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Chronic hepatitis C virus infection, a new cardiovascular risk factor?

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This article contains 2,860 words, an abstract with 186 words, key points 80 words, 53 references and 3 tables.

Key words: HCV; cardiovascular risk factor; stroke; ischemic heart diseases; extrahepatic manifestations.

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List of abbreviations in the order of appearance.

HCV : Hepatitis C Virus

HIV : Human Immunodeficiency Virus

OR : Odds Ratio

HR : Hazard Ratio

CI : Confidence interval

NASH : Non-Alcoholic Steato-Hepatitis

HBV : Hepatitis B Virus

RNA : Ribonucleic Acid

IMT : Intima-Media thickness

CVA : Cerebro Vascular Accident

IBT : Interferon Based Therapy

Conflict of interest.

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Key points' box

- The risk of major cardiovascular events - stroke, ischemic heart disease - is increased in HCV patients, independent of the severity of the liver disease or the common cardiovascular risk factors.
- HCV infection appears as an independent risk factor for the occurrence of ischemic cerebrovascular accidents, after adjusting for known prognostic factors.
- HCV infected patients have higher prevalence of carotid artery plaques compare to HCV negative subjects.
- HCV infection seems to be an independent risk factor for ischemic heart disease.

Abstract

Background: Among the large scope of extrahepatic manifestations related to hepatitis C virus (HCV) infection, many studies recently evaluated the frequency and characteristics of cardiovascular involvement.

Objective: To assess the current published data on HCV infection and cardiovascular diseases.

Methods: Published studies on cardiovascular disease, i.e. cerebrovascular accident and ischemic heart disease in subjects with HCV infection were analyzed from literature databases.

Results: Subjects with HCV chronic infection have an increased prevalence of carotid atherosclerosis and increased intima-media thickness compared to healthy controls or those with hepatitis B or nonalcoholic steatohepatitis. Active chronic HCV infection appears as an independent risk factor for ischemic cerebrovascular accidents. Active chronic HCV infection is associated with increased risk of ischemic heart disease. In some studies, successful interferon-based therapy showed a beneficial impact on the cardiovascular risk.

Conclusion: The risk of major cardiovascular events is higher in patients with HCV infection compared to controls, independent of the severity of the liver disease or the common cardiovascular risk factors. The beneficial impact of interferon-based therapy needs to be confirmed with new direct antiviral interferon-free agents in prospective studies with extended follow-up.

In addition to common cardiovascular risk factors (i.e. diabetes, hypertension, obesity, smoking, dyslipidemia, etc.), there appears to be new risk factors associated with certain infectious agents. Several infectious agents, notably *Chlamydia pneumoniae*, Cytomegalovirus and Human Immunodeficiency Virus (HIV), have been associated with the occurrence of cardiovascular manifestations. Hepatitis C virus (HCV) infection has been associated to a very large number of extrahepatic manifestations in various tissues and organs (1–6). Some authors have hypothesized that infections could contribute to the inflammatory cascade and result in atherosclerosis (7). Associations have been found between HCV infection and cardiomyopathies (8,9); coronary (10,11) or carotid (12,13) atherosclerosis; and hypertension (14). A recent epidemiological study showed that blood donors who were seropositive for HCV had higher mortality rates for cardiovascular diseases than non-HCV-infected blood donors without comorbidities (15). The pathogenic mechanisms connecting HCV infection, chronic liver disease, and atherogenesis are not completely understood. It has been hypothesized that HCV may promote atherogenesis and its complications through several direct and indirect biological mechanisms involving HCV colonization and replication within arterial walls, liver steatosis and fibrosis, enhanced and imbalanced secretion of inflammatory cytokines, oxidative stress, endotoxemia, perturbed cellular and humoral immunity, hyperhomocysteinemia, insulin resistance, type 2 diabetes...

As cardiovascular risk factors rates increase with age and patients with HCV chronic infection aging, it seems of major interest to assess the impact of HCV infection on the occurrence of cardiovascular events. This review assesses the current published data on HCV infection and cardiovascular diseases.

HCV infection and carotid atherosclerosis (*Table 1*)

