Published in final edited form as:

J Card Fail. 2009 June ; 15(5): 451–456. doi:10.1016/j.cardfail.2008.12.003.

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

JUDITH I. TSUI, MD, MPH¹, MARY A. WHOOLEY, MD^{2,3,4}, ALEXANDER MONTO, MD^{3,5}, KAREN SEAL, MD, MPH^{2,3}, PHYLLIS C. TIEN, MD^{3,6}, and MICHAEL SHLIPAK, MD, MPH^{2,3,4}

¹ Section of General Internal Medicine, Department of Medicine, Boston University School of Medicine/Boston Medical Center

² Divisions of General Internal Medicine, Department of Medicine, University of California, San Francisco, CA

³ Department of Medicine, Veterans Affairs Medical Center, San Francisco, CA

⁴ Department of Epidemiology and Biostatistics, University of California, San Francisco, CA

⁵ Gastroenterology and Hepatology, University of California, San Francisco, CA

⁶ Infectious Diseases, Department of Medicine, University of California, San Francisco, CA

Abstract

Background—How hepatitis C virus (HCV) affects coronary heart disease (CHD) risk factors and outcomes is largely unknown.

Methods and Results—Among a cohort of patients with stable CHD, we examined the association between HCV seropositivity and levels of inflammatory markers (C-reactive protein [CRP], fibrinogen, interleukin-6, and tumor necrosis factor [TNF]- α) and risk for the following outcomes: death, cardiovascular (CV) events, and heart failure events. A total of 84 (8.6%) participants were found to be seropositive for HCV. HCV-seropositive patients were found to have significantly lower adjusted mean levels of CRP (2.6 vs. 4.4; $P < .01$) and fibrinogen (340 vs. 398; $P < .01$), but higher levels of TNF- α (7.1 vs. 4.8; $P < .01$). Age-adjusted rates for HCV seropositive vs. seronegative were as follows: death 93 vs. 42/1,000 p-y ($P < .01$), CV events 62 vs. 40 ($P = .13$), and heart failure 76 vs. 29 ($P < .01$). After adjustment for demographic and clinical factors, HCV remained significantly associated with an increased risk for heart failure events (HR = 2.13; 95% CI: 1.19–3.80).

Conclusions—In this cohort with CHD, HCV seropositive participants had higher rates of death, CV events, and heart failure hospitalizations during follow-up. After adjustment for CV risk factors, HCV seropositivity remained independently associated with risk for heart failure events.

Keywords

Hepatitis C virus; inflammatory markers; heart failure

Reprint requests: Judith I. Tsui, MD, MPH, General Internal Medicine, Boston Medical Center, 801 Massachusetts Ave, Boston, MA 02118. Tel: (617) 414-6912; Fax: (617) 414-4676. judith.tsui@gmail.com.

All decisions regarding this manuscript were made by a Guest Editor.

Conflict of interest: none.

Approximately 4 million Americans are estimated to have been infected with hepatitis C virus (HCV) and the majority of those infected are currently in their 4th and 5th decades of life.¹ As individuals with HCV begin to age, they will inevitably face common comorbidities such as cardiovascular diseases. It is unknown how infection with HCV affects coronary heart disease (CHD) progression and outcomes.

Infectious etiologies have been hypothesized to contribute to the inflammatory cascade leading to atherosclerosis.² Some studies have found cross-sectional associations between HCV and cardiomyopathies,^{3,4} coronary atherosclerosis,^{5–7} carotid artery plaque,^{8,9} and increased pulse wave velocity,¹⁰ although not all studies support these findings.^{11–15} A recent epidemiologic study showed that HCV-seropositive blood donors had higher rates of cardiovascular mortality compared to uninfected donors.¹⁶ Furthermore, HCV infection is recognized to cause chronic immune stimulation, leading to an inflammatory response and cytokine production.¹⁷ These altered cytokine profiles observed in the setting of chronic HCV could potentially lead to adverse cardiovascular outcomes.¹⁸

Based on these prior findings, we conducted this study to explore the relationship between HCV seropositivity and inflammatory markers and clinical outcomes among individuals with established CHD. We hypothesized that HCV-seropositive participants might be distinguished by different levels of inflammatory markers and increased risk for subsequent CHD events.

