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Risk of Acute Myocardial Infarction Among Hepatitis C Virus (HCV)-Positive and HCV-Negative Men at Various Lipid Levels: Results From ERCHIVES

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(See the Editorial Commentary by Tien on pages 566–7.)

Background. Risk of acute myocardial infarction (AMI) among hepatitis C virus (HCV)-positive versus HCV-negative persons with similar lipid levels is unknown. We determined incident AMI rates among HCV-positive and HCV-negative men among various lipid strata.

Methods. We created a propensity score matched (PSM) cohort and a low cardiovascular disease (CVD) risk cohort. Primary outcome was incident AMI rates by HCV status in each lipid strata using National Cholesterol Program guidelines for lipid strata.

Results. We identified 85 863 HCV-positive and HCV-negative men in the PSM population. The incidence rates/1000 patient-years (95% confidence interval [CI]) for AMI among total cholesterol (TC) 200–239 stratum were 5.3 (4.89, 5.71) for HCV-positive versus 4.71 (4.42, 5) for HCV-negative men ($P = .02$) and for TC >240 mg/dL were 7.38 (6.49, 8.26) versus 6.17 (5.64, 6.71) ($P = .02$). For low-density lipoprotein cholesterol (LDL) of 130–159 mg/dL, AMI rates were 5.44 (4.97, 5.91) for HCV-positive and 4.81 (4.48, 5.14) for HCV-negative men ($P = .03$). The rise in risk with increasing lipid levels was greater in younger HCV-positive than in HCV-negative men (e.g., TC > 240 mg/dL: age >50 HR 1.38 [HCV-positive] and 1.12 [HCV-negative]; age ≤50 HR 1.6 [HCV-positive] and 1.29 [HCV-negative]), and more profoundly altered in HCV-positive men by lipid lowering therapy (change in HR with lipid-lowering therapy for TC >240 mg/dL from 1.82 to 1.19 [HCV-positive] from 1.48 to 1.03 [HCV-negative]).

Conclusions. HCV-positive men have a higher risk of AMI than HCV-negative men at higher TC/LDL levels; this risk is more pronounced at a younger age. Lipid lowering therapy significantly reduces this risk, with more profound reduction among HCV-positive versus HCV-negative men at similar lipid levels.

Keywords. hepatitis C virus; acute myocardial infarction; lipid; cholesterol; ERCHIVES.

There is significant controversy about the association of hepatitis C virus (HCV) infection with coronary artery disease (CAD) [1–5]. Some studies have demonstrated a higher risk of CAD among HCV-infected persons and a higher degree and severity of angiographically proven CAD [1, 5], whereas others have not found such an association. The understanding of cardiovascular disease (CVD) risk in HCV-infected populations is complicated by the differing prevalence of various CVD risk factors in HCV-infected compared with uninfected persons and the poorly understood interaction of those factors. Of particular note, untreated HCV-infected persons have substantially lower total and low-density lipoprotein cholesterol (LDL) levels compared with demographically similar HCV-uninfected persons [6, 7]. Increasing severity of liver disease has

also been associated with progressively lower lipid levels, further complicating the association [8]. It is unknown whether the lower serum lipid levels in HCV-infected persons confer lower risk of CVD events in this population independent of other CVD risk factors. Knowledge of any association, and how that might differ from HCV-uninfected persons, may be useful in developing targeted guidelines for lipid management in HCV-infected persons. The primary objective of our study was to determine the association of lipid levels with the risk of acute myocardial infarction (AMI) in HCV-infected and uninfected persons. We performed our analysis in propensity score matched HCV-infected and uninfected persons, as well as in persons free of most traditional CVD risk factors, so as to quantify the independent contribution of lipids to the risk of AMI in this population.

METHODS

Study Population

We used ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans), a well-established, previously described

national cohort of HCV-infected Veterans and demographically matched HCV-uninfected controls for our study [9–13]. Demographic, clinical, pharmacy, laboratory, and mortality data are retrieved from multiple well-characterized sources in the Department of Veterans Affairs (VA) Healthcare System and merged using previously described methods [1, 14–16]. From the main ERCHIVES database spanning 2001–2015, we created 2 data sets. First, we created a "propensity score matched" data set as follows: among HCV-infected and uninfected persons we excluded those with baseline CVD (based on ICD-9 codes for AMI, stroke, heart failure, peripheral vascular disease, unstable angina, angioplasty, and coronary artery bypass graft surgery), human immunodeficiency virus (HIV) coinfection, those missing baseline lipid measurement or body mass index (BMI), and females (due to small numbers). Within the HCV-infected group, we also excluded those who received treatment for HCV for >2 weeks. We then matched HCV infected and uninfected persons on a difference of propensity score of <0.001 on age, race, BMI, receipt of lipid lowering therapy, hypertension, diabetes, smoking, chronic obstructive pulmonary disease, and stage of chronic kidney disease. Second, we created a "low CVD risk" data set as follows: among HCV-infected and uninfected persons, we excluded those with a diagnosis of CVD, diabetes mellitus, hypertension, stage 3–5 chronic kidney disease, HIV coinfection, chronic obstructive pulmonary disease and smoking at baseline. Those who received HCV treatment for >2 weeks, had missing baseline lipid levels or BMI measurement and women (due to small numbers) were also excluded.

Definitions

AMI was defined by the presence of at least one inpatient or two outpatient codes for AMI. These codes have been shown to have a high positive predictive value (PPV 96.9%) [17] and high correlation with adjudicated events based on chart reviews [18]. Other comorbidities (diabetes, hypertension, chronic kidney disease, smoking, chronic obstructive pulmonary disease, HIV infection) were identified at baseline (diagnosed any time prior and up to and 6 months after HCV diagnosis) using definitions provided in our prior publications [14, 19, 20].

Lipid levels were retrieved from the routine labs performed during the course of care. Total cholesterol, LDL, high-density lipoprotein cholesterol (HDL), and triglyceride (TG) levels were retrieved and divided into groups based on the desirable levels set forth by the National Cholesterol Education Program, whereby the optimal or the desirable level was used as the comparator group, except for high-density lipoprotein, for which the comparator group was low HDL (HDL < 40 mg/dL) [21].

