



# Risk of Cardiovascular Disease Due to Chronic Hepatitis C Infection: A Review

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## Abstract

Hepatitis C (HCV) infection has an estimated global prevalence of 2.5%, causing chronic liver disease in 170 million people worldwide. Recent data has identified HCV infection as a risk factor for subclinical and clinical cardiovascular disease (CVD), but these data have been mixed and whether HCV is an independent risk factor for development of CVD remains controversial. In this review, we present the literature regarding the association of HCV with subclinical and clinical CVD and the possible underlying mechanisms leading to increased CVD among those infected with HCV. HCV infection leads to increased CVD via direct and indirect mechanisms with chronic inflammation, endothelial dysfunction and direct invasion of the arterial wall cited as possible mechanisms. Our review showed that HCV infection, particularly chronic HCV infection, appears to lead to increased subclinical CVD most consistently and potentially also to increased clinical CVD outcomes, leading to increased morbidity and mortality. Furthermore, the majority of studies evaluating the impact of HCV therapy on CVD morbidity and mortality showed an

improvement in subclinical and clinical CVD endpoints in patients who were successfully treated and achieved sustained viral suppression. These results are of particular interest following the development of new direct antiviral agents which have made HCV eradication simple and feasible for many more patients globally, and in doing so may possibly reduce CVD morbidity and mortality in those with chronic HCV infection.

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## Introduction

Hepatitis C virus (HCV) is a single-stranded RNA virus belonging to the Flaviviridae family.<sup>1</sup> HCV infection has an estimated global prevalence of 2.5%, causing chronic liver disease in 170 million people worldwide, and is the leading cause of progressive liver fibrosis, resulting in cirrhosis, liver cancer, liver failure and death.<sup>2,3</sup> Chronic HCV (CHC) infection progresses slowly for most individuals, and patients often remain asymptomatic for decades until they develop clinically apparent liver disease resulting in delayed diagnosis. In addition to liver disease, CHC infection has been associated with many extrahepatic comorbidities, including cryoglobulinemia, lymphoproliferative disease, renal disease, cardiovascular disease (CVD), diabetes mellitus (DM) and insulin resistance.<sup>4,5</sup> Recently, HCV treatment has been transformed by the availability of oral, once-daily, and well-tolerated direct-acting antiviral agents (DAAs), which achieve >90% sustained viral response (SVR) rates (SVR defined as an undetectable HCV RNA level 12 weeks after completing HCV treatment) among CHC patients.

Recent data has identified HCV infection as a risk factor for subclinical and clinical CVD. However, results of these studies are mixed and whether HCV is an independent risk factor for development of CVD remains controversial.<sup>6–8</sup> In this review, we present the literature regarding the association of HCV with subclinical and clinical CVD and the possible underlying mechanisms leading to increased CVD among those infected with HCV.

**Keywords:** Hepatitis C; Cardiovascular disease; Coronary heart disease; Atherosclerosis; Cerebrovascular disease.

**Abbreviations:** AA, African American; AB, antibody; ACS, acute coronary syndrome; aHR, adjusted hazard ratio; AMI, acute myocardial infarction; aRR, adjusted relative risk; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCV, cerebrocardiovascular; CHC, chronic hepatitis C; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CIMT, carotid intima media thickness; CRP, C-reactive protein; CVA, cerebrovascular accident; CVD, cardiovascular disease; DAAs, direct-acting antiviral agents; DCM, dilated cardiomyopathy; DM, diabetes mellitus; DVT, deep venous thrombosis; FMD, flow-mediated dilation; HBV, hepatitis B virus; HCM, hypertrophic cardiomyopathy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HLD, hyperlipidemia; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IDCM, idiopathic DCM; IFN, interferon; IHD, ischemic heart disease; IL, interleukin; IMT, intima media thickness; IR, insulin resistance; IRR, incidence rate ratio; MA, Mexican American; MI, myocardial infarction; NASH, non-alcoholic steatohepatitis; NMH, non-Mexican Hispanic; OR, odds ratio; PAD, peripheral arterial disease; PE, pulmonary embolism; PR, prevalence ratio; PVD, peripheral vascular disease; PVT, peripheral venous thrombosis; PWV, pulse wave velocity; RF, risk factor; RNA, ribonucleic acid; SMR, standardized mortality ratio; SVR, sustained viral response; TIA, transient ischemic attack; TNF, tumor necrosis factor; VA, Veterans Affairs; UA, unstable antigen; UK, United Kingdom; US, ultrasound; USA, United States of America. Received: 13 March 2017; Revised: 15 July 2017; Accepted: 27 July 2017

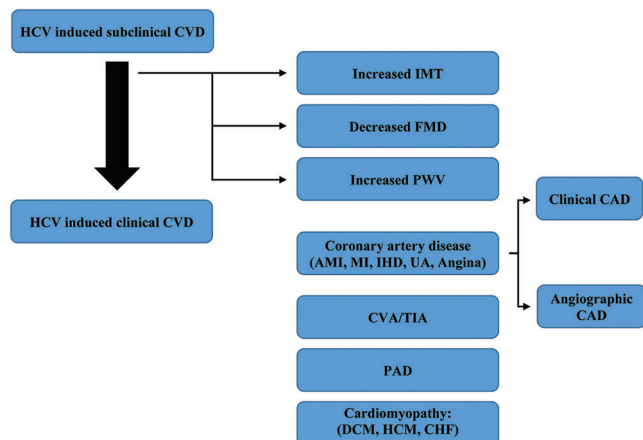
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## Methodology

We searched PubMed for English language articles published between January 1, 1995 through December 31, 2016 using the following keywords: "hepatitis C, hepatitis C virus, hepatitis non-A non-B, HCV, cardiovascular disease, cardiac outcomes, carotid atherosclerosis, intima-media thickness, cerebrovascular disease, stroke, cardiovascular outcomes, myocardial infarction, peripheral arterial disease (and its abbreviation PAD), and coronary artery disease. A total of 553 references were found, and of those 499 references were not selected because they were abstracts, poster presentations, correspondences or other report types, or were deemed not relevant to the scope of this review upon reading their abstracts. An additional 37 articles were added after performing ancestry and bibliography searches of all relevant articles, meta-analyses, systematic reviews, and narrative reviews on HCV and CVD. Ultimately, 91 full-length articles were reviewed. Study designs included randomized clinical trials, prospective cohorts, retrospective analyses, case-control studies, cross-sectional studies and meta-analysis.

We have presented the data from our literature review by first reporting studies that investigated possible pathogenic mechanisms of HCV on CVD in order to understand the plausible biological basis for findings reported subsequently, then presenting studies that investigated the effect of HCV infection on both subclinical and clinical outcomes of CVD, and finally presenting studies that assessed HCV infection on the myocardium. Subclinical CVD was defined as evidence of atherosclerotic disease using a surrogate measure of atherosclerosis (such as with carotid intima media thickness (CIMT), flow-mediated dilation (FMD) and pulse wave velocity (PWV)) whereas clinical CVD was defined as any clinical CVD event (such as coronary artery disease (CAD), myocardial infarction (MI), unstable angina (UA), cerebrovascular accident (CVA), transient ischemic attack (TIA), PAD, and congestive heart failure (CHF)) (Fig. 1).



**Fig. 1. Flowchart.**

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; IHD, ischemic heart disease; IMT, intima media thickness; FMD, flow-mediated dilation; MI, myocardial infarction; PAD, peripheral arterial disease; PWV, pulse wave velocity; UA, unstable angina.

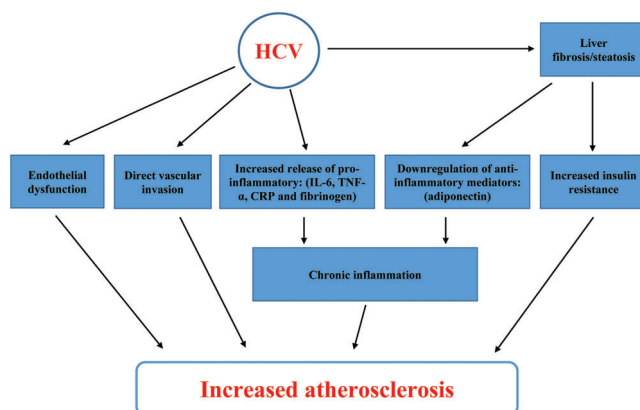
## Pathogenesis

The role of infectious agents in the development of atherosclerotic disease was first described over a century ago.<sup>9</sup> Chronic infection with certain organisms is believed to promote the atherogenic process by inducing a systemic inflammatory state.<sup>10</sup>

HCV infection interferes with glucose and lipid metabolism, resulting in a high prevalence of insulin resistance (IR), steatosis and type 2 diabetes, which are directly associated to atherosclerosis development. However, current literature suggests that HCV infection leads to increased CVD via direct and indirect mechanisms beyond these metabolic pathways (Fig. 2). Chronic inflammation, endothelial dysfunction and direct invasion of the arterial wall have also been cited as possible mechanisms.<sup>8</sup>

CHC infection has been shown to result in chronic immune stimulation and increased inflammation associated with increased levels of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)- $\alpha$ , C-reactive protein (CRP) and fibrinogen, which have all been associated with increased CVD.<sup>11-15</sup> Adinolfi *et al.*<sup>16</sup> demonstrated that the increase in pro-inflammatory cytokines among HCV patients was associated with a significantly higher prevalence of carotid atherosclerosis in HCV-infected patients compared to controls (53.7% vs. 34.3%,  $p > 0.0001$ ) after adjusting for presence of steatosis (77.7% vs. 57.8%,  $p = 0.0001$ ). In addition, the study reported a significant association between HCV RNA level and elevated levels of serum fibrinogen and CRP, suggesting a pro-inflammatory state as the underlying mechanism independent of steatosis.