Methods

Study Participants

The Heart and Soul study is an ongoing prospective cohort study designed to determine how psychosocial factors influence disease progression in persons with coronary disease. Methods have been described in depth previously.^{19,20} In brief, administrative databases were used to identify outpatients with documented CHD at two Department of Veterans Affairs Medical Centers (San Francisco and Palo Alto), 1 university medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had known CHD documented by at least 1 of the following: a history of myocardial infarction (MI), angiographic evidence of $\geq 50\%$ stenosis in one or more coronary vessels, prior evidence of inducible ischemia by treadmill or nuclear testing, or a history of coronary revascularization. Between September 2000 and December 2002, 1024 participants were enrolled and attended a baseline study appointment that included a medical history interview, a physical examination, and a comprehensive health status questionnaire, as well as blood draw for serum and plasma samples. This study cohort was restricted to 981 participants with HCV antibody test results. HCV serostatus was determined from documentation of a prior positive HCV antibody test in the patient's medical record ($n = 27$), or if no evidence of prior testing existed, from testing baseline serum samples ($n = 964$) using a 3rd-generation anti-HCV immunoassay (Johnson & Johnson's Vitros Anti-HCV Assay). Results were reported as positive, negative, or indeterminate as recommended by Centers for Disease Control and Prevention guidelines.²¹ Indeterminate results were excluded from the analysis ($n = 10$).

Measurement of Inflammatory Markers

Participants were instructed to fast for 12 hours (except for medications), not to take aspirin for 1 week, and not to smoke for 5 hours before their study appointment. Venous blood samples were obtained, and plasma and serum samples were stored at -70°C until the time of the assay. Laboratory technicians who assayed the inflammatory markers were blinded to clinical characteristics. We used the Roche Integra high-sensitivity assay to measure C-reactive protein (CRP) in 229 participants and (because of a change in lab protocol) the Beckman Extended

Range high-sensitivity CRP assay to measure CRP in the remaining 756 participants. Serum fibrinogen levels were determined by the Clauss assay.²² We used the R&D Systems (Minneapolis, MN) Quantikine HS IL-6 immunoassay to determine the concentration of interleukin (IL)-6. We used the Human Serum Adipokine Panel B LINCOplex Kit (Linco Research, Inc., St. Charles, MO) to measure tumor necrosis factor (TNF)- α .

Longitudinal Outcome Measures

We examined the following outcomes: all-cause mortality; cardiovascular (CV) events defined as CHD death, MI, or stroke; and heart failure (HF). We conducted annual telephone follow-up interviews with participants (or their proxy) and asked about death or hospitalization for “heart trouble.” For any reported event, medical records, electrocardiograms, death certificates, and coroner’s reports were retrieved and reviewed by 2 independent and blinded adjudicators. If the adjudicators agreed on the outcome classification, their classification was binding. In the event of disagreement, consultation from a third blinded adjudicator was performed. All-cause mortality was determined by review of death certificates. Nonfatal MI was defined using the American Heart Association diagnostic criteria.²³ A CHD death was defined as a death occurring during the same hospitalization in which an acute MI was documented or a death occurring within 1 hour of the onset of terminal symptoms not explained by other etiologies. Stroke was defined as a new neurologic deficit not known to be secondary to brain trauma, tumor, infection, or other cause. An HF event was based on Framingham criteria and defined as hospitalization for a clinical syndrome involving at least 2 of the following: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, and cardiomegaly or pulmonary edema on chest radiography.²⁴

Other Covariates

We examined the following characteristics as potential confounding variables: age, gender, race (white vs. non-white), education status (high school vs. non-high school graduate), body mass index (BMI), being physically active, current smoking, regular alcohol use (>4 drinks per week), recent (past year) illicit drug use, diabetes, hypertension, HIV, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, systolic and diastolic blood pressure, and use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), aspirin, β -blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARBs). Data on age, race/ethnicity, education, physical activity level, smoking status, alcohol use, illicit drug use, and medical comorbidities were determined by participant self-report. Study personnel recorded use of all medications at baseline study visit. Medication categories were categorized using Epocrates Rx (San Mateo, CA). Serum cholesterol was measured from fasting venous blood samples.

