HHS Public Access

Author manuscript

Gastroenterology. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

Gastroenterology. 2016 February ; 150(2): 430–440.e1. doi:10.1053/j.gastro.2015.10.007.

Statins are Associated with a Decreased Risk of Decompensation and Death in Veterans with Hepatitis C-related Compensated Cirrhosis

Arpan Mohanty, MD[1,2], **Janet Tate, ScD**[3], and **Guadalupe Garcia-Tsao, MD**[1,2]

[1]Section of Digestive Diseases, VA-CT Healthcare System, West Haven, CT, USA

[2]Section of Digestive Diseases, Yale University School of Medicine, New Haven, CT, USA

[3]Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA and VA-CT Healthcare System, West Haven, CT, USA

Abstract

Background & Aims—Statins decrease portal pressure in patients with cirrhosis and increase survival times of those who have bled from varices. However, statins can be hepatotoxic. It is important to determine whether long-term statin use will be beneficial or detrimental for patients with cirrhosis because physicians are reluctant to prescribe statins to patients with liver disease. We investigated effects of statins on decompensation and survival times in patients with compensated cirrhosis.

Methods—We performed a retrospective cohort using the Veteran Affairs Clinical Case Registry, which contains nationwide data from veterans infected with the hepatitis C virus (HCV). We identified patients with compensated cirrhosis from January 1996 through December 2009. Statin use was according to filled prescriptions. Cirrhosis and decompensation were determined from ICD9 codes, using a validated algorithm.

Results—Among 40,512 patients with HCV compensated cirrhosis (98% male, median age of 56 years), 2802 statin users were identified. We developed a propensity score model using variables associated with statin prescription, and new statin users were matched with up to 5 non-users; 685

Address for correspondence: Guadalupe Garcia-Tsao, MD, Section of Digestive Diseases, Yale University School of Medicine, 333 Cedar St – 1080 LMP, P.O. Box 208019, New Haven, CT 06510, Phone (203)737-6063, Fax: (203)785-7273, guadalupe.garcia-tsao@yale.edu.

Conflict of interest: None

Author contributions: Dr. Garcia-Tsao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis
Study concept and design: Mohanty, Garcia-Tsao
Acquisition, analysis and interpretation of data: All authors
Drafting of manuscript: Mohanty
Critical revision of manuscript for intellectual content: All authors
Statistical analysis: Tate
Study supervision: Garcia-Tsao
Approval of final version of manuscript: All authors

statin users were matched with 2062 non-users. Discrimination of the propensity score model was 0.92. Statin users had lower risk of decompensation (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.39–0.77)] and death (HR, 0.56; 95% CI, 0.46–0.69), compared with non-users. Findings persisted after adjustment for age, FIB-4 index score, serum level of albumin, model for end-stage liver disease and Child scores (HR for decompensation, 0.55; 95% CI, 0.39–0.78) and HR for death, 0.55; 95% CI, 0.45–0.68).

Conclusions—Based on data from the Veteran Affairs Clinical Case Registry, statin use among patients with HCV and compensated cirrhosis is associated with over 40% lower risk of cirrhosis decompensation and death. Although statins cannot yet be widely recommended for these patients, their use should not be avoided.

Keywords

Simvastatin; Prognosis; Decompensation; Mortality

Cirrhosis results from any chronic liver disease and has two distinct stages: compensated and decompensated. Median survival in compensated cirrhosis is over 12 years, while it is less than 2 years once decompensation occurs, that is, when complications of cirrhosis (ascites, variceal hemorrhage, and/or encephalopathy) become clinically apparent[1]. Main predictors of decompensation are the presence of clinically significant portal hypertension (determined by portal pressure measurement) and a low serum albumin (an indicator of liver dysfunction)[2, 3]. A decrease in portal pressure of only 10% has been shown to significantly decrease the development of varices[4] and reduce the incidence of first variceal hemorrhage, ascites and death in patients with compensated cirrhosis[5, 6].

Most drugs currently used to decrease portal pressure do so through splanchnic vasoconstriction thereby reducing portal blood inflow. However, an important component of portal hypertension is increased intrahepatic vascular resistance partially due to sinusoidal endothelial dysfunction with decreased nitric oxide. Statins increase nitric oxide availability at the intrahepatic level[7] and decrease portal pressure both in experimental animals[8] and in patients with cirrhosis[9]. Their beneficial effect may go beyond reducing portal pressure by increasing flow into the liver, thereby potentially improving liver function[9]. While statins can also be hepatotoxic, a small retrospective study recently suggested that statins are safe in cirrhosis and their use was a negative predictor of death[10].

The objective of this study was to assess the association between statin use, decompensation and death, in a large cohort of patients with compensated cirrhosis. We hypothesized that statins would be associated with lower risk of decompensation and death. Patients with more severe liver disease are less likely to be prescribed a statin but more likely to decompensate and die. Patients with more severe cardiovascular risk are more likely to receive a statin but may be at higher risk of death. To account for this confounding by indication we used propensity score matching. This technique provides an analysis that emulates a randomized trial.

Methods

Study design and data source

This is a retrospective cohort study, approved by the Institutional Review Board of the Veterans Affairs (VA) Connecticut Health Care System. Data was obtained from the US Departments of VA HCV Clinical Case Registry (CCR); a database of HCV infected Veterans receiving care in any VA facility nationwide. Subjects were included in the CCR if they had positive HCV antibody or an International Classification of Diseases, Ninth Revision (ICD-9) code for hepatitis C; 80% of patients had a positive HCV-RNA, a confirmatory test was not available in the remaining 20%. Data elements in the CCR include demographics, inpatient and outpatient visits (including ICD -9 diagnosis and procedure codes, and Current Procedural Terminology [CPT] codes), laboratory results and pharmacy data. Mortality was determined from the VA vital status file which is compiled from combined sources including inpatient mortality, social security data, and national death benefits data, a method shown to provide excellent mortality ascertainment.[11]Details on the creation and contents of CCR data have been published elsewhere[12]. The dataset used in the current study consisted of HCV patients in CCR in care between January 1, 1996 and December 31, 2009.

Study patients

Included patients had cirrhosis, defined by the presence of one inpatient or 2 outpatient codes (ICD 9 codes 571.2, 571.5, 571.6, as previously validated)[13] and who attended, primary care/internal medicine, cardiology, endocrinology, gastroenterology, geriatrics, hepatology, infectious diseases, or women's health clinics. These clinics were chosen because they were the source of 85% of statin use and we wanted to ensure that users and non-users came from the same source population and had an equal opportunity to receive a statin prescription. Patients with HIV (ICD-9 code 042, 044, V08) or hepatitis B infection (positive surface antigen or positive HBV DNA) were excluded.

