Title: Long-term Liver-related Outcomes and Liver Fibrosis Progression of Statin Usage in Steatotic Liver Disease.

Running Title: Statin Use for MASLD

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Abstract

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

Aim: This observational multicenter cohort study aimed to explore the effect of statins on long-term risk of liver-related clinical events (LRE), steatosis and liver fibrosis progression in patients with MASLD.

Methods: This cohort study collected data on MASLD patients undergoing at least two vibration-controlled transient elastography (VCTE) examinations at 16 tertiary referral centers from February 2004 to January 2023. Statin use was defined as 30 or more cumulative defined daily dose.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). Fibrosis progression was defined as LSM increase of ≥20% for cACLD and from <10 kPa to ≥10 or LSM for non-cACLD. Fibrosis regression was defined as a LSM reduction from ≥10 kPa to <10 or LSM decrease of ≥20% for cACLD.

Results: We followed 7,988 patients with baseline LSM 5.9 kPa (IQR 4.6-8.2) for 3.0 (IQR 1.9-4.5) years. At baseline, statin usage was present in 40.5% of patients, and cACLD was present in 17%. Statin usage was significantly associated with a lower risk of all-cause death (adjusted HR=0.233; 95% 0.127-0.426) and LREs (adjusted HR=0.380; 95% 0.268-0.539). Statin usage was also associated with lower fibrosis progression rates in cACLD (HR=0.542; 95% 0.389-0.755) and non-cACLD (HR=0.450; 95% 0.342-0.592), but not with fibrosis regression (HR=0.914; 95% 0.778-1.074).

Conclusions: Statin usage was associated with a markedly lower risk of all-cause death, liver-related events and fibrosis progression in patients with MASLD.

Keywords: metabolic dysfunction-associated fatty liver disease, metabolic dysfunction-associated steatotic liver disease, vibration-controlled transient elastography, liver fibrosis, prognosis.

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 are currently no FDA-approved agents but resmetirom specifically addressing metabolic dysfunction-associated steatohepatitis, as the current ones have not yet met the required liver-related histological endpoints.[3,4]

Statin medications are widely recognized for their effectiveness in lowering the risk of cardiovascular disease (CVD) by reducing plasma LDL- cholesterol concentrations by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase.[5,6] This leads to it being commonly prescribed for MAFLD patients with dyslipidemia, pre-existing CVD or at high risk of CVD.[7] Statins exert anti-inflammatory, anti-fibrotic, anti-thrombogenic, and antioxidant effects, which might 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 of people with MASLD, in which CVD represents the leading cause of death.[10-12] However, statins are still not widely used among patients with liver disease, mainly due to concerns about possible statin-induced liver damage and muscle weakness. Several studies have shed light on the safety of statin usage in patients with noncirrhotic MASLD or cirrhosis and have also shown promising results in recent years.[13] In clinical practice, healthcare providers are often hesitant to prescribe statins to patients with MASLD, and particularly those with cirrhosis because of safety concerns. Consequently, recent expert recommendations

have strongly recommended the use of statin therapy to treat patients with MASLD who have pre-existing CVD or are at high risk of CVD.[14]

Patients with MASLD are generally at high risk of CVD morbidity.[13] In this context, statin therapy represents the backbone for primary and secondary prevention of CVD and might be particularly beneficial if a hepatoprotective effect on liver fibrosis and liver-related clinical events was also confirmed. Therefore, this observational multicenter cohort study aimed to explore the effects of statins on long-term clinical outcomes and liver fibrosis progression in patients with MASLD.

Methods

Study Design and Participants

This cohort study was conducted on patients with MASLD who underwent vibration-controlled transient elastography (VCTE) examination at 16 centers in the United States, Europe, and Asia. Our detailed information regarding this multicenter VCTE cohort has been presented in previously published work.[15] Patients aged ≥18 years with MASLD diagnosed by histologic methods (steatosis in ≥5% of hepatocytes) or imaging studies (ultrasonography, computed tomography, magnetic resonance imaging, or controlled attenuation parameter ≥ 248 dB/m by VCTE) were eligible. 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), secondary causes of hepatic steatosis (e.g., usage of systemic steroids), or a history of hepatocellular carcinoma (HCC), hepatic decompensation, liver resection, liver transplant, or other malignant carcinomas were excluded (**Figure 1**).