Analyses

We separately analyzed the propensity score matched group and the low CVD risk group. Baseline characteristics and lipid levels were compared between HCV-infected and uninfected persons using χ^2 test or t-test for normally distributed data and Wilcoxon-Mann-Whitney test for nonnormally distributed data, as appropriate. We calculated the incident AMI rates per 1000 patient-years of follow-up for each lipid stratum for HCV-infected and uninfected persons. We used a Cox proportional hazards model to determine the hazards ratios (HRs) for AMI diagnosis within each lipid stratum in the HCV-infected and uninfected groups separately, using the optimal level as the comparator group. Assumptions of proportionality were tested using the Schoenfeld residuals. When the assumptions were not met, we stratified the analysis by the variable.

Additionally, we compared AMI rates within the HCV infected propensity score matched and low CVD risk groups by HCV RNA positivity. We also determined the risk of AMI conferred by HCV infection by analyzing the combined (HCV-positive and HCV-negative) propensity score matched group and determining the HR for AMI for each lipid stratum among the HCV-positive using HCV-negative as the comparator.

We used SAS® (version 9.4, SAS Institute Inc., Cary, NC, USA) and Stata® version 11 (Stata Corp., College Station, TX, USA) for analyses. The study was approved by the Institutional Review Board at VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania.

RESULTS

Baseline Characteristics

From 274 225 HCV infected and 351 671 HCV uninfected persons in ERCHIVES, we identified 85 863 HCV-infected and uninfected persons in propensity score matched population and 55 814 HCV-infected and 84 772 HCV-uninfected persons in the low CVD risk population. (Figure 1) In the propensity score matched population, the median age was 54 years (interquartile range [IQR] 49, 58), 63.3% were white, median BMI was 27.7 kg/m^2 (IQR 24.8, 31.1), and 24.8% had received lipid lowering therapy. In the low CVD risk population, HCV-infected persons had a lower median BMI compared with HCV-uninfected (26.7 kg/m^2 [IQR 23.8, 30.1] vs 28.3 kg/m^2 [IQR 25.3, 31.8], $P < .001$), lower total cholesterol (TC), LDL, and TG levels. HDL levels were similar in both groups. HCV-infected persons were less likely to be on a lipid lowering agent compared with HCV-uninfected persons (11.1% vs 24.5%, $P < .001$). (Table 1)

Propensity Score Matched Population

In the propensity score matched population, a total of 2710 AMI events were identified in the HCV-infected and 3239 in the HCV-uninfected persons. The incidence rate for AMI/1000 patient years was higher among HCV-infected persons with higher TC levels compared with the HCV-uninfected persons in the same TC level strata (e.g., for TC >240 mg/dL rates [95% CI] were 7.38 [6.49, 8.26] for HCV-infected vs 6.17
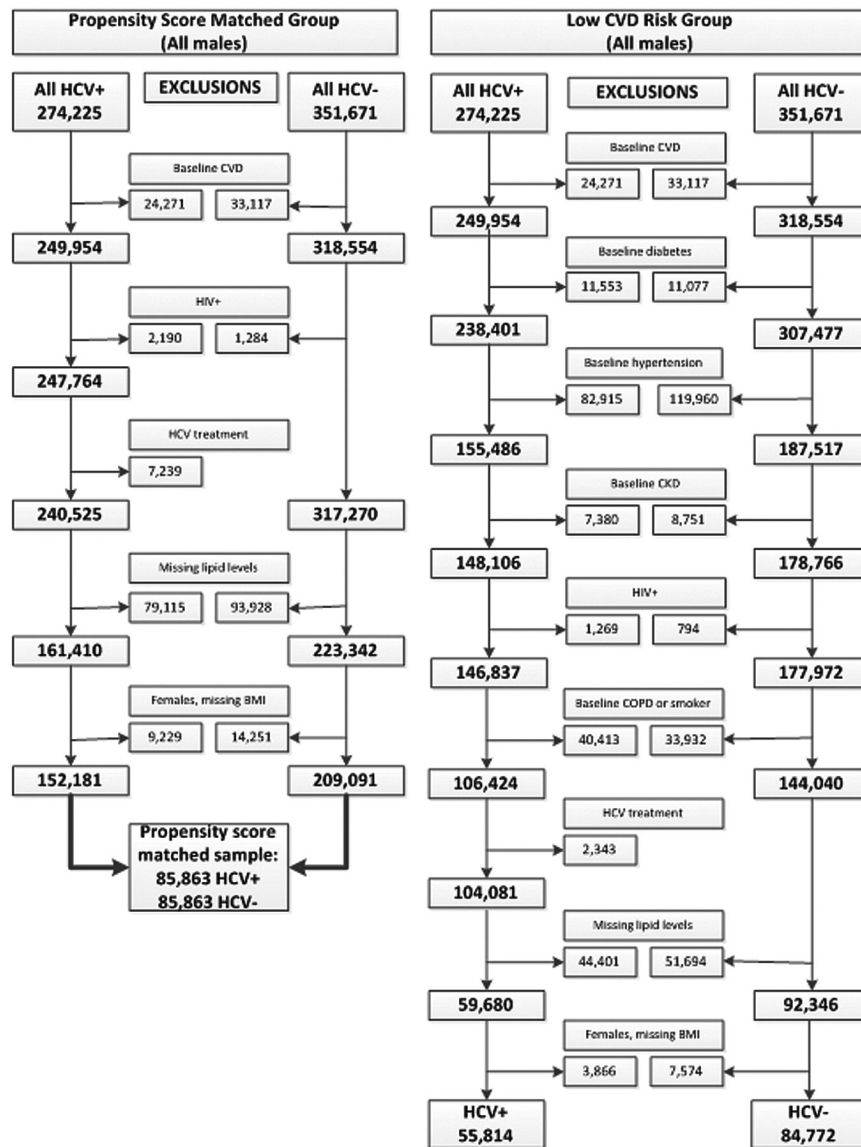
Figure 1. Creation of the data set for the current study from ERCHIVES. Abbreviations: BMI, body mass index; COPD, chronic obstructuve pulmonary disease; CVD, cardiovascular disease; CKD, chronic kidney disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