Since 2002, Japanese studies have reported an association between HCV infection and an increased risk of carotid atherosclerosis. HCV seropositivity is associated with an increased frequency of

carotid atherosclerosis plaques, with an odds ratio (OR) of 1.92 [95% CI 1.56-2.38] and an increased carotid intima-media thickness, OR 2.85 [2.28-3.57] (10,11). In multivariate analysis, the presence of HCV capsid proteins is an independent predictive factor of the presence of carotid plaques, OR 5.61 (95% CI 2.06-15.26; $p < 0.001$). Another Japanese study, in 2003, found that in patients with HCV antibody and type 2 diabetes a statistically significant association between HCV and ultrasonographic evidence of carotid atherosclerosis (16). Two Italian studies showed that HCV infection is predictive of increased carotid intima-media thickness (17,18). Patients with non-alcoholic steatohepatitis (NASH), chronic hepatitis C (presence of anti-HCV antibodies and HCV-RNA+) or chronic hepatitis B (HBs antigen, HBc antibodies and HBe antibodies, but negative for HBe antigen) showed a higher prevalence of carotid plaques compared to non-infected controls. Increased of carotid intima-media thickness was observed in the three groups of patients though not in the controls (r -value=0.63, $p < 0.001$ for NASH; r -value=0.44, $p < 0.001$ for HCV; r -value=0.32, $p < 0.05$ for HBV). Therefore, NASH, HCV and hepatitis B (HBV) seem to be associated with the early occurrence of atherosclerosis independent of common cardiovascular risk factors, including insulin resistance and metabolic syndrome. Another study that focused on the presence of HCV-RNA in carotid plaques suggests a local pro-atherogenic action of HCV. The prevalence of carotid atherosclerosis appears to be similar in patients with active hepatitis C (RNA+) or with a history of hepatitis C (RNA-) (19), with no influence of the viral replication on carotid atherosclerosis. Normalization of hepatic function after elimination of HCV results in improvement of the lipid abnormalities. An Italian working group demonstrated the importance of hepatic steatosis in the occurrence of atherosclerosis, particularly in patients with hepatitis C (20). The prevalence of carotid atherosclerosis was greater in HCV positive subjects with steatosis versus HCV positive subjects without steatosis (26.0% versus 14.8%; $p < 0.015$). The prevalence of carotid atherosclerosis was also greater in HCV positive patients with steatosis versus those with NASH (77.7% versus 57.8%; $p < 0.0001$). In multivariate analysis, steatosis related to HCV is an independent risk

factor of carotid atherosclerosis, with an OR of 32.35 (95% CI: 5.4-230; $p < 0.0001$). Some studies have not found an association between HCV infection and carotid atherosclerosis, but they were done on cohorts with small sample sizes (21) and in patients with high cardiovascular risk like in hemodialysis patients (22)

A Spanish study, in a limited group of HCV/HIV co-infected patients ($n=70$) demonstrated that HCV infection was associated with higher levels of sICAM-1 and sVCAM-1 (23). However, no evidence of increased subclinical atherosclerosis was found when endothelial function was evaluated through flow media dilatation, or when assessing the carotid intima-media thickness. An American study examined the relationship of HIV and hepatitis C virus with carotid artery intima-media thickness and the presence of carotid plaques in the Women's Interagency HIV Study. Hepatitis C virus infection was not associated with greater carotid artery intima media thickness after adjustment for demographic and traditional cardiovascular risk factors (24).

Chronic HCV infection seems to predispose patients to the development of atherosclerosis and leads to carotid plaques modifications (25), even though blood lipid levels and the prevalence of metabolic syndrome are lower in HCV-infected subjects. The mechanisms that are potentially involved include a chronic immunological challenge by HCV that results in an inflammatory response and in the production of pro-inflammatory cytokines (26). Persistent infection disturbs the balance between immunostimulation and inhibitory cytokines, which could thus maintain a significant level of inflammation. The alteration in the cytokine balance observed in patients with chronic hepatitis C could result in these cardiovascular complications (27). Otherwise, a recent Italian study has showed that severe hepatic fibrosis was independently linked to the presence of carotid plaques (OR 2.177, 95% CI: 1.043-4.542, $p < 0.03$) (28). In a recent cohort study from Taiwan, HCV-infected patients followed for thirteen years showed higher risk of developing peripheral arterial disease (HR 9.25; 95% CI 6.35-13.5) (29). However, discordant results have been reported in a study on 233 HCV seropositive patients and 4033

HCV negative controls that did not find an independent association between HCV seropositivity and carotid intima-media thickness, carotid plaques and carotid stenoses (30).

HCV infection and cerebrovascular involvement (*Table 2*)

Several recent publications have reported the association between hepatitis C and the occurrence of cerebrovascular accidents (CVA). A prospective Taiwanese study over a 17-year period estimated a 1% risk of mortality from CVA in HCV seronegative subjects versus 2.7% in those who were seropositive, with a HR of 2.18 (95% CI 1.5-3.16; $p < 0.001$) after adjusting for common CVA risk factors (31). There was a correlation between the increased CVA risk and the extent of viral replication (HCV-RNA). Conversely, a very recent Italian case-control study found an HCV seroprevalence of 26.8% in patients hospitalized for a CVA versus 6.6% in controls ($p = 0.0001$) (32). Patients with HCV infection compared to HCV-negative controls were younger and had lower cholesterol and triglyceride levels whereas they had higher levels of serum inflammatory markers (CRP, fibrinogen ...). In multivariate analysis, HCV infection was an independent risk factor of ischemic CVA (OR 2.02; 95% CI 1.69-2.46; $p = 0.0001$). Inflammation could play a key role in atheromatous plaque instability. A longitudinal cohort study conducted in Taiwan also showed that HCV infection independently increases the risk of CVA, with a hazard ratio adjusted for common cardiovascular risk factors of 1.27 (95% CI 1.14-1.41) (33). The only study that did not find an association between CVA and HCV is difficult to interpret, since there are many confounding factors that differ significantly between the HCV-positive group and the HCV seronegative patients (34).

