Published in final edited form as:

J Viral Hepat. 2017 October ; 24(10): 814–822. doi:10.1111/jvh.12705.

Performance of the Pooled Cohort Atherosclerotic Cardiovascular Disease Risk Score in Hepatitis C Virus-infected Persons

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Statement of Interests

Authors' declaration of personal interests: K.W.C. has received research support (to the institution) from Merck and Gilead. D.B. has received grant support (to the institution) from Merck, AbbVie and Bristol-Myers Squibb. J.S.C. has received grant support (to the institution) from Theratechnologies. A.A.B. has received grant support (to the institution) from Merck, AbbVie and Gilead. All other authors report no conflicts of interest.

Declaration of Funding Interests: This study was supported by a seed grant from the UCLA AIDS Institute/Center for AIDS Research (National Institute of Allergy and Infectious Diseases at the National Institutes of Health P30AI028697). This material is the result of work supported with resources and the use of facilities at the VA Pittsburgh Healthcare System and the central data repositories maintained by the VA Information Resource Center, including the National Patient Care Database, Decisions Support System Database and Pharmacy Benefits Management Database. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

Abstract

Chronic hepatitis C virus (HCV) infection has been associated with an increased risk for cardiovascular disease (CVD). The recommended Pooled Cohort Atherosclerotic Cardiovascular Disease (ASCVD) risk equation for estimation of 10-year CVD risk has not been validated in HCV-infected populations. We examined the performance of the ASCVD risk score in HCV-infected persons, using the national Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) to derive a cohort of HCV-infected and uninfected subjects without baseline ASCVD, hepatitis B, or HIV infection, and with low-density lipoprotein cholesterol level <190 mg/dL. Performance of the ASCVD risk equation was assessed by Cox proportional hazard regression, C-statistics, and Hosmer-Lemeshow statistic. The cohort included 70,490 HCV-infected and 97,766 HCV-uninfected men with mean age of 55 years, 56% white and 29% black. Incident CVD event rates were similar between the two groups (13.2 and 13.4 events/1000 person-years), with a higher incidence of coronary heart disease events in the HCV-uninfected group and of stroke events in the HCV-infected group. Adjusting for ASCVD risk score, HCV infection was associated with higher risk for an ASCVD event in the subgroup with baseline ASCVD risk 7.5% (HR 1.19, $p < 0.0001$). C-statistics were poor in both the HCV-infected and uninfected groups (0.60 and 0.61, respectively). By Hosmer-Lemeshow test, the ASCVD risk equation overestimated risk amongst lower risk patients and underestimated risk amongst higher risk patients in both the HCV-infected and uninfected groups. Further investigation is needed to determine if a modified equation to accurately predict ASCVD risk in HCV-infected persons is warranted.

Keywords

ASCVD score; cardiovascular disease; cardiovascular risk assessment; hepatitis C virus

Introduction

Data from an increasing number of studies suggest that chronic hepatitis C virus (HCV) infection is independently associated with an increased risk for cardiovascular disease (CVD) (1–8). Current American College of Cardiology/American Heart Association guidelines recommend use of the pooled cohort atherosclerotic cardiovascular disease (ASCVD) risk equation for assessment of 10-year CVD risk (9); however, this equation has not been validated in HCV-infected populations. Two of the ASCVD components, prevalence of hypertension and total cholesterol, are decreased in the setting of HCV infection. Lower serum cholesterol in HCV-infected persons has been noted in numerous studies and is independent of degree of liver disease (2, 5, 7). Interpreted traditionally, the lower blood pressure and cholesterol suggest that HCV infection may confer a protective effect for CVD, but increasingly the literature suggests that risk of atherosclerotic disease and clinical cardiovascular events including myocardial infarction (MI), heart failure, and ischemic stroke are in fact increased with HCV infection (7, 8, 10–13). Thus, routine clinical predictors of CVD risk such as a lipid profile may not be reliable for CVD risk estimation in HCV-infected persons and new or modified tools may be needed to optimize CVD risk

assessment in this population. Our aim was to assess performance of the ASCVD risk score in HCV-infected compared with HCV-uninfected persons.