[5.64, 6.71] for HCV-uninfected; P = .02). For LDL stratum of 130–159 mg/dL, AMI rates (95% CI) were 5.44 (4.97, 5.91) for HCV-infected and 4.81 (4.48, 5.14) for HCV uninfected persons (P = .03). For TC <200 mg/dL and LDL <100 mg/dL, AMI rates were lower in the HCV-positive compared with HCV-negative population (4.23 vs 4.57, P = .02 for TC; 4.16 vs 4.71, P = .007 for LDL). For the HDL stratum of <40 mg/dL, AMI rates (95% CI) were conversely higher among HCV-uninfected persons (6.23 [5.91, 6.55]) than HCV-infected persons (5.49 [5.18, 5.79]), P = .001. There were no significant differences between HCV-infected and uninfected persons for any of the TG strata (Table 2).

The risk of AMI was higher with increasing TC, LDL, and TG levels, and lower with increasing HDL levels compared with optimal levels within HCV-infected and uninfected persons

(Figure 2). The HRs were numerically higher in the HCV-infected persons with higher TC and LDL levels but not for TG levels.

Low Cardiovascular Disease Risk Population

In the low CVD risk population, a total of 1231 AMI events were identified in the HCV infected and 2222 in the HCV-uninfected persons. The incidence rates of AMI/1000 patient years of follow-up were higher and statistically significant among HCV-infected versus HCV uninfected for the TC stratum of 200–239 mg/dL (4.01 [3.57, 4.44] vs 3.47 [3.22, 3.71], P = .03) and numerically higher but not statistically significant for the TC stratum of >240 mg/dL (5.13 [4.24, 6.03] vs 4.35 [3.94, 4.77], P = .12) (Table 3). For LDL stratum of ≥160 mg/dL, the rates were higher for HCV-infected versus

Table 1. Baseline Characteristics of the Final Evaluable Study Population

	Propensity Score Matched Population			Low Cardiovascular Disease Risk Population		
	HCV Positive N = 85 863	HCV Negative N = 85 863	P-Value	HCV Positive N = 55 814	HCV Negative N = 84 772	P-Value
Age, median (IQR)	54 (49, 58)	54 (49, 58)	Matched	53 (48, 57)	52 (46, 58)	<.001
Race						
White	63.6%	63.6%	Matched	59.0%	59.2%	.007
Black	26.2%	26.2%		22.0%	22.0%	
Hispanic	1.7%	1.7%		4.6%	4.9%	
Other/Unknown	8.54%	8.5%		14.3%	13.9%	
Body mass index, median (IQR) kg/m²	27.7 (24.8, 31.1)	27.7 (24.8, 31.0)	Matched	26.73 (23.85, 30.13)	28.31 (25.27, 31.78)	<.001
Lipid lowering therapy	24.8%	24.8%	Matched	11.1%	24.5%	<0.001
Hypertension	40.2%	37.4%	<.001	Excluded	Excluded	N/A
Diabetes	3.7%	3.2%	<.001	Excluded	Excluded	N/A
Smoking	26.3%	25.4%	<.001	Excluded	Excluded	N/A
Chronic obstructive pulmonary disease	1.5%	1.5%	.8	Excluded	Excluded	N/A
Chronic kidney disease stage						
1	14.0%	14.0%	Matched	20.3	13.8	N/A
2	38.6%	38.6%		25.3	28.6	
3	5.8%	5.8%		Excluded	Excluded	
4–5	0.5%	0.5%		Excluded	Excluded	
Missing	41.2%	41.2%		54.4	57.6	
Mean FIB-4 score (SD)	2.2 (4.3)	1.3 (1.3)	<.001	2.2 (5.1)	1.2 (1.0)	<.001
FIB-4 >3.5, %	12.0	2.3	<.001	11.9	1.5	<.001
Total cholesterol, median (IQR) mg/dL	174.5 (150.5, 200.0)	193.5 (169.0, 218.5)	<.001	174 (150, 200)	195 (171, 221.5)	<.001
<200	74.4%	56.8%		74.4%	54.4%	
200–239	19.8%	31.5%		19.5%	32.1%	
>240	5.8%	11.7%		5.8%	13.5%	
LDL, median (IQR) mg/dL	102.8 (81.5, 125.8)	117.5 (95.7, 140.0)	<.001	102 (81, 126)	120.5 (98, 144)	<.001
<100	46.4%	29.2%		46.9%	26.6%	
100–129	32.0%	35.1%		31.2%	34.0%	
130–159	15.7%	24.6%		15.7%	26.2%	
≥160	5.9%	11.0%		6.2%	13.2%	
HDL, median (IQR) mg/dL	43 (35.0,53.0)	44 (36.5,54.0)	<.001	44 (36, 54)	44 (37, 53)	<.001
<40	39.8%	35.4%		36.7%	35.3%	
40–59	44.5%	48.1%		46.0%	50.1%	
≥60	15.7%	16.5%		17.4%	14.5%	
Triglycerides, median (IQR) mg/dL	115 (81.0, 168.0)	128 (87.0, 192.0)	<.001	107 (76, 156)	127 (86, 191)	<.001
<150	68.3%	60.5%		72.6%	60.7%	
150–199	14.9%	16.5%		13.5%	16.5%	
200–499	15.9%	21.6%		13.3%	21.5%	
≥500	0.9%	1.3%		0.6%	1.3%	

Abbreviations: HCV, hepatitis C virus; HDL, high density lipoprotein cholesterol; IQR, interquartile range; LDL, low density lipoprotein cholesterol; N/A, not applicable; SD, standard deviation.

HCV-uninfected persons (5.43 [4.54, 6.32] vs 4.30 [3.88, 4.72], P = .02). For TC <200 mg/dL and LDL <100 mg/dL, AMI rates were lower in the HCV-positive compared with HCV-negative population (2.69 vs 2.97, P = .04 for TC; 2.5 vs 3.08, P < .01 for LDL). For HDL and TG, there were no significant differences among HCV infected versus HCV-infected persons at the higher strata.