Statistical Analysis

We examined differences in demographic and clinical variables between HCV seropositive and seronegative participants using *t*-tests for continuous variables and chi-squared tests for categorical variables. We compared the adjusted means of inflammatory markers and cholesterol of HCV-seropositive and HCV-seronegative participants, using linear regression to adjust for age, sex, race, smoking, BMI, diabetes, hypertension, HIV, drug use, physical activity, aspirin, statin, β -blocker and ACE inhibitor/ARB use. These covariates were chosen on the basis of literature review and significant associations with HCV status observed in univariate analysis. All inflammatory marker values, except for fibrinogen, were transformed for analysis using natural logarithm because of highly skewed data, and were back transformed for presentation of results. For cholesterol, we experimented with log transforming to account for more mild skewness in the data, but found that results were similar; we chose therefore to use non-transformed variables in the analyses.

To compare the risk of outcomes among anti-HCV-positive and negative participants, we compared age-adjusted incidence rates using Poisson regression and constructed Cox proportional hazards models for each outcome: all-cause death; CV events; and HF events. For our Cox proportional hazards models, we adjusted for age, sex, race, smoking, BMI, HIV, diabetes, hypertension, physical activity, illicit drug use, statin use, aspirin use, β -blocker use, ACE inhibitor/ARB use, total cholesterol, HDL, log CRP, fibrinogen, log IL-6, and log TNF- α . We adjusted sequentially for demographic variables, clinical variables, and inflammatory markers. To avoid overfitting the model, we used a stepwise backward selection procedure for covariates, retaining all demographic variables in each model. Other covariates were retained in the adjusted models if they had either a $P < .2$ for the outcome, or if their inclusion in the model caused the parameter estimate for HCV to change by more than 5%. Cox models were created for each outcome; additionally, to differentiate whether HCV was associated with new cases of HF vs. HF exacerbations, we excluded participants with preexisting diagnoses of HF and reran models examining HF events. Cox models were checked for violation of the proportional hazards assumption by assessing log-minus-log survival plots for patterns of nonproportionality and performing the Schoenfeld test. All statistical analyses were conducted using Stata 8.2 (Stata Corporation, College Station, TX).

Results

Of the 981 participants with CHD, 84 (8.6%) were seropositive for HCV. HCV-seropositive participants were younger, had lower BMI, and were more likely to be current smokers and to have recently used illicit drugs (Table 1). HCV-seropositive participants were also more likely to be HIV positive, although the proportion was still relatively low ($n = 8$ or 10%). There were significant differences in the receipt of CHD treatments: HCV-seropositive participants were less likely to be taking statins, aspirin, β -blockers, ACE inhibitors, or ARBs than seronegative participants. There was no difference in the prevalence of diabetes or in measured blood pressure or resting left ventricular ejection fraction between the groups at baseline.

At baseline, patients with HCV had lower levels of fibrinogen and higher levels of TNF- α (Table 2). They also tended to have lower levels of HDL, but this finding was not statistically significant. After adjustment for age and other covariates, including statin use (which was substantially lower in HCV seropositive patients), we found that participants with HCV had significantly lower levels of all lipid measures. There were also differences in levels of inflammatory markers: adjusted mean levels of CRP and fibrinogen were lower, whereas TNF- α levels were significantly higher for HCV seropositive participants.

Data on follow-up outcomes were available for 970 participants (11 lost to follow-up), and the mean follow-up was 4.1 years (range, 0.1–6.1 years). There were 182 deaths (161 HCV–, 21 HCV+), 151 CV events (137 HCV–, 14 HCV+), and 119 HF hospitalizations (103 HCV–, 16 HCV+) in the follow-up period. Age-adjusted incidence rates were higher among HCV-seropositive participants for all outcomes (Fig 1). Specific rates for HCV-seropositive vs. seronegative patients were as follows: for death, 93 vs. 42 ($P < .01$); for CV events 62 vs. 40 ($P = .13$); for HF hospitalizations 76 vs. 29 ($P < .01$).

