46% lower risk of liver stiffness progression in the cACLD group (both p<0.001) (table 4). Conversely, the association between statin usage and liver stiffness regression was not statistically significant (HR=0.914; 95% CI 0.778 to 1.074, p=0.275). In the Kaplan-Meier survival analysis, we found that statin users had a significantly lower incidence of liver stiffness progression than non-statin users in both cACLD and non-cACLD groups (figure 4).

Table 2 Rates of all-cause death and liver-related outcomes stratified by statin usage

	No statin use	Statin use	P value
Subjects, n (%)	4755 (59.5%)	3233 (40.5%)	
Follow-up time, years	4.2 (2.7, 6.4)	5.0 (3.7 6.5)	<0.001
All-cause death, n (%)	68 (1.4%)	19 (0.6%)	<0.001
LRE, n (%)	156 (3.3%)	52 (1.6%)	<0.001
HCC	72 (1.5%)	32 (1.0%)	0.044
Ascites	65 (1.4%)	9 (0.3%)	<0.001
Spontaneous bacterial peritonitis	4 (0.1%)	4 (0.1%)	0.722
Variceal haemorrhage	40 (0.8%)	18 (0.6%)	0.179
Hepatic encephalopathy regression	28 (0.6%)	5 (0.2%)	0.002
Hepatorenal syndrome regression	3 (0.1%)	2 (0.1%)	1.000
Liver transplantation regression	9 (0.2%)	7 (0.2%)	0.803
Liver related death	20 (0.4%)	0 (0%)	<0.001

HCC, hepatocellular carcinoma; LREs, liver-related events.

Sensitivity analyses

Our results remained robust and consistent in all sensitivity analyses (online supplemental table 3). We also categorised statin users into those using lipophilic or hydrophilic statins and found that the results remained unchanged (online supplemental figures 2 and 3). In an analysis where we considered only individuals who had been event-free for at least 3 years after their initial VCTE, we found that statin usage was significantly associated with a lower risk of all-cause death and LREs, with an HR of 0.277 (95% CI 0.145 to 0.529) and 0.411 (95% CI 0.283 to 0.596). For liver stiffness changes, statin usage remained an independent predictor of liver stiffness progression in the whole cohort (HR=0.389; 95% CI 0.308 to 0.491, p<0.001). In a competing risk regression analysis with all-cause deaths as the competing risk, the HRs showed similar results for LREs (SHR=0.441; 95% CI 0.321 to 0.604, p<0.001) and liver stiffness progression (SHR=0.501; 95% CI 0.410 to 0.611). When setting the LSM-change cut-off from 20% to 30%, statin usage was found to lower the risk of liver stiffness progression compared with those who did not assume statins (HR=0.414; 95% CI 0.332 to 0.515, p<0001). Following a PSM analysis, we balanced baseline clinical and biochemical characteristics between patients with statin usage and those without. Each group, consisting of 2499 patients, was paired based on the congruence of their demographic and clinical profiles, as detailed in online supplemental table 4. This PSM process ensured that

Table 3 Cox regression models for adverse clinical outcomes stratified by cACLD and statin usage

	Events in no-statin user	Events in statin user	Adjusted HR	P value
All				
All-cause death	68 (1.4%)	19 (0.6%)	0.233 (0.127–0.426)	<0.001
LRE	156 (3.3%)	52 (1.6%)	0.380 (0.268–0.539)	<0.001
Non-cACLD				
All-cause death	28 (0.7%)	15 (0.5%)	0.262 (0.118–0.582)	<0.001
LRE	30 (0.8%)	17 (0.6%)	0.476 (0.243–0.930)	<0.001
cACLD				
All-cause death	40 (4.0%)	4 (1.0%)	0.200 (0.068–0.593)	0.004
LRE	126 (12.7%)	35 (9.2%)	0.562 (0.372–0.849)	<0.001

Adjusted for age, sex, BMI, diabetes, hypertension, baseline LSM and baseline CAP.
BMI, body mass index; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; LREs, liver-related events; LSM, liver stiffness measurement.

the standardised mean differences for most underlying factors remained below the threshold of 0.1. The results of PMS analysis were consistent and confirmed a substantially lower risk of all-cause death, LREs and liver stiffness progression rates for statin usage even after adjusting for potential confounders (all-cause death: HR=0.273; 95% CI 0.131 to 0.566, p<0.001; LREs: HR=0.524; 95% CI 0.343 to 0.802, p=0.003; liver stiffness progression: HR=0.449; 95% CI 0.354 to 0.570, p<0.001).