To further understand the contribution of HCV infection to the risk of AMI, we determined the hazards of AMI among the overall group at each lipid stratum using the HCV-uninfected group in the same stratum as the comparator group in the propensity score matched cohort. The hazards were higher for TC strata of 200–239 mg/dL (1.13 [1.02, 1.25]) and >240 mg/dL (1.19 [1.03, 1.38]) and LDL stratum of 130–159 mg/Dl (1.13 [1.01, 1.26] (Table 4). The association was not significant for higher TG or HDL levels.

We further analyzed the risk of AMI among HCV-infected and uninfected persons in the low CVD risk

Table 2. Incidence Rate of Acute Myocardial Infarction (per 1000 Patient Years) at Various Lipid Levels Among Hepatitis C Virus Infected and Uninfected Persons in the Propensity Score Matched Population

Variable	Category	HCV-Positive N = 85 863			HCV-Negative N = 85 863			P-Value
		Follow-up Years	N*	AMI Rate (95% CI)	Follow-up Years	N*	AMI Rate (95% CI)	
Total cholesterol, mg/dL	<200	424 412	1796	4.23 (4.04, 4.43)	370 421	1693	4.57 (4.35, 4.79)	.02
	200–239	121 891	646	5.30 (4.89, 5.71)	220 430	1038	4.71 (4.42, 5.00)	.02
	>240	36 330	268	7.38 (6.49, 8.26)	82 290	508	6.17 (5.64, 6.71)	.02
LDL cholesterol, mg/dL	<100	259 519	1079	4.16 (3.91, 4.41)	187 414	882	4.71 (4.40, 5.02)	.007
	100–129	190 096	856	4.50 (4.20, 4.80)	237 368	1061	4.47 (4.20, 4.74)	.89
	130–159	95 362	519	5.44 (4.97, 5.91)	170 974	822	4.81 (4.48, 5.14)	.03
	≥160	37 656	256	6.80 (5.97, 7.63)	77 384	474	6.13 (5.57, 6.68)	.19
HDL cholesterol, mg/dL	<40	228 234	1252	5.49 (5.18, 5.79)	237 457	1479	6.23 (5.91, 6.55)	.001
	40–59	262 394	1160	4.42 (4.17, 4.68)	326 685	1400	4.29 (4.06, 4.51)	.45
	≥60	92 006	298	3.24 (2.87, 3.61)	108 999	360	3.30 (2.96, 3.64)	.83
Triglycerides, mg/dL	<150	390 367	1575	4.03 (3.84, 4.23)	398 761	1603	4.02 (3.82, 4.22)	.93
	150–199	89 362	494	5.53 (5.04, 6.02)	112 019	618	5.52 (5.08, 5.95)	1.00
	200–499	97 124	590	6.07 (5.58, 6.56)	153 112	936	6.11 (5.72, 6.50)	.93
	≥500	5781	51	8.82 (6.40, 11.2)	9248	82	8.87 (6.95, 10.8)	.95

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HCV, hepatitis C virus; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol.

population stratified by age (<50 vs ≥50 years; Figure 3A), BMI (<30 vs ≥30; Figure 3B) and receipt of lipid lowering therapy (Figure 3C). Among the HCV-infected, the risk of AMI with increasing TC and LDL levels was higher among the younger age group, whereas in the HCV-uninfected persons, a more traditional risk profile with increasing risk in the older age group was observed (Figure 3A). When stratified by BMI categories, the risk profile was also more traditional in the HCV-infected group with higher risk of AMI observed in those with higher BMI (Figure 3B). Those who received lipid lowering agents experienced a significant protective effect compared with those who did not receive lipid lowering therapy in the same lipid level strata in both the HCV-infected and uninfected groups (Figure 3C).

Supplementary Analyses

We also determined the incidence rate of AMI at various lipid levels among the full cohort of HCV-infected and uninfected persons after excluding those with baseline CVD, HIV coinfection, >2 weeks of HCV treatment, missing lipid levels, and females (Supplementary Table 1). The trends were similar to those in the propensity score matched and low CVD risk populations.

To determine the possible impact of excluding patients for missing information, we compared the demographics and lipid
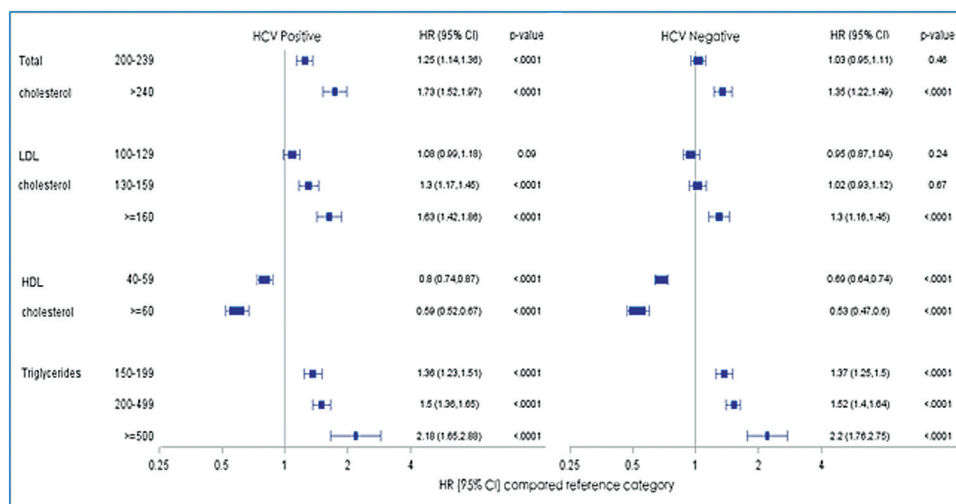
Figure 2. Risk of acute myocardial infarction in the propensity score matched population in various lipid groups (Cox proportional hazards model). Reference categories were total cholesterol < 200, LDL cholesterol < 100, HDL cholesterol <40, and triglycerides < 150 mg/dL. Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HDL, high density lipoprotein cholesterol; HR, hazards ratio; LDL, low density lipoprotein cholesterol.

