Effect of Addition of Statins to Antiviral Therapy in Hepatitis C Virus–Infected Persons: Results From ERCHIVES

Adeel A. Butt,1,2,3 Peng Yan,1 Hector Bonilla,4 Abdul-Badi Abou-Samra,3 Obaid S. Shaikh,1,2 Tracey G. Simon,5 Raymond T. Chung,6,7 and Shari S. Rogal,1,2 for the ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans) Study Team

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have been variably noted to affect hepatitis C virus (HCV) treatment response, fibrosis progression, and hepatocellular carcinoma (HCC) incidence, with some having a more potent effect than others. We sought to determine the impact of adding statins to antiviral therapy upon sustained virological response (SVR) rates, fibrosis progression, and HCC development among HCV-infected persons using the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES), an established, longitudinal, national cohort of HCV-infected veterans. Within ERCHIVES, we identified those who received HCV treatment and a follow-up of >24 months after treatment completion. We excluded those with human immunodeficiency virus coinfection, hepatitis B surface antigen positivity, cirrhosis, and HCC at baseline. Our main outcomes were liver fibrosis progression measured by FIB-4 scores, SVR rates, and incident HCC (iHCC). Among 7,248 eligible subjects, 46% received statin therapy. Statin use was significantly associated with attaining SVR (39.2% vs. 33.3%; P<0.01), decreased cirrhosis development (17.3% vs. 25.2%; P<0.001), and decreased iHCC (1.2% vs. 2.6%; P<0.01). Statins remained significantly associated with increased odds of SVR (odds ratio = 1.44; 95% confidence interval [CI] = 1.29, 1.61), but lower fibrosis progression rate, lower risk of progression to cirrhosis (hazard ratio [HR] = 0.56; 95% CI = 0.50, 0.63), and of incident HCC (HR = 0.51; 95% CI = 0.34, 0.76) after adjusting for other relevant clinical factors. Conclusions: Statin use was associated with improved virological response (VR) rates to antiviral therapy and decreased progression of liver fibrosis and incidence of HCC among a large cohort of HCV-positive Veterans. These data support the use of statins in patients with HCV. (Hepatology 2015;62:365-374)

Therapy for hepatitis C virus (HCV) is evolving rapidly. Recent introduction of oral direct-acting antiviral agents (DAAs) has led to dramatic improvement in sustained virological response (SVR) rates, such that over 90% of HCV-infected persons achieve SVR. With such high rates of VR, the
focus should now shift to achieving reduction in clinical consequences of HCV, including hepatic fibrosis and cirrhosis, hepatocellular carcinoma (HCC), and extrahepatic complications.

In patients with chronic HCV infection, the host cell lipid metabolism is critical for HCV infectivity and viral replication. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have been studied widely for their impact on VR, fibrosis progression, and incidence of HCC. However, their benefit is not entirely clear. Use of statins in HCV-infected persons has been shown to improve VR to interferon (IFN)-based regimens in some, but not all studies. Use of statins has also been associated with a reduced risk of liver fibrosis progression and a reduction in incidence of HCC. There is some disagreement about the antifibrotic effects of statins in other major organs, with some studies showing a protective effect of statins on cardiac and vascular fibrosis, whereas others have shown no benefit or a possible deleterious effect in persons with pulmonary fibrosis. These associations are further complicated by the fact that different statins may have varying effects on viral replication and fibrosis progression, with fluvastatin showing the most potent, and atorvastatin showing the least potent, antiviral activity. Previous studies were limited by small numbers and convenience samples at single centers. We conducted this study in a large, national cohort of HCV-infected persons to understand the impact of statins upon SVR, fibrosis progression, development of liver cirrhosis (LC), and incidence of HCC.

**Patients and Methods**

**Study Population.** Study participants included persons with HCV infection in the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES). ERCHIVES is a well-established national cohort of HCV-infected veterans and uninfected controls assembled from multiple national databases and has been described in multiple previous publications. Briefly, all HCV-infected veterans observed at any of the Department of Veterans Affairs (VA) facilities were identified based on a positive HCV antibody test between 2002 and 2013. Demographic, clinical, and laboratory data were retrieved from the National Patient Care Database and the Corporate Data Warehouse and pharmacy information, including all prescriptions written along with doses, duration, and number of refills, were retrieved from the Pharmacy Benefits Management database. Data were merged based on established algorithms. For the current study, we retained those subjects who received at least 14 days of treatment for HCV. We excluded those with human immunodeficiency virus (HIV) coinfection, positive hepatitis B surface antigen (HBsAg), LC, and HCC at baseline. We further excluded persons with missing baseline HCV RNA or lab data to calculate FIB-4 score, those in whom we could not determine SVR owing to missing post-treatment HCV-RNA levels, and those in whom we could not determine FIB-4 score at least once after 24 months of HCV treatment completion.