An index date was defined as date of first statin fill for statin users and a randomly chosen clinic visit date for statin non-users (Supplementary figure 1) between 2000 and 2009 (scarce statin use prior to 2000). Baseline period was defined as 365 days before the index date. Baseline labs used for the study were from this period and were the closest available to the index date. Statin users had to be newly initiating and were required to have at least 2 fills of any statin (simvastatin, lovastatin, rosuvastatin, atorvastatin, pravastatin and fluvastatin). To ensure that patients received medications from the VA (and minimize the possibility of statin prescription outside the VA) all patients had to have filled at least one VA prescription for any drug in the year before the index date (Figure 1, Supplementary Figure 1). To ensure that statin users were new initiators, the index date had to be at least 180 days after the first VA non-statin prescription of any kind. Patients were excluded if they had decompensation (as defined below) or hepatocellular carcinoma (ICD-9 code 155.0) before or within 180 days after the index date, no labs, or no follow-up. They were also excluded if they died within 180 days after the index date (Figure 1, Supplementary Figure 1). Statin users were excluded if they had only one statin prescription fill, or >365 days between first and second fill.

Study outcomes

The primary outcomes were cirrhosis decompensation and death. Decompensation was defined by the presence of one inpatient or two outpatient ICD -9 codes for (A)esophageal varices with bleeding (ICD9 code 456.0) (B) esophageal varices in diseases classified elsewhere, with bleeding (ICD9 code 456.20), (C) ascites (ICD 9 code 789.5) or (D) spontaneous bacterial peritonitis (ICD 9 code 567.23). This definition was modified from the original[14] by excluding the code for esophageal varices without bleeding (ICD-9 code 456.1, 456.21) and portal hypertension (572.3) as these are not decompensating events[1].

Outcomes analysis was restricted to patients with index dates prior to December 31, 2008 to allow all the opportunity for at least one year of follow-up. Follow-up began 180 days after the index date (Supplementary Figure 1) to avoid immortal time bias[15]. That is, as statin users were guaranteed to be alive long enough to have a second fill, a similar allowance had to be made for non-users. Most statin users had the second fill by 180 days. Follow-up for decompensation ended at the earliest of date of diagnosed decompensation liver transplant, death, or last visit recorded at the VA as of Dec 31, 2009. Follow-up for death was similar but patients were not censored at decompensation or transplant.

Data collection

Data collected included age, sex, race, body mass index (BMI), geographic site and its statin prescribing pattern, comorbid conditions and laboratory data as well as any prescription of antiviral therapy with pegylated interferon plus ribavirin during the study period. Co-morbid conditions were defined as those recorded any time prior to index date (Supplementary Figure 1). Hypertension, peripheral artery disease, chronic kidney disease, coronary artery disease, cerebrovascular disease smoking, diabetes, alcohol dependence and drug abuse were determined based on occurrence of at least one inpatient or two outpatient ICD -9 codes for the respective diagnoses. Baseline laboratory data on total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, albumin, total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), international normalized ratio (INR), platelet count and hemoglobin was collected prior to and closest to the index date and within 365 days of the same. The number of lipid and non-lipid laboratory tests performed in the year prior to the index date was also obtained. The FIB-4 index was calculated at baseline as [age in years × AST in U/L]/ [(platelet count × 10^9/L) × (ALT in U/L)[16]. Prior studies have shown that it is useful in ruling in cirrhosis in patients with chronic liver disease17 and, in compensated cirrhosis, it can identify patients with clinically significant portal hypertension with reasonable accuracy (unpublished observations). Liver transplantation was identified using ICD-9 procedure codes and diagnosis codes. Adherence to therapy was assessed by an extensively studied method, the proportion of days covered (PCD), which is calculated as the cumulative number of days during which the medication was available divided by the number of days of follow-up.[18, 19]

Statistical analysis

Development of propensity score—In order to minimize confounding by indication, the study employed a propensity score matched cohort design.[20] Propensity scores were developed using covariates associated with statin use, both well-established predictors and

also those specific to the patient population. The final multivariable logistic regression model included 33 variables and 3 interaction terms. We included age, body mass index, year of index visit, frequently occurring diagnoses in statin users (e.g. coronary artery disease, cerebrovascular disease, smoking, diabetes), laboratory values predictive of statin use (e.g. LDL, total cholesterol), healthcare utilization variables (e.g. number of laboratory tests, specialty clinic visited) and negative correlates of statin use (laboratory values indicating severity of liver disease e.g. albumin, total bilirubin, INR, platelet count and FIB-4 index. Additionally, prescribing patterns were developed by determining the proportion of patients in the visit pool who initiated statin use at each site by years (1997–2001, 2002–2003, 2004–2009). Sites below the 25th percentile were deemed as low statin-prescribing sites; those above the 75th percentile were deemed high statin-prescribing sites; all others were classified as medium. This attribute was assigned to each record and used in the propensity score model. Adding prescribing patterns by geographic site and year, and interactions with diabetes and HDL by year improved model fit and discrimination. The c-statistic for the propensity score model was 0.92, which indicates an excellent discrimination between statin users and non-users[21].

Matching—Statin users were matched by propensity scores to non-users with a greedy matching algorithm[22]. First, all possible 5 decimal place matches were made, then 4 decimal places and so on down to 1 decimal place. Next, the 5 best matches for each user were randomly selected with each non-user only selected once. The weighted average of each set of non-users was used to represent one non-user. Statin users who could not be matched were excluded from the matched cohort analysis. Subjects were assigned their original exposure status until the end of follow-up regardless of actual statin use during follow-up to emulate an intention to treat analysis of a randomized trial.

Outcome analysis—We performed parallel analyses in 1) an unmatched sample of all eligible statin users compared to a sample of all eligible unique non-users in whom the index date was randomly selected and 2) the propensity score matched sample of users and non-users. Kaplan-Meier curves were generated to compare primary outcomes in statin users and non-users. The association between statin use and risk of mortality and decompensation was estimated using Cox proportional hazards model with adjustment for age, FIB-4 index (as a surrogate of clinically significant portal hypertension), serum albumin, Model of End Stage Liver Disease (MELD) score and Child-Turcotte-Pugh (CTP) score; parameters that have been shown to predict decompensation and/or death in compensated cirrhosis[1, 2].