Materials and Methods

Subject selection/cohort derivation

We conducted a retrospective analysis utilizing the national Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES), 2001–2014, which includes HCV-infected veterans matched with HCV-uninfected controls. The creation of ERCHIVES has previously been described (13–16). Inpatient and outpatient data were derived from the Veteran Affairs (VA) National Patient Care Database, the VA Pharmacy Benefits Management database, and the Decisions Support System database in VA fiscal years 2001–2014. Discharge diagnoses and diagnoses from outpatient records are coded according to the *International Classification of Diseases, 9th Revision* (ICD-9). The validity of the administrative, pharmacy, and laboratory data has previously been reported (15, 17, 18), as has been the validity of the ICD-9 codes for select comorbid conditions, including myocardial infarction (MI) (17). HCV infection was defined by the presence of HCV antibody or a positive result from qualitative or quantitative testing for HCV RNA. HCV-uninfected controls were matched by age (in 5-year increments), sex, race, and year of HCV diagnosis in the VA health care system. Male participants aged 40–79 years were included. Only males were included as 97% of the ERCHIVES cohort is male. Participants were excluded if they had baseline CVD (defined as prevalent MI, history of coronary artery bypass grafting [CABG], percutaneous transluminal coronary angioplasty [PTCA], stroke, congestive heart failure, and atrial fibrillation), chronic hepatitis B (defined as positive hepatitis B surface antigen), HIV infection, low density lipoprotein (LDL) level ≥ 190 mg/dL, or if ASCVD risk was not calculable using the Pooled Cohort Equation due to missing variables (age, race, systolic blood pressure, antihypertensive treatment status, smoking status, high-density lipoprotein [HDL], total cholesterol level, and diabetes status). Diabetes was defined by the presence of any one of the following criteria: 1) glucose of >200 mg/dl on two separate occasions, 2) one inpatient or two outpatient ICD-9 codes plus glucose >126 mg/dl on two separate occasions, or 3) glucose > 200 mg/dl on one occasion plus treatment with an oral hypoglycemic or insulin for 30 days or longer. Antihypertensive therapy was defined as treatment with an antihypertensive agent for 30 days or longer. The systolic blood pressure value used for ASCVD risk calculation was the systolic blood pressure value closest to the baseline date, within a window of 1 year prior to and 6 months after baseline. HCV-infected participants who received HCV treatment during follow up were also excluded, given the potential for HCV treatment and clearance to modify clinical outcomes of interest, including mortality and cardiovascular disease. HCV-uninfected subjects who subsequently had a positive HCV serology or viral load during the follow-up period were also excluded. Figure 1 illustrates the derivation of the cohort.

The primary outcomes were: 1) incident MI, defined as 1 inpatient or 2 outpatient ICD-9 codes with date of diagnosis >6 months after study entry, 2) incident coronary heart disease (CHD), defined as incident MI, CABG, and/or PTCA occurring >6 months after entry, by 1 inpatient or 2 outpatient ICD-9 codes, 3) incident stroke, defined as 1 inpatient or 2

outpatient ICD-9 codes with date of diagnosis >6 months after study entry, 4) incident ASCVD event, defined as incident CHD plus stroke occurring 6 months after entry; and 5) incident ASCVD event plus death from any cause. Incident ASCVD event plus death was examined as an outcome to explore potential cardiovascular-related deaths that would not have been captured by an ICD-9 code for a CVD event. We examined the Pooled Cohort Equation ASCVD risk score, calculated for each participant using the published sex and race-specific equations (19), as a predictor for the above outcomes.

Statistical Analysis

Baseline demographic, clinical, and ASCVD risk score and risk category (low, <7.5% vs high, ≥7.5%) were examined and compared between HCV-infected and uninfected controls using t-tests, Wilcoxon tests, and chi-square tests. Event rates over the follow-up period were calculated for each of the outcomes of interest, by HCV status. Multivariable Cox proportional hazards models were constructed for incident ASCVD, adjusting for ASCVD score, HCV infection, and the interaction between ASCVD score and HCV infection, to determine if HCV status is associated with risk for incident ASCVD beyond that predicted by the ASCVD risk score. Performance of the Pooled Cohort Equation was measured by examining ASCVD risk discrimination and calibration of the score over the range of risk scores. To measure discrimination, C-statistics were calculated for the HCV infected and uninfected groups separately and within each group by race (white, black, other) for the ASCVD equation alone and with HCV status added to the model. Net reclassification index (NRI) values for the addition of HCV to the model were calculated in each group. Calibration of the score was measured by Hosmer-Lemeshow statistic, comparing observed vs predicted 10-year risk by deciles of predicted risk. All analyses were performed using SAS 9.4 (Cary, NC, U.S.A.).