HCV treatment resulted in reduction of inflammatory markers and improvement in surrogate measures of endothelial function, supporting the link between CHC infection, inflammation, and endothelial dysfunction. Chew *et al.*<sup>17</sup> demonstrated that HCV-infected patients who achieved SVR following treatment had decreased levels of SICAM-1 (a non-hepatically produced marker of endothelial dysfunction and inflammation) and sCD163 (a marker of monocyte/macrophage activation associated with the presence or burden of atherosclerotic plaque and arterial wall inflammation). In a case control study, Pateria *et al.*<sup>18</sup> demonstrated improvement in vascular stiffness assessed by carotid PWV in HCV-infected patients who underwent treatment and achieved SVR (PWV  $7.4 \pm 1.1$  m/s vs.  $6.5 \pm 0.6$  m/s,  $p = 0.04$ ).



**Fig. 2. Mechanism of HCV-induced CVD.**

HCV has been isolated from carotid plaque tissue and endothelial tissue of brain autopsy specimens taken from HCV-infected patients.<sup>19–21</sup> Additionally, HCV RNA has been demonstrated in the myocardium of patients with myocarditis and cardiomyopathy.<sup>22,23</sup> These interesting findings suggest a possible role for direct HCV infection in vascular and cardiac tissue, but these findings need to be reproduced in larger studies.

Not only is there an association between the presence of HCV and CVD but there also seems to be a causal link between the burden of HCV infection (as demonstrated by viral load or liver disease) and CVD risk. The pro-inflammatory state resulting from HCV infection which leads to increased CVD also promotes a pro-fibrogenic environment leading to hepatic steatosis and fibrosis.<sup>24</sup> Petta *et al.*<sup>25</sup> reported that the severity of hepatic fibrosis is directly linked to number of plaques. Adinolfi *et al.*<sup>24</sup> reported that viral load and hepatic steatosis were independently associated with atherosclerosis, and Maruyama *et al.*<sup>26</sup> found that patients with higher viral load and histology activity index had higher degrees of myocardial injury. Hence, increased HCV disease burden as measured by numerous indices (HCV viral load, hepatic steatosis, hepatic fibrosis) may cause patients with CHC to be more likely to develop HCV-associated CVD.

### HCV and subclinical CVD

Several functional and anatomical surrogate markers of subclinical CVD have been investigated in HCV-infected populations to assist in predicting CVD events (Table 1). Subclinical CVD was defined as atherosclerotic disease as measured by CIMT, FMD or PWV. CIMT is a well-validated method of detecting subclinical atherosclerosis, and increased CIMT is associated with CVD risk factors, coronary atherosclerosis and CVD events.<sup>27</sup> There were 18 studies that evaluated the effect of HCV infection on CIMT. FMD is a measure of nitric oxide-mediated endothelial-dependent vasodilation measured in the brachial arteries, which is closely linked to coronary endothelial function. Lower FMD can predict CVD events and early atherosclerotic disease in the general population.<sup>27</sup> There were two studies that evaluated the effect of HCV infection on FMD. PWV is a surrogate marker of arterial stiffness, and increased PWV has been associated with CVD and mortality. Three studies evaluated the effect of HCV infection on PWV.

Ishizaka and colleagues<sup>28,29</sup> first reported on the atherogenic potential of HCV by demonstrating that the presence of anti-HCV antibody was associated with an increased risk of carotid plaque (odds ratio (OR): 1.92, 95% confidence interval (CI): 1.56–2.38) and increased CIMT (OR: 2.85, 95% CI: 2.28–3.57),<sup>28</sup> and that circulating HCV core protein was a strong independent predictor of carotid plaques (OR: 5.61, 95% CI: 2.06–15.26;  $p < 0.001$ ).<sup>29</sup>

Following these initial studies, many authors have corroborated these findings. Fukui *et al.*<sup>30</sup> and Boddi *et al.*<sup>19</sup> found anti-HCV antibody positivity to be an independent factor of increased CIMT, and Adinolfi *et al.*<sup>24</sup> and Roed *et al.*<sup>15</sup> found a statistically significant difference in CIMT and carotid plaques between HCV-infected patients and HCV-uninfected controls. Both Targher *et al.*<sup>31</sup> and Tomiyama *et al.*<sup>32</sup> reported increased PWV and CIMT among HCV-infected patients when compared to controls and hepatitis B virus (HBV)-infected patients. Mostafa *et al.*<sup>33</sup> demonstrated that the prevalence of carotid atherosclerosis did not vary between patients with active infection compared to those with past infection who

had cleared the HCV, but chronically-infected patients were shown to have increased CIMT when compared to HCV-uninfected patients. More recently, Sosner *et al.*<sup>34</sup> reported an increased prevalence of carotid plaque in human immunodeficiency virus (HIV)/HCV co-infected patients compared to HIV mono-infected patients (8/18 (44%) vs. 3/22 (14%),  $p = 0.04$ ). All these studies further strengthen evidence for the relationship between HCV infection and atherosclerosis in different populations, and suggest that HCV is an independent risk factor of subclinical atherosclerosis.

Petta *et al.*<sup>25</sup> found significantly greater intima media thickness (IMT) among infected patients compared with controls ( $1.04 \pm 0.21$  vs.  $0.90 \pm 0.16$ ,  $p < 0.001$ ), and further demonstrated that severe hepatic fibrosis (OR: 2.177, 95% CI: 1.043–4.542;  $p = 0.03$ ) was independently associated with the presence of carotid plaques in multivariate logistic regression analysis.

In contrast to the above studies which demonstrated an association between CHC infection and carotid atherosclerosis, some other studies found no such association. Miyajima *et al.*<sup>35</sup> evaluated different patient groups consisting of uninfected controls, those who had cleared HCV infection and those who had CHC infection, and found, surprisingly, that IMT was reduced in patients with CHC infection compared to the other two groups. Similarly, Bilora *et al.*<sup>36,37</sup> examined the same cohort of patients with CHC infection in 2001 and 2006 and in both instances found a lower prevalence of carotid IMT and plaques in patients with chronic viral hepatitis compared to uninfected controls. Tien *et al.*<sup>38</sup> found that after adjustment for cardiovascular risk factors HCV was not associated with greater CIMT in HIV/HCV co-infected and HCV mono-infected patients compared to HIV mono-infected patients and uninfected controls; similarly, Masiá *et al.*<sup>39</sup> did not observe a statistically significant difference in CIMT or FMD between HIV/HCV co-infected and HIV mono-infected patients. Caliskan *et al.*<sup>40</sup> found that IMT of anti-HCV-positive and anti-HCV-negative hemodialysis patients did not differ significantly as well ( $0.76 \pm 0.11$  mm vs.  $0.7 \pm 0.15$  mm,  $p = 0.44$ ). In contrast, Matsumae *et al.*<sup>41</sup> and Oyake *et al.*<sup>42</sup> demonstrated an association between HCV and increased PWV among dialysis patients.

In a meta-analysis by Aslam *et al.*<sup>43</sup> HCV-infected patients were more likely to have carotid plaques than uninfected patients (48.2% vs. 20.7%,  $p = 0.05$ ), but there was no statistical difference in the CIMT among the groups (0.9 mm vs. 0.8 mm,  $p = 0.3$ ). In another meta-analysis by Petta *et al.*<sup>6</sup> HCV infection was associated with the presence of carotid plaques in eight of the nine studies, but this difference was statistically significant in only five of the studies. The pooled estimate of the effect of HCV infection on carotid plaques (OR: 2.27, 95% CI: 1.76–2.94;  $p < 0.001$ ) and IMT was significant (mean difference: 0.09, 95% CI: 0.03–0.16;  $p < 0.001$ ).

Taken together, the preponderance of these data suggests that HCV infection is a risk factor for subclinical CVD, as measured by both vascular stiffness and carotid atherosclerosis.