**Definitions.** Baseline was defined as the date of HCV treatment initiation. If multiple courses were administered, the most recent course was used for analysis. Treatment completion was defined according to approved U.S. Food and Drug Administration labeling guidelines. For boceprevir (BOC)- and telaprevir (TVR)-based regimens, previous treatment status and presence of cirrhosis were also taken into account. Cirrhosis was defined as a FIB-4 score of >3.5 based on previous work by our group and others and calculated as follows:

\[
\text{FIB-4} = \text{age [years] } \times \frac{\text{AST [IU/L]}}{\text{platelet count [platelets } \times 10^9/L] \times (\text{ALT}^{1/2} [\text{IU/L}] )}
\]

Laboratory data were obtained at yearly intervals and FIB-4 was calculated using these values. An average of two values closest to the chosen time point (± 6 months) was used to calculate FIB-4. Statin use was defined as receipt of a statin prescription for >14 days. SVR was defined as achieving a negative test for circulating HCV RNA 12 or more weeks after...
Subjects were considered to have diabetes if they met any of the following criteria: (1) glucose \( \geq 200 \text{ mg/dL} \) on two separate occasions; (2) International Classification of Diseases, Ninth Revision (ICD-9) codes (two or more outpatient or one or more inpatient) plus treatment with an oral hypoglycemic or insulin for \( \geq 30 \text{ days} \); (3) ICD-9 codes (two outpatient or one inpatient) plus glucose \( \geq 126 \text{ mg/dL} \) on two separate occasions; and (4) glucose \( \geq 200 \text{ mg/dL} \) on one occasion plus treatment with an oral hypoglycemic or insulin for \( \geq 30 \text{ days} \). History of alcohol and drug abuse or dependence and diagnosis of HCC were based on presence of at least one inpatient or two outpatient ICD-9 diagnoses.

Lipid profiles (total cholesterol [TC], low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglyceride [TG]) were obtained as part of routine clinical care, and the proportion of subjects fasting for these measurements is not known. Non-HDL cholesterol (non-HDL-C) was calculated by subtracting HDL from TC values.

**Outcomes.** Our primary outcome measures were (1) progression of liver fibrosis as measured by FIB-4 score; (2) development of cirrhosis defined as FIB-4 score of \( >3.5 \); and (3) incident HCC based on ICD-9 codes, as described above.

**Statistical Analysis.** Study population was divided into two groups: those who received statin therapy and those who did not receive any statin therapy. Baseline characteristics were compared between the two groups using the chi-squared test for categorical and the \( t \) test for continuous variables. Mean FIB-4 score was plotted over time for the two groups to compare fibrosis progression over time. FIB-4 score was also plotted dividing each group into those who achieved SVR and those who did not achieve SVR. Kaplan-Meier’s curves were generated to show and compare time to cirrhosis and HCC by statin use and further dividing them by attainment of SVR. Cox’s proportional hazards model was used to determine predictors of cirrhosis. Given that alcohol use is a strong independent predictor of liver complications, we repeated the above-described analysis after excluding all persons with a diagnosis of alcohol abuse and dependence at baseline. We also generated Kaplan-Meier’s curves for time to development of cirrhosis by HCV genotype for the persons with available results. A \( P \) value of \(<0.05\) was considered significant where comparisons were made. We used SAS (SAS Institute Inc., Cary, NC) and Stata software (version 11; Stata Corp LP, College Station, TX) for statistical analyses.

**Regulatory Approvals.** The study was approved by the institutional review board at VA Pittsburgh Healthcare System. Appropriate permissions were obtained from the data sources that provided data for ERCHIVES.

**Results**

Within ERCHIVES, we identified 33,899 persons who were initiated on HCV treatment. We excluded those with HIV coinfection (\( n = 941 \)), positive HBsAg (\( n = 4,449 \)), HCC at baseline (\( n = 321 \)), missing or undetectable HCV RNA at baseline (\( n = 7,042 \)), missing HCV RNA to determine SVR (\( n = 9,143 \)),
missing baseline or follow labs to calculate FIB-4 score (n = 2,982), and those with cirrhosis at baseline (n = 1,755; Fig. 1). After these exclusions, we had an evaluable dataset of 7,248 persons. Comparison of those on statins and those not on statins is provided in Table 1. Ninety-seven percent of the persons in the statin group had received statin therapy for more than 3 months and all had received it for more than 1 month. Median (interquartile range; IQR) age was 53 (49, 56) years and 52 (48, 56) years, respectively (P < 0.001); 68% and 66% were white (P = 0.01); and 96% and 95% were male (P = 0.003). Baseline HCV-RNA levels were similar. Baseline TC, LDL, TG, and non-HDL-C were higher and HDL was lower among those who received statins. In bivariate analysis, those who received statins were more likely to achieve SVR (39.2% vs. 33.3%; P < 0.001), decreased cirrhosis development (17.3% vs. 25.2%; P < 0.001), and less likely to have incident hepatocellular carcinoma (iHCC; 1.2% vs. 2.6%; P < 0.001).