To assess whether HCV seropositivity was associated with risk for clinical outcomes independent of other risk factors, we performed Cox-proportional hazards models, adjusting for age, clinical CVD risk factors, and inflammatory markers in a sequential fashion. Adjusting for age, sex, and race, we observed that HCV seropositivity was associated with a greater than 2-fold risk for death and HF hospitalizations, as well as an 80% increased risk for CV events (Table 3). After adjusting for other clinical variables, HCV remained associated with a 50% increase in risk of death and CV events, although the associations were no longer significant. The association of HCV with HF, however, remained 2-fold and significant. Further adjustment

for inflammatory markers had little effect on point estimates and *P* values of results. After excluding participants with a preexisting diagnosis of HF, the association between HCV and HF hospitalizations remained significant (fully adjusted HR =2.25; 95% CI: 1.02–4.97; *P* = .04)

Discussion

Among this cohort with CHD, we found HCV seropositivity to be associated with lower lipids, CRP and fibrinogen levels, and higher levels of IL-6 and TNF- α . Despite lower levels of LDL and CRP, HCV-seropositive participants experienced higher rates of death, CV events, and HF hospitalizations over time. After adjusting for risk factors, treatment differences, and inflammatory markers, HCV-seropositive participants still had a statistically significant 2-fold increase in risk of HF hospitalizations and a 50% elevated risk of death and CV events that did not reach statistical significance.

This is the first study to our knowledge to compare clinical outcomes by HCV serostatus in a cohort with CHD. Our finding that HCV is associated with HF hospitalizations is novel and warrants future investigation. A possible explanation for increased HF hospitalizations could be a higher incidence of cardiomyopathies or myocarditis among participants with HCV. Some studies, primarily from Japan, have noted a high prevalence of HCV infection among patients with cardiomyopathies and myocarditis,^{3,4} although other studies have not confirmed this association.^{14,15} A study of mice transgenic for the HCV core gene found increased development of cardiomyopathy, as evidenced by Doppler echocardiography and histologic changes.²⁵ Although HCV-seropositive participants in our study had similar baseline resting ejection fractions to seronegative participants, their ventricular function may have worsened over time. Another possibility is that HCV could be associated with progressive vascular changes because HCV seropositivity has been associated with accelerated coronary vasculopathy and decreased survival in heart transplant recipients.^{26,27} Also, inflammatory markers IL-6 and TNF- α have been associated with HF severity and outcomes,^{28–31} and our study did find higher levels of TNF- α in HCV-seropositive participants, as has been previously reported.^{32–35} However, adjustment for inflammatory markers did not attenuate the association between HCV and HF in this study, and therefore they do not appear to mediate the association. Another explanation could be that HCV is a marker for other variables that we did not adequately control for such as adherence, quality of care, or social factors that could influence hospitalization. Finally, side effects of chronic HCV such as fatigue or depression could lead to worsened symptoms of HF leading to hospitalization.

Our finding that HCV-seropositive participants had significantly different levels of lipids from HCV-seronegative participants is consistent with most prior research. Several moderately sized clinical studies have also demonstrated that patients with HCV have lower total cholesterol,^{36,37} HDL, and LDL³⁸ compared with healthy controls, and results have been confirmed in population-based studies as well.³⁹ The finding of lower adjusted CRP and fibrinogen levels is also supported by some prior research. One recent study of HIV-infected patients also found that HCV was associated with significantly lower CRP levels.⁴⁰ Another study of patients with chronic HCV demonstrated that CRP levels were lower than healthy controls and levels did not rise after treatment with interferon alpha-2b.⁴¹ Because CRP is synthesized by the liver, there is also biological plausibility to this finding. Physicians may want to use caution when interpreting CRP levels among patients with HCV infection, as standard cutoff ranges may not apply to this special population. We found only one relatively small study that examined fibrinogen in persons with and without HCV and it did not find a significant difference.³⁸