Institutional Review Board Approval

The study was determined by the University of California, Los Angeles Institutional Review Board (IRB) to be exempt from IRB review. ERCHIVES is approved by the IRB at VA Pittsburgh Healthcare System.

Results

A total of 70,490 HCV-infected and 97,766 HCV-uninfected male participants were included in the cohort. Baseline characteristics of the cohort are summarized in Table 1 and in Table 2, stratified by ASCVD risk category (<7.5% and ≥7.5%). The HCV-infected and uninfected groups were similar in age and distribution of race and ethnicity, prevalence of diabetes, systolic blood pressure, baseline treatment with antihypertensive medication, and HDL levels. The HCV-infected group had slightly lower BMI, higher alanine aminotransferase (ALT) levels, and lower total cholesterol, LDL, and triglyceride levels. HCV-infected participants were likely less likely to be on lipid-lowering therapy and more likely to be a current smoker and have a history of alcohol or drug abuse. Average predicted 10-year risk for first ASCVD event based on baseline characteristics was the same, 14% in both the HCV-infected and uninfected groups. The majority (approximately 70%) of patients in both groups had high predicted ASCVD risk ≥7.5%. Amongst the high ASCVD risk group, only

25.3% were on statin therapy compared to 45.1% of HCV-uninfected persons (Table 2). Amongst both the HCV-infected and HCV-uninfected groups, the ASCVD risk score (high vs low) appeared driven by similar magnitudes of difference in the risk equation components of age, race, blood pressure, diabetes, and total and HDL cholesterol.

Unadjusted event rates for incident MI, CHD, stroke, ASCVD, and ASCVD + death during the follow-up period are presented in Table 3. Rates of incident MI and CHD were higher amongst HCV-uninfected persons than HCV-infected persons, whereas the rate of incident stroke was higher amongst HCV-infected persons. Overall, the incident ASCVD rate was not different between the groups, but the rate of death from any cause was higher among HCV-infected than in HCV-uninfected persons. In the Cox proportional hazards model for incident ASCVD, after adjusting for ASCVD risk score, HCV infection was not associated with incident ASCVD event (hazard ratio [HR] 0.96, 95% CI [0.90–1.02], $p=0.14$), but there was a significant interaction effect between ASCVD risk score and HCV infection on incident ASCVD, where the presence of HCV infection increased the hazard of having an ASCVD event with increasing ASCVD score (HR 1.34, 95% CI [1.02, 1.76], $p=0.04$) (Table 4a). Adjusting for ASCVD score, amongst participants with low predicted ASCVD risk ($<7.5\%$), HCV infection was associated with a 41% lower risk for incident ASCVD event, whereas amongst participants with high predicted ASCVD risk ($\geq 7.5\%$), HCV infection was associated with a 19% higher risk for incident ASCVD event (Table 4b).

Performance of the ASCVD risk score

Discrimination of ASCVD risk by the ASCVD risk score in HCV-infected and uninfected persons in the cohort—Examining C-statistics in the HCV-infected and uninfected groups and within each group by race (white, black, other), the ASCVD risk score performed poorly in discriminating between individuals who had an ASCVD event and those who did not across all groups, with C-statistic values of 0.58–0.63 (see Table 5). The addition of HCV infection to the model marginally improved C-statistic values in the training set (by 0.01–0.02), with improvement in classification measured by NRI overall and in all subgroups except amongst those of black race.