We plotted FIB-4 score over time for various comparison groups. Subjects who received statin therapy had minimal or no increase in fibrosis score over time, whereas those who did not receive statin therapy had gradual progression of fibrosis (Fig. 2A). When we further divided these groups by attainment of SVR, fibrosis progression was highest among those who did not receive statin therapy and did not achieve SVR,

| Characteristic                        | On Statins (N = 3,347) | Not on Statins (N = 3,901) | P Value |
|---------------------------------------|------------------------|-----------------------------|---------|
| Age in years, median (IQR)            | 53 (49, 56)            | 52 (48, 56)                 | <0.0001 |
| Race, %                               |                        |                             | 0.01    |
| White                                 | 67.7                   | 65.9                        |         |
| Black                                 | 17.2                   | 16.3                        |         |
| Hispanic                              | 5.3                    | 5.7                         |         |
| Other/unknown                         | 9.8                    | 12.1                        |         |
| Sex, % male                           | 96.4                   | 94.9                        | 0.003   |
| Baseline median HCV RNA (IQR), IU/mL  | 1,610,000 (229,000, 9,380,000) | 1,600,000 (226,000,670,000) | 0.63    |
| Baseline median HCV RNA (IQR), log_{10} IU/mL | 6.21 (5.36, 6.97) | 6.2 (5.35, 6.99) | 0.21    |
| HCV genotype, %                       |                        |                             |         |
| 1                                     | 24.2                   | 28.6                        |         |
| 2                                     | 8.6                    | 8.2                         |         |
| 3                                     | 4.0                    | 5.5                         |         |
| 4                                     | 0.2                    | 0.5                         |         |
| Mix                                   | 0.06                   | 0.1                         |         |
| Missing                               | 62.9                   | 57.1                        | <0.0001 |
| BMI, mean (SD)                        | 29.64(6.74)            | 28.24(5.09)                 | <0.0001 |
| Diabetes, %                           | 22.1                   | 6.8                         | <0.0001 |
| Alcohol abuse or dependence, %        | 30.4                   | 33.2                        | 0.01    |
| Drug abuse or dependence, %           | 30.4                   | 32.5                        | 0.06    |
| Mean ALT, IU/mL (SD)                  | 78.0 (66.16)           | 80.4 (66.35)                | 0.12    |
| Mean AST, IU/mL (SD)                  | 51.9 (32.78)           | 55.6 (35.24)                | <0.0001 |
| Baseline FIB-4 score, mean (SD)       | 1.58 (0.75)            | 1.66 (0.77)                 | <0.0001 |
| Baseline lipid levels, mean (SD)      |                        |                             | <0.0001 |
| TC                                    | 170.58 (38.97)         | 157.7 (32.76)               | <0.0001 |
| LDL-C                                 | 101.79 (34.46)         | 92.31 (29.35)               | <0.0001 |
| HDL-C                                 | 36.82 (12.67)          | 40.8 (14.64)                | <0.0001 |
| TG                                    | 178.07 (136.12)        | 135.99 (103.5)              | <0.0001 |
| Non-HDL cholesterol                   | 133.35 (36.62)         | 117.07 (30.86)              | <0.0001 |
| Treatment regimen (most recent), %    |                        |                             | <0.0001 |
| PEG/RBV only                          | 97.3                   | 95.3                        |         |
| PEG/RBV/BOC                          | 2.4                    | 4.2                         |         |
| PEG/RBV/TPV                          | 0.3                    | 0.4                         |         |
| Mean duration of statin treatment, months (IQR) | 31.7 (13.3, 58.5) |                     |         |
| Mean duration of HCV treatment, months (IQR) | 9.0 (5.5, 11.1) | 8.9 (5.5, 11.1) | 0.86    |
| Follow-up variables, %                |                        |                             |         |
| Completed a course of HCV treatment   | 18.3                   | 20.1                        | 0.06    |
| Developed incident cirrhosis          | 17.3                   | 25.2                        | <0.0001 |
| Attained SVR                          | 39.2                   | 33.3                        | <0.0001 |
| HCC                                   | 1.2                    | 2.6                         | <0.0001 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PEG, pegylated interferon; RBV, ribavirin; SD, standard deviation.
followed by those who received statins but did not achieve SVR. Those who achieved SVR and received statin therapy had the lowest fibrosis progression rate (Fig. 2B). Time to diagnosis of cirrhosis was longer in persons who received statin therapy, compared to those who did not. Persons who did not receive statin therapy and did not achieve SVR had the fastest progression to cirrhosis, whereas those who received statin therapy and achieved SVR has the slowest progression to cirrhosis (Fig. 3). Similarly, time to diagnosis of HCC was longer in those who received statin therapy, compared to those who did not. Persons who did not receive statin therapy and did not achieve SVR had the fastest progression to HCC, whereas those who received statin therapy and achieved SVR has the slowest progression to HCC (Fig. 4). In multivariate Cox's regression analysis adjusted for baseline FIB-4 score, treatment with statins was associated with significantly lower risk of developing cirrhosis (hazard ratio [HR] = 0.56; 95% confidence interval [CI] = 0.50, 0.63; Table 2). Factors associated with a higher risk of cirrhosis were increasing age, male sex, higher baseline HCV RNA, infection with HCV genotype 1 (vs. non-1), diabetes mellitus, and alcohol use or dependence. Black race and attaining SVR were associated with a lower risk of cirrhosis. In a separate
multivariate Cox’s regression analysis, treatment with statins was associated with a higher likelihood of achieving SVR (odds ratio [OR] = 1.44; 95% CI = 1.29, 1.61; (Table 3). Treatment with statins was also associated with a lower risk of HCC (HR = 0.51; 95% CI = 0.34, 0.76). Factors associated with a higher risk of HCC included increasing age, nonwhite race, development of cirrhosis, diabetes, and alcohol abuse or dependence (Table 4).