DISCUSSION

In this large multicentre VCTE-prognosis study, compared with non-statin usage, statin usage was associated with a substantially lower long-term risk of all-cause mortality, LREs and liver stiffness progression in individuals with MASLD.

Effect of statin usage on all-cause death and LREs

An important finding of our cohort study is that statin usage was associated with a marked reduction in the risk of all-cause death and LREs over a median follow-up of 4.6 years. Limited by the short follow-up period and low incidence of liver clinical outcomes, there have been few studies investigating the relationship between statin usage and the risk of adverse clinical outcomes, such as all-cause death and LREs, especially in MASLD patients without cACLD.[16 25 26] A longitudinal retrospective analysis of 12 538 patients with MASLD using the National Health and Nutritional Examination Survey (NHANES) 1999–2018 database found that statin usage was significantly associated with a lower risk of all-cause and cancer-related mortality.[25]

A post-hoc analysis of three large randomised controlled trials (RCTs) involving over 11 000 patients with MASLD showed that atorvastatin usage significantly reduced serum liver enzyme levels and improved liver fat content.[8] Compared with MASLD/MASH patients who did not receive statins, those taking statins had a 50% reduction in CVD morbidity and mortality.[8] Phase 3 RCTs are ongoing to evaluate the effect of statins on the long-term risk of LREs in patients with MASLD or MASH.[27–29] This patient population is at high risk of developing fatal and non-fatal CVD events, and the use of statins may offer a substantial reduction in adverse cardiovascular and liver-related outcomes, which could also be of potential benefit for reducing the progression of liver disease over time. Previous studies have reported some protective effects of statin usage on chemoprevention and treatment of various cancer types, including HCC prevention in patients with MASLD.[26] A recent meta-analysis including 242 751 patients showed that statin use was associated with a lower risk of HCC overall (HR=0.52; 95% CI 0.37 to 0.72) and in subgroup analyses for MASLD (HR=0.68; 95% CI 0.59 to 0.77; p<0.01).[16]

Effect of statin usage on liver stiffness progression

Another important finding of our cohort study is that statin usage was significantly associated with a lower risk of liver stiffness progression in both cACLD and non-cACLD patients but did not reach statistical significance for liver stiffness regression. To our knowledge, this is the largest observational cohort study involving approximately 8000 individuals exposed to statins, with serial VCTE results for each individual,

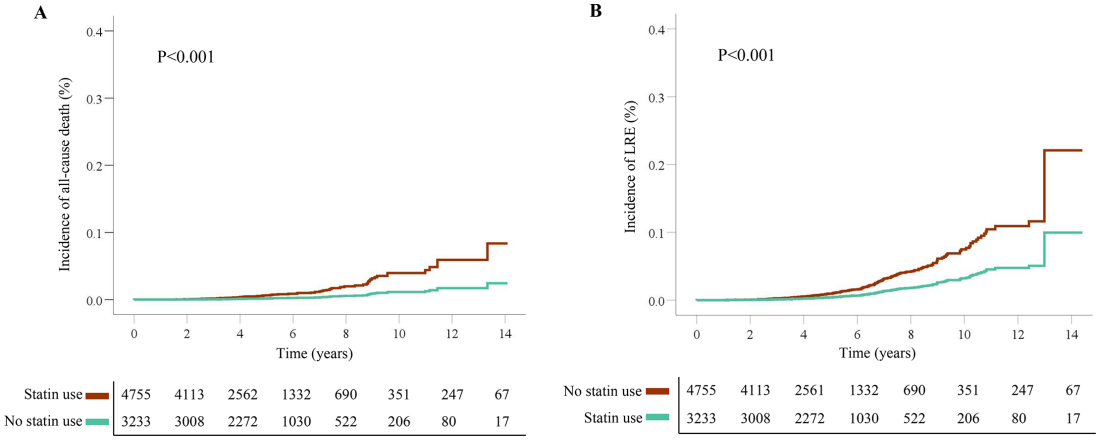

Figure 2 Kaplan-Meier survival analysis of the incidence of clinical outcomes in the whole cohort of participants stratified by statin usage. LRE, liver-related clinical events.