Table 3. Incidence Rate of Acute Myocardial Infarction (per 1000 patient-years) at Various Lipid Levels Among Hepatitis C Virus Infected and Uninfected Persons in the Low CVD Risk Population

| Variable | Category | HCV Positive | | | HCV Negative | | | |
| | | N = 55814 | | | N = 84772 | | | |
		Follow-up Years	Number of Events	AMI Rate (95% CI)	Follow-up Years	Number of Events	AMI Rate (95% CI)	P-Value
Total cholesterol, mg/dL	<200	289073.3	777	2.69 (2.50, 2.88)	348627.5	1034	2.97 (2.79, 3.15)	.04
	200–239	81853.31	328	4.01 (3.57, 4.44)	222195.6	771	3.47 (3.22, 3.71)	.03
	>240	24556.29	126	5.13 (4.24, 6.03)	95795.58	417	4.35 (3.94, 4.77)	.12
LDL cholesterol, mg/dL	<100	178697.4	447	2.50 (2.27, 2.73)	168587.5	519	3.08 (2.81, 3.34)	<.01
	100–129	125517.4	397	3.16 (2.85, 3.47)	226242.5	683	3.02 (2.79, 3.25)	.48
	130–159	64937.96	244	3.76 (3.29, 4.23)	179057.9	621	3.47 (3.20, 3.74)	.31
	≥160	26330.07	143	5.43 (4.54, 6.32)	92730.85	399	4.30 (3.88, 4.72)	.02
HDL cholesterol, mg/dL	Ref <40	143122	519	3.63 (3.31, 3.94)	234886.4	992	4.22 (3.96, 4.49)	.01
	40–59	183583	557	3.03 (2.78, 3.29)	336803.4	998	2.96 (2.78, 3.15)	.67
	≥60	68777.86	155	2.25 (1.90, 2.61)	94928.99	232	2.44 (2.13, 2.76)	.47
Triglycerides, mg/dL	<150	280482.4	775	2.76 (2.57, 2.96)	393124.9	1095	2.79 (2.62, 2.95)	.88
	150–199	55523.38	211	3.80 (3.29, 4.31)	112145.6	410	3.66 (3.30, 4.01)	.68
	200–499	57018.39	233	4.09 (3.56, 4.61)	152075.5	660	4.34 (4.01, 4.67)	.45
	≥500	2458.74	12	4.88 (2.12, 7.64)	9272.63	57	6.15 (4.55, 7.74)	.56

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HCV, hepatitis C virus; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol.

levels of subjects who were included in the dataset with those who were excluded for the comorbidities listed in Figure 1 in the low CVD risk population. The results were similar (Supplementary Table 2).

Among the full cohort, baseline HCV RNA data were available for 113 503 persons in the HCV-infected group, of whom 26 946 (23.7%) were HCV RNA negative (Supplementary Table 3). Among the propensity score matched population, HCV RNA levels were available for 39 101 persons in the HCV-infected group. Of those, 9275 (23.7%) were HCV RNA negative

(Supplementary Table 4). In both analyses, there were no significant differences in the rates of incident AMI among HCV RNA positive versus HCV RNA negative persons in the highest lipid level strata (Supplementary Tables 3 and 4). We also analyzed AMI rates among various groups after excluding those with baseline FIB-4 score >3.5. Results were similar to those provided in the main analyses (Supplementary Tables 5a and 5b).

DISCUSSION

In our large cohort of HCV-infected and uninfected persons, HCV-infected persons had a higher risk of AMI compared with HCV-uninfected persons with TC and LDL levels in the higher strata. This higher risk was seen in the propensity score matched population as well as those at a low risk of CVD due to exclusion of most traditional CVD risk factors. In the within-group (HCV-infected and HCV-uninfected) analyses, rate of AMI was lower in HCV-positive persons with optimal TC and LDL levels compared with HCV-negative persons in the same stratum; however, the risk of AMI increased more rapidly with each subsequent higher lipid stratum in the HCV-infected group than observed in the HCV-uninfected group, suggesting that incremental increases in lipid levels may have greater implications for risk for AMI in HCV-infected persons than in HCV-uninfected persons. Rates of AMI were lower in HDL <40 mg/dL stratum for HCV-positive compared with HCV-negative persons. In the low CVD risk population, a higher risk was observed in the younger age group (<50 years old) compared with older persons within the TC and LDL strata, and this was more pronounced in the HCV-infected compared with HCV-uninfected persons. Additionally, treatment with lipid lowering agents was associated with a greater reduction in risk of AMI

Table 4. Risk of Acute Myocardial Infarction Associated With Hepatitis C Virus (HCV) Infection at Various Lipid Levels in the Overall Propensity Score Population, With HCV Uninfected in the Same Lipid Stratum Serving as the Comparator (Cox Proportional Hazards Model)

| Variable | N = 171 726 | HCV+ (Ref HCV-) | |
	Category	HR (95% CI)	P-Value
Total cholesterol, mg/dL	<200	0.93 (0.87, 0.99)	.03
	200–239	1.13 (1.02, 1.25)	.02
	>240	1.19 (1.03, 1.38)	.02
LDL cholesterol, mg/dL	<100	0.88 (0.81, 0.97)	.01
	100–129	1.01 (0.93, 1.11)	.76
	130–159	1.13 (1.01, 1.26)	.03
	≥160	1.11 (0.96, 1.29)	.17
HDL cholesterol, mg/dL	<40	0.88 (0.82, 0.95)	.001
	40–59	1.04 (0.96, 1.12)	.36
	≥60	0.98 (0.84, 1.15)	.83
Triglycerides, mg/dL	<150	1.01 (0.94, 1.08)	.81
	150–199	1.00 (0.89, 1.13)	.97
	200–499	0.99 (0.9, 1.10)	.90
	≥500	1.00 (0.71, 1.42)	.99