Given that alcohol use is a strong independent predictor of liver fibrosis progression in all populations, we conducted supplementary sensitivity analyses excluding those with a diagnosis of alcohol abuse or dependence at baseline or during follow up. Statin use remained strongly associated with a lower risk of cirrhosis (HR = 0.60; 95% CI = 0.51, 0.71; Supporting Table 1). We plotted mean fibrosis scores over time by receipt of statin therapy as well as by attainment of SVR after excluding those with a diagnosis of alcohol abuse or dependence (Supporting Fig. 1). The results were similar to main analyses. Kaplan-Meier’s curves for time to cirrhosis for this population were also similar to the main analyses (Supporting Fig. 2). Genotype results were available for less than half of the HCV-infected study population. A plot of mean fibrosis score over time by HCV genotype showed more progression in HCV genotypes 1 and 2, compared with genotype 3 (Supporting Fig. 3). Kaplan-Meier’s curves by genotype showed slower time to diagnosis of cirrhosis among HCV genotype 2–infected persons (Supporting Fig. 4). There were too few subjects with cirrhosis among genotype 4–infected persons (n = 6) to make any meaningful comparison.

Because a large number of subjects were missing HCV-RNA results to calculate SVR, we conducted further sensitivity analyses classifying all subjects with missing SVR data as non-SVR. The direction and magnitude of the association did not change significantly for the association of statin use with cirrhosis, SVR, or HCC (Supporting Table 2).

Finally, given that metformin use has been associated with a lower risk of HCC in some studies,22,23 we assessed the association between metformin use and risk of developing cirrhosis or HCC. Metformin use was not associated with either outcome, nor did it significantly mitigate the effect of statins (data not shown).

### Table 2. Predictors of Cirrhosis, Adjusted for Baseline FIB-4 score*

| Characteristic                      | HR     | 95% CI   | P Value |
|------------------------------------|--------|----------|---------|
| Statin use                         | 0.56   | 0.50, 0.63| <0.0001 |
| Age, per 10-year increase          | 1.46   | 1.34, 1.58| <0.0001 |
| Race (white vs. non-white)         | 1.28   | 1.15, 1.43| <0.0001 |
| Sex (male)                         | 1.27   | 0.92, 1.74| 0.14    |
| Baseline HCV RNA, for each log10 increase| 1.06   | 1.03, 1.09| <0.0001 |
| HCV genotype (1 vs. non-1)         | 1.23   | 1.04, 1.46| 0.02    |
| BMI, per unit increase             | 1.002  | 0.99, 1.01| 0.7     |
| Dyslipidemia                       | 1.05   | 0.93, 1.18| 0.5     |
| Diabetes                           | 1.37   | 1.19, 1.58| <0.0001 |
| Alcohol abuse or dependence        | 1.37   | 1.20, 1.56| <0.0001 |
| Drug abuse or dependence           | 1.07   | 0.94, 1.22| 0.3     |
| Treatment regimen (PEG/RBV vs. DAA-containing) | 0.95   | 0.74, 1.22| 0.7     |
| Attained SVR (vs. no SVR)          | 0.72   | 0.64, 0.81| <0.0001 |

*Multivariate Cox’s regression analysis. Abbreviations: PEG, pegylated interferon; RBV, ribavirin.