HCV infection and ischemic heart disease (*Table 3*)

In 2009, an American study showed more cardiovascular events in HCV-seropositive patients than in those who were seronegative (6.2% versus 4%). Similar results were found for heart failure (7.6 % versus 2.9%; $p < 0.01$) and overall mortality (9.3% versus 4.2%; $p < 0.01$) (35). After adjustment for common cardiovascular risk factors, HCV seropositivity remained independently associated with

the risk for heart failure events. In a case-control study, HCV infection emerged as an independent factor of proven coronary artery disease (adjusted OR = 4.2; 95% CI 1.4-13.0)(11). A recent retrospective Italian study found an increase in ischemic heart events in HCV seropositive patients compared to those who were seronegative (22% versus 13%; $p < 0.031$) (20). HCV seropositive American veterans showed an increased risk of coronary artery disease [HR 1.25 (95% CI 1.2-1.3)] although HCV-seropositive versus HCV-seronegative patients had lower levels of plasma cholesterol (175 ± 41 vs. 198 ± 41 mg/dL), LDL cholesterol (102 ± 37 vs. 119 ± 38 mg/dL) and triglycerides (144 ± 119 vs. 179 ± 151 mg/dL) (all $p < 0.001$)(36). In a UK study, HCV-seropositive patients versus HCV-seronegative patients had less dyslipidemia but higher median glycated hemoglobin levels (6.2% versus 5.7%; 95% CI 0.3-0.8) and more frequent metabolic syndrome (28% versus 18%; relative risk 1.6; 95% CI 0.8-3.0) (37). Several inflammatory pro-atherosclerotic biomarkers were increased in HCV-positive versus HCV-negative patients, including C-reactive protein, soluble intracellular adhesion molecule 1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1) and soluble E-selectin. A recent American study has established that in an HCV positive cohort (1,434 persons), patients with detectable HCV RNA had a significantly higher incidence of coronary heart disease events compared with patients HCV antibody positive with no detectable RNA (5.9% versus 4.7%, $p = 0.04$). In multivariate analyses, both HCV antibody positivity (OR 1.32 95% IC 1.09-1.60) and HCV RNA positivity (OR 1.59 95% IC 1.13-2.26) were independent risk factors for incident coronary heart disease (38). A Japanese study showed elevated concentrations of NT-pro BNP in 42 out of 42 patients with HCV antibodies, at a mean level significantly greater than in 1,276 patients without HCV antibody (10000 ± 5860 versus 2508 ± 160 pg/mL, respectively; $p < 0.0001$). This result suggested that HCV infection may be an important cause of myocarditis and heart failure (9).

Myocardial perfusion was assessed using thallium-201 scintigraphy in HCV-seropositive subjects before and after antiviral treatment (39). A total of 217 Japanese patients with chronic hepatitis C, without previously known cardiac involvement, underwent thallium-201 myocardial scintigraphy before and after HCV treatment (Interferon/ribavirin). A severity score of ischemic

cardiac involvement was defined by the sum of myocardial defects visualized on the scintigraphy. Before any antiviral treatment, 87% of patients had an abnormal thallium-201 scintigraphy severity score. The severity score was closely correlated to the type of virological response. In patients with SVR, there was a lasting reduction in the severity score. In patients with virological relapse, there was an initial decrease in the severity score followed by an increase in the score during virological relapse. Patients who were non-responders to the antiviral treatment maintained a high severity score throughout the study. Another severity score based on angiographic coronary data was used (modified scoring system of Reardon et al.) to compare HCV-seronegative subjects to seropositive subjects with similar characteristics (i.e. gender, age, common cardiovascular risk factors)(40). The Reardon score is calculated by attributing 1 to 4 points according to the degree of occlusion (<50%, 50-74%, 75-100%) of proximal coronary arteries. The Reardon score was higher in HCV seropositive than in seronegative patients (8.75 ± 1.69 versus 6.01 ± 1.80 ; $p < 0.001$). The levels of C-reactive protein were higher in seropositive versus seronegative patients (2.073 ± 1.358 versus 1.190 ± 1.005 mg/L; $p < 0.001$), as were those of fibrinogen (5.323 ± 1.567 versus 4.104 ± 1.648 g/L; $p < 0.001$). Of note, American veterans with HIV-HCV coinfection showed an increased risk of coronary artery disease compared to patients with HIV mono-infection [HR 2.45 (95% CI 1.02-3.52)] and non-infected subjects [1.46 (95% CI 1.03 to 2.07)](41).