There are several important limitations of this study. This study used HCV antibody status rather than HCV RNA testing, which would more accurately characterize whether participants

had chronic HCV. However, prior research has shown that the great majority (approximately 80%) of individuals with a positive HCV serology will have chronic infection.¹ Furthermore, incorrectly labeling HCV status should have the effect of biasing our results to the null, thus strengthening our positive findings. We did not have information HCV viral genotype or histologic data to determine stage of liver disease. We also did not have data on HCV treatment which is known to effect cholesterol levels and inflammatory markers; however, given that this was a population of predominantly older patients with preexisting heart disease, it seems unlikely that many participants would be actively undergoing HCV treatment at the time of this study. Finally, we examined HF hospitalizations, rather than true incident HF. However, when we excluded individuals who were diagnosed with HF at baseline, we found that HCV was still associated with HF hospitalizations (presumably representing new cases of HF), although we did not have echocardiography data during hospitalizations to confirm.

In conclusion, among this cohort with established CHD, we found that HCV-seropositive participants had higher rates of death, CV events, and HF hospitalizations over time, despite lower cholesterol and CRP levels. After adjustment for other factors, HCV seropositivity remained independently associated with risk for HF hospitalizations, and this was true when excluding participants with a preexisting diagnosis of HF. Levels of CRP, fibrinogen, IL-6, and TNF- α did not appear to mediate the association between HCV and HF, so other causal pathways must be evoked. Further research is needed to confirm these results and explore mechanisms through which HCV might impact risk for cardiovascular disease and disease outcomes.

Acknowledgments

This work was supported by grants from the Department of Veterans Affairs (Epidemiology Merit Review Program); the National Heart, Lung and Blood Institute (R01 HL079235); the Robert Wood Johnson Foundation (Generalist Physician Faculty Scholars Program); the American Federation for Aging Research (Paul Beeson Faculty Scholars in Aging Research Program); and the Ischemia Research and Education Foundation. This publication was also made possible by Grant Number KL2RR024130 from the NCRR, a component of the National Institutes of Health. None of these funding sources had any role in the collection of data, interpretation of results, or preparation of this manuscript. The contents are solely the responsibility of the authors and do not necessarily represent the official view of the organizations listed above. The authors have no conflicts of interest or financial disclosures to report.

References

1. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006;144:705–14. [PubMed: 16702586]
2. Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link? *Lancet* 1997;350:430–6. [PubMed: 9259669]
3. Matsumori A, Matoba Y, Sasayama S. Dilated cardiomyopathy associated with hepatitis C virus infection. *Circulation* 1995;92:2519–25. [PubMed: 7586353]
4. Matsumori A, Shimada T, Chapman NM, Tracy SM, Mason JW. Myocarditis and heart failure associated with hepatitis C virus infection. *J Card Fail* 2006;12:293–8. [PubMed: 16679263]
5. Freiberg MS, Cheng DM, Kraemer KL, Saitz R, Kuller LH, Samet JH. The association between hepatitis C infection and prevalent cardiovascular disease among HIV-infected individuals. *AIDS* 2007;21:193–7. [PubMed: 17197810]
6. Fukui M, Kitagawa Y, Nakamura N, Yoshikawa T. Hepatitis C virus and atherosclerosis in patients with type 2 diabetes. *JAMA* 2003;289:1245–6. [PubMed: 12633185]
7. Vassalle C, Masini S, Bianchi F, Zucchelli GC. Evidence for association between hepatitis C virus seropositivity and coronary artery disease. *Heart* 2004;90:565–6. [PubMed: 15084562]
8. Ishizaka N, Ishizaka Y, Takahashi E, Tooda E, Hashimoto H, Nagai R, et al. Association between hepatitis C virus seropositivity, carotidartery plaque, and intima-media thickening. *Lancet* 2002;359:133–5. [PubMed: 11809259]