### Table 3. Predictors of SVR*

| Characteristic                      | OR     | 95% CI   | P Value |
|------------------------------------|--------|----------|---------|
| Statin use                         | 1.44   | 1.29, 1.61| <0.0001 |
| Age, per 10-year increase          | 0.88   | 0.81, 0.95| 0.0008  |
| Race (white vs. non-white)         | 1.51   | 1.35, 1.68| <0.0001 |
| Sex (male)                         | 0.95   | 0.75, 1.20| 0.65    |
| Baseline HCV RNA, for each log10 increase| 0.94   | 0.92, 0.96| <0.0001 |
| Baseline FIB-4, for each unit increase| 0.93   | 0.87, 1.00| 0.04    |
| HCV genotype (1 vs. non-1)         | 0.42   | 0.36, 0.49| <0.0001 |
| BMI, per unit increase             | 1.002  | 0.99, 1.01| 0.69    |
| Dyslipidemia                       | 0.94   | 0.84, 1.05| 0.28    |
| Diabetes                           | 0.66   | 0.56, 0.77| <0.0001 |
| Alcohol abuse or dependence        | 0.81   | 0.71, 0.92| 0.001   |
| Drug abuse or dependence           | 1.19   | 1.04, 1.35| 0.01    |
| Treatment regimen (PEG/RBV vs. DAA-containing) | 0.28   | 0.22, 0.36| <0.0001 |

*Multivariate logistic regression analysis. Abbreviations: PEG, pegylated interferon; RBV, ribavirin.

### Discussion

In this large, national cohort study assessing the impact of statin use upon progression of fibrosis controlling for known confounders, we found that statin use was significantly associated with decreased progression of fibrosis independent of having attained an SVR. This is also the first study to demonstrate the effects of statins on all three critical clinical outcomes of HCV, including fibrosis progression, SVR, and HCC development, in an unselected group of patients with various stages and genotypes of HCV.

Most previous clinical studies of statin use in HCV-infected persons have been in small,
Previous studies have reported a variable effect of statins upon VR in HCV-infected persons. Some studies have shown a clear improvement of VR with statin use in addition to antiviral therapy, whereas others have demonstrated little or no effect. Part of this may be owing to the variable activity of different statins upon HCV replication and to the different doses of statins used in studies. There is biological plausibility of an antiviral effect of statins in HCV-infected persons. In HCV-infected persons, the virus circulates as a lipoviral particle and resembles very-low-density lipoprotein, rich in cholesterol esters and containing apolipoproteins ApoE and ApoB. These apolipoproteins are important for virus entry, serving as ligands for the LDL receptor and scavenger receptor class B type 1. HCV infection alters lipid metabolism through activation of the sterol response element-binding protein. These interactions lead to up-regulation of genes involved in lipid metabolism at onset of viremia. Furthermore, HCV infection also inhibits fatty acid β-oxidation by down-regulating expression of the transcription factor, peroxisome proliferator-activated receptor alpha. Last, adenosine monophosphate–activated protein kinase, a key regulator of lipid metabolism, which augments fatty acid oxidation, appears to be inactive (dephosphorylated) in HCV-infected cells. Inhibition of cholesterol, geranylgeranylation of cellular proteins, and other genes related to synthesis and transport of fatty acids lead to a subsequent block of HCV replication.

Statins have been shown to consistently reduce fibrosis progression in the liver and other solid organs. The effect of statins on fibrosis may be partially related to their antiviral and immunomodulatory effects. Statins have been found to mitigate portal hypertension by increasing splanchnic nitric oxide. Statins also up-regulate transcription factors that exert vasoprotective effects in the liver and inhibit stellate cells, thus potentially decreasing fibrosis. Because of these findings, there has been interest in clinical trials. However, this interest has been tempered by fears about statins inducing hepatic injury, which have only recently been assuaged. The effects of statins truly have not been uniformly positive, with hepatotoxicity associated with high-dose statins in the setting of chronic liver disease. In contrast, one small retrospective study demonstrated that statin use may be associated with delayed decompensation of cirrhosis. A recent study assessing HCV patients randomized to long-term IFN use found that those on statins experienced decreased histological progression of fibrosis in multivariate models adjusted for several known predictors of fibrosis, but not in final/inclusive multivariable models. This was likely related to the limited study power, given that only 29 subjects were on statins and the majority of subjects had relatively advanced baseline liver disease (Ischak score of ≥3/6).

