

Review

Expert opinion on managing chronic HCV in patients with cardiovascular disease

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Extrahepatic manifestations of chronic HCV infection include cardiovascular diseases and an increase in cardiovascular mortality. The pathogenic mechanisms by which HCV contributes to cardiovascular disease are not well defined, however, it is likely that systemic inflammation, and the promotion of other metabolic diseases are involved. In this Review, the evidence for HCV infection as a non-traditional risk factor for cardiovascular disease

is evaluated. Furthermore, practical advice to evaluate cardiovascular disease risk and disease in chronic hepatitis C patients are included for help in daily clinical practice. Despite the advances in therapies for the treatment of HCV, there remains a need for increased awareness among specialists so that patients are more likely to obtain the treatment required to mitigate disease progression.

Introduction

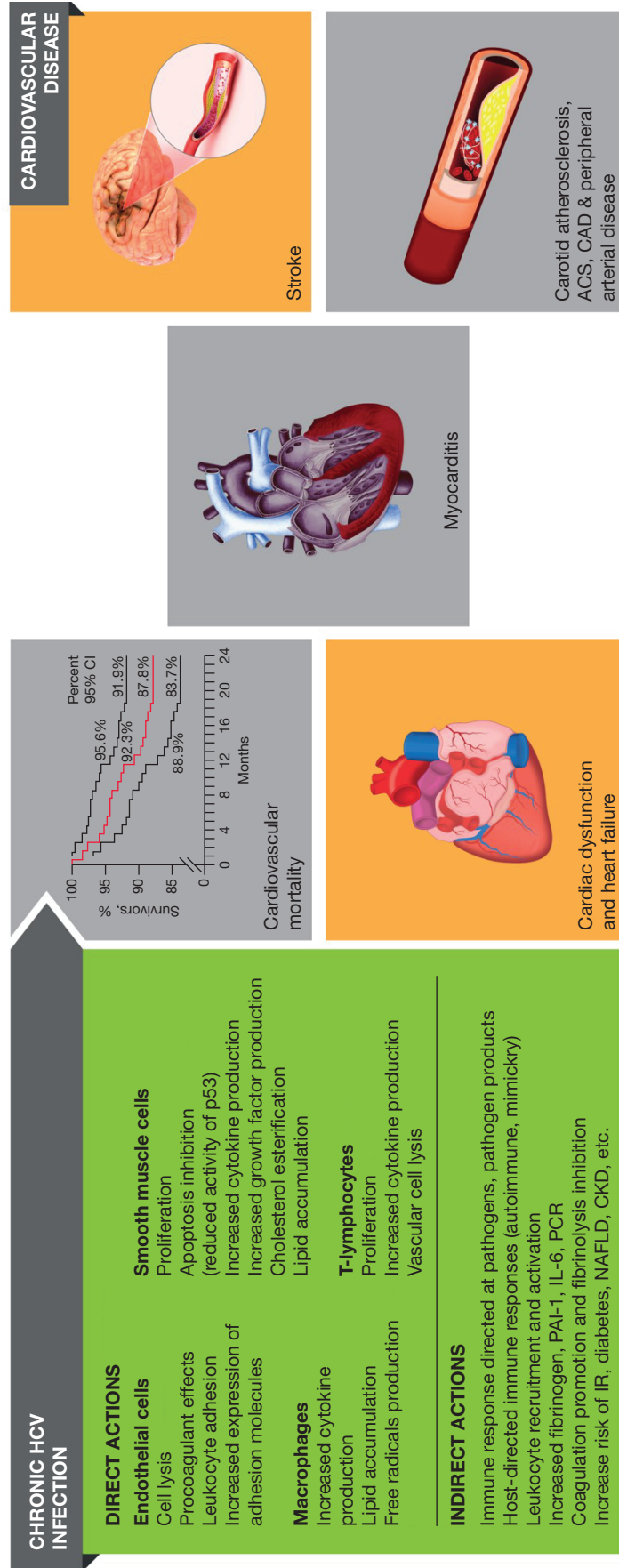
Chronic HCV infection accounts for a high proportion of chronic liver disease worldwide and consequently is a leading cause of liver-related morbidity and mortality [1]. In addition, chronic HCV infection is considered a systemic infection that can lead to extrahepatic manifestations [2,3]. In particular, HCV could be added to the list of infectious agents that play a clinically relevant role in the aetiology of cardiovascular disease (CVD) [4]. American Association for the Study of Liver Disease guidelines cite the evidence for the benefits of HCV treatment in patients with CVD or associated risk factors, for example, type 2 diabetes mellitus, and recommend that all patients with chronic HCV infection should be treated with anti-HCV therapies [5]. In addition, European Association for the Study of the Liver guidelines recommend that patients at risk of rapid evolution of liver disease (for example, those with diabetes) should be treated without delay [6].