### HCV and CVD

Numerous epidemiological cohort studies have sought to delineate whether the suggested link between subclinical CVD and HCV translates to an increased risk of clinical CVD among HCV-infected patients (Table 2). We have defined clinical CVD as any of the following clinical outcomes: CAD, MI,

**Table 1. Studies assessing the association between HCV infection and subclinical CVD surrogate markers**

Study (year)	Design	HCV study population: age in years; sex, %; race/ethnicity; country	Method of assessment of subclinical CVD; Endpoint	Sample Size, follow up time, calendar time	Outcome	Ref.
Ishizaka N et al. (2002)	Case-control	Age range: 24–86 Male: 67% Japan	B-mode US; CIMT >1.0 mm, Carotid plaques >1.0 mm	n = 4784, 104 HCV patients 1994–2000	- HCV seropositivity associated with an increased risk of carotid artery plaques (p = 0.002) and CIMT (p < 0.0001)	28
Ishizaka Y et al. (2003)	Case-control	Age range: 33–87 Male: 68% Japan	B-mode US; CIMT >1.0 mm, Carotid plaques >1.0 mm	n = 1992, HCV patients: 25 2000–2002	- HCV core protein positivity is an independent predictor of carotid plaques	29
Fukui et al. (2003)	Cross-sectional	Mean age: 65.6 Japan	Carotid US; plaques (distinct area of thickening), plaque score	n = 210, HCV patients: 31, controls: 179	- Presence of plaques and median plaque score (p < 0.001) and mean IMT (p = 0.004) significantly higher in HCV+ vs. controls - HCV seropositivity was an independent risk factor for atherosclerosis after adjustment for RF (p < 0.01)	30
Tomiyyama et al. (2003)	Case-control	Age range: 30–74 Japan	PWV	n = 7514, HBV AB+: 218, HBV Ag+: 76, HCV: 87	- HCV+ vs. HCV- had higher PWV (p < 0.01) - HCV+ but not HBV+ or HBV carrier was significantly associated with PWV (p < 0.05)	32
Targher et al. (2007)	Case-control	Mean age: 46 Male: 34 Italy	Carotid US; CIMT, plaques >1.2 mm	n = 155, NASH: 60, HCV: 60, HBV: 35, controls: 60	- IMT measurements markedly different among groups: 1.23 ± 0.2 mm (NASH) vs. 1.09 ± 0.2 (HBV) vs. 0.97 ± 0.1 (HCV) vs. 0.84 ± 0.1 (controls); p < 0.001 - HCV significantly associated with IMT (p < 0.001)	31
Boddi et al. (2007)	Case-control	Age range: 64–80 Male: 55% Italy	B-mode US; CIMT >1 mm or plaques ≥2 mm	n = 151, HCV patients: 31, controls: 120 January–April 2003	- Prevalence of IMT >1 mm significantly higher in HCV+ vs. controls (p < 0.001) - Prevalence and severity of internal carotid plaques not different in HCV+ vs. controls	19
Oyake et al. (2008)	Prospective cohort	Mean age: 65 Male: 76% Japan	Carotid-femoral PWV	n = 94, HCV RNA-positive: 17, HCV RNA-negative: 77 October 2002–October 2004	- PWV significantly higher in serum HCV RNA-positive vs. HCV RNA-negative (p < 0.01) - HCV+ status was an independent predictor of high PWV in multiple logistic regression analysis	42
Matsumae et al. (2010)	Prospective cohort	Mean age: 67.3 Male: 73.3% Japan	Carotid-femoral PWV; ankle-brachial blood pressure index	n = 148, HCV patients: 15 3 years	- HCV infection was an independent determinant of change in PWV - HCV resulted in an estimated annual rate of increase in PWV of 0.34 ms <sup>-1</sup> per year (p = 0.02)	41

(continued)

Table 1. (continued)

Study (year)	Design	HCV study population: age in years; sex, %; race/ethnicity; country	Method of assessment of subclinical CVD; Endpoint	Sample Size, follow up time, calendar time	Outcome	Ref.
Mostofa et al. (2010)	Cross-sectional	Mean age: 51 Male: 195 - Egypt	B-mode US, Doppler; CIMT, plaques >1.3 mm	n = 1297, chronic infection: 329, cleared infection: 173, never infected: 795 - 2002	- IMT increased in chronic infection vs. never infected, after adjustment for RF: 0.76, 95% CI: 0.72-0.79 vs. 0.70, 95% CI: 0.67-0.73; p = 0.02	33
Aslam et al. (2010)	Meta-analysis	Mean age: 57.3 Male/female ratio: 1.6 - Germany, Italy, Japan, Turkey, UK, USA	CIMT, carotid plaques	n = 12265, HCV patients: 655, articles: 10 -	- Carotid plaques more likely in HCV+ vs. HCV- groups (p = 0.05) - No significant difference observed in the mean CIMT between two groups (p = 0.30)	43
Sosner et al. (2012)	Case-control	Age range: 36-50 Male: 12 - France	Doppler US; carotid plaques >1.5 mm, femoral plaques >2.0 mm, CIMT	n = 40, HIV/HCV co-infected: 18, HIV mono-infected: 22 - December 2006-January 2008	- Prevalence of plaques significantly higher in the HIV/HCV co-infected vs. mono-infected (p = 0.04) - HCV chronic infection associated with CIMT (p = 0.02)	34
Adinolfi et al. (2012)	Case-control	Median age (range): 54 (22-70) Male: 51 - Italy	B-mode US; CIMT >1 mm or plaques ≥1.5 mm	n = 803, HCV patients: 326, controls: 477 - 2005-2011	- Higher prevalence of carotid atherosclerosis in HCV+ vs. controls (p < 0.0001) - Viral load independently associated with carotid atherosclerosis (p < 0.0001)	24
Petta et al. (2012)	Case-control	Mean age: 53.2 Male: 75 - Italy	B-mode US; CIMT, plaques >1.3 mm	n = 348, chronic HCV patients: 174, controls: 174 -	- IMT greater in HCV+ vs. controls (p < 0.001) - Hepatic fibrosis associated with presence of carotid plaques (p = 0.03)	25
Roed et al. (2014)	Case-control	Mean age: 50.8 Male: 61.7 - Denmark	Carotid US; CIMT value >75th percentile	n = 120, HCV patients: 60, controls: 60 - December 2010-July 2011	- Higher numbers of HCV+ had an increased CIMT above the standard population 75th percentile than controls: 9% vs. 3%; PR: 1.7, 95% CI: 0.4-6.7	15
Petta et al. (2016)	Meta-analysis	- - - Egypt, Turkey, Italy, Japan, Taiwan, USA, UK	Carotid plaques, CIMT	n = 9083, patients (9 studies) -	- HCV+ vs. HCV- had increased risks of carotid plaques (p < 0.001) without significant heterogeneity (I <sup>2</sup> = 31%; p = 0.17) and increased CIMT (p < 0.001), with heterogeneity (I <sup>2</sup> = 90%; p = 0.007)	6

(continued)

Table 1. (continued)

Study (year)	Design	HCV study population: age in years; sex, %; race/ethnicity; country	Method of assessment of subclinical CVD; Endpoint	Sample Size, follow up time, calendar time	Outcome	Ref.
Bilora et al. (2002)	Case-control	Mean age: 58.1 Male: 24 Italy	B-mode US and Doppler; mean CIMT comparisons, carotid and femoral plaques >2.0 mm	n = 98, chronic viral hepatitis: 48 (HCV: 46), controls: 50 12 months 2001	<ul style="list-style-type: none"> <li>- Carotid atherosclerosis less prevalent in chronic viral hepatitis patients vs. controls: 27% vs. 56%, <math>p &lt; 0.005</math></li> <li>- Patients with chronic viral hepatitis had fewer plaques and lower degree of vessel stenosis vs. controls: 16 vs. 59, <math>p &lt; 0.001</math></li> </ul>	36
Bilora et al. (2008)	Prospective cohort	Mean age: 57.1 Male: 18 Italy	B-mode US and Doppler; mean carotid and femoral IMT, carotid and femoral plaques >2.0 mm	n = 67, chronic viral hepatitis: 33 (HCV: 46), controls: 34 5 years 2006	<ul style="list-style-type: none"> <li>- Number of plaques remained unchanged in both groups</li> <li>- IMT remained unchanged in HCV+ vs. increased in controls (<math>p &lt; 0.05</math>)</li> </ul>	37
Tein et al. (2009)	Cross-sectional	Mean: 48.5 Male: 0 USA	B-mode US; CIMT, plaques >1.5 mm	n = 1675, HIV/HCV+: 220, HCV+: 53, HIV +: 95, control: 452 2004-2005	<ul style="list-style-type: none"> <li>- CIMT was significantly higher in HCV + groups vs. HIV-mono-infected group</li> <li>- HCV infection was not associated with greater CIMT after adjustment for RF</li> </ul>	38
Caliskan et al. (2009)	Prospective cohort	Age range: 25-67 Male: 13 Turkey	B-mode US, Doppler; brachial artery FMD; CIMT, plaques >1.0 mm	n = 72, HCV patients: 36, controls: 36 59 months	<ul style="list-style-type: none"> <li>- IMT of anti-HCV+ and anti-HCV- patients did not differ significantly (<math>p = 0.44</math>)</li> <li>- Plaque score also did not differ significantly between the two groups</li> </ul>	40
Masiá et al. (2011)	Cross-sectional	Median age: 43.7 Male: 53 Spain	B-mode US, brachial artery FMD, CIMT, carotid plaques >1.0 mm	n = 201, HCV+ patients: 63, controls: 138 February-June 2009	<ul style="list-style-type: none"> <li>- No significant difference in CIMT (<math>p = 0.39</math>) or FMD (<math>p = 0.37</math>) in HIV/HCV + vs HIV+ (<math>p = 0.37</math>)</li> </ul>	39
Miyajima et al. (2013)	Cross-sectional	Mean age: 68.5 Male: 17 Japan	Carotid US; CIMT comparisons	n = 1908, chronic infection (+anti-HCV/+HCV RNA): 40, transient infection (+anti-HCV/-HCV RNA): 88, controls: 1708 2009	<ul style="list-style-type: none"> <li>- IMT reduced in chronic infection vs. uninfected group (<math>p = 0.02</math>) and vs. transient infections (<math>p = 0.003</math>)</li> <li>- Significant intergroup difference (<math>p = 0.003</math>)</li> </ul>	35

Abbreviations: CI, confidence interval; CIMT, carotid intima media thickness; CVD, cardiovascular disease; FMD, flow-mediated dilatation; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IMT, intima media thickness; NASH, non-alcoholic steatohepatitis; OR, odds ratio; PR, prevalence ratio; PWV, pulse wave velocity; RF, risk factor; RNA, ribonucleic acid; US, ultrasound; USA, United States of America.