Statins have been shown, in various studies, to be associated with decreased HCC risk. This was reviewed in a recent meta-analysis that found a 37% decreased risk, which is similar to the 49% found in the present study. Subsequent to this meta-analysis,
two large case-control studies corroborated this association,\textsuperscript{7,32} and a nested case-control study had similar findings, though without a dose-response relationship described previously.\textsuperscript{33} This relationship requires further study, but may be related to inhibition of hepatic expression of thioredoxin, an enzyme that is increased in premalignant hepatic nodules that aids in cell survival.\textsuperscript{34} Statins have also been found to induce tumor apoptosis and cell-cycle arrest \textit{in vitro} by mitochondrial mechanisms,\textsuperscript{35} inhibition of cyclins and cyclin-dependent kinases,\textsuperscript{36} and induction of microtubule bundling.\textsuperscript{14} \textit{In vitro}, HCC cells have been found to decrease expression of cell adhesion molecules, thus preventing cell growth and invasion possibly through a rho-dependent kinase.\textsuperscript{37} Furthermore, adjuvant statin use along with standard chemotherapy regimens in patients with existing HCC has been demonstrated to prolong survival in several recent prospective studies as well as one small, randomized trial.\textsuperscript{38,39} Though much progress has been made in understanding the role of statins in HCC therapy, more work is required to understand the \textit{in vivo} effects of statins, including the type of statin (i.e., hydrophilic vs. hydrophobic) that may offer the greatest chemoprotective effect, as well as the optimal dosage and duration needed for effect.

Despite growing evidence of the beneficial effects of statins on liver disease, there remains a likely underutilization of the medications, in particular, in patients with advanced liver disease. This was evaluated in a survey of primary care providers in which more than one third underutilized statins and less than half were willing to prescribe them to patients with HCV.\textsuperscript{40} Based on studies demonstrating their safety in liver disease and, particularly, in HCV,\textsuperscript{41} expert recommendations state that statins should not be withheld even in advanced liver disease.\textsuperscript{42,43} HCV in particular is associated with MetS that includes insulin resistance, obesity, and dyslipidemia\textsuperscript{44} and may be associated with accelerated atherosclerosis,\textsuperscript{45} thus increasing the risk of coronary artery disease as well as liver disease progression.\textsuperscript{46}

Though this is a large, national cohort study, there are several limitations. Owing to the nonrandomized nature of the study, there is the potential for selection bias and unmeasured confounders. However, given that this was a large cohort, we were able to control for many known confounders. Additionally, this study included only subjects who had undergone HCV therapy and included predominantly males, which may limit its application to other patient populations. The use of FIB-4 rather than biopsy or FibroScan to determine the stage of fibrosis is a potential limitation. However, FIB-4 has been used in many studies and has a sensitivity and specificity of 55%-74% and 92%-98%, respectively, with an area under the receiver operating characteristic curve of 0.85 for identifying cirrhosis in patients with HCV.\textsuperscript{47-49} We did not assess the effect of individual statins. There are data to suggest that fluvastatin and simvastatin have more potent antiviral activity than other statins. We were unable to assess a dose-related effect of the statins, which could further support our hypothesis and should be a focus of future studies. Though use of ICD-9 codes to identify HCC is a potential limitation, these codes have been previously validated to identify patients with HCC in the VA.\textsuperscript{50}

In conclusion, to our knowledge, this is the first large, national cohort study to demonstrate that statin use is significantly associated with increased SVR rates and decreased progression to cirrhosis and HCC. Future studies should assess the impacts of statins in the presence of all-oral therapies, the mechanisms of their action, and dose-related effects of statins. The role of individual statins upon these outcomes also needs to be clarified.

References

1. Syed GH, Amako Y, Siddiqui A. Hepatitis C virus hijacks host lipid metabolism. Trends Endocrinol Metab 2010;21:33-40.
2. Selic KT, Lesnicar G, Poljak M, Meglic VJ, Rajter M, Prah J, et al. Impact of added fluvastatin to standard-of-care treatment on sustained virological response in naive chronic hepatitis C patients infected with genotypes 1 and 3. Intervirology 2014;57:23-30.
3. Bader T, Hughes LD, Fazzili J, Frost B, Dunnan M, Gonterman A, et al. A randomized controlled trial adding fluvastatin to peginterferon and ribavirin for naïve genotype 1 hepatitis C patients. J Viral Hepat 2013;20:622-627.
4. Patel K, Jhaveri R, George J, Qiang G, Kendeci O, Brown K, et al. Open-label, ascending dose, prospective cohort study evaluating the antiviral efficacy of Rosuvastatin therapy in serum and lipid fractions in patients with chronic hepatitis C. J Viral Hepat 2011;18:331-337.
5. Forde KA, Law C, O’Flynn R, Kaplan DE. Do statins reduce hepatitis C RNA titers during routine clinical use? World J Gastroenterol 2009;15:5020-5027.
6. Simon TG, King LY, Zheng H, Chung RT. Statin use is associated with a reduced risk of fibrosis progression in chronic hepatitis C. J Hepatol 2015;62:18-23.
7. Tsan YT, Lee CH, Ho WC, Lin MH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis C virus infection. J Clin Oncol 2013;31:1514-1521.
8. Yamamoto C, Fukuda N, Jumabay M, Saito K, Matsumoto T, Ueno T, et al. Protective effects of statin on cardiac fibrosis and apoptosis in arterial medullin-knockout mice treated with angiotensin II and high salt loading. Hypertens Res 2011;34:348-353.
9. Rodrigues DR, Rodrigues-Diez R, Lavor C, Rayego-Mateos S, Civeratos E, Rodriguez-Vita J, et al. Statins inhibit angiogenesis II/Smad pathway and related vascular fibrosis, by a TGF-beta-independent process. PLoS One 2010;5:e14145.
10. Xu JF, Washko GR, Nakahira K, Hatabu H, Patel AS, Fernandez IE, et al. Statins and pulmonary fibrosis: the potential role of NLRP3 inflammasome activation. Am J Respir Crit Care Med 2012;185:547-556.

