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Risk of Myocardial Infarction Associated with Chronic Hepatitis C Virus Infection: A Population-Based Cohort Study

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SUMMARY

Hepatitis C virus (HCV) infection is associated with systemic inflammation and metabolic complications that might predispose patients to atherosclerosis. However, it remains unclear if HCV infection increases the risk of acute myocardial infarction (MI). To determine whether HCV infection is an independent risk factor for acute MI among adults followed in general practices in the United Kingdom (UK), a retrospective cohort study was conducted in The Health Improvement Network (THIN), from 1996 through 2008. Patients 18 years of age with at least 6 months of follow-up and without a prior history of MI were eligible for study inclusion. HCV-infected individuals, identified with previously validated HCV diagnostic codes (n=4,809), were matched on age, sex, and practice with up to 15 randomly selected patients without HCV (n=71,668). Rates of incident MI among patients with and without a diagnosis of HCV infection were calculated. Adjusted hazard ratios (HRs) were estimated using Cox proportional hazards regression, controlling for established cardiovascular risk factors. During a median follow-up of 3.2 years, there was no difference in the incidence rates of MI between HCV-infected and uninfected patients (1.02 versus 0.92 events per 1,000 person-years; p=0.7). HCV infection was not associated with an increased risk of incident MI (adjusted HR, 1.10; 95% confidence interval (CI), 0.67 to 1.83). Sensitivity analyses including the exploration of a composite outcome of acute MI and coronary interventions yielded similar results (adjusted HR, 1.16; 95% CI, 0.77 to 1.74). In conclusion, HCV infection was not associated with an increased risk of incident MI.

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STATEMENT OF INTERESTS

Declaration of Personal Interests: The authors have no conflicts of interest to disclose.

Keywords

Hepatitis C virus; myocardial infarction; inflammation

INTRODUCTION

Hepatitis C virus (HCV) infection affects 1.6% of the adult population in the United States and 1% in the United Kingdom (UK) (1, 2). After exposure, the majority of HCV-infected patients develop chronic infection, manifested by the persistence of HCV RNA in the blood (3–8). HCV exerts its main effects on the liver, inducing inflammation that leads to progressive hepatic fibrosis and ultimately cirrhosis in approximately 20% of those chronically infected (8). HCV infection may also affect organ systems outside of the liver and induce direct or indirect effects on dermatologic, endocrine, hematologic, neurologic, renal, and ophthalmic function (9). However, its impact on cardiovascular disease remains unclear.

A number of factors related to chronic HCV infection have been hypothesized to contribute to atherosclerosis. HCV infection stimulates the host immune response, activating T helper cells and releasing a number of pro-inflammatory cytokines, including interferon-alpha, interleukin-1, interleukin-6, and tumor necrosis factor-alpha (10). Since inflammation is important to the development of atherosclerosis and ultimately myocardial infarction (MI) (11–13), the inflammatory state associated with HCV infection might contribute to an increased cardiovascular disease risk. Furthermore, HCV infection has been associated with metabolic complications, including diabetes mellitus (14–16), the metabolic syndrome (17), and hepatic steatosis (18), all of which are important risk factors for the development of cardiovascular and peripheral vascular disease.

Existing studies examining the association between HCV infection and cardiovascular diseases have reported conflicting results (19–29), and the impact of HCV infection on acute MI has been evaluated primarily among men (21, 29). Given the prevalence of HCV infection, affecting approximately 170 million people worldwide (3), and the morbidity and mortality associated with cardiovascular disease, it is important to determine if HCV infection increases the risk of MI among HCV-infected individuals. Thus, our primary objective was to examine whether HCV infection is an independent risk factor for MI within a broadly representative population-based cohort.

MATERIALS AND METHODS

Data Source

The Health Improvement Network (THIN) is a database of electronic medical records on over 7.5 million patients from over 1,500 general practitioners (GPs) in 415 UK practices (30) (31). Data recorded in THIN include demographic information, medical diagnoses, lifestyle characteristics, measurements taken during medical practice, prescriptions, laboratory results, and coded free text comments. Diagnoses are recorded using the Read diagnostic code scheme (32), and prescriptions are recorded using codes from the UK Prescription Pricing Authority (33). This study was approved by the University of Pennsylvania Institutional Review Board.