**Table 2. Studies assessing the association between HCV infection and composite clinical cardiovascular disease endpoints**

Study (year)	Design	HCV study population: age in years; sex, %; race/ethnicity, %; country	Cardiovascular disease outcomes/endpoint, n	Sample size, person-years, follow-up, calendar Time	Outcome	Ref.
Freiburg et al. (2007)	Cross-sectional	Mean age: 43.9; Male: 144; White: 34, Non-white: 66; USA	Self-reported CVD (MI, PVD, CVA, TIA)	n = 395, HIV/HCV co-infected: 198, HIV mono-infected: 197 – August 2001–July 2003	– HIV/HCV+ vs. HIV+ had higher prevalence of CVD – Risk of CVD adjusted for age was significantly higher among HIV/HCV co-infected	45
Tsui et al. (2009)	Prospective cohort	Mean age: 59; Male: 80; Non-white: 46; USA	All-cause mortality: 182; CVD: 151: CHD death, MI, stroke, CHF: 119	n = 981 CHD patients, HCV negative: 84, HCV 4.6 years September 2000–December 2002	– HCV+ patients had higher rates of death, CVD events, and heart failure hospitalizations – HCV seropositivity remained independently associated with the risk for heart failure events after adjustment for RF	13
Bedimo et al. (2010)	Retrospective cohort	Mean age: 47; Male: 97.8; White: 27.5, Black: 61.34, Other: 11.16; USA	MI, CCV: TIA, stroke	n = 19424, HIV/HCV co-infected: 6136 3.93 years/76376 person-years 1996–2004	– HIV/HCV co-infected vs. HIV+ had higher rates of MI and CCV	46
Gillis et al. (2014)	Retrospective cohort	Age range: 31–42; Male: 81; White: 74, Black: 5, Aboriginal: 15; Canada	Time to first CVD event (CAD, chronic IHD, arteriosclerotic vascular disease, MI, CHF, CVA, CABG, coronary artery angioplasty, sudden cardiac death: 167	HIV: 3416, HIV/HCV: 736, HIV/HBV: 736 2.32 years January 1995–January 2011	– HIV/HCV+ vs. HIV+ had higher incidence of CVD – HCV co-infected patients had a higher risk for CVD after adjustment for RF	44
Enger et al. (2014)	Matched retrospective cohort	Mean age: 49; Male: 62.4; African American: 5.2, Hispanic: 4.2, White: 43.9; USA	Thromboembolic events: DVT, PE, PVT, MI, JA, ischemic stroke, TIA, and other thromboembolic events	n = 90931, HCV patients: 22733, controls: 68198 12 months January 1, 2000–September 30, 2006	– HCV+ vs. controls had higher incidence of thromboembolic events – HCV+ vs. controls had increased IRR for thromboembolic events after adjustment for RF	50
Petta et al. (2016)	Meta-analysis	– – – Egypt, Turkey, Italy, Japan, Taiwan, USA, UK	CVD-related mortality carotid atherosclerosis, CIMT, CCV events	n = 468050 patients (22 studies) – –	– HCV+ vs. HCV– had increased risks of: a. CVD-related mortality (p = 0.02) b. carotid plaques (p = 0.17) c. CCV events (p < 0.001).	6

(continued)

Table 2. (continued)

Study (Year)	Design	HCV study population: age in years; sex, %; race/ethnicity, %; country	Cardiovascular disease outcomes/endpoint, n	Sample size, person-years, follow-up, calendar Time	Outcome	Ref.
Völzke et al. (2008)	Cross-sectional study	Mean age: 61.2; Male: 51; – Germany	MI, stroke, CIMT, carotid plaques, carotid stenosis	n = 4266, cases: 233, controls: 4033 – October 1997–May 2001	– No independent association detected between anti-HCV antibody seropositivity and MI, stroke, CIMT, carotid plaques or carotid stenosis	47
Younossi et al. 2013	Retrospective cohort	Age groups: <45: 43.72%; 45–55: 41.89%; 55–65: 10.7%; >65: 3.7% Male: 66.58 Caucasian: 62.04 AA: 23.51 NMH: 4.78 MA: 6.66 USA	IHD (CAD or MI), stroke, CHF	Chronic HCV patients: 173 – 1999–2010	– Chronic HCV infection was associated with CHF but not IHD or stroke	48
Coppo et al. (2015)	Retrospective cohort	Mean age: 55.7 Male: 47 – Italy	Macroangiopathic diabetic complications MI (3) CVA	CHC patients: 54, controls: 119 7.2 years –	– Rates of MI (5.5 vs. 1.68%, p = 0.16) and stroke (3.7% vs. 9.2%, p = 0.20) were similar between CHC patients and controls – HCV positivity was not associated with development of microangiopathic and macroangiopathic diabetic complications (HR: 0.74, 95% CI: 0.33–1.71; p = 0.49)	49

Abbreviations: AA, African American; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCV, cerebrovascular; CHD, coronary heart disease; CHF, congestive heart failure; CIMT, carotid intima media thickness; CVD, cardiovascular disease; CVA, cerebrovascular accident; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IHD, ischemic heart disease; IRR, incidence rate ratio; MA, Mexican American; MI, myocardial infarction; NMH, Non-Mexican Hispanic; TIA, transient ischemic attack; PVD, peripheral vascular disease; PVT, peripheral venous thrombosis; RF, risk factor; UA, unstable angina; USA, United States of America.



UA, CVA, TIA, PAD and CHF. Eight studies investigated the effect of HCV infection on composite clinical CVD endpoints that included two or more of the above clinical CVD events.

Tsui *et al.*<sup>13</sup> assessed the rate of CVD events (cardiovascular mortality, MI, stroke, heart failure hospitalizations) among coronary heart disease (CHD) patients and found that HCV seropositive patients had higher rates of death, CVD events, and heart failure hospitalizations during follow-up compared to HCV seronegative patients, but after adjustment for CVD risk factors the HCV seropositivity remained independently associated with the risk for heart failure events only (hazard ratio (HR): 2.13, 95% CI: 1.19–3.80).

In the Ontario HIV Treatment Network Cohort Study, Gillis *et al.*<sup>44</sup> examined the rates of CVD events (CAD, chronic ischemic heart disease (IHD) and arteriosclerotic vascular disease, MI, CHF, CVA, coronary bypass, angioplasty, or sudden cardiac death) in a large cohort of HIV mono-infected and HIV/HCV co-infected patients. There was a higher incidence of CVD events (9.62 vs. 7.59) and an elevated risk of CVD in HIV co-infected patients compared to HIV mono-infected patients (adjusted hazard ratio (aHR): 1.44, 95% CI: 0.97–2.13;  $p = 0.07$ ). Freiburg *et al.*<sup>45</sup> reported significantly increased rates of CVD and acute myocardial infarction (AMI) among HIV/HCV co-infected patients compared to HIV mono-infected patients (11.1% vs. 2.5%,  $p < 0.05$ ), and after adjusting for age, HIV/HCV co-infected patients had a significantly high OR for the prevalence of CVD (adjusted OR: 4.65, 95% CI: 1.70–12.71) in the HIV Clinical Case Registry of the Veterans Affairs (VA) Center for Quality Management cohort. Bedimo *et al.*<sup>46</sup> evaluated a cohort of HIV-infected patients and found that rates of AMI and cerebrovascular disease (CVA and TIA) were significantly higher in HIV/HCV co-infected patients than in HIV mono-infected patients: 4.19 vs. 3.36 events/1000 patient-years, respectively ( $p < 0.001$ ) for AMI and 12.47 vs. 11.12 events/1000 patient-years, respectively ( $p < 0.001$ ) for cerebrovascular disease.

In contrast, Völzke *et al.*<sup>47</sup> found no significant association between hepatitis B or C infection status and MI, stroke (CVA), CIMT, and carotid plaques or stenosis, though the CI was skewed towards an increased risk of AMI with HCV infection status. In a cohort study of patients with CHC infection, Younossi *et al.*<sup>48</sup> found that HCV-infected patients had a significantly higher prevalence of CHF (3.8% vs. 0.9%,  $p = 0.047$ ) compared to controls, but there was no statistically significant difference in the prevalence of stroke, IHD, or CVD (a composite outcome including the presence of stroke, CHF, and IHD). In multivariate analysis adjusted for age, obesity and smoking, HCV infection was significantly associated with CHF only (adjusted OR: 2.49, 95% CI: 1.04–5.96). Coppo *et al.*<sup>49</sup> found no difference in the rates of microangiopathic (neuropathy, nephropathy, retinopathy and peripheral vascular disease (PVD)) and macroangiopathic (MI and CVA) complications among HCV-positive and HCV-negative patients.