11. Nadrous HF, Ryu JH, Douglas WW, Decker PA, Olson EJ. Impact of angiotensin-converting enzyme inhibitors and statins on survival in idiopathic pulmonary fibrosis. Chest 2004;126:438-446.

12. Ikeda M, Abe K, Yamada M, Dassalo H, Naka K, Kato N. Different anti-HCV profiles of statins and their potential for combination therapy with interferon. Hepatology 2006;44:117-125.

13. Wüstenberg A, Kah J, Singheran K, Sirma H, Keller AD, Rosal SR, et al. Matrix conditions and KLF2-dependent induction of heme oxygenase-1 module inhibition of HCV replication by fluvastatin. PLoS One 2014;9:e96533.

14. Ali N, Allam H, Bader T, May R, Basalingappa KM, Berry WL, et al. Fluvastatin interfaces with hepatitis C virus replication via microtubule bundling and a doublestranded-like kinase-mediated mechanism. PLoS One 2013;8:e80304.

15. Bader T, Fazili J, Madhoun M, Aston C, Hughes D, Rizvi S, et al. Fluvastatin inhibits hepatitis C replication in humans. Am J Gastroenterol 2008;103:1383-1389.

16. Butt AA, Wang X, Budoff M, Leaf DA, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. Clin Infect Dis 2009;49:225-232.

17. Butt AA, Wang X, Moore CM. Effect of HCV and its treatment upon survival. Hepatology 2009;50:387-392.

18. Butt AA, Yan P, Lo Re V, III, Rimmel D, Goetz MB, Leaf DA, et al. Liver fibrosis progression in hepatitis C virus infection after seroconversion. JAMA Intern Med 2015;175:178-185.

19. Butt AA, McGinnis KA, Skanderson M, Justice AC. A comparison of treatment eligibility for HCV in HCV monoinfected vs. HCV/HIV coinfected persons in ERICHIVES (Electronically Retrieved Cohort of HCV Infected Veterans). AIDS Res Hum Retroviruses 2011;27:973-979.

20. Yee HS, Currie SL, Darling JM, Wright TL. Management and treatment of hepatitis C viral infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center program and the National Hepatitis C Program office. Am J Gastroenterol 2006;101:2360-2378.

21. Butt AA, Khan UA, Shaikh OS, McMahon D, Dorey-Stein Z, Tsevat J, et al. Rates of HCV treatment eligibility among HCV monoinfected and HCV/HIV-coinfected patients in tertiary care referral centers. HIV Clin Trials 2009;10:25-32.

22. Zhang ZJ, Zheng ZJ, Shi R, Su Q, Jiang Q, Kip KE. Metformin for liver cancer prevention in patients with type 2 diabetes: a systematic review and meta-analysis. J Clin Endocrinol Metab 2012;97:2347-2353.

23. Hassan MM, Curley SA, Li D, Kaseb A, Davila M, Abdalla EK, et al. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer 2010;116:1938-1946.

24. Kapadia SB, Chisari FV. Hepatitis C virus RNA replication is regulated by host gene regulation and fatty acids. Proc Natl Acad Sci U S A 2005;102:2561-2566.

25. Sun HY, Singh N. Antimicrobial and immunomodulatory attributes of statins: relevance in solid-organ transplant recipients. J Infect Dis 2009;48:745-755.

26. Zafra C, Abraldes JG, Turnes J, Berzigotti A, Fernandez M, Garcia-Espana C, et al. Statins and pulmonary fibrosis: the potential role of NLRP3 inflammasome activation. Am J Respir Crit Care Med 2012;185:547-556.