Study Design and Subjects

We conducted a matched retrospective cohort study among patients in THIN aged 18 years or older who were registered with a THIN practice for at least 6 months. Patients were

identified as HCV-infected if they had: 1) a diagnosis of HCV infection, or 2) a diagnosis of nonspecific viral hepatitis with “hepatitis C” noted in a free text comment field (34). HCV-uninfected patients had no diagnosis recorded for either HCV infection or another cause of viral hepatitis during follow-up. Patients were excluded if prior to the start of follow-up (defined below), they had a diagnosis of: 1) MI, or 2) active hepatitis B virus infection, defined by diagnostic codes for chronic hepatitis B or a positive hepatitis B surface antigen.

All eligible HCV-infected patients were selected and matched to randomly selected HCV-uninfected patients based on age (± 5 years), sex, and THIN practice (35). Up to fifteen HCV-uninfected patients were matched to each HCV-infected subject to ensure sufficient sample sizes for planned subanalyses.

Follow-up for HCV-infected patients began on the date of initial HCV diagnosis or the registration date plus 180 days, whichever was later. Follow-up for HCV-uninfected patients began on the same date as that of their matched HCV-infected subject. Follow-up continued until an acute MI, death, transfer out of THIN, end of study data (November 5, 2008), or end of data collection for the THIN practice. Subjects whose principal cause of death was an acute MI were classified as having this endpoint on their death date.

Main Outcome Measures

The primary outcome was first occurrence of acute MI after the start of follow-up. Patients were classified as having an acute MI if they received a Read code consistent with this diagnosis during follow-up (36).

As a secondary outcome measure, we examined a composite outcome of either incident MI or revascularization procedure (e.g., percutaneous transluminal coronary angioplasty, coronary artery bypass grafting) during follow up.

Measurement of Covariates

We collected the following data on or prior to the start of follow-up: age; sex; height; weight; family history of cardiovascular disease; diagnoses of diabetes, hypertension, hyperlipidemia, and chronic kidney disease, defined by diagnostic codes or prescriptions for relevant medications; tobacco, cocaine, and alcohol use, as assessed by the general practitioner; and selected prescriptions (aspirin, non-aspirin non-steroidal anti-inflammatory agents, 3-hydroxy-3-methyl-glutaryl [HMG]-CoA reductase inhibitors, oral hypoglycemic agents, insulin, anti-hypertensive drugs). Patients were considered exposed to a medication of interest at the start of follow-up if a prescription was recorded within 90 days prior to the start of follow-up. All prescriptions for aspirin were collected during follow-up to determine continued exposure.

Statistical Analyses

Incidence rates (37) of MI with 95% confidence intervals (CIs) were determined for HCV-infected and -uninfected subjects. Hazard ratios (HRs) with 95% CIs of first incident MI and a composite outcome of first incident MI or coronary revascularization procedure were estimated using Cox proportional hazards regression adjusted for the matching variables, so that standard errors appropriately reflected the clustering induced by the matched sets (38). HRs were adjusted for established cardiovascular risk factors (i.e., hypertension, diabetes, hyperlipidemia, family history of cardiovascular disease, and smoking). Additional potential confounding variables evaluated included: age; sex; body mass index (BMI); alcohol consumption; cocaine use; chronic kidney disease; and use of a medication of interest. Confounders were retained in the model if their inclusion changed the unadjusted HR of incident acute MI by more than 15% or were proposed *a priori* (39). We also assessed

interactions between HCV infection and both age and sex. Standard model checking procedures were employed, including visual inspection of diagnostic log-log plots. Missing values of height and weight were multiply imputed based on fully observed covariates including age and sex (40, 41). The imputation algorithm employed the Markov chain Monte Carlo method and 20 imputed data sets were created (42, 43). Final estimates were obtained using standard formulae to combine estimates from the 20 analyses (40). All reported results derive from the imputed data sets.

We performed several sensitivity analyses to determine the robustness of our results. We repeated analyses treating aspirin as a time-varying covariate. We performed a sub-analysis evaluating the risk of incident MI among patients documented as having chronic HCV infection by their GP compared to uninfected persons. Finally, since antiviral therapy for HCV infection might affect the risk of acute MI, we repeated our analyses excluding patients who received standard or pegylated interferon prior to or during follow-up.