The protocol of this study underwent approval by the institutional review boards of all participating centers. Adherence to the Declaration of Helsinki principles was undertaken and the need for informed written consent was waived due to its retrospective nature.

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 meters. After at least 8 hours of fasting, a venous blood sample was taken to examine kidney and liver biochemistry and full blood cell count. The VCTE equipment (FibroScan; Echosens) was used to assess the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) by trained operators, as described previously. Healthcare professionals who were trained as per the manufacturer's instructions performed the LSMs, and these were considered valid if 10 measurements were obtained with interquartile ranges (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 patients 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.[16] 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%. Our primary study outcome was a composite outcome inclusive of all-cause death and liver-related events (LREs), including development of cirrhosis (cirrhosis, decompensation, or portal hypertension ICD codes), HCC or liver-related mortality (includes liver transplantation). The second study outcome was the change of hepatic steatosis and fibrosis. For MASLD patients with cACLD at baseline (baseline LSM ≥ 10 kPa), a clinically relevant increase in LSM was defined as at least 20% (i.e. Fibrosis progression). A clinically relevant decrease in LSM was defined as a follow-up LSM of less than 10 kPa or follow-up LSM of less than 20 kPa, along with a decrease of at least 20% (Fibrosis regression). For MASLD patients without cACLD at baseline (baseline LSM < 10 kPa), a clinically relevant LSM increased if the follow-up LSM was ≥ 10 kPa (Fibrosis progression). The remaining patients were considered to be "Fibrosis stable.”

Statin exposure

All patients who were prescribed statin medications during the study observation period were identified. Statin prescriptions included simvastatin, atorvastatin, pravastatin, osuvastatin, fluvastatin, lovastatin, and pitavastatin. The usage of statins was defined as having been exposed to a statin if they filled a statin prescription for ≥ 30cDDD during both inpatient and outpatient visits from 1 February 2004 to 1 year before the date of outcome or the end of follow-up, consistent with prior studies.[17-19] Individuals who had any statin prescription during the ≤ 365-day period before the

first attainment of cDDD ≥ 30 were excluded to ensure that we captured incident statin use.

Statistical Analysis

All statistical analyses were performed using the IBM SPSS software, version 23.0 for Windows. Continuous variables were expressed as means ± SD or medians (interquartile ranges, 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 chi-squared test (for categorical variables). During the follow-up, we performed unadjusted and adjusted Cox proportional hazards models to examine the association between status usage and the risk of long-term clinical outcomes (all-cause death and liver-related events) and LSM changes using hazard ratios (HR) and 95% confidence intervals (CI). Kaplan-Meier survival analysis was also performed to calculate the event-free survival curves, and the log-rank test was used to test the presence of 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 minimize the effect of lead-time bias (people with longer survival may have a greater possibility for events), we left-truncated the follow-up period at 3-year and conducted time-to-event analyses again. Second, to test if the LSM cutoff used to define liver fibrosis regression and progression may impact the results, we have also provided HRs for the primary outcome by increasing the LSM cutoff 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 using the Fine and Gray's model to estimate subdistribution hazard ratios (SHR) for all-cause mortality. Fourth, we conducted an analysis using propensity score matching (PSM) to confirm our findings. We performed PSM to balance the baseline characteristics between the groups with unfavorable and favorable clinical outcomes. We used one-to-one propensity score matching to select similar groups of individuals prescribed statins and those not, based on age, sex, BMI, hypotension, diabetes, LSM, and CAP at baseline VCTE. The adjustment was made following the calibration of the caliper width to 0.1 of the standard deviation found in the logit-transformed propensity scores. The balance of potentially associated factors between the two-propensity score-matched groups was evaluated using standardized mean differences. Adjusted Cox proportional hazards models was also applied, with robust standard errors accounting for the clustering of matched pairs.