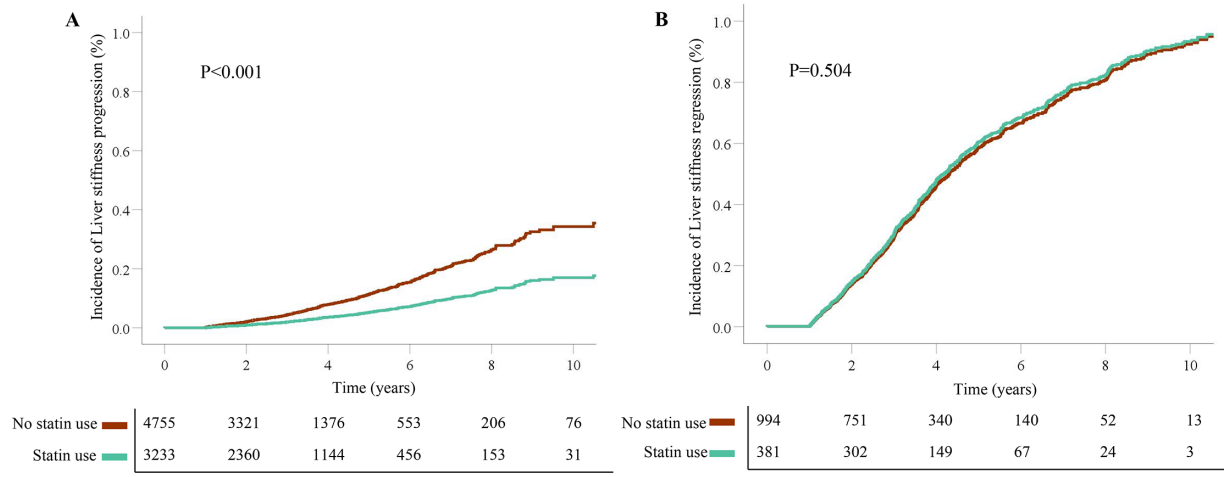

Figure 3 Kaplan-Meier survival analysis of the incidence of liver stiffness changes in the whole cohort of participants stratified by statin usage. LRE, liver-related clinical events.

which allowed for a more accurate diagnosis and dynamic staging of liver fibrosis. Currently, there are few studies on the long-term effects of statins on liver stiffness progression in MASLD.[30] Using liver histopathology data from a nationwide Swedish cohort of 3862 non-cirrhotic individuals with various chronic liver diseases and statin exposure, Sharma *et al* reported that statin usage was associated with lower rates of progression to cirrhosis (HR=0.62; 95%CI 0.49 to 0.78), HCC (HR=0.44; 95%CI 0.27 to 0.71) and liver-related mortality (HR=0.55; 95%CI 0.36 to 0.82).[23] In a cross-sectional analysis of the NHANES 2017–2018 database involving 744 patients with type 2 diabetes and VCTE results, Ciardullo and Perseghin found that statin use was associated with lower odds of advanced liver fibrosis (OR 0.35; 95%CI 0.13 to 0.90), but no significant interaction was found between statin usage and hepatic steatosis (as assessed with CAP).[30] In another recent cross-sectional study of 346 patients with biopsy-proven MASLD and type 2 diabetes, Nascimbeni *et al* showed that statin use was negatively associated with significant liver fibrosis (≥F2).[31] A large population-based study was conducted on 712 262 subjects with MASLD (defined as fatty liver index >60) using data from the National Health Information Database of the Republic of Korea, collected in 2010 and followed up until 2016.[32] Of these, 111 257 subjects had a BARD score ≥2 and were categorised as liver fibrosis cases. The results of this cross-sectional study showed that statin usage was associated with a lower likelihood of significant liver fibrosis (adjusted OR 0.43; 95%CI 0.42 to 0.44), independent of diabetes status. In a European study of 1201 patients with biopsy-proven MASH (107 took statins for at least 6 months), the authors reported that individuals on statin treatment had significantly lower odds for hepatic steatosis, NASH and advanced fibrosis than those who were not on statins.[33] It is plausible that the potential benefits of statin usage, such as its anti-inflammatory, vascular and tissue healing properties, could help prevent liver fibrosis progression. However, while no long-term phase 3 RCTs have been undertaken on the effect of statins on liver fibrosis in humans, available evidence suggests that statins generally have a beneficial effect on the severity of MASLD.[11 34]