Assuming an incidence rate of acute MI of 1.33 per 1,000 person-years (44), an average follow-up of 2.5 person-years, and a 15:1 ratio of unexposed to exposed subjects, we estimated that 3,000 HCV-infected patients would provide 80% power to detect a relative hazard of acute MI of 2.0 between HCV-infected and -uninfected patients, using a two-sided, 0.05-level test. Analyses were performed using Stata version 11.0 (StataCorp, College Station, TX).

RESULTS

Among 4.5 million patients with at least 6 months of follow-up in THIN between February 1996 and November 2008, 5,218 HCV-infected individuals were identified. A total of 40 patients were excluded due to an acute MI recorded prior to the start of follow-up or prior to their HCV diagnosis, 31 were excluded because a date of HCV diagnosis was not available, 214 for active hepatitis B virus infection, and 124 for an age below 18 years. Hence, 4,809 HCV-infected subjects were matched to 71,668 HCV-uninfected patients.

The characteristics of the HCV-infected and -uninfected subjects are shown in Table 1. Compared to HCV-uninfected individuals, patients with HCV infection more frequently had diabetes mellitus and chronic kidney disease but less often had hyperlipidemia. HCV-infected patients also more commonly had a lower BMI, were smokers, drank alcohol, used cocaine, and received prescriptions for aspirin and an antihypertensive medication compared to HCV-uninfected patients.

During a median follow-up of 2.41 years for HCV-infected and 3.22 years for HCV-uninfected patients, 264 subjects had an incident acute MI (16 HCV-infected versus 248 HCV-uninfected; $p=0.9$). The incidence rate of acute MI was not statistically different between HCV-infected and -uninfected persons (1.02 versus 0.92 events per 1,000 person-years; $p=0.67$).

Results examining the association between HCV infection and acute MI are summarized in Table 2. In unadjusted analysis, HCV infection did not increase the risk of incident MI (HR, 1.12; 95% CI 0.68 to 1.84). After controlling for established cardiovascular risk factors including age, sex, hypertension, diabetes, hyperlipidemia, family history of cardiovascular disease, and smoking as well as chronic kidney disease, BMI, and baseline aspirin use, the only additional confounding variables identified, HCV infection did not increase the risk of acute MI (adjusted HR, 1.10; 95% CI 0.67 to 1.83). Similar results were observed when examining the association between HCV infection and a composite outcome of first acute MI or a revascularization procedure (adjusted HR, 1.16; 95% CI 0.77 to 1.74). Furthermore,

stratification of the results based on age category (less than 50, 50–65, and greater than 65 years) and sex did not change the results (data not shown).

Sensitivity analyses including aspirin as a time-varying covariate did not appreciably alter the results (adjusted HR, 1.07; 95% CI 0.64 to 1.78). After exclusion of subjects who received antiviral therapy for HCV infection prior to or during follow-up, the overall results remained unchanged (adjusted HR 1.13; 95% CI 0.68 to 1.87). Sub-analyses examining the risk of acute MI between patients documented as having chronic HCV by their GP compared to uninfected persons showed similar results to the primary analysis (adjusted HR 0.67; 95% CI 0.16 to 2.71). Finally, given that HCV infection may increase acute MI risk through diabetes or decrease this risk through hyperlipidemia and may therefore be in the causal pathway, we re-ran multivariable models without adjusting for diabetes or hyperlipidemia. No appreciable change in the risk of acute MI was observed (adjusted HR 1.10; 95% CI 0.67 to 1.83 and adjusted HR 1.10; 95% CI 0.66 to 1.82 for diabetes and hyperlipidemia, respectively).

DISCUSSION

A number of chronic inflammatory diseases, including psoriasis, rheumatoid arthritis, and systemic lupus erythematosus, have been associated with an increased risk of MI (45–50). However, in this retrospective analysis of HCV-infected and HCV-uninfected patients followed in UK general practices, HCV infection was not associated with an increased incidence of either acute MI or a composite outcome of MI or coronary revascularization procedures. This suggests that not all chronic inflammatory conditions are associated with cardiovascular disease. The hypothesized association between HCV infection and MI was not observed despite the increased prevalence of several known cardiovascular risk factors among the HCV-infected patients, including diabetes, hypertension, and smoking.