The potential burden of CVD in patients with HCV infection is relevant owing to the high proportion of

HCV-infected patients with CVD-associated risk factors such as diabetes, chronic kidney disease or hypertension ([7,8]; S Petta *et al.* unpublished data). These data, together with evidence of associations with atherosclerosis, stroke, myocardial infarction (MI), coronary artery disease (CAD), peripheral arterial disease, myocarditis [9–11] and heart failure [12,13] suggest that HCV infection increases the risk of CVD [3].

Two reviews [14,15] have looked at the potential direct and indirect mechanisms by which HCV could increase cardiovascular risk (Figure 1). However, patients with chronic HCV infection tend to be middle aged or older, and both HCV infection and cardiovascular risk factors are common in the general population, which makes it difficult to establish a causal association between HCV infection and CVD. Whether HCV is causative or not of CVD, it is important that clinicians are aware of the increased risk of CVD in HCV-infected patients. Evidence shows that CVD affects survival in cirrhotic patients [16–18] and is a leading cause of mortality in HCV patients.

Figure 1. Direct and indirect mechanisms of HCV-related cardiovascular disease



ACS, acute coronary syndrome; CAD, coronary artery disease; CKD, chronic kidney disease; IL-6, interleukin 6; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; PAI-1, plasminogen activator inhibitor-1.

HCV as a non-traditional risk factor for cardiovascular disease

Carotid atherosclerosis

The presence of HCV infection is associated with low grade chronic systemic inflammation, which may induce chronic endothelial lesions and accelerate atherosclerosis.

Japanese patients with HCV infection were shown to have a significantly higher prevalence of carotid plaques compared with HCV-negative controls after adjusting for cardiometabolic confounders [19]. Consistent with this finding, Italian patients with chronic HCV infection had significantly higher carotid intima media thickness than uninfected controls [20,21]. Consistent with these data, several studies have reported a higher prevalence of carotid atherosclerosis in HCV-infected patients compared with uninfected controls [19,22,23].

A meta-analysis of data from nine case-control studies, showed an approximate twofold higher risk of carotid plaques in HCV-infected individuals compared with uninfected controls [24]. Similar results were obtained when intima-media thickness was considered as the outcome, instead of carotid plaques. Moreover, the overall impact of HCV on the presence of carotid plaques was greater in populations with higher smoking prevalence than in those with lower smoking prevalence [24].

Stroke

Several epidemiological studies have reported a significantly increased incidence of stroke in people with HCV infection compared with HCV-negative controls [25,26] or a higher prevalence of HCV infection in patients with stroke than in age- and sex-matched controls [27]. HCV infection has been identified as an independent risk factor for stroke in HCV-infected patients [27]; the presence of HCV has been correlated with higher levels of inflammatory markers in patients with stroke [27]; and the risk of cerebrovascular death has been significantly and positively correlated with HCV RNA levels [28]. It must be noted however, that a significantly lower prevalence of stroke has also been observed in HCV-infected individuals compared with control subjects [29].

Coronary artery disease

The prevalence of HCV infection has been reported to be significantly higher in patients with angiographic evidence of CAD compared with patients without CAD (6.3% versus 2.0%; $P<0.05$), and the presence of HCV remained a significant predictor of CAD even after correction for cardiometabolic risk factors (odds ratio [OR] 4.2; 95% CI 1.4, 13.0) [30].