Enger *et al.*<sup>50</sup> demonstrated that the proportion of patients with thromboembolic events (deep venous thrombosis (DVT), pulmonary embolism (PE), portal venous thrombosis, MI, UA, ischemic stroke, TIA, and other thromboembolic events) was more than 50% higher in the HCV-infected group compared to controls, and the incidence rate ratio (IRR) among HCV-infected patients was 1.62 (95% CI: 1.48–1.77) for any thromboembolic event after adjustment for baseline characteristics.

These studies which investigated the risk of developing clinical CVD (that included more than one CVD endpoint) conferred by CHC infection varied in their definitions of CVD, and therefore have reported conflicting results. Overall, they showed a trend towards a positive association between HCV and different composite endpoints of CVD, especially among the larger cohort studies, such as those conducted by Gillis *et al.*,<sup>44</sup> Freiburg *et al.*,<sup>45</sup> Bedimo *et al.*<sup>46</sup> and Enger *et al.*<sup>50</sup> as well as in the meta-analysis by Petta *et al.*<sup>6</sup>

## HCV and clinical CAD

Nine studies have evaluated the effect of HCV infection focused only on CAD endpoints (Table 3). CAD was defined variably among the studies, and the study-specific descriptions are reported when reporting study results in the text or corresponding table. Studies that examined composite CVD endpoints were reported in the section above.

The first evidence for an association between HCV and CAD (defined as angiographic documentation of CAD of 50% stenosis or more) was reported by Vassalle *et al.*<sup>51</sup>, who reported an increased rate of HCV seropositivity among CAD patients and that HCV seropositivity was an independent predictor of CAD after adjusting for confounding CVD risk factors (OR: 4.2, 95% CI: 1.4–13.0). Similar results were reproduced by Ramdeen *et al.*<sup>52</sup> In a large database from the United States of America (USA), Pothineni *et al.*<sup>53</sup> showed that HCV antibody positivity (OR: 1.32, 95% CI: 1.09–1.60;  $p < 0.001$ ) and HCV RNA positivity (OR: 1.59, 95% CI: 1.13–2.26;  $p < 0.001$ ) were independent risk factors for CHD events and that patients with detectable HCV RNA had a significantly higher incidence of CHD events compared to those with only HCV antibody positive but no detectable RNA (5.9% vs. 4.7%,  $p = 0.04$ ).

In contrast, Arcari *et al.*<sup>54</sup> found no association between HCV and AMI (relative risk (RR): 0.91, 95% CI: 0.52–1.6) among young, active-duty USA military personnel. Momiyama *et al.*<sup>55</sup> reported comparable rates of HCV antibody positivity among angiographically documented CAD (at least 50% stenosis in a major coronary artery) patients and controls.

Butt *et al.*<sup>56</sup> performed two large studies utilizing the USA VA National Patient Care Database. In data from 1999 to 2003 including 126,926 HCV-infected and uninfected patients, the authors found that after adjusting for demographics and CVD risk factors the odds of CAD (defined by implantable cardioverter defibrillator (ICD) 9 codes for AMI, other acute and subacute forms of IHD, old MI, angina pectoris, and other forms of chronic IHD, aortocoronary bypass and percutaneous transluminal coronary angioplasty) were significantly lower in HCV-positive patients compared to HCV-negative patients (adjusted OR: 0.74, 95% CI: 0.71–0.76). However, in the 2001 to 2006 analysis of over 80,000 HCV-infected and uninfected patients each, Butt *et al.*<sup>57</sup> found that HCV-infected patients had a higher risk of CAD when compared to HCV-uninfected patients (HR: 1.27, 95% CI: 1.22–1.31), despite HCV-infected patients having more favorable lipid profiles compared to controls in multivariate regression models. There were subtle differences between these two studies that may potentially explain their different results. In the first study HCV status was determined by ICD coding, while in the second study HCV status was determined by serological status. Also, the study periods were different, which may have reflected changing HCV treatment options since the

**Table 3. Studies assessing the association between HCV infection and clinical CAD**

Study (year)	Design	Study Population: Age in years; Sex, %; Race/Ethnicity; Country	CAD Definition/ Endpoint, n	Person-Years Follow-up, Calendar Time	Outcome	Ref.
Vassalle et al. (2004)	Case-control	Mean age: 66; Male: 81.3; - Italy	HCV seropositivity	n = 491 CAD patients, Controls: 195 - -	- Increased rate of HCV seropositivity in CAD patients vs. controls (6.3 vs. 2; p = 0.05), which increased with the number of vessels affected (p < 0.05) - HCV seropositivity was an independent predictor of coronary artery disease	51
Ramdeen et al. (2008)	Case-control	Mean age: 53; - USA	CAD (>50% obstruction of ≥1 major coronary artery): 32	n = 72. HCV patients: 36, controls: 36 - -	- CAD was more prevalent in HCV+ vs. controls (p < 0.005) - Two-three vessel CAD was more prevalent in HCV+ vs. controls (p < 0.005)	52
Butt et al. (2009)	Matched retrospective cohort	Mean age: 51.2; Male: 97.1; White: 55.4, Black: 29.5, Hispanic: 1.9; USA	ICD-9 codes for MI, CHF CABG, PCI, CAD	n = 171665, HCV patients: 823,083, controls: 89,582 - 2001–2006	- HCV infection associated with a higher risk of CAD	57
Pothineni et al. (2014)	Retrospective cohort	Mean age: 47.3 (antibody-positive)/48.6 (RNA-positive group); Male: 56.3/57; White: 76.2/77.1, African American: 18.5/18.4, Others: 5.3/4.5; USA	ICD-9 codes of CHD. CHD: chronic stable angina, UA, CAD, AMI: 471	n = 24484, HCV antibody-positive: 8251, HCV RNA-positive: 1434, controls: 14799 - 2001–2013	- Higher incidence of CHD events among HCV+ vs. controls - HCV antibody and RNA positivity and HCV RNA were independent risk factors for occurrence of CHD events	53
Ambrosino et al. (2016)	Meta-analysis	- - - -	- Cardiocerebrovascular disease	HCV patients: 297613, controls: 557814, articles: 27 - -	- Significantly increased risk of CAD and CVA (p < 0.0001) in HCV+ vs. controls	60
Arcari et al. (2006)	Case-control	Mean age: 40.2; Male: 100; White (non-Hispanic): 60.6, Black: 30.1, Other: 9.25; USA	ICD-9 codes for MI HCV seropositivity: 52	MI patients: 292, controls: 290 - 1991–2000	- No difference in the prevalence of HCV infection between MI patients vs. controls (p = 0.44) - No association found between HCV positivity and acute MI	54

(continued)

Table 3. (continued)

Study (year)	Design	Study Population: Age in years; Sex, %; Race/Ethnicity; Country	CAD Definition/Endpoint, n	Person-Years Follow-up, Calendar Time	Outcome	Ref.
Momiyama et al. (2005)	Case-control	Mean age: 64; Male: 82; - Japan	>50% stenosis on angiography; HCV AB: 15 or HCV core antigen: 5 positivity among CAD patients; MI: 211	n = 630, CAD patients: 524, controls: 106 - -	- No difference in prevalence of HCV AB positivity in CAD patients vs. controls - HCV positivity was not an independent factor for CAD or MI	55
Butt et al. (2007)	Retrospective cohort	Mean age: 51.8; Male: 96.8; White: 48.5, Black: 24.6, Hispanic: 6; USA	ICD-9 codes for CAD, stroke, PVD	HCV patients: 126926, controls: 126926 - 1999-2003	- Prevalence of CAD and strokes were lower in the HCV+ vs. control group (p < 0.001) - Prevalence of PVD was similar between the two groups (p = 0.3) - HCV+ had a lower risk of CAD and strokes than controls after adjustment	56
Forde et al. (2012)	Retrospective cohort	Median age: 38.6; Male: 61.03; - UK	Read code for MI	HCV patients: 4809, controls: 71668 3.2 years 1996-2008	- No difference in the incidence rates of MI found in HCV+ vs. controls - HCV infection was not associated with an increased risk of MI after adjustment	58
D.A.D Study Group (2010)	Prospective cohort	- - White: 55.2, Black: 3.7, Other: 1.3, Unknown: 39.8 USA	MI MI: 517; stroke: 295	n = 33347, HCV patients: 5084 157912 person-years 1999-2007	- Similar CVD event rates per 1000 person-years in the HCV+ and HCV- groups - No association between HCV seropositivity and the development of MI or stroke	59

Abbreviations: AB, antibodies; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHC, chronic hepatitis C; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; CVA, cerebrovascular accident; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary angioplasty; PVD, peripheral vascular disease; RNA, ribonucleic acid; OR, odds ratio; UA, unstable angina; UK, United Kingdom; USA, United States of America.

regimen of pegylated-interferon (IFN) alpha-2a and ribavirin was approved in 2002. Other large cohorts in the United Kingdom (UK)<sup>58</sup> and across several continents (the so-called D:A:D collaboration<sup>59</sup> of 11 cohorts) also demonstrated no effect of HCV infection and rates of MI.