Results

Participants Characteristics

Between February 2004 and January 2023, we found 17,949 patients who underwent twice or more VCTE examinations. After screening for inclusion and exclusion criteria, we excluded 9961 patients, leaving us with 7988 patients with MASLD in the final analysis, as shown in **Figure 1**. Compared to 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 follow-up of 3.0 (IQR: 1.9 - 4.5) years, 87 deaths occurred for all-cause mortality and 208 LREs occurred in the whole cohort (**Table 2**). In particular, 68 all-cause deaths and 156 LREs occurred in non-statin users with an incidence event rate of 2.9 and 6.7 per 1000 person-years, while 19 all-cause deaths and 52 LREs occurred in statin users with an incidence event rate of 1.1 and 3.0 per 1000 person-years (**Table 3**). Compared to non-statin users, people who used 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 associated with a lower risk of all-cause mortality (HR = 0.233; 95% CI 0.127 - 0.426, P < 0.001) and LRE (HR = 0.380; 95% CI 0.268 - 0.539, P < 0.001). Subgroup analysis also demonstrated the association persisted in non-cACLD and cACLD groups (all P < 0.001). The KM curve indicated a sustained decrease in the cumulative incidence of all-cause mortality and LRE in statin users compared to non-users **(Figure 2**).

Association between Statin Usage and LSM Changes

Patients with liver fibrosis progression were more likely to experience clinical outcomes, including all-cause mortality and LRE compared to those with fibrosis stable in both cACLD and non-cACLD groups (**Supplementary Figure 1 &**

Supplementary Table 1). In non-cACLD patients, we found a 3.8-fold risk of all-cause mortality (HR = 3.797; 95% CI 1.522 - 9.474, P < 0.001) and a 7.5-fold risk of developing incident LREs (HR = 7.548; 95% CI 3.844 - 14.823, P < 0.001) in patients with fibrosis progression than those with stable fibrosis. In cACLD patients, 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 fibrosis progression compared those with stable fibrosis.

We also assessed the association between the statin usage and changes in LSMs (**Figure 3 & Supplementary Table 2**). Statin users had a 55% low risk of fibrosis progression in non-cACLD patients and a 46% lower risk of fibrosis progression in cACLD patients compared to non-statin users (both P < 0.01) (**Table 4**). However, the association between statin usage and regression of liver fibrosis was not statistically significant (HR = 0.914; 95% CI 0.778 - 1.074, P = 0.275). In the K-M analysis, we found that statin users had a significantly lower incidence of liver fibrosis progression than non-statin users in both cACLD and non-cACLD groups (**Figure 4**).

Sensitivity Analyses

Our results remained robust and consistent in all sensitivity analyses (**Supplementary Table 3**). We also categorized statin users into those using lipophilic or hydrophilic statins and found that the results remained unchanged (**Supplementary Figure 2 & Supplementary Figure 3**). In an analysis where we considered only individuals who had been event-free for at least 3-year after their initial VCTE, we found that statin usage was significantly associated with a lower risk of all-cause death and LRE incidence, with an HR of 0.277 (95%CI 0.145 - 0.529) and 0.411 (95%CI 0.283 -

0.596). For liver fibrosis changes, statin usage remained a strong and independent predictor of liver fibrosis progression in the whole cohort (HR = 0.389, 95% CI 0.308 - 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 LRE (SHR = 0.441 95% CI 0.321 - 0.604, P < 0.001) and liver fibrosis progression (SHR = 0.501, 95% CI 0.410 - 0.611). When setting the LSM-change cutoff from 20% to 30%, statin usage was found to lower the risk of fibrosis progression compared to those who did not take statins (HR = 0.414; 95% CI 0.332 – 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 **Supplementary Table 4**. This PSM process ensured that the standardized mean differences for most underlying factors remained below the threshold of 0.1. The results of PMS analysis were consistent and showed a substantially lower risk of all-cause death, LREs and fibrosis progression rates for statin usage even after adjusting for potential confounders (all-cause death: HR = 0.273 95% CI 0.131 - 0.566, P < 0.001; LREs: HR = 0.524, 95% CI 0.343 - 0.802, P = 0.003; liver fibrosis progression: HR = 0.449, 95% CI 0.354 - 0.570, P < 0.001).