Calibration of the ASCVD risk score for HCV-infected and uninfected persons in the cohort—Table 6 provides the number of observed vs expected individuals with an ASCVD event during the follow-up period. At the lower spectrum of predicted ASCVD risk (deciles 1–4), there were fewer observed ASCVD events than expected. For deciles 7–9 of predicted risk, there were more events than predicted by the ASCVD risk score. Across all deciles, there was a significant difference in expected vs observed events by chi-square test, $p<0.0001$, suggesting inadequate calibration of the ASCVD risk equation for prediction of ASCVD events in the cohort, with overestimation of risk at lower predicted risk and underestimation at higher predicted risk. This pattern was similarly found by HCV subgroup (infected and uninfected).

Discussion

We found that the performance of the ASCVD risk score and the impact of HCV infection on incident CVD events in our cohort varied depending on the level of ASCVD risk. While

in the overall cohort there was not an independent association of HCV with incident ASCVD risk, the association of HCV with ASCVD risk was modified by estimated ASCVD risk score. At higher predicted risk ($\geq 7.5\%$), HCV was associated with increased risk for an ASCVD event, whereas at lower risk ($<7.5\%$), HCV was associated with decreased risk for an ASCVD event. Correspondingly, examining the calibration of the ASCVD risk equation for prediction of ASCVD event, it appears that the equation performs well (observed and predicted number of events being similar) for the average risk patient in the cohort, but performs poorly at lower and higher risk. This is of particular concern with higher risk patients, where ASCVD risk appears to be underestimated. Notably, in the cohort, HCV-infected persons were much less likely than HCV-uninfected persons to be on a lipid-lowering medication, and only 21% of HCV-infected patients were on a lipid-lowering agent, despite the majority (71%) having an ASCVD risk score $\geq 7.5\%$. This discrepancy suggests under-treatment for CVD prevention in HCV-infected persons, perhaps driven by both low cholesterol levels (well-established now to be associated with chronic HCV infection) and unproven concern for hepatotoxicity with statin therapy (20, 21), and highlights a missed opportunity for CVD prevention.

Based on traditional risk factors included in the ASCVD risk equation, there was no difference in calculated ASCVD risk score between HCV-infected and uninfected subjects. We also interestingly found no difference in overall incident ASCVD event rates comparing HCV-infected and uninfected patients. However, there appear to be potential differences in the type of ASCVD event experienced by HCV-infected and uninfected persons, with higher rates of coronary disease events (incident MI and CHD) amongst HCV-uninfected persons compared to a higher rate of stroke amongst HCV-infected persons in our cohort. The association of HCV with ischemic stroke and carotid atherosclerosis has been reported in multiple studies, where HCV infection was associated with both higher risk of stroke and younger age at stroke event (10, 22). Interestingly, HCV has been isolated in carotid plaque, including in patients without detectable serum HCV RNA (23). Data published previously from ERCHIVES demonstrated higher rates of CVD amongst HCV-infected persons compared to uninfected controls after adjustment for traditional risk factors, but CHF was included in the CVD definition (whereas we focused in this analysis on atherosclerotic CVD) (2), which may have driven the higher CVD event rates in the HCV-infected group. The association of HCV infection with heart failure is supported by other studies (8, 24). We also saw higher rates of death amongst HCV-infected vs HCV-uninfected subjects, some of which may have been cardiac-related deaths, but cause of death was not available for analysis.

In our analysis, the ASCVD risk equation performed poorly by C-statistics in discriminating between high and low risk individuals in both the HCV-infected and uninfected groups. A limitation to interpretation of the performance characteristics of the risk equation is that the ASCVD risk score was derived utilizing a different dataset, without adjustment. The limited follow-up time (mean of 4.8 years in the HCV group) may also have impacted the performance of the risk score, particularly in the lower risk participants, where observed events were fewer than predicted by the ASCVD risk score.

Our study highlights that as traditional risk factors for CVD accumulate in aging HCV patients, HCV may significantly increase risk for a CVD event, and the recommended Pooled Cohort ASCVD risk equation may underestimate such risk. Including HCV status as a predictor, in addition to the ASCVD risk score, did not meaningfully improve risk prediction. Either adjustment of the ASCVD Cox model or further adjustment for other CVD risk factors that may variably be associated with HCV (such as hepatic steatosis, fibrosis stage, drug or alcohol use, and chronic kidney disease) may be needed to improve CVD risk prediction for HCV-infected persons.