9. Ishizaka Y, Ishizaka N, Takahashi E, Unuma T, Tooda E, Hashimoto H, et al. Association between hepatitis C virus core protein and carotid atherosclerosis. *Circ J* 2003;67:26–30. [PubMed: 12520147]
10. Tomiyama H, Arai T, Hirose K, Hori S, Yamamoto Y, Yamashina A. Hepatitis C virus seropositivity, but not hepatitis B virus carrier or seropositivity, associated with increased pulse wave velocity. *Atherosclerosis* 2003;166:401–3. [PubMed: 12535755]
11. Volzke H, Schwahn C, Wolff B, Mentel R, Robinson DM, Kleine V, et al. Hepatitis B and C virus infection and the risk of atherosclerosis in a general population. *Atherosclerosis* 2004;174:99–103. [PubMed: 15135257]
12. Momiyama Y, Ohmori R, Kato R, Taniguchi H, Nakamura H, Ohsuzu F. Lack of any association between persistent hepatitis B or C virus infection and coronary artery disease. *Atherosclerosis* 2005;181:211–3. [PubMed: 15939074]
13. Moritani M, Adachi K, Arima N, Takashima T, Miyaoka Y, Niigaki M, et al. A study of arteriosclerosis in healthy subjects with HBV and HCV infection. *J Gastroenterol* 2005;40:1049–53. [PubMed: 16322949]
14. Dalekos GN, Achenbach K, Christodoulou D, Liapi GK, Zervou EK, Sideris DA, et al. Idiopathic dilated cardiomyopathy: lack of association with hepatitis C virus infection. *Heart* 1998;80:270–5. [PubMed: 9875087]
15. Grumbach IM, Heermann K, Figulla HR. Low prevalence of hepatitis C virus antibodies and RNA in patients with myocarditis and dilated cardiomyopathy. *Cardiology* 1998;90:75–8. [PubMed: 9778541]
16. Guiltinan AM, Kaidarova Z, Custer B, Orland J, Strollo A, Cyrus S, et al. Increased all-cause, liver, and cardiac mortality among hepatitis C virus-seropositive blood donors. *Am J Epidemiol* 2008;167:743–50. [PubMed: 18203734]
17. Jacobson Brown PM, Neuman MG. Immunopathogenesis of hepatitis C viral infection: Th1/Th2 responses and the role of cytokines. *Clin Biochem* 2001;34:167–71. [PubMed: 11408013]
18. Hansson GK. Immune mechanisms in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2001;21:1876–90. [PubMed: 11742859]
19. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. *JAMA* 2003;290:215–21. [PubMed: 12851276]
20. Bibbins-Domingo K, Gupta R, Na B, Wu AH, Schiller NB, Whooley MA. N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. *JAMA* 2007;297:169–76. [PubMed: 17213400]
21. Alter MJ, Kuhnert WL, Finelli L. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2003;52:1–13. 15. [PubMed: 12585742]quiz CE1-4
22. Clauss A. Rapid physiological coagulation method in determination of fibrinogen. *Acta Haematol* 1957;17:237–46. [PubMed: 13434757]
23. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation* 2003;108:2543–9. [PubMed: 14610011]
24. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194–202. [PubMed: 12517230]
25. Omura T, Yoshiyama M, Hayashi T, Nishiguchi S, Kaito M, Horiike S, et al. Core protein of hepatitis C virus induces cardiomyopathy. *Circ Res* 2005;96:148–50. [PubMed: 15618537]
26. 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;23:277–83. [PubMed: 15019636]