Six different sensitivity analyses were performed in the matched cohort: 1) in patients who did not receive HCV anti-viral therapy; 2) in patients who were HCV RNA positive; 3) excluding patients with FIB 4 <1.45 (patients who are less likely to have cirrhosis and may have been miscoded); (4) in statin users with > 50% adherence; 5) excluding statin users with >180 days before the second fill and 6) using an alternative definition of decompensated cirrhosis. Analyses were conducted using SAS version 9.4 (SAS Institute, Inc. Cary, North Carolina).

Results

Of 342,157 HCV infected patients in the CCR, 45,350 (14%) patients had cirrhosis and no HIV infection. Among 40,512 patients with a visit to one of the included clinics, we identified 2,802 statin users. After applying exclusion criteria 1,323 statin users and 12,522 non-users were eligible for unmatched analysis (Figure 1). Most patients used simvastatin (85%), followed by lovastatin (10%), pravastatin (3%), rosuvastatin (1%) and fluvastatin (1%).

We were able to match 685 statin users with 2,062 statin non-users. As shown in Figure 2, statin users had a wider range of propensity scores than non-users and therefore we were only able to match users with propensity scores in the lower range. Only 16 % of non-users had a score >0.04, compared with 87% of users. Statin users with high propensity scores (i.e. those very likely to be prescribed statins) could not be matched and were excluded from matched analysis. Among the 2062 non-users, the propensity score of the user matched to 5 decimal places for 16%, 37% were within 0.0001, 36% to 0.001, 10% to 0.02 and 1% matched to one decimal place. Of 685 statin users, 134 were matched to 5 non-users, 238 to 4 non-users, 3 to 212 non-users 87 to 2 non-users and 14 to one non-user.

Baseline characteristics of unmatched and propensity score-matched users and non-users are shown in Table 1. The weighted average of each set of non-users was used to represent one non-user. In the unmatched cohort there were many clinically and statistically significant differences between users and non-users, specifically, statin users were older, had a higher prevalence of smoking, coronary artery disease, hypertension, diabetes, chronic kidney disease, peripheral artery disease and cerebrovascular disease; as well as higher cholesterol, LDL, albumin and platelet count. As expected, in the propensity matched cohort there were no differences in these parameters between statin users and nonusers, demonstrating the validity of our model. Antiviral therapy was prescribed in 23% of the patients (20.7% of non-statin users; 25.4% of statin users; p=0.04). Median adherence, as determined by the proportion of days covered (PDC) was 0.79 (IQR 0.45, 1.00) for cirrhosis decompensation and 0.77 (IQR 0.41, 1.00) for death

Cirrhosis decompensation

In the unmatched cohort, in a median follow-up of 2.5 years for statin users and 1.5 years for statin nonusers, statin use was associated with lower risk of decompensation [HR 0.22 (95% CI 0.17, 0.28)] that remained after adjusting for age, BMI, serum albumin, FIB4, MELD and CTP scores (Table 2).

In the matched cohort, median follow-up for decompensation was 2.3 years for statin users and 1.7 years for statin non-users. There were 220 decompensation events (39 statin users and 181 non-users). Statin use was associated with lower risk of decompensation [HR 0.55 (95% CI 0.39, 0.77)] compared to non-use. These findings persisted after adjustment for antiviral therapy [HR 0.56 (95% CI 0.39, 0.79)].

We further analyzed the effect of statin use on the type of decompensation. As shown in Table 3, statin use was associated with a lower risk of variceal hemorrhage [HR 0.39 (95%

CI 0.19, 0.78)] and ascites [HR 0.59 (95% CI 0.39, 0.91)]. Development of spontaneous bacterial peritonitis was not different between study groups [HR 0.93 (95% CI 0.29, 2.90)].

Death

In the unmatched cohort, statin use was associated with a lower risk of death [HR 0.39 (95% CI 0.34, 0.44)] that remained significant after adjusting for age, BMI, serum albumin, FIB 4, MELD and CTP scores (median follow-up 2.6 years for statin users, 1.9 years for statin non-users) (Table 2).

In the matched cohort, median follow-up for death was 2.4 years for users and 1.9 years for non-users. There were 667 deaths (121 users and 546 non-users). Statin use was associated with lower risk of death [HR 0.56 (95% CI 0.46, 0.69)] compared to non-use. These findings persisted after adjustment for antiviral therapy [HR 0.57 (95% CI 0.47, 0.70)].

Statin use was also associated with a significantly lower risk of development of HCC [HR 0.42 (95% CI 0.27, 0.64)] and lower rate of liver transplantation [HR 0.37 (95% CI 0.15, 0.96)] (Table 4).

Probability of decompensation and death—Kaplan-Meier plots for both unmatched and matched cohorts showed an advantage for statin users for both outcomes (decompensation and death) beginning about one year after the start of follow-up that persisted over the full 8 years of available follow-up time (Figure 3). Differences were attenuated in the matched cohort but remained significant, $p < 0.001$ (log-rank test and Wilcoxon test).

Sensitivity analyses

All six sensitivity analyses yielded similar results to that of the main analysis in the matched cohort. Compared to non-users, statin users had a lower risk of decompensation and death after 1) excluding patients who received HCV antiviral therapy [HR 0.59 (95% CI 0.41, 0.85)]and [HR 0.56 (95% CI 0.45, 0.69)]; 2) excluding patients who did not have HCV RNA confirmation [HR 0.63 (95% CI 0.43, 0.93)] and [HR 0.58 (95% CI 0.46, 0.73)]; 3) excluding patients with FIB 4 < 1.45 [HR 0.61 (95% CI 0.42, 0.88)] and [HR 0.55 (95% CI 0.44, 0.70)]; 4) excluding 208 statin users with <50% adherence [HR 0.50 (95% CI 0.32, 0.77)] and [HR 0.57 (95% CI 0.45, 0.72)]; 5) excluding 55 statin users whose second fill was 181 to 365 days after the end of the first fill [HR 0.52 (95% CI 0.36, 0.75)] and [HR 0.57 (95% CI 0.46, 0.70)]; and 6) using an alternate (previously published) definition[14] for decompensation [HR 0.65 (95% CI 0.47, 0.89)].

Discussion

In this propensity score matched study we demonstrate 40% lower risk of decompensation and death with statin use, in a large cohort of U.S. veterans with compensated HCV cirrhosis. As expected, given appropriate[3] matching, multivariable analysis adjusting for predictors of death and decompensation did not alter the results. Unmatched analyses showed overly wide differences, illustrating the importance of properly accounting for confounding by indication.

