

Risk of Acute Liver Injury Among Chronic Hepatitis C Virus-Infected Patients After Statin Initiation

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Abstract

Background: Patients with chronic hepatitis C virus (HCV) infection may be prescribed statins for metabolic/cardiovascular disease, but it remains unclear if the risk of acute liver injury (ALI) associated with statin use is higher for chronic HCV-infected persons.

Methods: We conducted a cohort study among 3,768 chronic HCV-infected statin initiators, 23,535 HCV-uninfected statin initiators, 12,073 chronic HCV-infected statin non-users, and 30,808 HCV-uninfected statin non-users in the Veterans Aging Cohort Study from 2000-2012. We determined development of: 1) liver aminotransferases >200 U/L, 2) severe ALI (international normalized ratio ≥ 1.5 and total bilirubin >2 times upper limit of normal (ULN)), 3) hospitalization with an ALI diagnosis, and 4) all-cause mortality. Cox regression was used to determine propensity score-adjusted hazard ratios (HRs) with 95% confidence intervals (CI).

Results: Chronic HCV-infected statin initiators had higher risks of liver aminotransferases >200U/L, severe ALI, hospitalization with ALI, and death, than HCV-uninfected statin initiators. In contrast, HCV-infected statin initiators had lower risks of liver aminotransferases >200 U/L, severe ALI, hospitalization with severe ALI, and death compared those HCV-infected not using statins. The risk of death was lower for HCV-infected statin initiators than HCV-uninfected statin non-users.

Background

- Chronic hepatitis C virus (HCV) is associated with increased rates of metabolic syndrome, diabetes, and coronary artery disease.
- The 3-hydroxy-3methylglutaryl-coenzyme A reductase inhibitors (statins) are commonly prescribed for patients affected by the above conditions, and are one of the most frequently prescribed medication classes in the US.
- Statins have been shown to have other beneficial effects, specific to HCV, including higher rates of sustained virologic response, decreased rates of liver cancer, and decreased risk of hepatic decompensation among cirrhotics.
- Statins have been associated with acute liver injury (ALI) and also as causes of acute liver failure.
- The effects of statins on the risk of acute, clinically significant liver injury in the chronic HCV-infected population remains unknown.

Objective

- Determine the risk of acute liver injury amongst chronic HCV-infected persons initiating on statins as compared to HCV-uninfected statin initiators, as well as to HCV-infected and HCV-uninfected statin non-users.