27. Gasink LB, Blumberg EA, Localio AR, Desai SS, Israni AK, Lautenbach E. Hepatitis C virus seropositivity in organ donors and survival in heart transplant recipients. *JAMA* 2006;296:1843–50. [PubMed: 17047214]
28. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). *Circulation* 2001;103:2055–9. [PubMed: 11319194]
29. Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation* 2000;102:3060–7. [PubMed: 11120695]
30. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 1996;27:1201–6. [PubMed: 8609343]
31. Tsutamoto T, Hisanaga T, Wada A, Maeda K, Ohnishi M, Fukai D, et al. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. *J Am Coll Cardiol* 1998;31:391–8. [PubMed: 9462584]
32. Nelson DR, Lim HL, Marousis CG, Fang JW, Davis GL, Shen L, et al. Activation of tumor necrosis factor- α system in chronic hepatitis C virus infection. *Dig Dis Sci* 1997;42:2487–94. [PubMed: 9440625]
33. Blackard JT, Kang M, St Clair JB, Lin W, Kamegaya Y, Sherman KE, et al. Viral factors associated with cytokine expression during HCV/HIV co-infection. *J Interferon Cytokine Res* 2007;27:263–9. [PubMed: 17477814]
34. Knobler H, Zhornicky T, Sandler A, Haran N, Ashur Y, Schattner A. Tumor necrosis factor- α -induced insulin resistance may mediate the hepatitis C virus-diabetes association. *Am J Gastroenterol* 2003;98:2751–6. [PubMed: 14687828]
35. Zylberberg H, Rimaniol AC, Pol S, Masson A, De Groote D, Berthelot P, et al. Soluble tumor necrosis factor receptors in chronic hepatitis C: a correlation with histological fibrosis and activity. *J Hepatol* 1999;30:185–91. [PubMed: 10068094]
36. Serfaty L, Andreani T, Giral P, Carbonell N, Chazouilleres O, Poupon R. Hepatitis C virus induced hypobetalipoproteinemia: a possible mechanism for steatosis in chronic hepatitis C. *J Hepatol* 2001;34:428–34. [PubMed: 11322205]
37. Maggi G, Bottelli R, Gola D, Perricone G, Posca M, Zavaglia C, et al. Serum cholesterol and chronic hepatitis C. *Ital J Gastroenterol* 1996;28:436–40. [PubMed: 9032585]
38. Ferroni P, Mammarella A, Martini F, Paoletti V, Cardarello CM, Labbadia G, et al. Increased soluble P-selectin levels in hepatitis C virus-related chronic hepatitis: correlation with viral load. *J Investig Med* 2001;49:407–12.
39. Marzouk D, Sass J, Bakr I, El Hosseiny M, Abdel-Hamid M, Rekacewicz C, et al. Metabolic and cardiovascular risk profiles and hepatitis C virus infection in rural Egypt. *Gut* 2007;56:1105–10. [PubMed: 16956918]
40. Floris-Moore M, Howard AA, Lo Y, Schoenbaum EE, Arnsten JH, Klein RS. Hepatitis C infection is associated with lower lipids and high-sensitivity C-reactive protein in HIV-infected men. *AIDS Patient Care STDS* 2007;21:479–91. [PubMed: 17651029]
41. Kalabay L, Nemesanszky E, Csepregi A, Pusztay M, David K, Horvath G, et al. Paradoxical alteration of acute-phase protein levels in patients with chronic hepatitis C treated with IFN- α 2b. *Int Immunol* 2004;16:51–4. [PubMed: 14688060]

Fig. 1.
Age-adjusted incidence of outcomes by hepatitis C virus status.

Table 1**Sample Characteristics by Hepatitis C Antibody Status**

	HCV Ab Negative	HCV Ab Positive	<i>P</i> Value *
	(n = 897)	(n = 84)	
	Mean ± SD or n (%) [†]	Mean ± SD or % [†]	
Age (y)	67 ± 11	59 ± 11	<.01
Female	161 (18%)	17 (20%)	.61
Non-white	350 (39%)	39 (46%)	.15
High school graduate	783 (88%)	71 (85%)	.42
BMI (kg/m ²)	29 ± 5	26 ± 6	.01
Physically active	567 (64%)	49 (58%)	.34
Current smoker	147 (16%)	46 (57%)	<.01
Regular alcohol use	264 (30%)	21 (25%)	.36
Recent illicit drug use	51 (6%)	24 (29%)	<.01
Diabetes mellitus	230 (26%)	23 (27%)	.75
Hypertension	634 (71%)	52 (62%)	.08
HIV	17 (2%)	8 (10%)	<.01
Statin use	605 (67%)	21 (25%)	<.01
Aspirin use	699 (78%)	57 (68%)	.04
b-blocker use	522 (58%)	37 (44%)	.01
ACE inhibitor/ARB use	470 (52%)	30 (36%)	<.01
Systolic BP	133 (±20)	134 (±23)	.52
Diastolic BP	74 (±11)	76 (±11)	.15
Resting LV ejection fraction	0.62 (±0.1)	0.62 (±0.1)	.89
Low platelets (<130 × 103 μL)	30 (3%)	7 (8%)	.02

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LV, left ventricular; SD, standard deviation.