Analysis of specific decompensating events in our study showed that statins were associated with a significant decrease in the development of ascites and variceal hemorrhage, the two main decompensating events in cirrhosis. Major determinants of decompensation in patients with compensated cirrhosis are the severity of portal hypertension (as determined by hepatic venous pressure gradient ≥10 mmHg) and slight impairment in liver synthetic function (serum albumin <4 g/dL and MELD score >10)[2].

Simvastatin has been shown to reduce portal pressure both in experimental animals[8, 23] and in patients with cirrhosis[9]. It does this by ameliorating endothelium-dependent vasorelaxation of the liver vasculature by increasing bioavailability of the vasodilator, nitric oxide[7]. Intrahepatic vasodilatation also improves flow to the liver and may improve liver function as demonstrated by improved clearance of indocyanine green in patients with cirrhosis[9]. Commonly used portal pressure- reducing agents such as non-selective beta-blockers lack this effect because they that act by decreasing portal venous inflow, without an effect on hepatic flow. In a recent placebo-controlled study performed in patients with cirrhosis who had recently bled from varices, simvastatin improved survival without an effect on recurrent variceal hemorrhage[24], indicating that its beneficial effect may be mostly related to liver flow amelioration and consequent improvement in liver function. Furthermore, it has also been shown that statins may decrease liver fibrosis in experimental cirrhosis and decrease progression of fibrosis in patients with viral hepatitis[25].

Statins also have important anti-inflammatory properties in hepatocytes as well as vascular cells (endothelial, smooth muscle, immune cells)[26]. Statins reduce IL-6 mediated C-reactive protein[27], an acute phase reactant, produced mostly in the hepatocytes and marker of poor prognosis in cirrhosis[28]. Pre-clinical data suggest that simvastatin may attenuate liver inflammation and liver injury associated with infections or bleeding[29] and data in humans show that statins are protective in ischemic hepatitis[30]. Statin use has also been shown to suppress hepatitis C activity in-vitro and in-vivo[31, 32], with recent data suggesting that the concomitant use of statins while undergoing antiviral treatment increases the likelihood of sustained virologic response[33].

Therefore, our results could be explained by various effects of statins not only in ameliorating mechanisms of portal hypertension but also potentially an anti-inflammatory and antiviral effect, although the latter effect may not be as important since a simvastatin survival benefit has been described in decompensated cirrhosis of mostly an alcoholic etiology[24]. Furthermore, our results could not be explained on the basis of antiviral therapy since only a minority of patients received pegylated interferon and ribavirin and sensitivity analysis excluding patients receiving antiviral therapy demonstrated the same results as in the overall group.

Ours is the first study evaluating the effect of statins in a homogeneous nationwide cohort of patients with compensated HCV cirrhosis. A previous small single-center study that combined patients with compensated and decompensated cirrhosis and that concluded that statins were not harmful, had shown that statin use was a negative predictor of death[10].

In order to emulate a randomized placebo-controlled trial, propensity score matching was performed and resulted in excellent balance between statin users and non-users. This matching corrected for confounding that may have occurred because of less statin use in patients with more severe liver disease or more statin use in patients with a greater cardiovascular risk and potentially higher mortality[20]. As noted, only statin users with low propensity scores could be matched, thereby excluding those with a higher probability of receiving statins. These patients would have likely been ineligible to participate in a randomized trial as they would have had a strong indication for statin use and it would have been unethical to withhold a statin. Although the cause of death cannot be obtained from this database and the decrease in mortality could be due to a reduction in cardiovascular-related deaths, the fact that patients with high propensity for statin use (i.e. patients with a high risk of dying a cardiovascular-related death) were excluded reduces this possibility. Additionally, decompensation and HCC are important predictors of death in patients with cirrhosis[1, 34]and as both decompensation and HCC were reduced in this cohort, it seems more likely that the observed decrease in mortality was in fact due to a reduction in decompensation and HCC. Our study confirms evidence in the literature showing a decrease in HCC with statins[35], although the mechanisms may be different from those by which statins would decrease decompensation.

We note other limitations as ICD 9 codes were used for diagnoses, misclassification bias is a possibility and patients without cirrhosis could have been included in the study. However, cirrhosis is more likely to be underdiagnosed and even if patients without cirrhosis had been included, one would expect them to be equally distributed between study groups. All patients in this cohort had chronic HCV infection but concomitant etiologies for cirrhosis cannot be excluded as more than 50% had an ICD 9 diagnosis of alcohol dependence and median BMI was in the overweight range. Another limitation is that the study cohort is predominantly male. This may affect the generalizability of the results but does not limit its internal validity

Although statins can be hepatotoxic, this is usually mild and self-limited and their safety has been previously demonstrated in patients with chronic liver disease.[36, 37] The beneficial effect of statins in our study, as it relates to decompensation and death, further supports a lack for significant deleterious hepatotoxic effect. Statin prescription in patients with chronic liver disease remains low[38] as indicated by the relatively low number of statin users in our cohort, even in those with a high cholesterol (less than half the patients with cholesterol >200 mg/dL received a statin).

This retrospective propensity-matched cohort study performed in veterans with HCV compensated cirrhosis demonstrates the association of statin use with decreased risk of cirrhosis decompensation and death. Results should lead to multicenter prospective placebo-controlled randomized trials in the general non-veteran population that should stratify patients by etiology of cirrhosis. While we cannot yet recommend statin use in all patients with compensated cirrhosis, it is important that practitioners recognize that statins should not be avoided in these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/support: Yale Liver Center NIH P30 DK34989

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CCR	clinical case registry
CPT	current procedural terminology
CTP	Child-Turcotte-Pugh
HBV	hepatitis B Virus
HCV	hepatitis C virus
HDL	high density lipoprotein
HR	hazards ratio
HIV	human immunodeficiency virus
ICD	International Classification of Diseases
INR	international normalized ratio
LDL	low density lipoprotein
MELD	model for end stage liver disease
VA	Veterans Affairs