Some data for the risk of coronary artery disease in HCV infected patients appear to be more discordant. In 126,000 HCV-seropositive veterans paired for age with 126,000 HCV-seronegative veterans, there was a lower prevalence of coronary artery disease in patients with hepatitis C compared to non-infected patients (8.3% vs. 10.8%, $p = 0.001$) (42). However, the subjects' comorbidities prevalence and characteristics were significantly different between the two groups and the follow-up period was relatively short (4 years). A similar methodology was used by the same group in 2009 in another study with contradictory results (36). Explanations given for this contradiction were the greater frequency of HBV co-infection and the fact that tobacco use, obesity and lipid levels were not taken into account (33). A retrospective study in the United Kingdom

showed that the incidence rate of myocardial infarction did not increase in HCV-infected patients (37). A review of very recent American literature did not confirm the association between hepatitis C and coronary artery disease (43). An American cohort of young men from the US Military included 292 patients with coronary artery disease and 290 patients without (controls). Some patients were HCV antibody positive, 7.6% in the coronary artery disease group vs 9.8% in controls. In multivariate analysis adjusted for age, gender, smoking, hyperlipidemia, race/ethnicity, education level, marital status, hypertension, overweight/obesity, and work stress, no significant association between HCV seropositivity and coronary artery disease was observed (adjusted OR 0.94; 95% IC 0.52-1.68) (44). An American study has showed that in HCV-infected patients with stable liver function, the rates of major adverse cardiac events (i.e. death, myocardial infarction, target-vessel revascularization) and of all-cause mortality were similar in the Bare-Metal Stents and Drug Eluting Stent groups (45).

Cardiovascular disease-related mortality in HCV infected patients

A retrospective cohort study from United States showed an increased cardiovascular mortality among more than 10,200 HCV seropositive blood donors compared to more than 10,200 HCV seronegative subjects (HR 2.21; 95% CI 1.41-3.46) (15). A prospective Japanese study of 1077 adult hemodialysis patients without hepatitis B virus infection included 968 HCV seronegative, 55 HCV seropositive HCV RNA negative and 79 HCV RNA positive patients (46). The sex- and age-adjusted mortality rate was 71.9, 80.4, and 156 respectively. The RRs (95% CI) for death in HCV RNA negative versus HCV RNA positive patients were 1.23 (0.72 to 2.12) vs 1.60 (1.13 to 2.28) for all-cause death and 0.75 (0.28 to 2.02) vs 1.64 (0.98 to 2.73) for cardiovascular death. A recent meta-analysis on 22 studies that compared the occurrence of cardiovascular diseases between HCV-infected and HCV-uninfected subjects found that HCV-infected patients had increased risks of cardiovascular diseases-related mortality (OR 1.65; 95%CI, 1.07-2.56; P =0.02), even greater in patients with diabetes and hypertension (47). A meta-analysis in hemodialysis patients found that anti-HCV

antibody positivity is an independent and significant risk factor for death, with an adjusted RR for cardiovascular mortality of 1.26 (95% CI 1.10-1.45) (48).

Impact of HCV treatment on cardiovascular outcomes

Few studies have evaluated the effect of Pegylated interferon α plus ribavirin (Interferon Based Therapy), the standard of care treatment for chronic HCV infection before the advent of new direct acting antiviral therapy, on main cardiovascular outcomes.

A retrospective study from the Taiwan National Health Insurance Program included 3,113 subjects with a newly detected HCV infection and 12,452 age- and gender-matched subjects without HCV infection followed up to 5 years (49). Use of IBT significantly reduced the risk of stroke in HCV patients (adjusted HR = 0.39, 95% CI = 0.16-0.95, P = 0.039) after adjusting for known prognostic factors. Another Taiwanese study showed IBT to be associated with improved cardiovascular outcomes in HCV-infected diabetic patients (50). After a mean follow up of 8 years, the cumulative incidence of CVA in HCV-seropositive diabetic patients significantly decreased after treatment with IBT 3.1% (95% CI 1.1-5.0%) compared to non-treated HCV infected diabetics (5.3%; 95% CI 3.0-7.5%) or diabetic HCV-seronegative subjects (6.1%; 95% CI 4.8-7.4%). In another study from the Taiwan nationwide cohort, 12,384 HCV patients treated with IBT matched 1:2 with 24,768 untreated controls showed a 8-year cumulative incidence of stroke of 1.31% versus 1.76% (p=0.001). Of note, the multivariate analysis showed that a 16 weeks-IBT was associated with a lower risk of stroke (HR 0.62, IC 95% 0.46-0.83; p=0.001) and of acute coronary disease (HR 0.77, 95% CI 0.62-0.97 ; p=0.01) (51). Such beneficial cardiovascular impact was not found in patients who received less than 16 weeks IBT. Use of IBT in chronic hepatitis C seems to reduce the risk of stroke as well as non-liver related mortality (20).