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HDL, high density lipoprotein cholesterol; HR, hazard ratio; LDL, low density lipoprotein cholesterol.
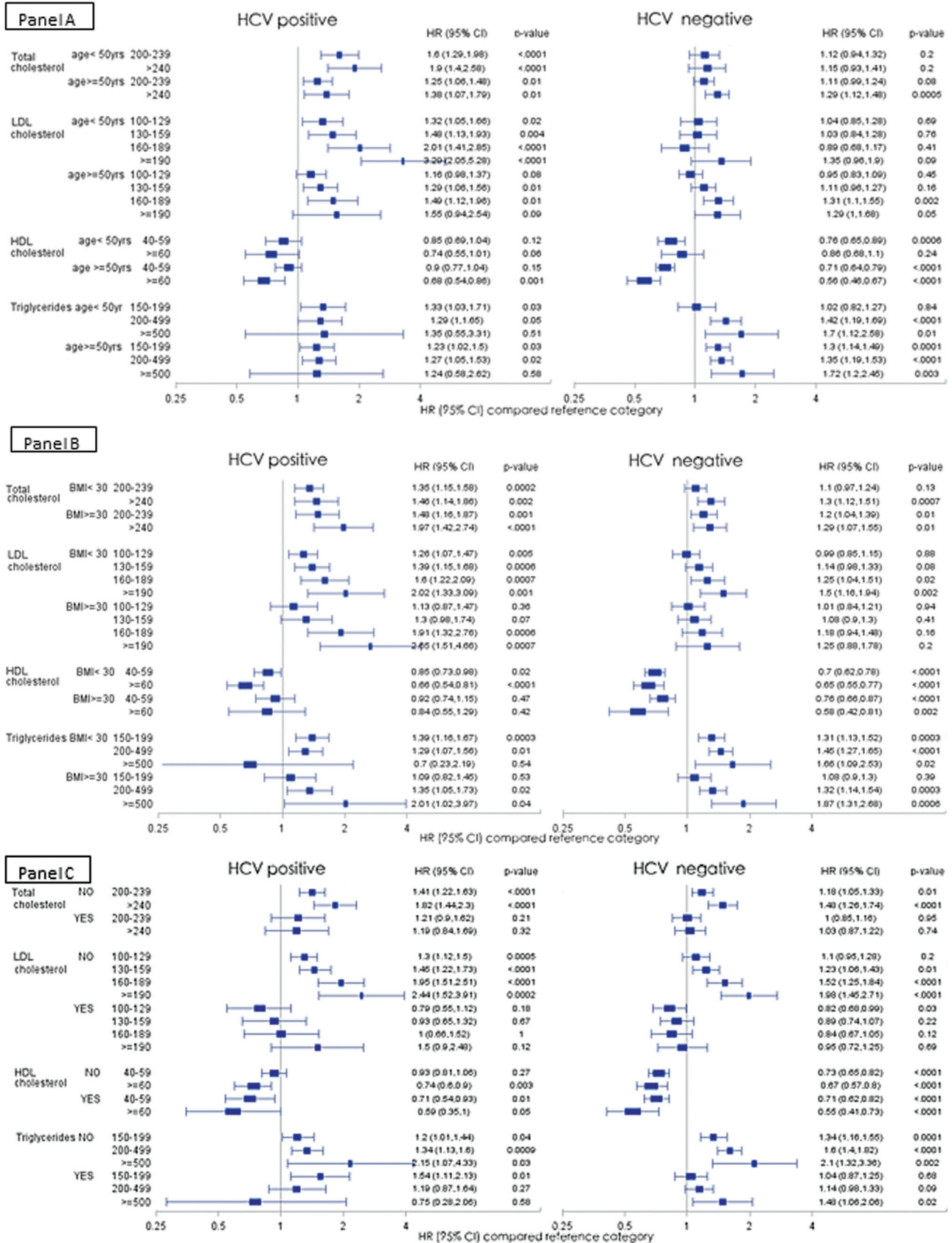
PanelA

HCV positive — HR (95% CI), p-value

Total cholesterol
- age< 50yrs 200-239: 1.6 (1.29,1.98), <.0001
- >240: 1.9 (1.4,2.58), <.0001
- age>=50yrs 200-239: 1.25 (1.06,1.48), 0.01
- >240: 1.38 (1.07,1.79), 0.01

LDL cholesterol
- age< 50yrs 100-129: 1.32 (1.05,1.66), 0.02
- 130-159: 1.48 (1.13,1.93), 0.004
- 160-189: 2.01 (1.41,2.85), <.0001
- >=190: 3.29 (2.05,5.28), <.0001
- age>=50yrs 100-129: 1.16 (0.98,1.37), 0.08
- 130-159: 1.29 (1.06,1.56), 0.01
- 160-189: 1.49 (1.12,1.96), 0.01
- >=190: 1.55 (0.94,2.54), 0.09

HDL cholesterol
- age< 50yrs 40-59: 0.85 (0.69,1.04), 0.12
- >=60: 0.74 (0.55,1.01), 0.06
- age >=50yrs 40-59: 0.9 (0.77,1.04), 0.15
- >=60: 0.68 (0.54,0.86), 0.001

Triglycerides
- age< 50yr 150-199: 1.33 (1.03,1.71), 0.03
- 200-499: 1.29 (1.1,1.65), 0.05
- >=500: 1.35 (0.55,3.31), 0.51
- age>=50yrs 150-199: 1.23 (1.02,1.5), 0.03
- 200-499: 1.27 (1.05,1.53), 0.02
- >=500: 1.24 (0.58,2.62), 0.58

HCV negative — HR (95% CI), p-value

Total cholesterol
- age< 50yrs 200-239: 1.12 (0.94,1.32), 0.2
- >240: 1.15 (0.93,1.41), 0.2
- age>=50yrs 200-239: 1.11 (0.99,1.24), 0.08
- >240: 1.29 (1.12,1.48), 0.0005