Discussion

In this large multicenter VCTE cohort study, compared with non-statin usage, our findings indicate that statin usage is associated with a substantially lower risk of all-cause mortality, LREs and liver fibrosis progression in adult individuals with MASLD.

Effect of statin usage on all-cause death and LREs

An important finding of our prospective cohort study is that statin usage was associated with a marked reduction in the risk of all-cause death and LREs over the follow-up. 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.[20-22] A longitudinal retrospective analysis conducted on 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 reduced overall and cancer-related mortality.[20] A post-hoc analysis of three large randomized controlled trials (RCTs) involving over 11,000 patients with MASLD showed that atorvastatin usage reduced serum liver enzymes and improved liver fat accumulation.[8] Compared to MASLD/metabolic dysfunction-associated steatohepatitis (MASH) patients who did not receive statins, those who received 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.[23-25] This patient population is at high risk of fatal and nonfatal 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.[21] A recent meta-analysis including 242,751 patients showed that statins use

was associated with a lower risk of HCC overall (HR: 0.52; 95% CI: 0.37–0.72) and in subgroup analyses for MASLD (HR: 0.68; 95% CI: 0.59–0.77; $p < 0.01$).[22]

Effect of statin usage on liver fibrosis progression

Another important finding of our prospective cohort study is that statin usage was significantly associated with a lower risk of liver fibrosis progression both in cACLD and non-cACLD but did not reach statistical significance for liver fibrosis 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, 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 fibrosis progression in individuals with MASLD.[26] Using liver histopathology data from a nationwide Swedish cohort of 3,862 noncirrhotic 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 0.49-0.78), HCC (HR 0.44; 95% CI 0.27-0.71), and liver-related mortality (HR 0.55; 95% CI 0.36-0.82).[18] In a cross-sectional analysis of the NHANES 2017-18 database, involving 744 patients with type 2 diabetes and VCTE results, Ciardullo et al. found that statin use was associated with a lower odds of advanced liver fibrosis (odds ratio = 0.35; 95% CI 0.13 - 0.90), but no significant interaction was found between statin usage and hepatic steatosis (as assessed with CAP).[26] In another recent cross-sectional study of 346 patients with diabetes and biopsy-proven MASLD, Nascimbeni et al. confirmed that statin use was independently and negatively associated with significant liver fibrosis (≥ F2).[27] A large population-based study was conducted on 712,262 subjects with MASLD (defined as FLI >60) using data from the National Health

Information Database of the Republic of Korea, collected in 2010 and followed up until 2016.[28] Of these, 111,257 subjects had a BARD score ≥ 2 and were categorized as liver fibrosis cases. The results of such cross-sectional study showed that statin usage was significantly associated with a reduced likelihood of significant liver fibrosis (adjusted OR 0.43; 95% CI 0.42–0.44), independent of diabetes status. In an European study of 1,201 patients with biopsy-proven NASH (107 took statins for at least 6 months) the authors reported that individuals on statin treatment had a significantly lower odds for steatosis, NASH and advanced fibrosis than those who were not on statins.[29] It is plausible that the potential benefits of statin usage, such as its anti-inflammatory, vascular, and tissue healing properties, could help prevent 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 this class of drugs generally has a beneficial effect on the severity of MASLD.[11,30]