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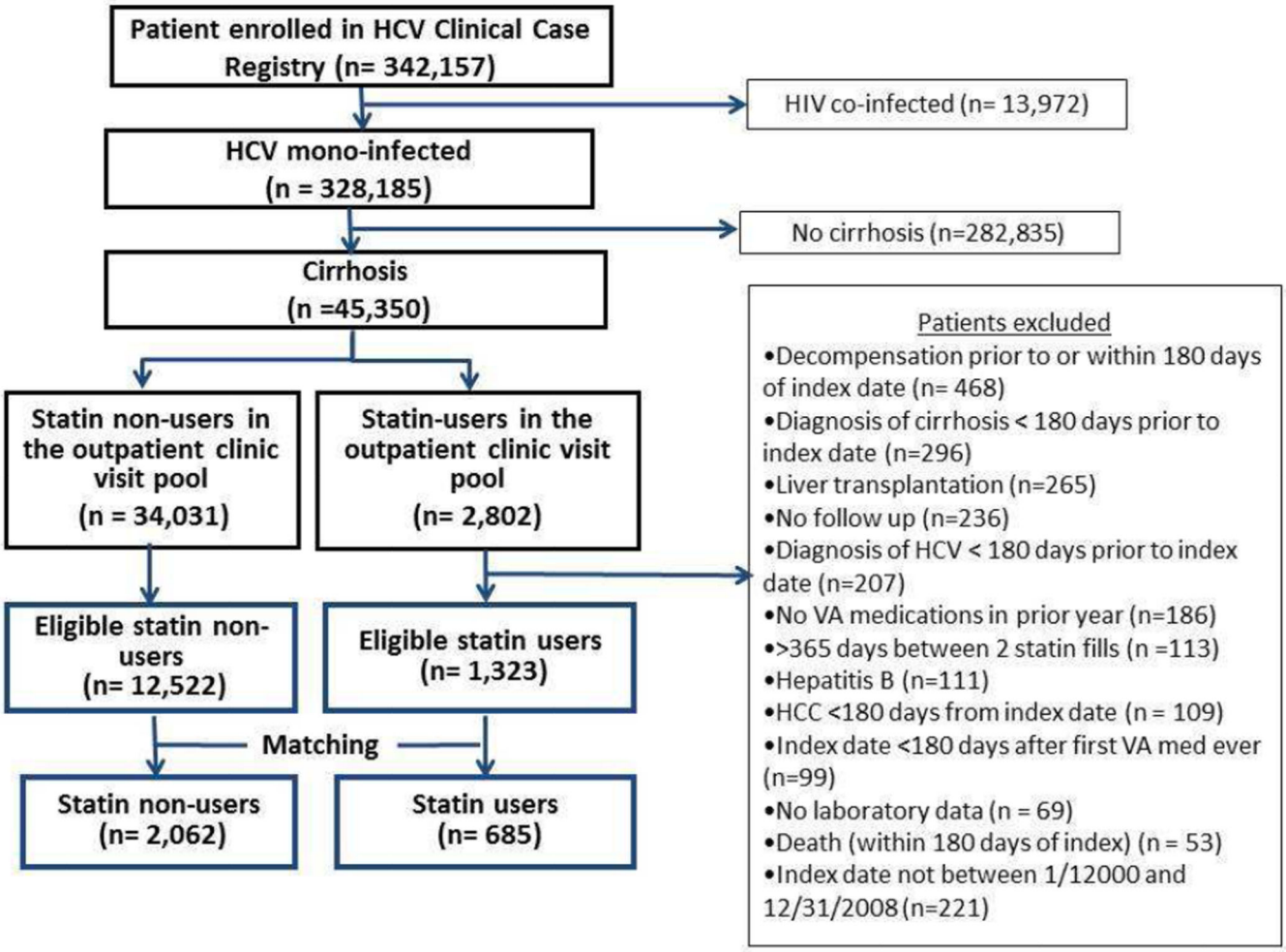

Figure 1.
Study Flow diagram

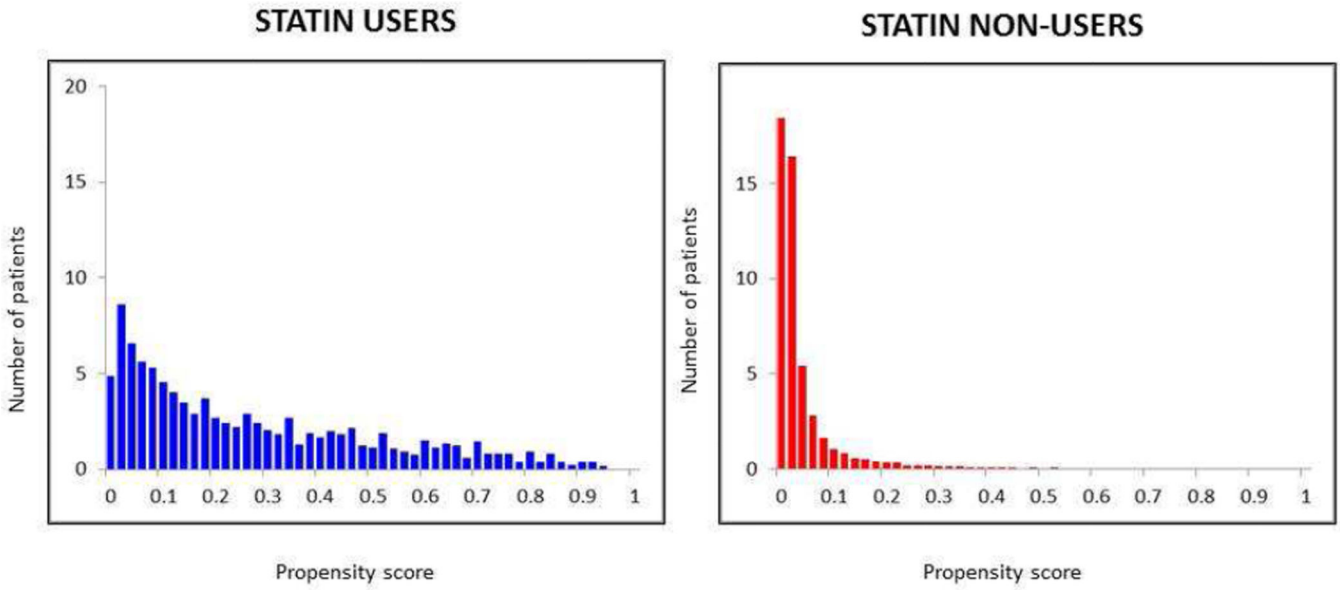

Figure 2.