Other studies showed beneficial impact of IBT on surrogate markers of atherosclerosis. A cross sectional study showed that HCV patients who achieved a SVR compared to non-SVR patients

had a significant improvement in their arterial stiffness as measured by pulse wave velocity (7.4 ± 1.1 versus 6.5 ± 0.6 m/s, respectively) (47). A Spanish study included 56 patients, 32 HCV-HIV co-infected and 24 HCV mono-infected. Compared with baseline, during IBT therapy there was a significant decrease in the concentrations of matrix metalloproteinase-9 ($P < 0.001$), intercellular cell adhesion molecule-1 (ICAM-1) ($P \leq 0.01$) and oxidized low-density lipoproteins ($P = 0.002$) (52). After IBT discontinuation, levels of ICAM-1, VCAM-1 and tumor necrosis factor- α were significantly lower compared with baseline, a change restricted to patients with sustained virological response.

Conclusion

Among the large number of extrahepatic manifestations related to chronic HCV infection, cardiovascular involvement has probably been underestimated. Recent studies showed increased risk of cardiovascular events in HCV infected patients, i.e. cerebrovascular, cardiac and renal events regardless of the severity of the liver disease or the common cardiovascular risk factors. The beneficial effects of successful antiviral treatment found in some studies (sustained virological response) on the cardiovascular risk offer new opportunities, particularly with the emergence of new interferon-free combinations more effective and well tolerated. These data need to be confirmed in prospective studies dedicated to these issues and including extended follow-up.

Table 1: Main studies assessing the association between hepatitis C virus (HCV) infection and carotid atherosclerosis.

References, year	Type of study	Country	HCV+ (n)	HCV- (n)	Statistics	Diagnosis method
Studies showing an association						
Ishizaka et al. (12), 2002	Cross-sectional	Japan	104	4784	OR=2.9 95% CI 2.3-3.6	HCV antibody
Ishizaka et al. (13), 2003	Cross-sectional	Japan	25	1967	OR=NA	HCV core protein
Tomiyawa et al. (14), 2003	Cross-sectional	Japan	87	7427	OR=NA	HCV antibody
Fukui et al. (16), 2003	Cross-sectional	Japan	31	179	OR=NA	HCV antibody
Boddi et al. (17), 2007	Cross-sectional	Italy	31	120	OR=4.4 95% CI 1.4-13.9	HCV antibody
Targher et al. (18), 2007	Cross-sectional	Italy	60	60	OR=1.6 95% CI 1.5-2.6	HCV antibody and HCV RNA
Mostafa et al. (19), 2010	Cross-sectional	Egypt	329	795	OR=3.5 95% CI 1.2-9.9	HCV antibody and HCV RNA
Petta et al. (28), 2012	Prospective	Italy	174	174	OR=NA	HCV genotype 1
Adinolfi et al. (25), 2012	Case-control	Italy	326	477	OR=5.2 95% CI 2.6-10.5	HCV RNA
Hsu et al (29), 2015	Cross sectional	Taiwan	7641	30564	OR=1.43 95% CI 1.23-1.67	ICD-9
Studies not showing an association						
Völzke et al.(30), 2004	Transversal	Germany	21	4033	OR=NA	HCV antibody
Bilora et al. (21), 2008	Case-control	Italy	40	40	OR=NA	HCV RNA
Caliskan et al. (22), 2009	Prospective*	Turkey	36	36	OR=NA	HCV antibody
Tien et al. (24), 2009	Cross-sectional**	USA	273	1502	OR=NA	HCV antibody +/- HCV RNA
Masia et al. (23) , 2011	Cross-sectional**	Spain	63	138	OR=0.61 95% CI 0.55-0.65	HCV RNA

* Hemodialysis patients, ** HIV patients, OR=odds ratio, 95% CI=95% confidence interval, NA=not available, ICD-9=International Classification of Diseases-9

Table 2: Main studies assessing the association between hepatitis C virus (HCV) infection and ischemic cerebrovascular accident.