LDL cholesterol
- age< 50yrs 100-129: 1.04 (0.85,1.28), 0.69
- 130-159: 1.03 (0.84,1.28), 0.76
- 160-189: 0.89 (0.68,1.17), 0.41
- >=190: 1.35 (0.96,1.9), 0.09
- age>=50yrs 100-129: 0.95 (0.83,1.09), 0.45
- 130-159: 1.11 (0.96,1.27), 0.16
- 160-189: 1.31 (1.1,1.55), 0.002
- >=190: 1.29 (1,1.68), 0.05

HDL cholesterol
- age< 50yrs 40-59: 0.76 (0.65,0.89), 0.0006
- >=60: 0.86 (0.68,1.1), 0.24
- age >=50yrs 40-59: 0.71 (0.64,0.79), <.0001
- >=60: 0.56 (0.46,0.67), <.0001

Triglycerides
- age< 50yr 150-199: 1.02 (0.82,1.27), 0.84
- 200-499: 1.42 (1.19,1.69), <.0001
- >=500: 1.7 (1.12,2.58), 0.01
- age>=50yrs 150-199: 1.3 (1.14,1.49), 0.0001
- 200-499: 1.35 (1.19,1.53), <.0001
- >=500: 1.72 (1.2,2.45), 0.003

HR (95% CI) compared reference category

PanelB

HCV positive — HR (95% CI), p-value

Total cholesterol
- BMI< 30 200-239: 1.35 (1.15,1.58), 0.0002
- >240: 1.46 (1.14,1.86), 0.002
- BMI>=30 200-239: 1.48 (1.16,1.87), 0.001
- >240: 1.97 (1.42,2.74), <.0001

LDL cholesterol
- BMI< 30 100-129: 1.26 (1.07,1.47), 0.005
- 130-159: 1.39 (1.15,1.68), 0.0006
- 160-189: 1.6 (1.22,2.09), 0.0007
- >=190: 2.02 (1.33,3.09), 0.001
- BMI>=30 100-129: 1.13 (0.87,1.47), 0.36
- 130-159: 1.3 (0.98,1.74), 0.07
- 160-189: 1.91 (1.32,2.76), 0.0006
- >=190: 2.65 (1.51,4.66), 0.0007

HDL cholesterol
- BMI< 30 40-59: 0.85 (0.73,0.98), 0.02
- >=60: 0.66 (0.54,0.81), <.0001
- BMI>=30 40-59: 0.92 (0.74,1.15), 0.47
- >=60: 0.84 (0.55,1.29), 0.42

Triglycerides
- BMI< 30 150-199: 1.39 (1.16,1.67), 0.0003
- 200-499: 1.29 (1.07,1.56), 0.01
- >=500: 0.7 (0.23,2.19), 0.54
- BMI>=30 150-199: 1.09 (0.82,1.45), 0.53
- 200-499: 1.35 (1.05,1.73), 0.02
- >=500: 2.01 (1.02,3.97), 0.04

HCV negative — HR (95% CI), p-value

Total cholesterol
- BMI< 30 200-239: 1.1 (0.97,1.24), 0.13
- >240: 1.3 (1.12,1.51), 0.0007
- BMI>=30 200-239: 1.2 (1.04,1.39), 0.01
- >240: 1.29 (1.07,1.55), 0.01

LDL cholesterol
- BMI< 30 100-129: 0.99 (0.85,1.15), 0.88
- 130-159: 1.14 (0.98,1.33), 0.08
- 160-189: 1.25 (1.04,1.51), 0.02
- >=190: 1.5 (1.16,1.94), 0.002
- BMI>=30 100-129: 1.01 (0.84,1.21), 0.94
- 130-159: 1.08 (0.9,1.3), 0.41
- 160-189: 1.18 (0.94,1.48), 0.16
- >=190: 1.25 (0.88,1.78), 0.2

HDL cholesterol
- BMI< 30 40-59: 0.7 (0.62,0.78), <.0001
- >=60: 0.65 (0.55,0.77), <.0001
- BMI>=30 40-59: 0.76 (0.66,0.87), <.0001
- >=60: 0.58 (0.42,0.81), 0.002

Triglycerides
- BMI< 30 150-199: 1.31 (1.13,1.52), 0.0003
- 200-499: 1.45 (1.27,1.65), <.0001
- >=500: 1.66 (1.09,2.53), 0.02
- BMI>=30 150-199: 1.08 (0.9,1.3), 0.39
- 200-499: 1.32 (1.14,1.54), 0.0003
- >=500: 1.87 (1.31,2.68), 0.0006

HR (95% CI) compared reference category

PanelC

HCV positive — HR (95% CI), p-value

Total cholesterol
- NO 200-239: 1.41 (1.22,1.63), <.0001
- >240: 1.82 (1.44,2.3), <.0001
- YES 200-239: 1.21 (0.9,1.62), 0.21
- >240: 1.19 (0.84,1.69), 0.32

LDL cholesterol
- NO 100-129: 1.3 (1.12,1.5), 0.0005
- 130-159: 1.45 (1.22,1.73), <.0001
- 160-189: 1.95 (1.51,2.51), <.0001
- >=190: 2.44 (1.52,3.91), 0.0002
- YES 100-129: 0.79 (0.55,1.12), 0.18
- 130-159: 0.93 (0.65,1.32), 0.67
- 160-189: 1 (0.66,1.52), 1
- >=190: 1.5 (0.9,2.48), 0.12

HDL cholesterol
- NO 40-59: 0.93 (0.81,1.06), 0.27
- >=60: 0.74 (0.6,0.9), 0.003
- YES 40-59: 0.71 (0.54,0.93), 0.01
- >=60: 0.59 (0.35,1), 0.05

Triglycerides
- NO 150-199: 1.2 (1.01,1.44), 0.04
- 200-499: 1.34 (1.13,1.6), 0.0009
- >=500: 2.15 (1.07,4.33), 0.03
- YES 150-199: 1.54 (1.11,2.13), 0.01
- 200-499: 1.19 (0.87,1.64), 0.27
- >=500: 0.75 (0.28,2.06), 0.58