Propensity score histograms for statin users and statin non-users

Statin users had a wider range of propensity scores than non-users. Stain users with propensity scores in the lower range were matched to statin non-users with similar propensity scores

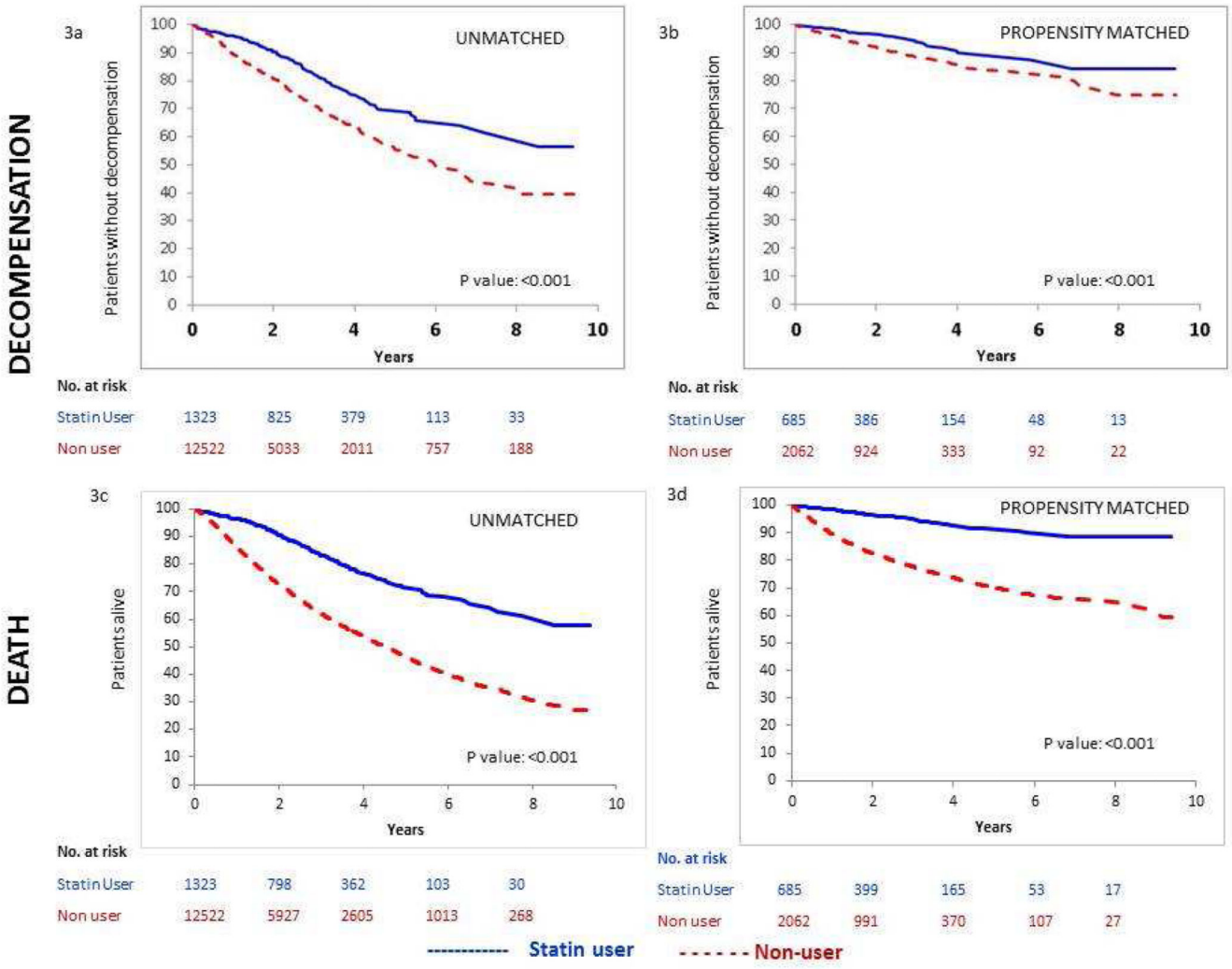

Figure 3.

a, b: Kaplan Meier estimates of percentages of patients reaching decompensation for unmatched and propensity matched cohorts

c, d: Kaplan Meier estimates of percentages of patients dying for unmatched and propensity matched cohorts

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Table 1

Baseline characteristics of unmatched and matched cohort

		Unmatched					Propensity Score Matched				
		Non-user (N = 12522)		Statin user (N = 1323)		p value	Non-user (N = 685)		Statin user (N = 685)		p value
Age	<45	499	(4.0)	23	(1.7)	<.0001	14	(2.0)	12	(1.8)	0.94
	45–49	2048	(16.4)	114	(8.6)		58	(8.4)	65	(9.5)	
	50–55	4010	(32.0)	385	(29.1)		190	(27.7)	197	(28.8)	
	55–59	3488	(27.9)	469	(35.4)		248	(36.2)	241	(35.2)	
	60–64	1277	(10.2)	174	(13.2)		88	(12.8)	91	(13.3)	
	≥65	1200	(9.6)	158	(11.9)		88	(12.8)	79	(11.5)	
	Median (IQR)	54	(50, 58)	56	(52, 60)		56	(52, 60)	56	(52, 59)	
Sex	Male	12236	(97.7)	1300	(98.3)	0.20	671	(97.9)	677	(98.8)	0.18
Race	White	6136	(49.0)	707	(53.4)	<.0001	341	(49.8)	359	(52.4)	0.67
	Black	1850	(14.8)	266	(20.1)		145	(21.2)	146	(21.3)	
	Hispanic	1064	(8.5)	78	(5.9)		45	(6.6)	38	(5.5)	
	Other	3472	(27.7)	272	(20.6)		154	(22.4)	142	(20.7)	
Year	2000	1091	(8.7)	48	(3.6)	<.0001	28	(4.1)	28	(4.1)	1.0
	2001	1016	(8.1)	49	(3.7)		19	(2.8)	19	(2.8)	
	2002	1133	(9.0)	76	(5.7)		41	(6.0)	41	(6.0)	
	2003	1075	(8.6)	82	(6.2)		41	(6.0)	41	(6.0)	
	2004	1216	(9.7)	193	(14.6)		80	(11.7)	80	(11.7)	
	2005	1367	(10.9)	183	(13.8)		84	(12.3)	84	(12.3)	
	2006	1466	(11.7)	207	(15.6)		112	(16.4)	112	(16.4)	
	2007	1713	(13.7)	229	(17.3)		122	(17.8)	122	(17.8)	
	2008	2445	(19.5)	256	(19.3)		158	(23.1)	158	(23.1)	
Site prescribing pattern **	Low	2106	(16.8)	114	(8.6)	<.0001	74	(10.8)	68	(9.9)	0.80
	Medium	7812	(62.4)	747	(56.5)		400	(58.3)	396	(57.8)	
	High	2604	(20.8)	462	(34.9)		212	(30.9)	221	(32.3)	
Clinic	Gastroenterology, Hepatology, Infectious Disease	3123	(24.9)	80	(6.0)	<.0001	59	(8.6)	55	(8.0)	0.96
	Primary Care	8886	(71.0)	1058	(80.0)		557	(81.4)	558	(81.5)	