References, year	Type of study	Country	HCV+ (n)	HCV- (n)	Statistics	Diagnosis method
<i>Studies showing an association</i>						
Lee et al. (31), 2010	Prospective cohort	Taiwan	1307	22,358	HR=2.2 95% CI 1.5-3.2	ICD-9
Liao et al. (33), 2012	Cross-sectional	Taiwan	4094	16,376	HR=1.27 95% CI 1.14-1.14	ICD-9
Adinolfi et al. (32), 2013	Cross-sectional	Italy	79	741	OR=2.4 95% CI 1.69-2.46	HCV antibody
Hsu et al. (49), 2013	Retrospective cohort	Taiwan	3113	12452	HR=1.23 95% CI 1.06-1.42	ICD-9
Hsu et al. (50), 2014	Cross-sectional	Taiwan	2875	12,450	HR=0.53 95% CI 0.30-0.93	ICD-9 and HCV antibody
Pothineni et al, (38), 2014	Retrospective cohort	USA	8,251	14,799	OR=1.32 95% CI 1.09-1.60	HCV antibody
Hsu et al. (51), 2015	Prospective cohort*	Taiwan	12,384	-	HR=0.62 95% CI 0.42-0.83	ICD-9
<i>Studies not showing an association</i>						
Younossi et al (34), 2013	Cross-sectional	USA	173	19,568	OR=2.49 95% CI 1.04-5.96	HCV RNA

HR=hazard ratio, OR=odds ratio, 95% CI=95% confidence interval. * 12,394 HCV treated patients vs 27,768 HCV untreated patients ICD-9=International Classification of Diseases-9

Table 3: Main studies assessing the association between hepatitis C virus (HCV) infection and ischemic heart disease.

References, year	Type of study	Country	HCV+ (n)	HCV- (n)	Statistics	Diagnosis method
Studies showing an association						
Vassalle et al. (11), 2004	Cross-over	Italy	491	195	OR=4.2 95% CI 1.4-13	HCV antibody
Alyan et al (40), 2008	Cross-sectional	Turkey	139	225	OR= 2.02 95% CI 1.58-2.58	HCV antibody
Butt et al. (36), 2009	Cross-sectional	USA	82,083	89,582	HR=1.25 95% CI 1.2-1.3	ICD-9
Tsui et al. (35), 2009	Cross-sectional	USA	84	897	HR=2.13 95% CI 1.19-3.80	HCV antibody
Ramdeen et al.(45), 2010	Retrospective cohort	USA	78	-	OR=NA	HCV antibody
Freiberg et al (41), 2011	Cross-sectional**	USA	1439	5453(HIV-) 1687(HIV+)	HR= 2.03 95% CI 1.28-3.21	ICD-9
Studies not showing an association						
Völzke et al.(30), 2004	Transversal	Germany	21	4033	OR=NA	HCV antibody
Butt et al.(42), 2007	Cross-sectional	USA	126,926	126,926	OR=NA	ICD-9
Forde et al.(53), 2012	Retrospective cohort	UK	4809	71,668	HR=1.1 95%CI 0.67-1.83	ICD-9
Younossi et al.(34), 2013	Cross-sectional	USA	173	19568	OR=NA	HCV-RNA

** HIV patients HR=hazard ratio, OR=odds ratio, 95% CI=95% confidence interval, NA=not available. ICD-9=International Classification of Diseases-9

References

1. Watanabe H, Ono T, Muso E, Matsumori A, Sasayama S. Hepatitis C virus infection manifesting as tubulointerstitial nephritis, cardiomyopathy, and hepatitis. *Am J Med.* 1 août 2000;109(2):176-7.
2. Okuse C, Yotsuyanagi H, Koike K. Hepatitis C as a systemic disease: virus and host immunologic responses underlie hepatic and extrahepatic manifestations. *J Gastroenterol.* nov 2007;42(11):857-65.
3. Nieto FJ. Infections and atherosclerosis: new clues from an old hypothesis? *Am J Epidemiol.* 15 nov 1998;148(10):937-48.
4. Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC, et al. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. *Arthritis Rheum.* oct 1999;42(10):2204-12.
5. Cacoub P, Gragnani L, Comarmond C, Zignego AL. Extrahepatic manifestations of chronic hepatitis C virus infection. *Dig Liver Dis.* 15 déc 2014;46 Suppl 5:S165-73.
6. Rosenthal E, Cacoub P. Extrahepatic manifestations in chronic hepatitis C virus carriers. *Lupus.* avr 2015;24(4-5):469-82.
7. Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link? *Lancet.* 9 août 1997;350(9075):430-6.
8. Matsumori A, Matoba Y, Sasayama S. Dilated cardiomyopathy associated with hepatitis C virus infection. *Circulation.* 1 nov 1995;92(9):2519-25.
9. Matsumori A, Shimada T, Chapman NM, Tracy SM, Mason JW. Myocarditis and heart failure associated with hepatitis C virus infection. *J Card Fail.* mai 2006;12(4):293-8.
10. 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.* 11 janv 2007;21(2):193-7.
11. Vassalle C, Masini S, Bianchi F, Zucchelli GC. Evidence for association between hepatitis C virus seropositivity and coronary artery disease. *Heart.* mai 2004;90(5):565-6.
12. Ishizaka N, Ishizaka Y, Takahashi E, Tooda E ichi, Hashimoto H, Nagai R, et al. Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening. *Lancet.* 12 janv 2002;359(9301):133-5.
13. 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.* janv 2003;67(1):26-30.
14. 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.* févr 2003;166(2):401-3.