References

1. Ishizaka N, Ishizaka Y, Takahashi E, Tooda E, Hashimoto H, Nagai R, et al. Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening. *Lancet*. 2002; 359(9301):133–5. [PubMed: 11809259]
2. Butt AA, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. *Clin Infect Dis*. 2009; 49(2):225–32. [PubMed: 19508169]
3. Alyan O, Kacmaz F, Ozdemir O, Deveci B, Astan R, Celebi AS, et al. Hepatitis C infection is associated with increased coronary artery atherosclerosis defined by modified Reardon severity score system. *Circ J*. 2008; 72(12):1960–5. [PubMed: 18957787]
4. Petta S, Macaluso FS, Craxi A. Cardiovascular diseases and HCV infection: a simple association or more? *Gut*. 2014; 63(3):369–75. [PubMed: 24295849]
5. Adinolfi LE, Restivo L, Zampino R, Guerrera B, Lonardo A, Ruggiero L, et al. Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis. *Atherosclerosis*. 2012; 221(2):496–502. [PubMed: 22385985]
6. Hsu YH, Muo CH, Liu CY, Tsai WC, Hsu CC, Sung FC, et al. Hepatitis C virus infection increases the risk of developing peripheral arterial disease: a 9-year population-based cohort study. *J Hepatol*. 2015; 62(3):519–25. [PubMed: 25263004]
7. Pothineni NV, Delongchamp R, Vallurupalli S, Ding Z, Dai Y, Hagedorn CH, et al. Impact of hepatitis C seropositivity on the risk of coronary heart disease events. *Am J Cardiol*. 2014; 114(12):1841–5. [PubMed: 25438910]
8. Tsui JI, Whooley MA, Monto A, Seal K, Tien PC, Shlipak M. Association of hepatitis C virus seropositivity with inflammatory markers and heart failure in persons with coronary heart disease: data from the Heart and Soul study. *J Card Fail*. 2009; 15(5):451–6. [PubMed: 19477406]
9. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 129(25 Suppl 2):S49–73. [PubMed: 24222018]
10. Adinolfi LE, Restivo L, Guerrera B, Sellitto A, Ciervo A, Iuliano N, et al. Chronic HCV infection is a risk factor of ischemic stroke. *Atherosclerosis*. 2013; 231(1):22–6. [PubMed: 24125405]
11. Ambrosino P, Lupoli R, Di Minno A, Tarantino L, Spadarella G, Tarantino P, et al. The risk of coronary artery disease and cerebrovascular disease in patients with hepatitis C: A systematic review and meta-analysis. *Int J Cardiol*. 2016; 221:746–54. [PubMed: 27428315]
12. Liao CC, Su TC, Sung FC, Chou WH, Chen TL. Does hepatitis C virus infection increase risk for stroke? A population-based cohort study. *PLoS One*. 2012; 7(2):e31527. [PubMed: 22363662]
13. Butt AA, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. *Clin Infect Dis*. 2009; 49(2):225–32. [PubMed: 19508169]
14. Butt AA, Khan UA, McGinnis KA, Skanderson M, Kent Kwok C. Co-morbid medical and psychiatric illness and substance abuse in HCV-infected and uninfected veterans. *J Viral Hepat*. 2007; 14(12):890–6. [PubMed: 18070293]
15. Butt AA, Justice AC, Skanderson M, Good C, Kwok CK. Rates and predictors of hepatitis C virus treatment in HCV-HIV-coinfected subjects. *Aliment Pharmacol Ther*. 2006; 24(4):585–91. [PubMed: 16907891]