		Unmatched				Propensity Score Matched				
		Non-user (N = 12522)		Statin user (N = 1323)		p value	Non-user (N = 685)		Statin user (N = 685)		p value
	Endocrinology, Nephrology	274	(2.2)	61	(4.6)		31	(4.5)	31	(4.5)	
	Cardiology	239	(1.9)	124	(9.4)		38	(5.5)	41	(6.0)	
Conditions	Smoking	7453	(59.5)	868	(65.6)	<.0001	453	(66.2)	451	(65.8)	0.89
	Alcohol abuse/dependence	7085	(56.6)	694	(52.5)	0.004	365	(53.3)	372	(54.3)	0.72
	Drug abuse/dependence	5401	(43.1)	576	(43.5)	0.78	290	(42.3)	322	(47.0)	0.08
	Coronary artery disease	1496	(11.9)	493	(37.3)	<.0001	210	(30.7)	241	(35.2)	0.08
	Hypertension	7443	(59.4)	1111	(84.0)	<.0001	553	(80.7)	568	(82.9)	0.29
	Diabetes	3613	(28.9)	725	(54.8)	<.0001	357	(52.1)	363	(53.0)	0.73
	Chronic kidney disease	335	(2.7)	78	(5.9)	<.0001	38	(5.5)	40	(5.8)	0.79
	Peripheral artery disease	466	(3.7)	113	(8.5)	<.0001	56	(8.2)	41	(6.0)	0.11
	Cerebrovascular disease	386	(3.1)	75	(5.7)	<.0001	39	(5.7)	40	(5.8)	0.92
Number of lipid tests	0	3774	(30.1)	49	(3.7)	<.0001	43	(6.2)	46	(6.7)	0.82
	1	4959	(39.6)	461	(34.8)		259	(37.9)	267	(39.0)	
	2 or more	3789	(30.3)	813	(61.5)		383	(55.9)	372	(54.3)	
Total Cholesterol	<200	7944	(63.4)	685	(51.8)	<.0001	438	(63.9)	444	(64.8)	0.80
	≥200	777	(6.2)	587	(44.4)		203	(29.6)	193	(28.2)	
	None found	3801	(30.4)	51	(3.9)		44	(6.4)	48	(7.0)	
LDL (mg/dL)	<100	5391	(43.1)	259	(19.6)	<.0001	204	(29.7)	211	(30.8)	0.94
	100 –129	1477	(11.8)	389	(29.4)		219	(32.0)	216	(31.5)	
	130–159	403	(3.2)	351	(26.5)		125	(18.2)	115	(16.8)	
	≥160	104	(0.8)	191	(14.4)		44	(6.4)	43	(6.3)	
	None found	5147	(41.1)	133	(10.1)		93	(13.6)	100	(14.6)	
HDL (mg/dL)	<40	3666	(29.3)	671	(50.7)	<.0001	325	(47.4)	319	(46.6)	0.65
	40–59	2874	(23.0)	451	(34.1)		225	(32.9)	212	(30.9)	
	≥60	5043	(40.3)	108	(8.2)		82	(12.0)	93	(13.6)	
	None found	939	(7.5)	93	(7.0)		53	(7.7)	61	(8.9)	
Triglyceride (mg/dL)	<150	5808	(46.4)	722	(54.6)	<.0001	391	(57.1)	381	(55.6)	0.84
	≥150	1873	(15.0)	512	(38.7)		221	(32.3)	227	(33.1)	
	None found	4841	(38.7)	89	(6.7)		73	(10.6)	77	(11.2)	

		Unmatched					Propensity Score Matched				
		Non-user (N = 12522)		Statin user (N = 1323)		p value	Non-user (N = 685)		Statin user (N = 685)		p value
Number of non-lipid labs	<10	4344	(34.7)	141	(10.7)	<.0001	87	(12.7)	90	(13.1)	0.75
	10–12	3467	(27.7)	511	(38.6)		243	(35.5)	254	(37.1)	
	≥13	4711	(37.6)	671	(50.7)		355	(51.8)	341	(49.8)	
Albumin (g/dL)	≥4.0	3066	(24.5)	560	(42.3)	<.0001	263	(38.4)	269	(39.3)	0.99
	3.6–3.9	2959	(23.6)	322	(24.3)		165	(24.0)	162	(23.6)	
	2.8–3.5	4289	(34.3)	259	(19.6)		166	(24.2)	168	(24.5)	
	<2.8	1502	(12.0)	70	(5.3)		35	(5.1)	34	(5.0)	
	None found	706	(5.6)	112	(8.5)		57	(8.3)	52.0	(7.6)	
	Median (IQR)	3.6	(3.1, 4.0)	3.9	(3.5, 4.2)		3.8	(3.4, 4.2)	3.9	(3.4, 4.2)	
Total bilirubin (mg/dL)	<2	10012	(80.0)	1221	(92.3)	<.0001	622	(90.8)	625	(91.2)	0.91
	2–3	1278	(10.2)	28	(2.1)		20	(3.0)	22	(3.2)	
	>3	598	(4.8)	6	(0.5)		7	(1.1)	5	(0.7)	
	None found	634	(5.1)	68	(5.1)		35	(5.1)	33	(4.8)	
	Median (IQR)	1	(0.7, 1.6)	0.7	(0.5, 1.0)		0.8	(0.6, 1.1)	0.7	(0.5, 1.1)	
INR	<1.7	8261	(66.0)	754	(57.0)	<.0001	421	(61.5)	405	(59.1)	0.77
	1.7–2.3	361	(2.9)	11	(0.8)		6	(0.9)	6	(0.9)	
	>2.3	122	(1.0)	31	(2.3)		9	(1.3)	12	(1.8)	
	None found	3778	(30.2)	527	(39.8)		249	(36.4)	262	(38.2)	
	Median (IQR)	1.2	(1.1, 1.3)	1.1	(1.0, 1.2)		1.1	(1.0, 1.2)	1	(1.0, 1.2)	
Platelets ($\times 10^9$ /L)	≥150	3866	(30.9)	801	(60.5)	<.0001	362	(52.8)	372	(54.3)	0.95
	100–149	3085	(24.6)	273	(20.6)		167	(24.4)	160	(23.4)	
	<100	5081	(40.6)	167	(12.6)		118	(17.2)	116	(16.9)	
	None found	490	(3.9)	82	(6.2)		39	(5.6)	37	(5.4)	
	Median (IQR)	112	(76, 171)	180	(129, 233)		155	(107, 211)	167	(116, 223)	
FIB4	<1.45	1209	(9.7)	375	(28.3)	<.0001	128	(18.7)	159	(23.2)	0.12
	1.45–3.25	2792	(22.3)	513	(38.8)		262	(38.2)	242	(35.3)	
	>3.25	7388	(59.0)	273	(20.6)		205	(29.9)	211	(30.8)	
	None found	1133	(9.0)	162	(12.2)		90	(13.1)	73	(10.7)	
Hemoglobin (g/dL)	≥14	6298	(50.3)	801	(60.5)	<.0001	387	(56.4)	414	(60.4)	0.25