HCV infection was associated with a higher risk of CAD (hazard ratio [HR] 1.25; 95% CI 1.20, 1.30) after

adjusting for confounding factors, in a comparison of a large cohort of HCV-infected (ERCHIVES) and HCV-negative patients [31]. HCV-infected men in the same cohort (ERCHIVES) had a higher risk of acute MI than HCV-negative men with higher total cholesterol/low-density lipoprotein levels; moreover, the risk of acute MI in HCV-infected men was more pronounced at a younger age [32]. Notably, lipid lowering therapy significantly reduced the risk of MI in HCV-infected individuals compared with HCV-negative individuals with similar lipid levels [32]. In contrast to these findings, similar rates of acute coronary syndrome (ACS) have also been reported in treatment-naive HCV-positive patients and HCV-negative individuals [33].

A meta-analysis has reported a significant but heterogeneous association between HCV infection and the combination of cerebrovascular and cardiovascular events (OR 1.30; 95% CI 1.10, 1.55; $P=0.002$), and between, when analysed separately, HCV infection and cardiovascular events (OR 1.20; 95% CI 1.03, 1.40; $P=0.02$), and cerebrovascular events (OR 1.35; 95% CI 1.00, 1.82; $P=0.05$) [24]. Notably, the impact of HCV on cerebro-cardiovascular events was significantly higher in studies involving older patients ($P<0.001$) and those with a higher proportion of participants with hypertension ($P=0.008$) or diabetes ($P<0.001$), suggesting that the effect of HCV infection is more pronounced in populations at increased cardiovascular risk [24].

Interestingly, non-obese, non-diabetic, treatment-naive patients with HCV mono-infection have been shown to have an intermediate Framingham risk score and significantly higher pro-inflammatory cytokine levels than controls (blood donors), which suggests that inflammation is the critical mechanism by which HCV can contribute to atherosclerosis [34].

Consistent with these results, an observational study in a cohort of >150,000 patients (82,082 of whom were HCV-positive) showed a significant association between HCV infection and the risk of developing CAD [31]. Similarly, HCV-infected patients had a significantly higher incidence of coronary heart disease events than HCV-negative patients (4.9% versus 3.2%; $P<0.001$) in a prospective cohort study [35]. Moreover, among HCV-positive patients the incidence of cardiovascular events were higher in individuals with detectable HCV RNA levels than in HCV antibody-positive patients with undetectable HCV RNA levels (5.9% versus 4.7%; $P=0.04$) [35], suggesting that active HCV infection increases cardiovascular risk. Further data also linked HCV infection, not only with the presence of CAD, but also with the severity of coronary atherosclerosis. Chronic HCV infection has also been associated with a significantly higher prevalence of coronary artery calcification and coronary plaques in HIV-positive patients than in HIV-mono-infected men [22].

Acute coronary syndromes

The incidence of ACS was significantly higher in 13,983 treatment-naive HCV-infected patients than in 55,932 HCV-negative individuals in a large cohort study; moreover, the presence of comorbidities (hypertension, heart failure, dyslipidaemia, type 2 diabetes) was associated with a significantly higher risk of ACS in HCV-positive patients [36]. In this analysis, the highest risk of ACS was observed in middle-aged patients [36].

Antiviral treatment may lower CVD risk in HCV-positive patients. Treatment with pegylated interferon (PEG-IFN) plus ribavirin (RBV) significantly decreased the risk of ACS (HR 0.77; 95% CI 0.62, 0.97; $P=0.026$), as well as end-stage renal disease (HR 0.15; 95% CI 0.07, 0.31; $P<0.001$) and ischaemic stroke (HR 0.62; 95% CI 0.46, 0.83; $P=0.001$) in a large population of HCV-infected patients ($n=293,480$), 12,384 of whom had received PEG-IFN/RBV [37]. This finding suggests that prior-antiviral treatment may be a confounding factor in studies of CVD risk in HCV-infected patients. Recent data from the ERCHIVES study demonstrate a higher rate of acute MI in untreated HCV-positive men than in HCV-negative men, with consistently higher cardiovascular event rates in HCV-positive patients with increasing total cholesterol and low-density lipoprotein levels, and conversely, significantly lower cardiovascular event rates in HCV-positive patients receiving lipid lowering therapy [32].

Some studies have also shown a lack of association between HCV infection and acute MI [38,39]; however, these studies have flaws. For example, a large retrospective observational study (>75,000 participants) [38] had a short follow-up period (median 3.2 years), and a broad definition of chronic HCV infection that included patients who had spontaneously cleared HCV infection. As such, the findings are susceptible to residual confounding by unmeasured factors [38].