15. 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*. 15 mars 2008;167(6):743-50.
16. Fukui M, Kitagawa Y, Nakamura N, Yoshikawa T. Hepatitis C virus and atherosclerosis in patients with type 2 diabetes. *JAMA*. 12 mars 2003;289(10):1245-6.
17. Boddi M, Abbate R, Chellini B, Giusti B, Solazzo V, Soft F, et al. HCV infection facilitates asymptomatic carotid atherosclerosis: preliminary report of HCV RNA localization in human carotid plaques. *Dig Liver Dis*. sept 2007;39 Suppl 1:S55-60.
18. Targher G, Bertolini L, Padovani R, Rodella S, Arcaro G, Day C. Differences and similarities in early atherosclerosis between patients with non-alcoholic steatohepatitis and chronic hepatitis B and C. *J Hepatol*. juin 2007;46(6):1126-32.
19. Mostafa A, Mohamed MK, Saeed M, Hasan A, Fontanet A, Godsland I, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. *Gut*. août 2010;59(8):1135-40.
20. Adinolfi LE, Zampino R, Restivo L, Lonardo A, Guerrera B, Marrone A, et al. Chronic hepatitis C virus infection and atherosclerosis: clinical impact and mechanisms. *World J Gastroenterol*. 7 avr 2014;20(13):3410-7.
21. Bilora F, Campagnolo E, Rinaldi R, Rossato A, Arzenton M, Petrobelli F. Carotid and femoral atherosclerosis in chronic hepatitis C: a 5-year follow-up. *Angiology*. janv 2008;59(6):717-20.
22. Caliskan Y, Oflaz H, Pusuroglu H, Boz H, Yazici H, Tamer S, et al. Hepatitis C virus infection in hemodialysis patients is not associated with insulin resistance, inflammation and atherosclerosis. *Clin Nephrol*. févr 2009;71(2):147-57.
23. Masiá M, Padilla S, Robledano C, Ramos JM, Gutiérrez F. Evaluation of endothelial function and subclinical atherosclerosis in association with hepatitis C virus in HIV-infected patients: a cross-sectional study. *BMC Infect Dis*. 2011;11:265.
24. Tien PC, Schneider MF, Cole SR, Cohen MH, Glesby MJ, Lazar J, et al. Association of hepatitis C virus and HIV infection with subclinical atherosclerosis in the women's interagency HIV study. *AIDS*. 24 août 2009;23(13):1781-4.
25. Adinolfi LE, Restivo L, Zampino R, Guerrera B, Lonardo A, Ruggiero L, et al. Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis. *Atherosclerosis*. avr 2012;221(2):496-502.
26. Jacobson Brown PM, Neuman MG. Immunopathogenesis of hepatitis C viral infection: Th1/Th2 responses and the role of cytokines. *Clin Biochem*. mai 2001;34(3):167-71.
27. Hansson GK. Immune mechanisms in atherosclerosis. *Arterioscler Thromb Vasc Biol*. déc 2001;21(12):1876-90.
28. Petta S, Torres D, Fazio G, Cammà C, Cabibi D, Di Marco V, et al. Carotid atherosclerosis and chronic hepatitis C: a prospective study of risk associations. *Hepatology*. mai 2012;55(5):1317-23.