Given the mixed findings in prior studies focusing exclusively on CAD endpoints, Ambrosino *et al.*<sup>60</sup> conducted a large meta-analysis to evaluate the impact of CHC infection on the risk of CAD. CAD was defined as the presence of at least one among the following: MI, UA, chronic stable angina, angiographic evidence of  $\geq 50\%$  stenosis in one or more coronary vessels, history of coronary revascularization, ischemic electrocardiogram according to validated criteria (major Q or QS wave, complete left-bundle branch block, small Q or QS wave, ST depression, T wave abnormality). A total of 20 studies including 273,219 HCV-infected and 473,928 HCV-uninfected patients showed a significantly increased risk of CAD associated with HCV positivity (OR: 1.382, 95% CI: 1.103–1.732;  $p = 0.005$ ;  $I^2 = 99\%$ ;  $p = 0.0001$ ). Therefore, the sum of these data among various studies remains inconclusive, with several large cohort studies reporting no association between HCV infection and CAD but a few others, including the large meta-analysis cited above, finding positive associations between HCV infection and CAD.

### HCV and angiographic CAD

Six studies investigated the effect of HCV on CAD based on coronary artery angiographic findings (Table 4). CAD severity was assessed using previously validated scoring systems. Both the Reardon severity scoring system<sup>61</sup> and the Gensini score<sup>62</sup> visual scoring systems of CAD severity are based upon coronary angiography findings which take into account the number of vessels involved, location of the vessel, significance of the myocardial territory supplied, and degree of vessel stenosis.

Alyan *et al.*<sup>11</sup> used a modified Reardon severity scoring system and demonstrated that CAD severity scores were significantly higher in the HCV seropositive group than in the control group ( $p < 0.001$ ), and HCV seropositivity was an independent predictor for the severity of coronary atherosclerosis (OR: 2.018, 95% CI: 1.575–2.579;  $p < 0.001$ ) after adjustment for age, sex, smoking, hypertension, DM, body mass index (BMI), CRP and fibrinogen.<sup>11</sup> In patients undergoing coronary angiography for evaluation of CAD, Satapathy *et al.*<sup>63</sup> observed a significantly higher prevalence of CAD (69.8% vs. 47.6%,  $p = 0.01$ ), significantly higher modified Reardon's severity scores ( $6.26 \pm 5.39$  vs.  $2.6 \pm 3.03$ ,  $p < 0.0005$ ), and significant multivessel CAD (defined as  $>50\%$  stenosis in  $\geq 2$  vessels involved; 57.1% vs. 15.9%,  $p < 0.0005$ ) among the HCV-infected patients compared to controls. Salam *et al.*<sup>64</sup> reported that HCV antibody-positive patients had more severe coronary lesions than seronegative patients among those referred for angiography. Unlike the previous studies, Pothineni *et al.*<sup>65</sup> found no significant differences between HCV-infected patients and controls in the number of vessels with obstructive coronary disease, and there was no correlation between HCV RNA titers and severity of CAD as assessed by the Gensini score ( $p = 0.90$ ).

Nonetheless, a meta-analysis by Olubamwo *et al.*<sup>66</sup> concluded that HCV infection may increase the risk of occurrence and the severity of coronary atherosclerosis, which seems consistent with the results of the vast majority of studies evaluating the effect of HCV infection on severity of CAD.

### HCV and CVA

There were nine studies that investigated the association between HCV infection and the development of CVA and/or mortality due to strokes. In the studies discussed below, CVA was defined by new onset neurological deficits not attributable to other causes based on ICD codes or supporting neuroimaging.

In a large prospective population-based cohort, Liao *et al.*<sup>67</sup> reported that the cumulative risk of stroke in HCV-infected patients was significantly higher than in HCV-uninfected patients (adjusted OR: 1.27, 95% CI: 1.14–1.41). Similar results by Adinolfi *et al.*<sup>16</sup> demonstrated that patients with ischemic stroke had a significantly higher prevalence of HCV infection than controls (26.2% vs. 6.6% respectively,  $p = 0.0001$ ), and that HCV infection was an independent risk factor for stroke (OR: 2.04, 95% CI: 1.69–2.46;  $p = 0.0001$ ). In a large Australian study, Lee *et al.*<sup>68</sup> observed that CHC infection was an independent risk predictor of cerebrovascular deaths and there was an increase in cerebrovascular mortality with increasing serum HCV RNA level. Hsu *et al.*<sup>69,70</sup> strengthened the relationship between HCV infection and CVA by showing that the incidence of stroke decreased following IFN treatment in one large retrospective and a recent prospective cohort study. Finally, while large artery atherosclerosis is certainly a risk factor for CVA among HCV-infected patients, small vessel disease may also play a role and HCV has been associated with an increase in mean arteriolar wall thickness in the deep cerebral white matter.<sup>71</sup> In contrast to the above studies, Younossi *et al.*<sup>48</sup> found no significant association between HCV infection and stroke (adjusted OR: 0.58, 95% CI: 0.16–2.02).

In a meta-analysis by Huang *et al.*<sup>72</sup> which included six studies, the authors concluded that HCV infection significantly increased the risk of stroke, and a second meta-analysis of 13 studies conducted by Ambrosino *et al.*<sup>60</sup> found a significantly increased risk of cerebrovascular disease in HCV patients compared to uninfected controls (OR: 1.485, 95% CI: 1.079–2.044). In conclusion, the association between CHC infection and cerebrovascular disease has been demonstrated consistently in many population cohort studies and in two separate meta-analyses with only Younossi *et al.*<sup>48</sup> reporting differing results.

### PAD

There was only one study that investigated the effect of HCV infection on the development of PAD. Hsu *et al.*<sup>73</sup> found that among 7,641 patients with CHC after adjusting for age, sex, urbanization level, and comorbidities (hypertension, HL, DM, IHD, chronic obstructive pulmonary disease, chronic kidney disease/end-stage renal disease, CVA, and acute alcoholic hepatitis), HCV-infected patients had a higher risk of developing PAD, as assessed by ICD codes for PAD, compared to age- and sex-matched controls (HR: 1.43, 95% CI: 1.23–1.67). The risk of PAD development increased substantially with the number of comorbidities, and HCV-infected patients with four comorbidities had the highest risk of developing PAD (HR: 9.25, 95% CI: 6.35–13.5). Further studies are needed to determine if HCV infection truly impacts the development of PAD.

**Table 4. Studies assessing the association between HCV and angiographic CAD**

Study (year)	Design	HCV Population: Age in years; Sex, %; Race/Ethnicity; Country	Endpoint, n	Person-Years Follow-up, Calendar Time	Outcome	Ref.
Alvan et al. (2008)	Case-control	Mean age: 61.2 Male: 76.3 - Turkey	CAD, Reardon severity score	n = 364, HCV patients: 139, controls: 225 - 2003–2007	- Increased rates of multi-vessel CAD (>2 vessels) in HCV+ vs. controls: 126 (91.6%) vs. 166 (74.1%), p < 0.001 - Increased Reardon severity scores in HCV+ vs. controls (p < 0.001) - HCV seropositivity was an independent predictor for severity of coronary atherosclerosis (p < 0.001)	11
Satapathy et al. (2013)	Case-control	Mean age: 60.9 Male: 41 White: 55.6, African American: 18, Hispanic: 3, Asian: 7 USA	CAD prevalence, Reardon score	n = 116, HCV patients: 63, controls: 63 - 2002–2008	- Higher prevalence (p = 0.01) and severity (p < 0.0005) of CAD in HCV+ vs. controls - HCV+ status was significantly associated with CAD (p = 0.007)	63
Salam et al. (2016)	Cross-sectional	Mean age: 54.08 Male: 55.9 - Egypt	CAD severity: Gensini score	n = 509, HCV patients: 118 - 2013–2014	- Increased HCV prevalence among CAD patients vs. controls (34.3% vs. 21.8%, p = 0.004) - Increased Gensini score among HCV+ vs. HCV- (p = 0.01)	64
Olubamwo et al. (2016)	Meta-analysis	- - - - USA	CAD, CAD severity, CAD-related coronary events	10 studies - - - 2001–2013	- Increased risk of CAD among HCV+ : OR: 3.06, 95% CI: 1.99–4.72	66
Pohtineni et al. (2015)	Case-control	Mean age: 52 Male: 60.6 - USA	CAD, Gensini score	n = 122, HCV patients: 61, controls: 61 - 2001–2013	- Obstructive CAD less frequent in HCV+ vs. controls: 23% vs. 39%, p < 0.05 - Gensini score was similar in both groups - No significant correlation found between HCV RNA titers and Gensini score (p = 0.9)	65

Abbreviations: CAD, coronary artery disease; CI, confidence interval; HCV, hepatitis C virus; HDL, high density lipoprotein; OR, odds ratio; RNA, ribonucleic acid; USA, United States of America.

### HCV and cardiomyopathy

Myocarditis and subsequent cardiomyopathy can be caused by several cardiotropic viruses. HCV has been among viruses associated with cardiomyopathy, and its effect has been hypothesized to be independent from its ischemic effects on the myocardium.<sup>74</sup> Both Younossi *et al.*<sup>48</sup> and Tsui *et al.*<sup>13</sup> reported increased rates of heart failure events among patients with CHC compared to controls, and HCV was found to be an independent factor for CHF events on multivariable analysis.