Peripheral arterial disease

HCV infection has been shown to be an independent risk factor for peripheral arterial disease, with the risk increasing with the number of comorbidities and age [40]. Chronic HCV infection is also independently associated with peripheral arterial stiffness (compliance index by photoplethysmography) [41].

Heart dysfunction and failure

Clinical studies have shown a link between HCV infection and cardiac dysfunction. In HCV-infected patients with otherwise normal cardiac function and structure, high levels of N terminal-pro-B-natriuretic peptide (NT-pro-BNP) were evidenced, suggesting the presence of sub-clinical cardiac dysfunction [4,12,13]. Correlations between echocardiography parameters indicating left ventricular dysfunction (left ventricular

diastolic diameter, left ventricular posterior wall diastolic thickness and mitral E/E') and NT-pro-BNP levels have also been observed in other studies [42,43]. Myocardial perfusion defects, evaluated with single-photon emission computed tomography, were found in 87% of chronic HCV infection patients without overt heart disease, and improved after viral eradication (sustained virological response [SVR]) by IFN therapy [44]. Of note, the majority of these studies have been conducted on asymptomatic patients, showing that patients with chronic HCV infection might have extremely mild signs of heart damage, and highlighting the importance of evaluating sub-clinical myocardial dysfunction in patients with chronic HCV infection.

Other studies have further investigated the extent of myocardial damage in patients with chronic HCV infection. Left ventricular mass was higher in patients with chronic HCV infection than in healthy normotensive controls, but similar to that in HCV-negative patients with hypertension ($n=104$) [45]. A link between HCV infection and myocardial injury was established by thallium-201 myocardial scintigraphy in a cohort of 217 patients with chronic HCV infection [44]. A small study that employed cardiac magnetic resonance imaging, demonstrated that HCV-infected patients had significantly lower left-ventricular end-diastolic volume, reduced stroke volume, lower postcontrast myocardial T1 time and higher partition coefficient expression of myocardial fibrosis when compared with HCV-negative individuals [46]. In line with these cross-sectional data, HCV seropositivity was associated with an approximate twofold increase in the risk of heart failure (HR 2.13; 95% CI 1.19, 3.80) when compared with seronegative individuals in a cohort of patients with stable coronary heart disease [47]. In addition, a significant association between HCV infection and the risk of congestive heart failure (OR 2.49; 95% CI 1.04, 5.96) was observed in the US National Health and Nutrition Examination Survey (NHANES) [48].

All in all, when looking at the interplay between HCV infection and cardiovascular damage, available clinical evidence – even if not always confirmed – reinforced by mechanistic studies suggest a role for HCV infection in the development of cardiovascular alterations. Further studies are necessary to better understand the importance of HCV infection in patients at different cardiovascular risks and with different degrees of HCV-related liver damage.

Myocarditis

HCV RNA has been identified in myocardial tissue of patients with dilated cardiomyopathy and myocarditis [49,50]. In addition, the prevalence of anti-HCV antibodies was higher (4.4%; $n=59/1,355$) in patients with idiopathic heart failure than in the general US population

(1.8%), with a higher prevalence in patients with myocarditis suggesting a potential role of HCV in myocardial damage [11]. Although a previous study did not find a link between myocarditis and HCV infection [51], the association is worthy of further investigation.

In patients with thalassaemia major, HCV infection appears to be involved in the pathogenesis of myocardial fibrosis through direct and indirect mechanisms [9]. In an autopsy study, HCV RNA was found in cardiac tissue from 26.0% of patients with hypertrophic cardiomyopathy, 11.5% of those with dilated cardiomyopathy and 33.3% of those with myocarditis [52].