Despite the hypothesized link between HCV infection and atherosclerosis, our results suggest that HCV infection does not increase the incidence of acute MI. Although HCV infection stimulates an inflammatory cascade, the resulting inflammation may not be of the magnitude, severity, or subtype sufficient to accelerate atherosclerosis and increase the risk of cardiovascular events. Further, cytokine receptor function and intracellular signaling may not be equally distorted in HCV infection as it is in other chronic inflammatory conditions. In addition, the lower serum lipid levels among the HCV-infected persons, which might be due to binding of HCV to low-density lipoprotein-C receptors or impairment of hepatic assembly of very low-density lipoproteins (51), may counteract the pro-atherosclerotic effects of HCV-associated inflammation. These factors might explain the lack of association between HCV infection and acute MI in this study.

Our results are consistent with those of Arcari et al. (21), who demonstrated no association between HCV infection and acute MI in a case-control study of 582 males in the US Army. However, our finding that HCV infection did not increase the risk of incident MI differs from that of several other studies (16, 20, 22). Vassale et al.(20) reported that HCV infection was an independent predictor of angiographically-documented coronary artery disease in a case-control study of 686 patients (adjusted odds ratio, 4.2; 95% CI 1.4 to 13.0). Ishizaka et al.(22) reported an association between HCV infection and carotid artery plaque and thickening of the intima media. Finally, Butt et al.(29) examined over 170,000 U.S. veterans over a 5-year period and observed that HCV infection was associated with a 27% increase in the incidence of cardiovascular events, defined as myocardial infarction, congestive heart failure, or coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. Our results might differ from these studies due to differences in the populations examined, outcomes evaluated, and confounding variables included in these analyses.

The current study has a number of strengths. It included data from over 80,000 patients followed in general practices in the United Kingdom. Since THIN's general practitioners are provided with incentives to maintain the electronic medical record, information within THIN is recorded with a high degree of accuracy (30), and GPs will have recorded information in the same manner between HCV-infected and -uninfected patients. Further, our analyses controlled for a number of established cardiovascular risk factors and other important confounding variables that might influence the incidence of MI, including baseline as well as chronic exposure to aspirin, and our results were robust to multiple sensitivity analyses. Finally, the THIN population has similar demographics to the broader UK and is considered to be highly representative of this population.

There are several potential limitations to this study. First, it is possible that some patients who spontaneously cleared HCV infection were included within the exposed group. However, up to 86% of patients infected with HCV develop chronic infection (8). Further, we examined the association between documented chronic HCV infection and incident acute MI and demonstrated similar results to those of our primary analyses. In addition, no HCV-uninfected patient was identified as being HCV antibody or RNA positive, minimizing the likelihood of misclassification of HCV status. Second, the duration of follow-up for both cohorts was short, and it remains unclear how HCV infection might affect the risk of MI over a longer duration of time. However, stratifying our results by age categories did not yield statistically significant differences and one can expect that the older population has had a longer duration of infection. Third, residual confounding by unmeasured confounders is always possible in observational studies. However, such confounding would not only have to be of considerable magnitude but also be substantially independent of the comprehensive list of factors already included to unmask an association between HCV infection and incident MI. Finally, height and/or weight results were missing in 20% of patients, but multiple imputation was performed to ensure that missing data did not affect the validity of our results.

In conclusion, HCV infection did not increase the risk of incident acute MI among a large sample of patients followed in UK general practices. The reduced lipid levels observed among HCV-infected persons might be sufficient to mitigate any pro-atherosclerotic effects of HCV-associated inflammation. The inflammation stimulated by HCV infection may also be different from that of other chronic inflammatory diseases. Regardless of the reason for the lack of association, these data suggest that not all chronic inflammation is associated with an increased risk of cardiovascular disease.

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Table 1

Baseline characteristics of the HCV-infected and -uninfected cohorts.