Effect of statin type

In our cohort study, we also observed a consistent beneficial effect on the risk of clinical outcomes and liver fibrosis 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.[31] 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.[31,32] Compared to hydrophilic statins, lipophilic statins may stimulate antitumor immunity more efficiently. They may also have antitumor effects by inducing G0/G1 cell cycle

arrest, inhibiting Ras/Raf/Mek/ERK signaling, and promoting apoptosis in preclinical studies.[19,33] A meta-analysis that examined individual types of statins found that rosuvastatin, a hydrophilic statin, was associated with the most significant reduction in the risk of developing HCC.[22]

Balance between potential risk and benefit of statin usage

Physicians are cautious when prescribing statins to patients with MASLD, even though statin usage is safe and may even significantly reduce serum aminotransferase levels without any increased risk of hepatotoxicity.[34] The most common side effects of statins are statin-associated muscle symptoms (SAMS), which include muscle pain, weakness, and even rhabdomyolysis.[35,36] 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.[11,37] The statin benefits generally outweigh the potential risks. There is evidence to suggest that statins may lower the risk of liver fibrosis progression, LRE and mortality among patients with or without compensated cirrhosis.[11,37] This evidence, combined with the known safety and tolerability of statins and their potential to reduce HCC risk, may lead Hepatologists to consider using statins to improve outcomes for cACLD or cirrhosis without incurring significant additional costs. However, we cannot draw any conclusions before confirming these promising results through large RCTs with long follow-ups that evaluate the use of statins at baseline versus on-trial as a possible confounder in patients with MASLD.

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 3.0 years median follow-up may be considered short, given the prolonged progression of chronic liver disease to cirrhosis and complications. Third, although in our observational cohort study we adjusted for potential confounders, the results might have overestimated the benefits of statins due to possible residual confounding in statin users. It is known that evidence from observational studies is prone to confounding by indication. Therefore, there is a need for long-term phase 3 RCTs to better evaluate the association between statin exposure and the risk of liver fibrosis progression, liver-related death and other hepatic clinical outcomes 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 DDD of statin therapy before being classified as "statin users", the index date was set only after this classification, potentially leading to immortal time bias. Last, the data included in this study were from tertiary referral centers, so the prognostic performance of VCTE should be confirmed in a more general setting in the future.

Conclusions

This is a large observational multicenter prospective cohort study that includes liver VCTE data both at baseline and follow-up. The results of this study suggest that statin

usage may help reduce CVD morbidity and mortality rates and slow down liver disease progression in both cACLD and non-cALCD patients. Although this prospective cohort study provides a reliable estimate of the risk between statin usage and adverse liver-related outcomes in people with MASLD, future long-term randomized controlled trials are needed before recommending statin usage in routine clinical practice in this patient population.

Author Contributions: Drs Zhou and Zheng had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Zhou, Yip, Petta, Bugianesi, Yoneda, Calleja, Newsome, Fan, Fournier-Poizat, G. Wong, Nakajima, Asgharpour, Kim, V. Wong. Acquisition, analysis, or interpretation of data: Lin, Lee, Yip, Tsochatzis, Bugianesi, Yoneda, Zheng, Hagström, Boursier, Calleja, Goh, W. Chan, Gallego-Durán, Sanyal, De Lédinghen, Newsome, Castéra, Lai, Fournier-Poizat, G. Wong, Pennisi, Armandi, Nakajima, Liu, Shang, Saint-Loup, Llop, Teh, Lara-Romero, Asgharpour, Mahgoub, M. Chan, Canivet, Romero-Gomez, Kim, Targher, Byrne, V. Wong, Zheng. Drafting of the manuscript: Zhou and Zheng. Critical review of the manuscript for important intellectual content: All authors. Statistical analysis: Zhou and Zheng. Administrative, technical, or material support: Zhou, Lee, Bugianesi, Yoneda, Zheng, Goh, Newsome, Lai, Fournier-Poizat, G. Wong, Nakajima, Liu, Shang, Saint-Loup, Asgharpour, M. Chan, V. Wong, Zheng. Supervision: Zhou, Yip, Tsochatzis, Bugianesi, Yoneda, W. Chan, Newsome, G. Wong, Armandi, Nakajima, Llop, Romero-Gomez, Kim, V. Wong, Zheng.