Effect of statin type

In our cohort study, we also observed a consistent beneficial effect on the risk of clinical outcomes and liver stiffness progression for both lipophilic and hydrophilic statins. Lipophilic statins, such as simvastatin, fluvastatin, pitavastatin, lovastatin and atorvastatin, can enter cells through passive diffusion and are present in various tissues.[35] Conversely, hydrophilic statins, including rosuvastatin and pravastatin, require a liver-specific, carrier-mediated mechanism for their uptake. Therefore, lipophilic statins are believed to have more pleiotropic effects on non-lipid tissues.[35 36] Lipophilic statins may stimulate antitumour immunity more efficiently compared with hydrophilic statins. They may also have antitumour effects by inducing G0/G1 cell cycle arrest, inhibiting Ras/Raf/Mek/ERK signalling and promoting apoptosis in preclinical studies.[24 37] A meta-analysis examining individual types of statins found that rosuvastatin, a hydrophilic statin, was associated with the most significant reduction in the risk of developing HCC.[16]

Balance between potential risk and benefit of statin usage

Physicians should be cautious when prescribing statins to patients with MASLD, even though statin usage is safe and may significantly reduce serum aminotransferase levels without any increased risk of hepatotoxicity.[38] The most common side effects of statins

Table 4 Cox regression models for liver stiffness change stratified by cACLD and statin usage

	No statin use	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
All					
Liver stiffness progression	Ref.	0.499 (0.412 to 0.604)	<0.001	0.411 (0.333 to 0.508)	<0.001
Non-cACLD					
Liver stiffness progression	Ref.	0.688 (0.507 to 0.933)	0.016	0.450 (0.342 to 0.592)	<0.001
cACLD					
Liver stiffness progression	Ref.	0.523 (0.408 to 0.670)	<0.001	0.542 (0.389 to 0.755)	<0.001
Liver stiffness regression	Ref.	1.052 (0.906 to 1.222)	0.504	0.914 (0.778 to 1.074)	0.275

Adjusted for age, sex, BMI, diabetes, hypertension, baseline LSM and baseline CAP.
BMI, body mass index; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; LSM, liver stiffness measurement.