29. Hsu Y-H, Muo C-H, Liu C-Y, Tsai W-C, Hsu C-C, Sung F-C, et al. Hepatitis C virus infection increases the risk of developing peripheral arterial disease: a 9-year population-based cohort study. *J Hepatol.* mars 2015;62(3):519-25.
30. Völzke 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.* mai 2004;174(1):99-103.
31. Lee M-H, Yang H-I, Wang C-H, Jen C-L, Yeh S-H, Liu C-J, et al. Hepatitis C virus infection and increased risk of cerebrovascular disease. *Stroke J Cereb Circ.* déc 2010;41(12):2894-900.
32. Adinolfi LE, Restivo L, Guerrera B, Sellitto A, Ciervo A, Iuliano N, et al. Chronic HCV infection is a risk factor of ischemic stroke. *Atherosclerosis.* nov 2013;231(1):22-6.
33. Liao C-C, Su T-C, Sung F-C, Chou W-H, Chen T-L. Does hepatitis C virus infection increase risk for stroke? A population-based cohort study. *PLoS One.* 2012;7(2):e31527.
34. Younossi ZM, Stepanova M, Nader F, Younossi Z, Elsheikh E. Associations of chronic hepatitis C with metabolic and cardiac outcomes. *Aliment Pharmacol Ther.* mars 2013;37(6):647-52.
35. Tsui JI, Whooley MA, Monto A, Seal K, Tien PC, Shlipak M. Association of hepatitis C virus seropositivity with inflammatory markers and heart failure in persons with coronary heart disease: data from the Heart and Soul study. *J Card Fail.* juin 2009;15(5):451-6.
36. Butt AA, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. *Clin Infect Dis.* 15 juill 2009;49(2):225-32.
37. Forde KA, Haynes K, Troxel AB, Trooskin S, Osterman MT, Kimmel SE, et al. Risk of myocardial infarction associated with chronic hepatitis C virus infection: a population-based cohort study. *J Viral Hepat.* avr 2012;19(4):271-7.
38. Pothineni NVKC, Delongchamp R, Vallurupalli S, Ding Z, Dai Y, Hagedorn CH, et al. Impact of hepatitis C seropositivity on the risk of coronary heart disease events. *Am J Cardiol.* 15 déc 2014;114(12):1841-5.
39. Maruyama S, Koda M, Oyake N, Sato H, Fujii Y, Horie Y, et al. Myocardial injury in patients with chronic hepatitis C infection. *J Hepatol.* janv 2013;58(1):11-5.
40. Alyan O, Kacmaz F, Ozdemir O, Deveci B, Astan R, Celebi AS, et al. Hepatitis C infection is associated with increased coronary artery atherosclerosis defined by modified Reardon severity score system. *Circ J.* déc 2008;72(12):1960-5.
41. Freiberg MS, Chang C-CH, Skanderson M, McGinnis K, Kuller LH, Kraemer KL, et al. The risk of incident coronary heart disease among veterans with and without HIV and hepatitis C. *Circ Cardiovasc Qual Outcomes.* juill 2011;4(4):425-32.
42. Butt AA, Khan UA, McGinnis KA, Skanderson M, Kent Kwok C. Co-morbid medical and psychiatric illness and substance abuse in HCV-infected and uninfected veterans. *J Viral Hepat.* déc 2007;14(12):890-6.
43. Wong RJ, Kanwal F, Younossi ZM, Ahmed A. Hepatitis C virus infection and coronary artery disease risk: a systematic review of the literature. *Dig Dis Sci.* juill 2014;59(7):1586-93.

44. Arcari CM, Nelson KE, Netski DM, Nieto FJ, Gaydos CA. No association between hepatitis C virus seropositivity and acute myocardial infarction. *Clin Infect Dis.* 15 sept 2006;43(6):e53-6.
45. Palaniswamy C, Aronow WS, Sukhija R, Chugh T, Ramdeen N, Kalapatapu K, et al. Major adverse cardiac events in patients with hepatitis C infection treated with bare-metal versus drug-eluting stents. *Clin Cardiol.* juin 2010;33(6):367-70.
46. Ohsawa M, Kato K, Tanno K, Itai K, Fujishima Y, Okayama A, et al. Seropositivity for anti-HCV core antigen is independently associated with increased all-cause, cardiovascular, and liver disease-related mortality in hemodialysis patients. *J Epidemiol.* 2011;21(6):491-9.
47. Pateria P, Jeffrey GP, MacQuillan G, Speers D, Ching H, Chinnaratha MA, et al. The association between chronic hepatitis C infection and cardiovascular risk. *Intern Med J.* 19 oct 2015;
48. Fabrizi F, Dixit V, Messa P. Impact of hepatitis C on survival in dialysis patients: a link with cardiovascular mortality? *J Viral Hepat.* sept 2012;19(9):601-7.
49. Hsu C-S, Kao J-H, Chao Y-C, Lin HH, Fan Y-C, Huang C-J, et al. Interferon-based therapy reduces risk of stroke in chronic hepatitis C patients: a population-based cohort study in Taiwan. *Aliment Pharmacol Ther.* août 2013;38(4):415-23.
50. Hsu Y-C, Lin J-T, Ho HJ, Kao Y-H, Huang Y-T, Hsiao N-W, et al. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. *Hepatology.* avr 2014;59(4):1293-302.
51. Hsu Y-C, Ho HJ, Huang Y-T, Wang H-H, Wu M-S, Lin J-T, et al. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut.* mars 2015;64(3):495-503.
52. Masiá M, Robledano C, López N, Escolano C, Gutiérrez F. Treatment for hepatitis C virus with pegylated interferon- α plus ribavirin induces anti-atherogenic effects on cardiovascular risk biomarkers in HIV-infected and -uninfected patients. *J Antimicrob Chemother.* août 2011;66(8):1861-8.
53. Forde KA, Haynes K, Troxel AB, Trooskin S, Osterman MT, Kimmel SE, et al. Risk of myocardial infarction associated with chronic hepatitis C virus infection: a population-based cohort study. *J Viral Hepat.* avr 2012;19(4):271-7.