* Student's *t*-test or chi-square test.

[†] Numbers/percentages may not sum due to missing data; <1% data missing for all covariates.

Table 2

Mean Levels of Inflammatory Markers and Cholesterol by HCV Serostatus*

	Unadjusted Results			Adjusted Results		
	HCV Seronegative		P value	HCV Seronegative		P value
	Mean (95%CI)	HCV Seropositive Mean (95%CI)		Mean (95% CI)	HCV Seropositive Mean (95% CI)	
Total cholesterol (mg/dL)	178 (175–181)	171 (160–181)	.15	180 (177–183)	153 (144–162)	<.01
LDL (mg/dL)	104 (102 to 107)	103 (95–111)	.8	106 (103–108)	91 (84–99)	<.01
HDL (mg/dL)	46 (45–47)	43 (40–46)	.08	46 (45–47)	43 (40–46)	.05
Triglycerides (mg/dL)	142 (133–151)	125 (106–144)	.12	144 (136–152)	105 (72–130)	.01
CRP (mg/L)	4.6 (4.1–5.2)	4.0 (2.5–5.4)	.41	4.4 (4.1–4.8)	2.6 (1.9–3.5)	<.01
Fibrinogen (mg/dL)	397 (391–403)	343 (324–362)	<.01	398 (391–403)	340 (324–362)	<.01
IL-6 (pg/mL)	3.3 (3.1–3.5)	3.7 (3.1–4.3)	.16	3.2 (3.0–3.3)	3.6 (3.0–4.2)	.13
TNF- α (pg/mL)	4.4 (4.2–4.7)	7.4 (5.6–9.2)	<.01	4.8 (4.6–5.1)	7.1 (5.8–8.7)	<.01

CRP, C-reactive protein; HCV, hepatitis C virus; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; TNF, tumor necrosis factor.

* Adjusted for age, sex, race, smoking, body mass index, diabetes, hypertension, human immunodeficiency virus, drug use, physical activity, aspirin, statin, β -blocker, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use.

Table 3

Relative Hazards for Outcomes Associated with HCV Seropositivity

	Death		CV Death, MI, or Stroke		HF Hospitalizations	
	HR (95% CI)	P Value	HR (95%)	P Value	HR (95%)	P Value
Model 1: adjusted for demographic factors [*]	2.57 (1.61–4.11)	<.01	1.83 (1.04–3.23)	.04	2.80 (1.63–4.83)	<.01
Model 2: adjusted for the above plus significant clinical factors [†]	1.58 (0.95–2.63)	.08	1.54 (0.83–2.84)	.17	2.13 (1.19–3.80)	.01
Model 3: adjusted for the above plus significant inflammatory markers [‡]	1.62 (0.95–2.75)	.07	1.74 (0.92–3.32)	.09	2.05 (1.11–3.78)	.02

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CRP, C-reactive protein; CV, cardiovascular; HDL, high-density lipoprotein; HF, heart failure; HR, heart rate; HIV, human immunodeficiency virus; IL, interleukin; MI, myocardial infarction; TNF, tumor necrosis factor.

^{*} Age, sex, and race.

[†] Retained covariates are as follows: 1) for death: smoking, drug abuse, HIV, BMI, diabetes, physical activity, statin, and ACE inhibitor/ARB use; 2) for CV outcomes: smoking, diabetes, hypertension, physical activity, statin use, ACE inhibitor/ARB use, total cholesterol, and HDL; 3) for HF hospitalizations: smoking, BMI, physical activity, diabetes, statin use, aspirin use, ACE inhibitor/ARB use.

[‡] Retained covariates are as follows: 1) for death: CRP and IL-6; 2) for CV outcomes: CRP and IL-6; 3) for HF hospitalizations: CRP, IL-6 and TNF- α .