16. Butt AA, Justice AC, Skanderson M, Rigsby MO, Good CB, Kwok CK. Rate and predictors of treatment prescription for hepatitis C. *Gut*. 2007; 56(3):385–9. [PubMed: 17005764]
17. Fultz SL, Skanderson M, Mole LA, Gandhi N, Bryant K, Crystal S, et al. Development and verification of a “virtual” cohort using the National VA Health Information System. *Med Care*. 2006; 44(8 Suppl 2):S25–30. [PubMed: 16849965]
18. McGinnis KA, Skanderson M, Levin FL, Brandt C, Erdos J, Justice AC. Comparison of two VA laboratory data repositories indicates that missing data vary despite originating from the same source. *Med Care*. 2009; 47(1):121–4. [PubMed: 19106740]
19. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D’Agostino RB Sr, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014; 63(25 Pt B):2935–59. [PubMed: 24239921]
20. Onofrei MD, Butler KL, Fuke DC, Miller HB. Safety of statin therapy in patients with preexisting liver disease. *Pharmacotherapy*. 2008; 28(4):522–9. [PubMed: 18363535]
21. Tandra S, Vuppalanchi R. Use of statins in patients with liver disease. *Curr Treat Options Cardiovasc Med*. 2009; 11(4):272–8. [PubMed: 19627660]
22. Huang H, Kang R, Zhao Z. Is hepatitis C associated with atherosclerotic burden? A systematic review and meta-analysis. *PLoS One*. 2014; 9(9):e106376. [PubMed: 25184517]
23. Boddi M, Abbate R, Chellini B, Giusti B, Giannini C, Pratesi G, et al. Hepatitis C virus RNA localization in human carotid plaques. *J Clin Virol*. 2010; 47(1):72–5. [PubMed: 19896417]
24. Perticone M, Miceli S, Maio R, Caroleo B, Sciacqua A, Tassone EJ, et al. Chronic HCV infection increases cardiac left ventricular mass index in normotensive patients. *J Hepatol*. 2014; 61(4):755–60. [PubMed: 24882051]

Figure 1.
Derivation of cohort

Table 1

Baseline characteristics of the cohort and predicted 10-year ASCVD risk by HCV status.

Characteristic	HCV-infected N=70,490	HCV-uninfected N=97,766	P-value
Age (years), mean (SD)	54.86 (6.79)	54.75 (7.56)	0.003
Race/Ethnicity			<.0001
White Non-Hispanic	55.6%	56.6%	
Black	28.5%	27.7%	
Hispanic	3.4%	4.0%	
Other	12.5%	11.7%	
BMI, mean (kg/m ²)	27.7 (6.2)	29.5 (7.1)	<.0001
Systolic blood pressure (mmHg), mean (SD)	133.7 (19.3)	134.0 (18.6)	0.0002
ALT (U/L), mean (SD)	63.6 (65.5)	34.1 (33.4)	<.0001
Chronic kidney disease			<.0001
Stage 1	35.6%	25.9%	
Stage 2	46.9%	55.0%	
Stage 3	12.4%	14.6%	
Stage 4	2.1%	1.8%	
Stage 5	3.0%	2.7%	
(Missing)	35167	53556	
Diabetes	15.62%	14.42%	<.0001
Baseline HCV RNA log ₁₀ IU/ml, mean (SD) (n=50,888)	3.9 (2.4)	N/A	
History of drug abuse	24.0%	8.7%	<.0001
History of alcohol abuse	24.8%	12.9%	<.0001
Total cholesterol (mg/dL), mean (SD)	173.7 (39.8)	192.5 (41.8)	<.0001
HDL-C (mg/dL), mean (SD)	46.5 (18.0)	45.8 (16.5)	<.0001
LDL-C (mg/dL), mean (SD)	100.8 (32.9)	114.4 (33.7)	<.0001
Triglycerides (mg/dL), mean (SD)	140.4 (129.8)	172.1 (167.6)	<.0001
Smoking status			<.0001
Current	70.1%	49.5%	
Former	16.8%	22.2%	
Never	13.1%	28.3%	
On antihypertensive medication	41.8%	41.8%	0.92
On lipid lowering medication	20.7%	38.7%	<.0001

Characteristic	HCV-infected N=70,490	HCV-uninfected N=97,766	P-value
Cirrhosis (FIB-4>3.5)	14.7%	2.2%	<.0001
Baseline predicted 10-year risk for first ASCVD event using the ASCVD Pooled Cohort Equation, %, mean (SD)	14 % (1%)	14 % (1%)	0.3
ASCVD risk category			<.0001
Low (<7.5%)	28.9%	30.1%	
High (7.5%)	71.1%	69.9%	
Mean follow-up (years), mean (SD)	4.82 (3.53)	6.03 (3.66)	<.0001

HCV = hepatitis C virus; BMI = body mass index; ALT = alanine aminotransferase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

Table 2

Baseline characteristics of the cohort by predicted 10-year ASCVD risk and HCV status.