Both dilated cardiomyopathy (DCM; characterized by dilation and impaired contraction of one or both ventricles) and hypertrophic cardiomyopathy (HCM; characterized by increased ventricular wall mass not caused by conditions causing volume overload) have been linked to HCV infection.<sup>75</sup> Matsumori *et al.*<sup>23</sup> reported an increased prevalence of HCV antibodies among patients with DCM, and detected HCV genomes within the samples of autopsied hearts from patients with myocarditis and patients with DCM or HCM. Matsumori *et al.*<sup>76</sup> later found a statistically significant increased prevalence of serum-detectable HCV RNA in patients with myocarditis or cardiomyopathy compared to those with IHD. However, Dalekos *et al.*<sup>77</sup> and Fujioka *et al.*<sup>78</sup> evaluated patients with idiopathic DCM (IDCM) and found no association between HCV infection and IDCM. Similarly, Grumbatch *et al.*<sup>79</sup> observed no association between DCM and HCV infection in patients with DCM and myocarditis compared to controls. Human leukocyte antigen (HLA) and non-HLA haplotypes have been identified in some patients with HCV-associated cardiomyopathy, suggesting a role of genetic predisposition which may differ among various patient populations, thus possibly explaining discordant results obtained in studies from Japan and Europe.<sup>74</sup>

Both Matsumori *et al.*<sup>23</sup> and Teragaki *et al.*<sup>80</sup> examined sera of HCM patients and matched controls and found a significantly increased prevalence of HCV antibodies among those with HCM. Matsumori *et al.*<sup>23</sup> also identified HCV genomes within heart tissue biopsies of patients with HCM, suggesting a causal link.

### HCV and cardiovascular mortality

Eight longitudinal cohort studies have evaluated mortality rates among HCV-infected patients (Table 5). Some of these studies demonstrated increased mortality rates among HCV-infected patients not only from liver related causes but also from CVD. However, other studies observed contrasting results.

Amin *et al.*<sup>81</sup> found that the incidence of mortality related to CVD (as defined by ICD-10 codes for circulatory disease) as well as all-cause mortality was increased among HCV patients compared to controls, with death from CVD being the most common cause of death (standardized mortality ratio: 1.3, 95% CI: 1.2–1.5). Guiltinan *et al.*<sup>82</sup> noted that HCV-positive blood donors had increased cardiovascular mortality compared to matched HCV-seronegative controls (HR: 2.21, 95% CI: 1.41–3.46), but their data lacked confounding factors on CVD. In the REVEAL prospective cohort of adults with positive anti-HCV antibodies (69% of whom had detectable HCV RNA), Lee *et al.*<sup>83</sup> showed that there was an increase in both hepatic and extrahepatic mortality when compared to seronegative controls and an increased risk of death from CVD based on diagnoses reported in the

Taiwanese National Death Certification Registry. Additionally, mortality from CVD was significantly higher among patients who had detectable HCV RNA levels compared to those with undetectable HCV RNA but positive anti-HCV antibodies, suggesting antiviral therapy may have a role in decreasing HCV related CVD mortality.

HCV-related CVD mortality has also been studied among renal patients. Younossi *et al.*<sup>84</sup> reported that death due to CHD was significantly increased in HCV-infected renal transplant recipients compared to HCV-uninfected recipients. A meta-analysis by Fabrizi *et al.*<sup>85</sup> in long-term dialysis patients demonstrated that anti-HCV antibody positivity was an independent and significant risk factor for death in patients on maintenance dialysis.

In contrast, Vadjic *et al.*<sup>86</sup> found no association between HCV infection and CVD mortality among opioid substitution therapy registrants. Kristiansen *et al.*<sup>87</sup> also observed no statistically significant increase in standardized mortality ratios due to CVD. In a meta-analysis of the three studies above involving non-renal patients, Petta *et al.*<sup>6</sup> reported that the pooled estimate of the effect of HCV infection on CVD mortality was significant (OR: 1.65, 95% CI: 1.07–2.56;  $p = 0.02$ ), but with significant heterogeneity ( $I^2 = 76\%$ ;  $p = 0.02$ ).

The data reported from the various studies, and some with large sample sizes, investigating the impact of HCV infection on cardiovascular mortality was mixed, and therefore the association remains inconclusive. However, there is a suggestion of increased CVD mortality due to HCV infection when the data are considered in total.

### Effect of HCV treatment on cardiovascular disease and outcomes

Advances in the development of DAAs has resulted in dramatic improvements in HCV treatment, with ability to achieve SVR >90% in most HCV-infected patients.<sup>88</sup> Notably, the clinical benefits of SVR have been shown to extend beyond hepatic disease.<sup>89</sup> Therefore, it is of great interest to determine whether these novel DAAs will further reduce CVD-attributable morbidity and mortality among HCV-infected patients because demonstration of improved CVD-attributable morbidity and mortality with HCV therapy would offer powerful data supporting the role of HCV infection on CVD outcomes.

In a case-control study of 50 patients with CHC infection, Pateria *et al.*<sup>18</sup> found significant improvement in PWV in HCV-treated patients who had achieved SVR compared to those who had not achieved SVR (PWV  $7.4 \pm 1.1$  m/s vs.  $6.5 \pm 0.6$  m/s,  $p = 0.04$ ). Maruyama *et al.*<sup>26</sup> performed thallium-201 myocardial scintigraphy on 217 patients with CHC infection, and 87% were found to have abnormal scintigraphy scans with liver histology activity index score and serum HCV RNA titers at baseline associated with greater abnormalities on scintigraphy scans. After interferon (IFN) therapy, scintigraphy scans improved in patients who achieved SVR.

In the French ANRS CO12 CirVir<sup>90</sup> prospective cohort of 1,323 CHC-infected patients treated with IFN and DAAs, the authors found that patients who achieved SVR had a lower risk of cardiovascular events, which included CHF, IHD, cardiac arrhythmia, CVA, valvular cardiomyopathy, PAD, cardiac arrest and aortic aneurysm (HR: 0.42; 95% CI: 0.25–0.69;  $p = 0.001$ ). Similarly, in a Scottish cohort<sup>91</sup> of 3,385 CHC-infected patients followed up to a median of 5.3 years,

**Table 5. Studies assessing the association between HCV and cardiovascular mortality**

Study (year)	Design	Study population: age in years; sex, %; race/ethnicity; country	Endpoint, n	Person-years, follow-up, calendar time	Outcome	Ref.
Younossi et al. (1999)	Retrospective cohort	Mean age: 49.7 Male: 67 - USA	Mortality, CHD (3), morbidity and allograft function	n = 54, HCV patients: 15, controls: 39 -	- No significant difference in CHD rates between HCV+ and controls: 46.6% vs. 20.5%, p = 0.09 - Death from CHD was significantly more frequent in the HCV+ group (p = 0.018)	84
Amin et al. (2006)	Retrospective cohort	Median age: 35 Male: 63 - Australia	All-cause mortality: 1233	n = 117547, HCV patients: 75834, HCV/HBV patients: 2604 3.5-5.4 years 1990-2002	- Significant increase in all-cause mortality and circulatory-related deaths in the HBV/HCV co-infected group vs. the HCV group	81
Guiltinan et al. (2008)	Retrospective cohort	Average age of death: 50 Male: 6627 White: 960, Black: 137, Hispanic: 166, Asian: 51 USA	All-cause mortality	n = 20518, HCV patients: 10259, controls: 10259 7.7 years 1991-2002	- Increased mortality in the HCV vs. control group (p < 0.00001) - HCV was significantly associated with cardiovascular deaths	82
Lee et al. (2012)	Retrospective cohort	Mean age: 50.8 Male: 42.5 - Taiwan	All-cause mortality: 2394	n = 23820, HCV patients: 1095, controls: 19636 16.2 years 1991-2008	- Increased all-cause mortality among HCV+ vs. controls: HR: 1.89, 95% CI: 1.66-2.1 - Increased mortality from circulatory disease among HCV+ vs. controls: HR: 2.77, 95% CI: 1.49-5.15 - Increased mortality from circulatory disease in patients with detectable HCV RNA vs. undetectable HCV RNA (p = 0.026)	83
Fabrizi et al. (2012)	Meta-analysis	Age range: 40-69.87 Male: 45.6-71.5 - Australia, Japan, Italy, Spain, Taiwan, USA	All-cause mortality	13 articles, n = 145608 patients -	- Increased risk of all-cause mortality with anti-HCV status: aRR: 1.35, 95% CI: 1.25-1.47 - Increased risk of CVD death with anti-HCV status: aRR: 1.26, 95% CI: 1.10-1.45	85
Petta et al. (2016)	Meta-analysis	- - - Egypt, Turkey, Italy, Japan, Taiwan USA, UK	CVD-related mortality	n = 468050 patients (22 studies)	- HCV+ vs. HCV- had increased risk of CVD-related mortality (p = 0.02)	6
Vajdic et al. (2015)	Retrospective cohort	Median age: 26 Male: 69 - Australia	Cause-specific mortality: 1834	n = 29571 HCV patients: 15523 7.3 years 1993-2007	- No increased risk of death from CVD among HCV+: HR: 1.4, 95% CI: 0.9-1.9	86

(continued)

Table 5. (continued)

Study (year)	Design	Study population: age in years; sex, %; race/ethnicity; country	Endpoint, n	Person-years, follow-up, calendar time	Outcome	Ref.
Kristiansen <i>et al.</i> (2011)	Retrospective cohort	Median age: 41 Male: 68 - Norway	All-cause mortality: 122	n = 1010 HCV patients: 122 7 years 2004–2006	- No statistically significant increase in mortality from cardiovascular disease among HCV+ patients - No significant reduction in mortality with anti-HCV treatment: HR: 0.807, 95% CI: 0.348–1.870; <i>p</i> 0.617	87

Abbreviations: aRR, adjusted relative risk; CHD, coronary heart disease; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; OR, odds ratio; RNA, ribonucleic acid; RR, risk ratio; SMR, standardized mortality ratio; USA, United States of America.