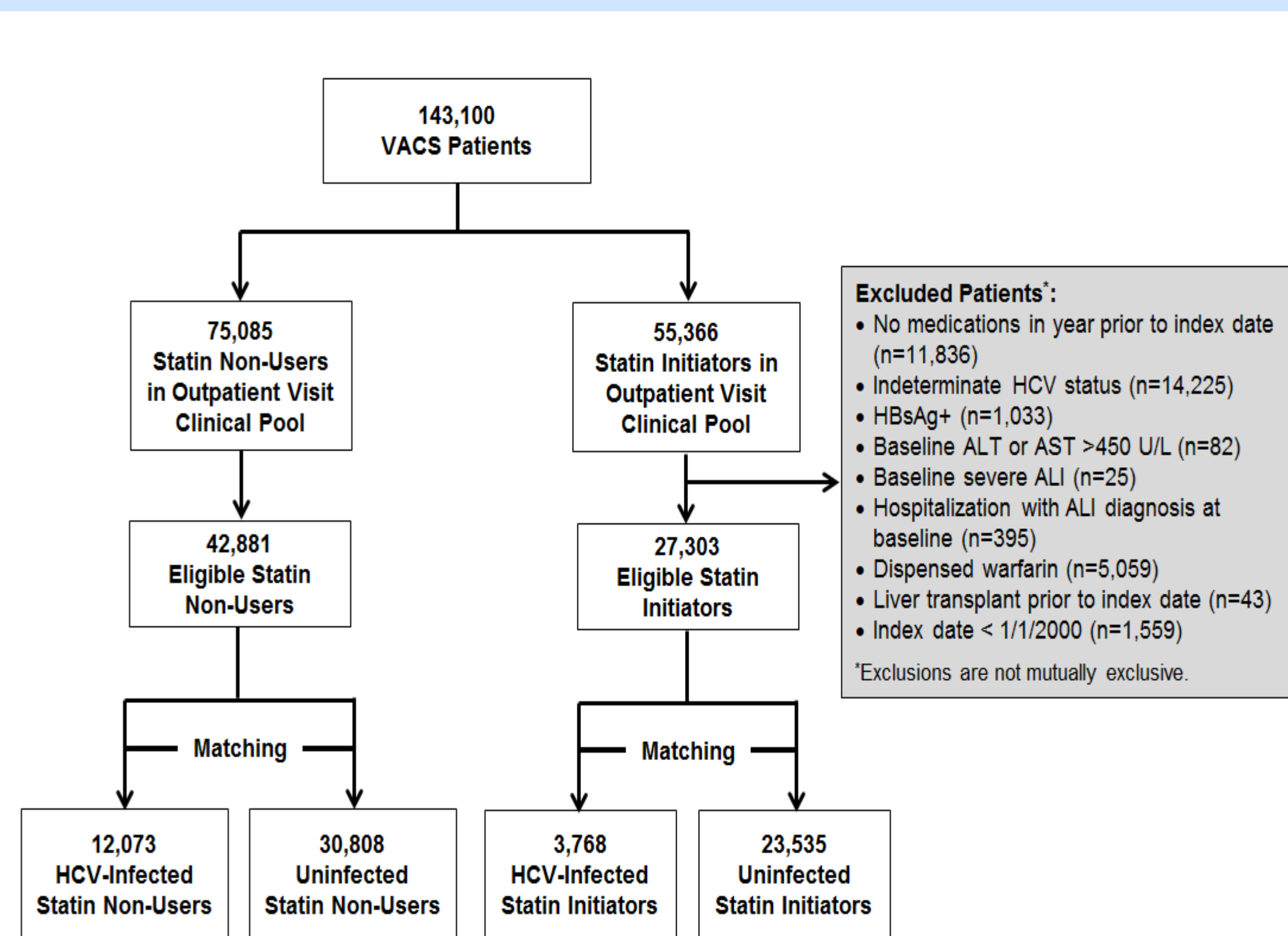
Methods

Study Design: Retrospective cohort study

Data Source: Veterans Aging Cohort Study (VACS)

January 1 2000-September 30, 2012.

Patient Selection for Inclusion:



Outcomes:

- Biochemical ALI: Liver aminotransferases >200 U/L
- Severe ALI (international normalized ratio ≥ 1.5 and total bilirubin >2 times upper limit of normal (ULN)),
- Hospitalization with an ALI diagnosis by ICD-9 code
- All-cause mortality

Statistical Analysis:

- Propensity scores were used to control for confounding variables and to minimize indication bias for statin use.
- Cox regression was used to estimate hazard ratios (HR) of the specified outcomes associated with statin use in chronic HCV-infected persons.
- A single Cox model was used for the three comparisons of interest for each outcome.

Results

Propensity Score-Adjusted Relative Hazards of Specified Outcomes in Chronic HCV-Infected Statin Initiators Compared to HCV-Uninfected Statin Initiators, Chronic HCV-Infected Statin Non-Users, and HCV-Uninfected Statin Non-Users

Cohort Comparison	Hazard Ratio of Outcome (95% Confidence Interval)			
	Liver Aminotransferase >200 U/L	Severe ALI*	Hospitalization with ALI	All-Cause Mortality
Chronic HCV+ statin initiators vs. HCV- statin initiators	4.15 (3.71-4.62)	3.79 (2.02-7.11)	7.38 (4.72-11.53)	2.87 (2.38-3.47)
Chronic HCV+ statin initiators vs. Chronic HCV+ statin non-users	0.23 (0.21-0.24)	0.19 (0.11-0.34)	0.26 (0.18-0.38)	0.38 (0.32-0.46)
Chronic HCV+ statin initiators vs. HCV- statin non-users	2.65 (2.37-2.97)	0.88 (0.49-1.56)	1.31 (0.89-1.94)	0.61 (0.51-0.73)