Conflicts of Interest Statement: Dr Yip reported serving as an advisory committee member and a speaker for Gilead Sciences outside the submitted work. Dr Tsochatzis

reported receiving personal fees as advisory board member for Boehringer, Novo Nordisk, Pfizer, and Siemens; receiving speaker fees from Echosens, Novo Nordisk, and AbbVie outside the submitted work. Dr Hagström reported personal fees from AstraZeneca, personal fees from Bristol Myers-Squibb, personal fees from MSD, personal fees from Novo Nordisk, personal fees from Boehringer Ingelheim, personal fees from KOWA, and personal fees from GW Phara outside the submitted work, and grants from AstraZeneca, grants from Echosens, grants from Gilead Sciences, grants from Intercept, grants from MSD, grants from Novo Nordisk, and grants from Pfizer outside the submitted work. Dr Boursier reported receiving grants and personal fees from Echosens outside the submitted work. Dr Calleja reported receiving other from Echosens Clinical Trials during the conduct of the study; grants from Roche Pharma and other from Gilead Advisory Board outside the submitted work. Dr W. Chan reported serving as consultant or advisory board member for Roche, AbbVie, Boehringer Ingelheim, and Novo Nordisk; and a speaker for Echosens, Viatris, and Hisky Medical. Dr Sanyal reported receiving grants from Intercept, personal consulting fees from Gilead, grants from Merck, personal consulting fees from Pfizer, grants and personal consulting fees from Eli Lilly, grants and personal consulting fees from Novo Nordisk, Boehringer Ingelheim, Novartis, Histoindex, and stock options from Genfit, Tiziana, Durect, Inversago, and personal consulting fees from Genentech, ALnylam, Regeneron, Zydus, LG chem, Hanmi, Madrigal, Path AI, 89 Bio, and stock options from Galmed outside the submitted work. Dr De Lédinghen reported receiving nonfinancial support from Echosens during the conduct of the study. Dr Newsome reported receiving grants from Novo Nordisk, advisory board and personal consulting fees, honoraria for lectures and travel expenses from Novo Nordisk, personal consulting and advisory board fees from Boehringer Ingelheim,

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Figure Legends

Figure 1. Study participant flow.

Figure 2. Kaplan-Meier curve of the incidence of clinical outcomes in the whole cohort by statin usage.

Figure 3. Kaplan-Meier curve of the incidence of liver stiffness changes in the whole cohort by statin usage.

Figure 4. Kaplan-Meier curve of the incidence of clinical outcomes and liver stiffness changes in the whole cohort by statin usage and cACLD.

Supplementary Figure 1. (A) Changes in liver stiffness between baseline and following VCTE examinations; (B) Kaplan-Meier curve of the incidence of clinical outcomes in the whole cohort by liver stiffness changes in patients with non-cALCD; (C) Kaplan-Meier curve of the incidence of clinical outcomes in the whole cohort by liver stiffness changes in patients with cACLD.

Supplementary Figure 2. Subgroup analysis (forest-plot) for clinical outcomes and liver stiffness changes in the whole cohort by types of statin usage.

Supplementary Figure 3. Subgroup analysis (Kaplan-Meier curve) for the incidence of clinical outcomes and liver stiffness changes in the whole cohort by types of statin usage.

Table Legends

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

Table 2. Rates of clinical outcomes stratified by statin usage.

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

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

Supplementary Table 1. Cox regression models for clinical outcomes stratified by cACLD and fibrosis change.

Supplementary Table 2. Rates of liver stiffness changes stratified by cACLD and statin usage.

Supplementary Table 3. Sensitivity analyses.

Supplementary Table 4. Clinical characteristics stratified by statin usage after propensity score matching.