		Unmatched					Propensity Score Matched				
		Non-user (N = 12522)		Statin user (N = 1323)		p value	Non-user (N = 685)		Statin user (N = 685)		p value
	12–13.9	3747	(29.9)	300	(22.7)		175	(25.5)	167	(24.4)	
	10–11.9	1438	(11.5)	104	(7.9)		62	(9.0)	54	(7.9)	
	<10	340	(2.7)	29	(2.2)		21	(3.0)	10	(1.5)	
	None found	699	(5.6)	89	(6.7)		41	(6.0)	40	(5.8)	
	Median (IQR)	14.1	(12.8, 15.3)	14.6	(13.3, 15.7)		14.4	(13.0, 15.6)	14.6	(13.3, 15.6)	
MELD	<10	5640	(45.0)	586	(44.3)	<0.000 1	318	(46.5)	313	(45.7)	0.70
	≥10	2688	(21.5)	191	(14.4)		106	(15.4)	98	(14.3)	
	None found	4194	(33.5)	546	(41.3)		261	(38.1)	274	(40.0)	
	Median (IQR)	8.3	(6.3, 10.9)	7.3	(5.6, 9.9)		8	(6, 10)	7	(6, 10)	
BMI (kg/m^2)	<18.5	165	(1.3)	9	(0.7)	<.0001	8	(1.2)	8	(1.2)	0.51
	18.5 –24.9	3095	(24.7)	249	(18.8)		156	(22.7)	129	(18.8)	
	25–29.9	4513	(36.0)	461	(34.8)		227	(33.1)	237	(34.6)	
	≥30	4377	(35.0)	583	(44.1)		285	(41.6)	299	(43.6)	
	None found	372	(3.0)	21	(1.6)		10	(1.5)	12	(1.8)	
	Median (IQR)	27.9	(24.7, 31.7)	29.3	(25.8, 32.9)		28.6	(25.1, 32.5)	29.3	(25.7, 33.2)	

* For the unmatched cohort, statin non-users sample were randomly selected by index date among all unique eligible non-users. For the matched cohort, the weighted average of each group of non-users was used to represent one non-user.

** Prescribing patterns were developed by determining the proportion of patients in the visit pool who initiated statin use at each site by years (1997–2001, 2002–2003, 2004–2009). Sites below the25th percentile were deemed as low statin-prescribing sites; those above the 75th percentile were deemed high statin-prescribing sites; all others were classified as medium.

Table 2

Hazard ratios of association of statin with decompensation and death in unadjusted and adjusted cohort.

		Unmatched			Propensity Score Matched		
		Events	**HR**	**(CI)**	**Events**	**HR**	**(CI)**
Decompensation	Unadjusted	2275	0.22	(0.17, 0.28)	220	0.55	(0.39, 0.77)
Adjusted for	Age		0.23	(0.18, 0.30)		0.54	(0.38, 0.76)
	Age+ BMI		0.23	(0.18, 0.29)		0.53	(0.37, 0.75)
	Age + BMI + albumin,		0.29	(0.23, 0.37)		0.53	(0.37, 0.75)
	Age + BMI+ albumin + FIB4		0.40	(0.31, 0.51)		0.55	(0.39, 0.78)
	Age + BMI + albumin + FIB4 + MELD		0.37	(0.29, 0.48)		0.55	(0.39, 0.78)
	Age + BMI + Child + FIB4		0.38	(0.30, 0.49)		0.55	(0.39, 0.77)
Death	Unadjusted	5015	0.39	(0.34, 0.44)	667	0.56	(0.46, 0.69)
Adjusted for	Age		0.36	(0.32, 0.41)		0.55	(0.45, 0.66)
	Age + BMI		0.36	(0.32, 0.42)		0.55	(0.45, 0.67)
	Age + BMI + albumin,		0.45	(0.40, 0.52)		0.56	(0.46, 0.69)
	Age + BMI+ albumin + FIB4		0.51	(0.45, 0.59)		0.57	(0.47, 0.69)
	Age + BMI + albumin + FIB4 + MELD		0.48	(0.42, 0.55)		0.55	(0.45, 0.68)
	Age + BMI + Child + FIB4		0.49	(0.43, 0.56)		0.55	(0.45, 0.67)

Table 3

Rates of decompensation and specific decompensating events in statin non-users and statin users

	N	PY	Decompensation		Ascites		VH		SBP	
			Events	Rate	Events	Rate	Events	Rate	Events	Rate
Non-user	2062	4615	181	3.9	112	2.4	58	1.3	11	0.24
User	685	1842	39	2.1	26	1.4	9	0.5	4	0.22
Total events			220		138		67		15	
Hazard ratio (UCL, LCL)			0.55 (0.39, 0.77) p=0.0007		0.59 (0.39, 0.91) p=0.02		0.39 (0.19, 0.78) p=0.01		0.92 (0.9, 2.9) p=0.89	

PY= person year; VH=variceal hemorrhage; SBP= spontaneous bacterial peritonitis; UCL= 95% upper confidence limit; LCL= 95% lower confidence limit; rates are per 100 PY

Table 4

Risk of HCC, liver transplantation and death in statin non-users and in statin users.

	HCC			Liver transplantation			Death		
	PY	**Events**	**Rate**	**PY**	**Events**	**Rate**	**PY**	**Events**	**Rate**
Non-user	4673	148	3.2	4771	34	0.7	4897	546	11.1
User	1881	25	1.3	1895	5	0.3	1913	121	6.3
Total		173			39			667	
Hazard ratio (UCL, LCL)	0.42 (0.27, 0.64) P <0.001			0.37 (0.15, 0.96) P=0.04			0.56 (0.46, 0.69) p <0.001		

HCC= hepatocellular carcinoma; PY= person year; UCL=95% upper confidence limit; CL= 95% lower confidence limit; rates are per 100 PY