Characteristic	HCV-infected ASCVD risk <7.5% N=20,337	HCV-infected ASCVD risk ≥7.5% N=50,153	HCV-uninfected ASCVD risk <7.5% N=29,454	HCV-uninfected ASCVD risk ≥7.5% N=68,312
Age (years), mean (SD)	50.2 (4.94)	56.8 (6.52)	49.4 (5.13)	57.1 (7.27)
Race/Ethnicity				
White Non-Hispanic	63.7%	52.4%	60.2%	55.1%
Black	16.3%	33.3%	20.6%	30.7%
Hispanic	5.0%	2.8%	5.2%	3.4%
Other	15.0%	11.5%	14.0%	10.8%
BMI, mean (kg/m ²)	27.0 (6.6)	27.9 (6.0)	28.9 (6.7)	29.8 (7.3)
Systolic blood pressure (mmHg), mean (SD)	123.8 (15.6)	137.7 (19.3)	124.8 (14.8)	138.0 (18.6)
ALT (U/L), mean (SD)	70.4 (74.0)	60.9 (61.5)	36.5 (33.3)	33.1 (33.4)
Chronic kidney disease				
Stage 1	45.1%	32.4%	33.1%	23.4%
Stage 2	45.0%	47.6%	56.9%	54.4%
Stage 3	6.8%	14.3%	7.3%	17.0%
Stage 4	1.1%	2.4%	0.7%	2.2%
Stage 5	2.1%	3.3%	1.9%	2.9%
(Missing)	11350	23817	18318	35238
Diabetes	2.8%	19.2%	3.2%	21.0%
Baseline HCV RNA log ₁₀ IU/ml, mean (SD) (n=14,371 and 36,517)	3.87 (2.35)	3.91 (2.42)		
History of drug abuse	27.5%	22.6%	10.2%	8.0%
History of alcohol abuse	28.8%	23.1%	14.3%	12.3%
Total cholesterol (mg/dL), mean (SD)	165.7 (37.1)	177.0 (40.43)	187.8 (37.05)	194.6 (43.45)
HDL-C (mg/dL), mean (SD)	51.9 (19.6)	44.3 (16.7)	50.4 (18.3)	43.8 (15.3)
LDL-C (mg/dL), mean (SD)	93.0 (30.9)	104.0 (33.2)	111.2 (32.6)	115.7 (34.0)
Triglycerides (mg/dL), mean (SD)	111.5 (75.7)	152.0 (144.4)	140.4 (103.3)	185.6 (187.0)
Smoking status				
Current	57.2%	75.3%	31.4%	57.2%
Former	23.3%	14.1%	27.4%	20.0%
Never	19.5%	10.6%	41.2%	22.8%
On antihypertensive medication	20.5%	50.4%	19.9%	51.2%

Characteristic	HCV-infected ASCVD risk <7.5% N=20,337	HCV-infected ASCVD risk ≥7.5% N=50,153	HCV-uninfected ASCVD risk <7.5% N=29,454	HCV-uninfected ASCVD risk ≥7.5% N=68,312
On lipid lowering medication	9.2%	25.3%	23.8%	45.1%
Cirrhosis (FIB-4>3.5)	14.1%	15.0%	1.7%	2.5%
Mean follow-up (years), mean (SD)	5.48 (3.72)	4.55 (3.42)	6.61 (3.68)	5.78 (3.63)

HCV = hepatitis C virus; BMI = body mass index; ALT = alanine aminotransferase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

Table 3

Cardiovascular events during follow-up, by HCV status

Event	HCV-infected N=70,490		HCV-uninfected N=97,766		P-value
	Number of events	Event rate/1000 person-years	Number of events	Event rate/1000 person-years	
Incident MI	2461	7.45 (7.16,7.75)	4879	8.60 (8.36,8.84)	<0.001
Incident CHD	2622	7.95 (7.65,8.26)	5266	9.31 (9.06,9.56)	<0.001
Incident stroke	1945	5.83 (5.57,6.08)	2700	4.65 (4.48,4.83)	<0.001
Incident ASCVD	4277	13.15 (12.76,13.55)	7476	13.38 (13.08,13.69)	0.37
Incident ASCVD + Death (from any cause)	6327	19.45 (18.98,19.93)	8762	15.69 (15.36,16.01)	<0.001