Characteristic	HCV-Infected (n=4,809)	HCV-Uninfected (n=71,668)	P-Value
Median age (years, IQR)	38.60 (31.57, 46.68)	38.57 (31.39, 46.45)	0.9
Sex (no., %)			
Male	2,935 (61.03%)	43,802 (61.12%)	0.9
Female	1,874 (38.97%)	27,866 (38.88%)	
Body mass index category (no., %)			
Underweight (<18.5 kg/m ²)	172 (3.58)	1,624 (2.27)	<0.001
Ideal (18.5 kg/m ² – 24.9 kg/m ²)	2,061 (42.86%)	26,384 (36.81%)	
Overweight (25.0 kg/m ² – 29.9 kg/m ²)	1,031 (21.44%)	17,982 (25.09%)	
Obese (>30.0 kg/m ²)	557 (11.58%)	9,914 (13.83%)	
Missing	988 (20.54 %)	15,764 (22.00%)	
Family history of cardiovascular disease (no., %)	607 (12.62%)	9,210 (12.82%)	0.7
Medical comorbidity (no., %)			
Diabetes mellitus	259 (5.39%)	2,310 (3.22%)	<0.001
Hypertension	466 (9.69%)	7,168 (10.00)	0.5
Hyperlipidemia	574 (11.94%)	9,421 (13.15%)	0.02
Chronic kidney disease	99 (2.06%)	529 (0.74%)	<0.001
Medication use (no., %)			
Aspirin	118 (2.65%)	1,303 (1.82%)	0.002
Anti-hypertensives	489 (10.17%)	5,088 (7.10%)	<0.001
HMG-CoA reductase inhibitors	90 (1.87%)	1,907 (2.66%)	0.001
Hypoglycemic agents	151 (3.14%)	1,228 (1.71%)	<0.001
Smoking (no., %)			
Ever	3,574 (74.32%)	44,423 (61.98%)	<0.001
Alcohol consumption (no., %)	3,870 (80.47%)	53,200 (74.23%)	<0.001
Cocaine use (no., %)	79 (1.64%)	16 (0.02%)	<0.001
Follow-up time (years, IQR)	2.41 (0.93, 5.10)	3.22 (1.34, 5.83)	< 0.001

IQR=interquartile range; HMG=3-hydroxy-3-methyl-glutaryl

Table 2

Unadjusted and adjusted hazard ratios of the risk of first incident myocardial infarction for baseline variables of interest.

Variable	Unadjusted Hazard Ratio [*]	95% CI	Adjusted Hazard Ratio [†]	95% CI
Hepatitis C virus infection	1.12	0.68–1.84	1.10	0.67–1.83
Sex				
Male	Reference		Reference	
Female	0.45	0.33–0.62	0.35	0.26–0.47
Age				
<50 years	Reference		Reference	
50–65 years	4.08	3.05–5.45	3.37	2.48–4.57
>65 years	9.68	7.10–13.18	9.25	6.48–13.19
Medical comorbidities				
Hypertension	3.17	2.40–4.19	1.04	0.73–1.49
Diabetes mellitus	2.69	1.66–4.37	0.97	0.57–1.64
Hyperlipidemia	3.18	2.38–4.24	1.35	0.96–1.90
Chronic kidney disease	7.10	3.84–13.11	3.67	1.96–6.83
Aspirin use	4.82	3.00–7.76	0.99	0.57–1.72
Body mass index (BMI) category				
18.5–24.9 kg/m ²	Reference		Reference	
25.0–29.9 kg/m ²	1.93	1.43–2.60	1.47	1.08–1.99
> 30.0 kg/m ²	2.06	1.48–2.87	1.59	1.13–2.24
Ever smoking	1.69	1.28–2.24	1.33	1.00–1.78
Family history of cardiovascular disease	2.46	1.87–3.24	2.22	1.66–2.99

^{*} Body mass index imputed based on height, weight and potential covariates for all subjects for whom a BMI was not available in the dataset.

[†] Adjusted model includes age, sex, co-morbidities as defined by medication usage 90 days prior to the index date or a diagnostic code entered into the medical record prior to the start of follow-up, aspirin use in the 90 days prior to the index date, body mass index measured closest to baseline or imputed if missing and tobacco prior to the start of follow-up.