27. Marrone G, Russo L, Rosado E, Hide D, Garcia-Cardena G, Garcia-Pagan JC, et al. The transcription factor KLF2 mediates hepatic endothelial protection and paracrine endothelial-stellate cell deactivation induced by statins. J Hepatol 2013;58:98-103.

28. Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Beldr R. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Hepatology 2007;46:1453-1463.

29. Chang CH, Chang YC, Lee YC, Liu YC, Chuang LM, Lin JW. Severe hepatic injury associated with different statins in patients with chronic liver disease: a nationwide population-based cohort study. J Gastroenterol Hepatol 2015;30:155-162.

30. Kumar S, Grace ND, Qamar AA. Statin use in patients with cirrhosis: a retrospective cohort study. Dig Dis Sci 2014;59:1958-1965.

31. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis. Gastroenterology 2013;144:323-332.

32. Lai SW, Liao KE, Lai HC, Sung FC, Chen PC. Statin use and risk of hepatocellular carcinoma. Eur J Epidemiol 2013;28:485-492.

33. McGlynn KA, Divine GW, Sahastrabuddhe VV, Engel LS, VanSlooten A, Wells K, et al. Statin use and risk of hepatocellular carcinoma in a U.S. population. Cancer Epidemiol 2014;38:523-527.

34. Skogastierna C, Johansson M, Patini P, Eriksson M, Eriksson LC, Ekstrom L, et al. Statins inhibit expression of chDroloxede reductase 1 in rat and human liver and reduce tumour development. Biochem Biophys Res Commun 2012;417:1046-1051.

35. Zhang W, Wu J, Zhou L, Xie HY, Zheng SS. Fluvastatin, a lipophilic statin, induces apoptosis in human hepatocellular carcinoma cells through mitochondria-operated pathway. Indian J Exp Biol 2010;48:1167-1174.

36. Relja B, Meder F, Wilhelm K, Henrich D, Marzi I, Lehnert M. Simvastatin inhibits cell growth and induces apoptosis and G0/G1 cell cycle arrest in hepatic cancer cells. Int J Mol Med 2010;26:735-741.

37. Relja B, Meder F, Wang M, Blaha R, Henrich D, Marzi I, et al. Simvastatin modulates the adhesion and growth of hepatocellular carcinoma cells via decrease of integrin expression and ROCK. Int J Oncol 2011;38:879-885.

38. Graf H, Jungst C, Straub G, Dogan S, Hoffmann RT, Jakobs T, et al. Chemoembolization combined with pravastatin improves survival in patients with hepatocellular carcinoma. Digestion 2008;78:34-38.

39. Kawata S, Yamasaki E, Nagase T, Inui Y, Ito N, Matsuda Y, et al. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. Br J Cancer 2001;84:886-891.

40. Rzouq FS, Volk ML, Hatoum HH, Talluri SK, Mummaid RR, Sood GK. Hepatotoxicity fears contribute to underutilization of statin medications by primary care physicians. Am J Med Sci 2010;340:89-93.

41. Henderson LM, Patel S, Giordano TP, Green L, El-Serag HB. Statin therapy and serum transaminases among a cohort of HCV-infected veterans. Dig Dis Sci 2010;55:190-195.

42. Onofrei MD, Butler KL, Fuke DC, Miller HB. Safety of statin therapy in patients with preexisting liver disease. Pharmacotherapy 2008;28:522-529.

43. Calderon RM, Cubeddu LX, Goldberg RB, Schiff ER. Statins in the treatment of dyslipidemia in the presence of elevated liver aminotransferase levels: a therapeutic dilemma. Mayo Clin Proc 2010;85:349-356.

44. Argiello MA, Loria P, Cardulli N. Dysmetabolic changes associated with HCV: a distinct syndrome? Intern Emerg Med 2008;3:99-108.

45. Haji SA, Starling RC, Avery RK, Mawhorter S, Tuzcu EM, Schoenhagen P, et al. Donor hepatitis-C seropositivity is an independent risk factor for the development of accelerated coronary vasculopathy and predicts outcome after cardiac transplantation. J Heart Lung Transplant 2004;23:277-283.

46. Rzouq F, Alahdab F, Olyaei M. Statins and hepatitis C virus infection: an old therapy with new scope. Am J Med 2014;348:426-430.

47. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. IFB-4: an inexpensive and accurate marker of fibrosis...
in HCV infection. comparison with liver biopsy and fibrotest. Hepatology 2007;46:32-36.
48. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology 2012;142:1293-1302.
49. Chou R, Wason N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. Ann Intern Med 2013;158:807-820.
50. Goldberg DS, Lewis JD, Halpern SD, Weiner MG, Lo RV, III. Validation of a coding algorithm to identify patients with hepatocellular carci-

Supporting Information

Additional Supporting Information may be found at http://onlinelibrary.wiley.com/doi/10.1002/hep.27835/suppinfo.