HCV = hepatitis C virus; MI = myocardial infarction; CHD = coronary heart disease; ASCVD = atherosclerotic cardiovascular disease

Tables 4a and 4b

Cox proportional hazards model for association of HCV infection with incident ASCVD

4a.		
	Hazard Ratio (95% CI)	P-value
HCV infection	0.96 (0.90, 1.02)	0.14
ASCVD risk score	20.87 (17.78, 24.49)	<.0001
ASCVD score by HCV infection	1.34 (1.02, 1.76)	0.04

4b.		
	Hazard Ratio (95% CI)	P-value
HCV Infection + low ASCVD <7.5% vs HCV–	0.59 (0.55, 0.63)	<.0001
HCV Infection + high ASCVD (score ≥ 7.5%) vs HCV–	1.19 (1.14, 1.24)	<.0001
ASCVD risk score	23 (20.20, 26.19)	<.0001

HCV = hepatitis C virus; ASCVD = atherosclerotic cardiovascular disease

Table 5

Performance of ASCVD risk equation in ASCVD risk discrimination by HCV status and race/ethnicity, with and without HCV status in the model

	HCV+	Uninfected	HCV+ White	Uninfected White	HCV+ Black	Uninfected Black	HCV+ Other	Uninfected Other
C-statistic for ASCVD equation alone (95% CI)	0.6 (0.59, 0.61)	0.61 (0.6, 0.62)	0.58 (0.57, 0.59)	0.6 (0.59,0.61)	0.6 (0.58, 0.61)	0.63 (0.62,0.64)	0.59 (0.57, 0.62)	0.62 (0.6, 0.64)
C-statistic for ASCVD equation + HCV status (95% CI)	All	White	Black	Other				
	0.61 (0.6, 0.61)	0.6 (0.6, 0.61)	0.61 (0.6, 0.62)	0.61 (0.6, 0.63)				
Net reclassification index for addition of HCV variable (p-value)	All	White	Black	Other				
	0.12 (p<0.0001)	0.16 (p<0.0001)	0.03 (p=0.08)	0.15 (p<0.0001)				

ASCVD = atherosclerotic cardiovascular disease; HCV = hepatitis C virus

Table 6

Observed vs predicted incident ASCVD events during follow-up in the cohort by ASCVD risk equation

6a. Whole cohort			
Decile of predicted 10-year ASCVD risk (lowest to highest)	Number of participants	Incident ASCVD event	
		Observed	Expected
1	16831	600	840.60
2	16829	797	893.41
3	16824	863	935.06
4	16830	950	977.96
5	16825	1029	1024.90
6	16826	1161	1081.68
7	16826	1265	1155.59
8	16828	1403	1263.31
9	16826	1626	1451.59
10	16811	2059	2129.04

6b. HCV-infected group only			
Decile of predicted 10-year ASCVD risk (lowest to highest)	Number of participants	Incident ASCVD event	
		Observed	Expected
1	7050	260	307.97
2	7049	311	327.38
3	7053	320	342.54
4	7047	343	357.37
5	7048	374	374.30
6	7049	392	394.69
7	7050	445	421.53
8	7050	497	460.09
9	7051	581	525.96
10	7043	754	765.22

6c. HCV-uninfected group only			
Decile of predicted 10-year ASCVD risk (lowest to highest)	Number of participants	Incident ASCVD event	
		Observed	Expected
1	9779	337	533.45
2	9777	488	566.44
3	9777	540	593.26
4	9776	607	620.64
5	9777	652	651.00
6	9778	775	687.34
7	9778	821	734.26
8	9777	910	802.94

6c. HCV-uninfected group only			
Decile of predicted 10-year ASCVD risk (lowest to highest)	Number of participants	Incident ASCVD event	
		Observed	Expected
9	9777	1052	925.72
10	9770	1294	1361.02

p<0.0001 by Hosmer Lemeshow goodness-of-fit

P=0.0052 by Hosmer Lemeshow goodness-of-fit

p<0.0001 by Hosmer Lemeshow goodness-of-fit