Characteristics of the Comparison Groups

Characteristic	HCV-Infected Statin Initiators (n=3,768)	HCV-Uninfected Statin Initiators (n=23,535)	HCV-Infected Statin Non-Users (n=12,073)	HCV-Uninfected Statin Non-Users (n=30,808)
Median age (years, IQR)	54 (46-62)	52 (40-64)	52 (44-60)	48 (34-62)
Male sex (n, %)	3,714 (98.5)	22,872 (97.2)	11,893 (98.5)	29,533 (95.9)
Race/ethnicity (n, %)				
Black	2,398 (63.6)	10,514 (44.7)	7,330 (60.7)	15,750 (51.1)
Caucasian	1,022 (27.1)	9,734 (41.4)	3,394 (28.1)	11,140 (36.2)
Hispanic	274 (7.3)	2,359 (10.0)	1,047 (8.7)	2,233 (7.2)
Other/Unknown	74 (2.0)	928 (3.9)	302 (2.5)	1,685 (5.5)
Body mass index (n, %)				
≤ 18.5 kg/m ²	52 (1.4)	178 (0.8)	432 (3.6)	828 (2.7)
18.5-24.9 kg/m ²	1,066 (28.3)	4,348 (18.4)	4,789 (39.7)	9,778 (31.7)
25-29.9 kg/m ²	1,377 (36.5)	6,079 (25.8)	8,414 (35.7)	10,194 (33.1)
≥ 30 kg/m ²	1,204 (32.0)	10,065 (42.8)	2,113 (17.5)	8,028 (26.1)
Missing weight and/or height	69 (1.8)	530 (2.3)	862 (7.1)	1,980 (6.4)
Medical comorbidities (n, %)*				
Alcohol dependence/abuse	1,712 (45.4)	5,058 (21.5)	5,859 (48.5)	7,533 (24.5)
Cerebrovascular disease	157 (4.2)	434 (1.8)	149 (1.2)	216 (0.7)
Chronic kidney disease	364 (9.6)	989 (4.2)	739 (6.1)	1,032 (3.3)
Cirrhosis	144 (3.8)	63 (0.3)	624 (5.2)	156 (0.5)
Congestive heart failure	209 (5.5)	556 (2.4)	226 (1.9)	379 (1.3)
Myocardial infarction	687 (18.2)	2,426 (10.3)	567 (4.7)	930 (3.0)
Diabetes mellitus	1,492 (39.6)	6,079 (25.8)	1,805 (15.0)	2,180 (7.1)
Hypertension	1,240 (32.9)	6,749 (28.7)	3,032 (25.1)	6,080 (19.7)
Injection/non-injection drug use	1,819 (48.3)	4,057 (17.2)	6,192 (51.3)	6,390 (20.7)
Peripheral vascular disease	202 (5.4)	717 (3.0)	275 (2.2)	413 (1.3)
Median ALT (U/L, IQR)	41 (28-59)	27 (20-38)	49 (32-76)	26 (19-38)
Median AST (U/L, IQR)	36 (27-51)	24 (20-30)	48 (33-74)	25 (20-33)
FIB-4 (n, %)				
<1.45	1,702 (45.1)	15,499 (65.9)	3,179 (26.3)	15,217 (49.4)
1.45-3.25	1,430 (38.0)	3,614 (15.3)	4,007 (33.2)	4,476 (14.5)
≥ 3.25	636 (16.9)	4,422 (18.8)	4,887 (40.5)	11,115 (36.1)
HIV infection (n, %)	894 (24%)	5,902 (25%)	6,249 (52%)	11,837 (38%)
Median propensity score (IQR) [†]	0.395 (0.118-0.744)	0.600 (0.247-0.863)	0.003 (0.001-0.010)	0.009 (0.003-0.034)

- Chronic HCV-Infected Statin Initiators had a higher risk of all ALI events and death than HCV Uninfected Statin Initiators
- Chronic HCV-Infected Statin Initiators had a lower risk of all ALI events and death than HCV-Infected patients not using statins.
- The risk of death was lower for HCV-infected statin-initiators than for HCV-uninfected statin users.

Conclusions:

- Statin initiation in HCV-infected patients is associated with an increased risk of biochemical liver injury, severe liver injury, and hospitalization with liver injury in the first 18 months of therapy, as compared to HCV-Uninfected Statin initiators.
- Amongst HCV-infected patients, statin initiation was associated with a decreased risk of biochemical liver injury, severe liver injury, hospitalization with liver injury, and a decreased risk of all-cause mortality in the first 18 months of therapy