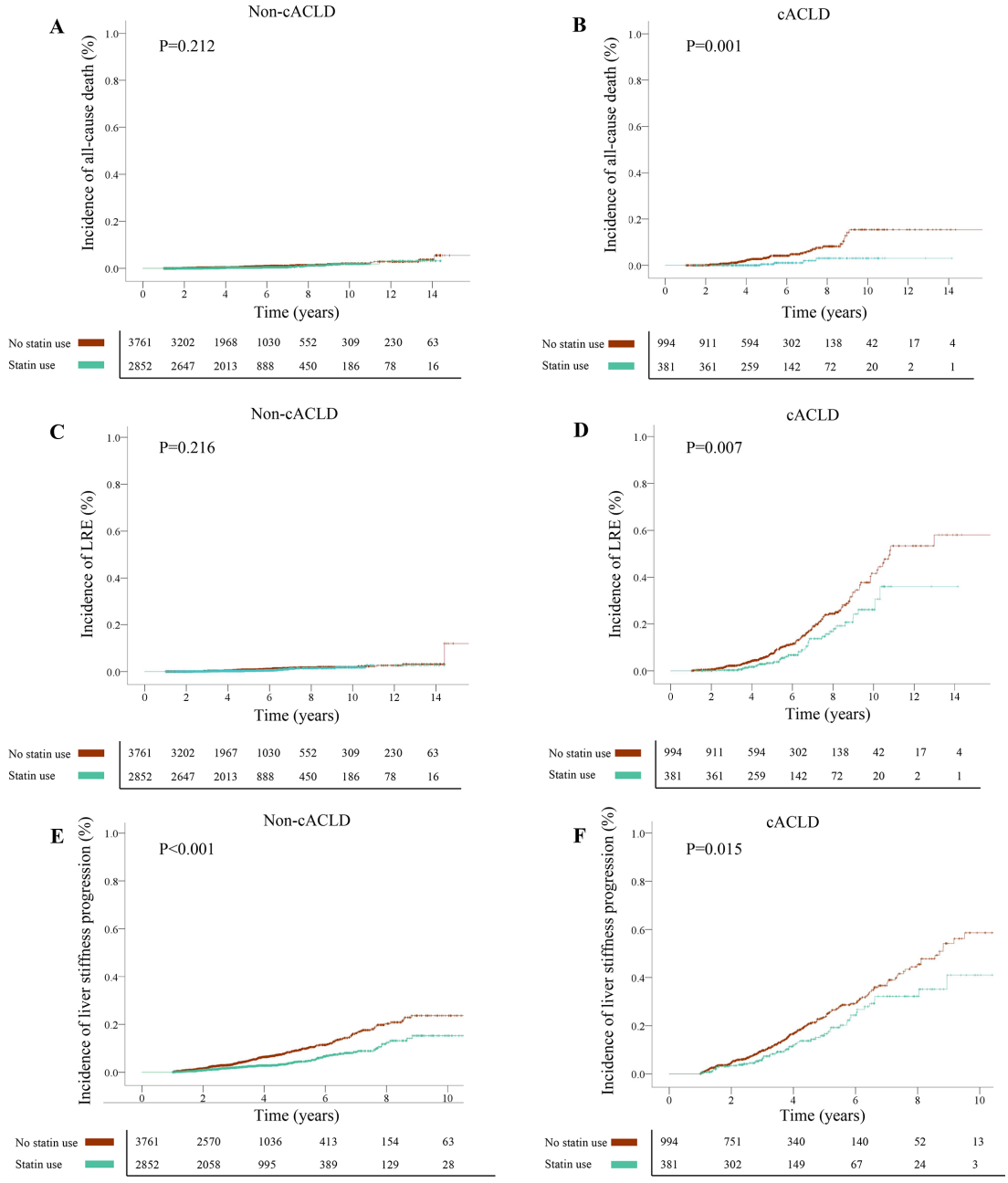

Figure 4 Kaplan-Meier survival analysis of the incidence of clinical outcomes and liver stiffness changes in the whole cohort of participants stratified by statin usage and cACLD. cACLD, compensated advanced chronic liver disease.

are statin-associated muscle symptoms, which include muscle pain, weakness and even rhabdomyolysis.[39 40] Extensive clinical experience with the widespread use of statins has shown that the risk of statin-induced severe liver injury is low, occurring in less than 1.2 out of 100 000 users, and is likely idiosyncratic.[11 41] The statin benefits generally outweigh the potential risks. There is evidence to suggest that statins may lower the risk of liver stiffness progression, LREs and mortality among patients with or without compensated cirrhosis.[11 41] This evidence, combined with the known safety and tolerability of statins and their potential to reduce HCC risk, may lead hepatologists/gastroenterologists to consider using statins to improve clinical outcomes for cACLD or cirrhosis without incurring significant additional costs. However, these promising results will be best confirmed by large RCTs with long follow-up duration that evaluate the use of statins at baseline versus on-trial in patients with MASLD to minimise potential confounders.

Limitations

Our study has several limitations that should be mentioned. First, when patients are assessed at different intervals, it can affect the interpretation of the data. However, we looked at changes in non-invasive testing and clinical outcomes after VCTE examinations, considering intervals. Second, although we had a sufficient sample size for evaluating clinical outcomes, the 3-year median follow-up may be considered short, given the prolonged progression of chronic liver disease to cirrhosis and complications. Third, although we adjusted for potential confounders in our cohort study, the results might have overestimated the benefits of statins due to possible residual confounding in statin users. Differences between groups that we could not fully account for (confounding by indication) likely exist. This is a well-known issue in observational studies. Therefore, there is a need for long-term phase 3 RCTs to better evaluate the association between statin exposure and the risk of liver stiffness progression, LREs and

mortality in patients with chronic liver diseases. Fourth, the intrinsic limitations of our database make it difficult to thoroughly study the complexities of drug interactions, especially between statins and glucose-lowering drugs, despite adjusting for antidiabetic drug use in the analysis. Fifth, our analysis included statin use as a time-dependent variable. However, patients had to have received at least 30 cDDDs of statin therapy before being classified as 'statin users', the index date was set only after this classification, potentially leading to immortal time bias. Finally, the data included in this study were from tertiary referral centres, so the prognostic performance of VCTE should be confirmed in a more general setting in the future.

CONCLUSIONS

This large observational multicentre prospective cohort study includes liver VCTE data at baseline and follow-up. The results of this cohort study suggest that statin usage may help reduce CVD morbidity and mortality rates and slow down liver stiffness progression in both cACLD and non-cALCD patients. Although this cohort study provides a reliable estimate of the risk between statin usage and adverse liver-related outcomes in people with MASLD, future long-term RCTs are needed to further confirm the findings.

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