SVR was significantly associated with CVD after 7.5 years of follow-up (aHR: 3.4, 95% CI: 0.5–6.1; *p* = 0.019).

Using data from the Taiwanese National Health Insurance Database, authors have repeatedly shown cardiovascular benefits associated with HCV clearance and achievement of SVR. Hsu *et al.*<sup>69,70</sup> demonstrated decreased incidence of stroke following IFN treatment and decreased HRs for ischemic strokes and acute coronary syndrome (ACS) associated with HCV clearance after IFN-based therapy among diabetic patients. Finally, in a prospective cohort study of 12,384 patients, multivariate analyses revealed that antiviral treatment with pegylated-IFN plus ribavirin was associated with a lower risk of ACS (HR: 0.77, 95% CI: 0.62–0.97; *p* = 0.026) and ischemic stroke (HR: 0.62; 95% CI: 0.46–0.83; *p* = 0.001).<sup>92</sup>

Unlike in the Taiwanese studies, the large, multicenter, longitudinal Italian HIV/HCV co-infection cohort study (MASTER cohort)<sup>93</sup> found that the pooled probability of CVD and death was significantly lower in patients who achieved SVR after treatment with IFN-based therapy compared to those did not achieve SVR (log-rank *p* = 0.0059, *p* = 0.04 and *p* < 0.0001, respectively). However, the significant association did not remain in the Cox regression analysis model in which achieving SVR was not associated with decreased CVD (CHD, cerebrovascular disease, chronic heart failure, or PVD). Notably, key CVD confounding factors (blood pressure, smoking, and BMI) were not available in the cohort.

The majority of the findings from studies evaluating the impact of HCV therapy on CVD morbidity and mortality showed an improvement in subclinical and clinical CVD endpoints in patients who achieved SVR. These results are of particular interest following the development of new DAAs which have revolutionized HCV treatment and made HCV eradication simple and feasible for many more patients globally, and in doing so may possibly reduce CVD morbidity and mortality in those with CHC infection.

### Discussion

HCV infection, particularly CHC infection, appears to result in increased subclinical and clinical CVD outcomes and to lead to increased morbidity and mortality. Large well conducted studies have produced compelling yet conflicting data. There is a large and robust body of data supporting the association between HCV and subclinical CVD, as measured by CIMT, FMD and/or PWV. Many large population-based studies<sup>28,29</sup> as well as case controls studies<sup>24,30</sup> have reported positive associations between CHC infection and increased risk of carotid atherosclerosis, whereas, in contrast, studies among smaller cohorts have not found this association in specific patient populations who represent high-risk groups for the development of atherosclerosis, such as those on hemodialysis<sup>40</sup> or HIV co-infected patients.<sup>38,39</sup> The association between HCV infection and subclinical CVD is further strengthened by meta-analyses which included studies with negative results and yet found significant pooled estimates of the effect of HCV on increased carotid atherosclerosis.<sup>6,43</sup>

On the other hand, studies investigating the association between HCV infection and different clinical CVD endpoints have shown mixed results. The differences in results may be due to differences in study designs, patient populations, varying definitions of HCV positive patients (ICD codes vs. serological testing), different types of endpoints assessed



(MI, UA, CAD, CVA, PAD) and how they were measured (angiography findings, self-reported CVD events, ICD codes), and lack of comprehensive and consistent collection of traditional cardiovascular risk factors among studies resulting in incomplete adjustments for these cardiovascular risk factors in the multivariate analyses. Among the clinical CVD endpoints, the association between HCV and CVA appears to be the strongest, with the majority of studies reporting a positive association. In addition, an association between HCV viral burden and increased risk of CVA has been noted.<sup>68,72</sup>

The preponderance of the data suggests an increased risk for the development of coronary artery atherosclerosis as well as an increase in the severity of CAD based on the majority of case-control studies in which HCV-infected patients underwent coronary angiography.<sup>11,51–53,63,64,66</sup> However, it is uncertain whether the likely increased risk of coronary atherosclerosis translates to an increased risk of MI among these patients since many studies were unable to demonstrate an association between HCV infection and rates of MI. For example in the study by Forde *et al.*,<sup>58</sup> HCV infection did not increase the risk of MI but the mean follow-up period was only 3.2 years, which may have limited the ability to detect an association given the chronic nature of atherosclerosis and the cumulative risk that eventually leads to the sentinel clinical event of MI.

Using the NHANES data Younossi *et al.*<sup>48</sup> also did not find any association between HCV and CVD except with CHF, but it is important to note that in this study patients with CHC infection were significantly older and had a higher rate of hypertension, insulin resistance and smoking history than those without HCV infection, which may have attenuated the ability to detect such an association. Notably, the D.A.D cohort study<sup>59</sup> that included 11 cohorts across multiple continents and which included adjustment for many though not all traditional CVD risk factors (large percentage of unknown race, rates of illicit drug use, hypertension, and DM) was unable to demonstrate an association between CHC infection and risk of stroke or MI.

Interestingly, while an initial study conducted by Butt *et al.*<sup>56,57</sup> reported that HCV infection (diagnosed using ICD codes) exhibited a protective effect on CVD, a subsequent follow up study using serological testing to define HCV infection reported the opposite finding that HCV-infected patients had an increased risk of developing CVD. These two studies by the same authors highlight that differences in defining study populations may be critical in explaining some of the observed differences among studies.

Other studies such as those by Völzke *et al.*<sup>47</sup> and Arcari *et al.*<sup>54</sup> were significantly limited by the very small number of HCV cases included, and/or by a special patient population, such as young and fit active military personnel in the latter. Despite the mixed results of individual cohort and case-control studies evaluating the association between HCV and MI, several meta-analyses have consistently found that HCV infection increased the risk of CAD among HCV-infected patients.<sup>6,60,66</sup>

If HCV truly increased risk of developing subclinical and consequently clinical CVD outcomes, then it would be expected that this increased CVD risk should lead to increased cardiovascular mortality. Indeed, studies that investigated the association between HCV infection and CVD mortality using death registries have generally reported increased mortality among HCV-infected patients. Furthermore, in the study by Lee *et al.*<sup>83</sup> which adjusted for many CVD factors and

included a mean follow-up of 16 years demonstrated not only increased mortality from circulatory disease but also that HCV eradication ameliorated the CVD risk. This finding has significant implications in the current era of DAA therapy, since large numbers of patients can be treated successfully for CHC, and suggests that HCV therapy could potentially mitigate CVD risk and outcomes among CHC-infected patients. Numerous studies have demonstrated that higher risk CHC-infected patients such as those with higher HCV viral load and HCV-related liver disease (hepatic steatosis and/or fibrosis) have increased CVD,<sup>24–26,53</sup> and so the potential to reduce morbidity and mortality in these higher risk CHC patient groups is of great public health significance.

There were several strengths to our systematic review. First, it presented a thorough, comprehensive description of the literature on the associations between HCV and subclinical and numerous different clinical CVD outcomes (severity of CAD, PAD, cardiomyopathy, CVD mortality) not included in many other reviews of this topic. Second, it reported data on the effect of HCV therapy on subclinical and clinical CVD outcomes, including CVD mortality, not reported in most other reviews. Our review was limited, however, by the heterogeneous study designs, study populations and subclinical and clinical outcomes examined, as well as inconsistent and incomplete capturing of traditional CV risk factors among studies, all of which made it challenging to reconcile differences in results among them and limited our ability to make firm conclusions. Another limitation was that we did not conduct a systemic meta-analysis, but we felt that excluding so many relevant studies in the pursuit of the meta-analysis would compromise the focus of reporting comprehensive data on a heterogeneous group of surrogate measures of subclinical CVD and different clinical CVD endpoints, which necessitated including studies with very heterogeneous designs. Furthermore, the scope of our review did not account for the possible contribution of genetic variations leading to genetic predisposition of different ethnic groups and different HCV genotypes with CHC infection to CVD outcomes.

## Conclusions

The current data support the assertion that CHC infection increases the risk of subclinical and likely clinical CVD, through a multifactorial cascade which may include direct and indirect immune and inflammatory effects, metabolic derangements and possibly direct cardiotropism exhibited by the HCV virus. There is an urgent need for translational research to delineate these proposed mechanisms for the apparent association between HCV and CVD. Additionally, more prospective cohort studies conducted in different patient populations are needed to confirm the findings of HCV infection and increased subclinical and clinical CVD. Furthermore, larger, well-designed therapeutic studies are critical to establish whether CHC truly increases CVD risk and to evaluate if HCV treatment can attenuate or even eliminate that increased CVD risk. The promise of large-scale HCV therapy ushered in by the highly efficacious and well tolerated DAAs has arrived, and therefore understanding the relationship between HCV and CVD and how this relationship is affected by HCV eradication with treatment has substantial public health implications.

## Conflict of interest

The authors have no conflict of interests related to this publication.

## Author contributions

Contributed to the analysis and interpretation of data, and critical revision of the manuscript (JJ, SK, MK, AS, AB, SB), conception of the study design, collection, analysis and interpretation of data, manuscript writing and serial critical revisions of the manuscript (AB, SB).

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