HCV negative — HR (95% CI), p-value

Total cholesterol
- NO 200-239: 1.18 (1.05,1.33), 0.01
- >240: 1.48 (1.26,1.74), <.0001
- YES 200-239: 1 (0.85,1.16), 0.95
- >240: 1.03 (0.87,1.22), 0.74

LDL cholesterol
- NO 100-129: 1.1 (0.95,1.29), 0.2
- 130-159: 1.23 (1.06,1.43), 0.01
- 160-189: 1.52 (1.25,1.84), <.0001
- >=190: 1.98 (1.45,2.71), <.0001
- YES 100-129: 0.82 (0.68,0.99), 0.03
- 130-159: 0.89 (0.74,1.07), 0.22
- 160-189: 0.84 (0.67,1.05), 0.12
- >=190: 0.95 (0.72,1.25), 0.69

HDL cholesterol
- NO 40-59: 0.73 (0.65,0.82), <.0001
- >=60: 0.67 (0.57,0.8), <.0001
- YES 40-59: 0.71 (0.62,0.82), <.0001
- >=60: 0.55 (0.41,0.73), <.0001

Triglycerides
- NO 150-199: 1.34 (1.16,1.55), 0.0001
- 200-499: 1.6 (1.4,1.82), <.0001
- >=500: 2.1 (1.32,3.36), 0.002
- YES 150-199: 1.04 (0.87,1.25), 0.68
- 200-499: 1.14 (0.98,1.33), 0.09
- >=500: 1.48 (1.06,2.06), 0.02

HR (95% CI) compared reference category

Figure 3. Risk of acute myocardial infarction in the low cardiovascular disease risk population in various lipid groups, stratified by age groups (A), BMI (B), and receipt of lipid lowering therapy (C). (Adjusted Cox proportional hazards model, adjusted for age, race, BMI, and receipt of lipid lowering agents, excluding adjustment for outcome of interest in each model). Abbreviations: BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; HDL, high density lipoprotein cholesterol; HR, hazards ratio; LDL, low density lipoprotein cholesterol.

among HCV-infected persons compared with HCV-uninfected persons with similar baseline TC, LDL, and TG levels.

There is increasing evidence that HCV is associated with a higher risk of CAD [1, 2, 22]. The increased risk associated with HCV extends to stroke and heart failure [23, 24]. Proposed mechanisms for this increased risk include a pro-inflammatory state with higher levels of pro-inflammatory cytokines associated with a higher risk of CVD events [22], severity of liver disease directly contributing to the risk of myocardial injury [25], and possible direct effects of the virus on the myocardium and endothelium [25, 26]. Infection with HCV is associated with alteration of the lipid profile, but the independent contribution of this to the risk of AMI has been unclear thus far. Our results suggest that higher TC (>200) and LDL (>100) levels among HCV-infected persons should prompt clinicians into evaluating the risk of AMI more carefully in the HCV-infected persons and considering a more aggressive approach to CVD prevention strategies in these persons.

The vast majority of the HCV-infected subjects who had HCV RNA results were HCV RNA positive. Because subjects who received any treatment were excluded, this represents true chronic infection. Our analysis did not demonstrate a consistent higher risk of AMI among HCV RNA positive versus HCV RNA negative and similar lipid levels. This suggests a role of HCV infection itself and not necessarily ongoing viral replication in the genesis of risk of AMI in this population. Future studies should assess the impact of successful HCV eradication upon future risk of AMI events.

The demonstration of a higher risk of AMI among the younger HCV-infected persons is a cause for concern. It is somewhat counterintuitive that younger persons with a similar risk profile would have a higher risk. One possible explanation of this observation is that with increasing age more people may have altered their lifestyle toward healthier behaviors. However, we adjusted for at least 1 possible effect of such behavior, namely, BMI. It is also possible that HCV-infected persons may have reached a censoring event at a younger age (namely, AMI, death), thus biasing the remaining older persons toward a lower risk of events. Also, when we analyzed the risk by BMI categories, the higher BMI categories were associated with a higher risk of AMI. Finally, these data may suggest that lipid levels are a more significant risk factor at a younger age, and with aging, other factors begin to contribute more to the risk of AMI in HCV-infected persons.

Lipid lowering therapy had profound effects on the risk of AMI in all lipid strata (except TG levels 150–199 mg/dL). In each of those strata, the risk of AMI dropped to insignificant levels compared with the baseline stratum in those taking lipid lowering agents. For several strata, the absolute difference in HRs was larger among HCV-infected persons compared with HCV-uninfected persons. Although the reasons for this are unclear, these findings have potential implications in management of HCV-infected persons. Our data suggest that guidelines for treatment of lipid abnormalities in HCV-infected persons may need to be revised to suggest earlier and more aggressive treatment of hyperlipidemia.

Certain limitations need to be considered when interpreting the results from our study. Lipid levels were measured in the course of routine clinical care, so it is unclear how many of these values were collected in a fasting state, although lipid levels change minimally with fasting and even nonfasting lipid levels are associated with cardiovascular events [27]. We used ICD-9 codes to determine AMI. Although this has been used and validated in previous studies, there is a potential for a bias when relying of such codes. It has also been suggested that Veterans with acute, life-threatening conditions like AMI may not present to the VA for their acute care and may seek care at the nearest facility, which may not be a VA facility. We have studied this extensively in the setting of AMI and have found that these codes have high positive predictive values and demonstrate good agreement with formal chart review adjudication processes [18]. The ICD-9 codes used in our study included both inpatient and outpatient records, allowing us to capture events that occurred outside the VA as the Veterans sought follow-up care in the VA system. Finally, our results may not be generalizable to women because we excluded women due to small numbers.

In conclusion, HCV-infected persons may be at a higher risk of AMI than HCV-uninfected persons with similar TC and LDL levels, and this risk may be more pronounced at a younger age. Lipid lowering therapy significantly alters the risk of AMI, with a more profound lowering of risk among HCV-infected persons than HCV-uninfected persons at similar lipid levels. These data suggest that there is a need to revise the guidelines for management of lipid levels in HCV-infected persons.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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