Therapy for myocarditis is controversial given that the mechanism by which HCV affects the myocardium is unknown. Treatment for chronic HCV infection may potentially lead to resolution of the cardiomyopathy, or potentially improve the clinical course in patients with myocarditis and HCV infection [53,54]. Immunosuppression may be helpful despite the persistence of the viral genome, suggesting an immune-mediated mechanism of damage [55,56]. The development of HCV-associated cardiomyopathy may be facilitated by viral and immunological factors in genetically susceptible subjects. In particular, the HLA and non-HLA systems have been implicated in the susceptibility for the development of HCV-associated cardiomyopathy. In this context, genes of the major histocompatibility complex II may drive the development of different phenotypes of HCV-associated cardiomyopathies. In particular, HLA-DQB1*0303 and HLA-DRB1*0901 were more prevalent in HCV-infected patients with hypertrophic cardiomyopathy, and DRB1*1201 was more prevalent in HCV-infected patients with dilated cardiomyopathy [57].

HCV and cardiovascular mortality

HCV infection has been associated with increased overall mortality (HR 3.13; 95% CI 2.60, 3.76) and cardiovascular death (HR 2.21; 95% CI 1.41, 3.46) in HCV-infected

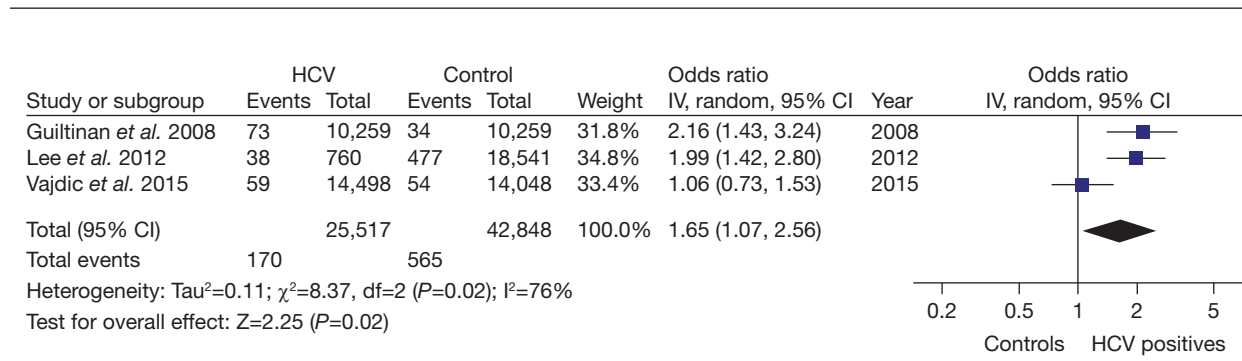
patients when compared with uninfected matched blood donors [58]. Similar significant increases in overall mortality and circulatory mortality rates in anti-HCV seropositive individuals were observed in the REVEAL HCV cohort [59]. In contrast, no association was found between HCV infection and cardiovascular mortality in a large population-based cohort study of 29,571 patients on opioid substitution therapy, 14,048 of whom were HCV-positive [60]. A meta-analysis of these three studies (total $n=68,365$) revealed a significant association (OR 1.65; 95% CI 1.07, 2.56) between HCV infection and cardiovascular death (Figure 2) [24]. Notably, the results have been confirmed in a prospective 5-year study in patients receiving haemodialysis ($n=1,077$), in which chronic HCV infection, but not cured HCV infection, was an independent risk factor for CVD mortality [61].

Evidence regarding the potential benefits of HCV treatment on cardiac-related outcomes

The availability of safe and effective antiviral regimens that eradicate HCV infection in most patients (independently of the severity of the underlying liver disease and of the number and severity of comorbidities), together with evidence that HCV infection promotes CVD, raises the clinically relevant question of whether eradicating HCV can improve cardiovascular outcomes.

As noted above, the risk of lethal cerebrovascular events was lowest in HCV-positive patients with undetectable HCV RNA and increased with viral load when compared with anti-HCV-antibody negative patients [28]. This suggests that eradication of HCV with antiviral therapy should reduce the risk of cerebrovascular death; however, this study does not provide evidence of a direct effect of virological eradication (SVR) and a reduction in cardiovascular risk. In a proof of concept study in a cohort of 200 Japanese individuals with chronic HCV infection and without overt heart disease,

Figure 2. Association between HCV infection and cardiovascular mortality



Reprinted with permission from Hepatitis C virus infection is associated with increased cardiovascular mortality: a meta-analysis of observational studies by Petta S, Maida M, Macaluso FS, *et al.* (2016) *J Gastroenterology* 150:145–155 [24]. Meta-analysis of three studies that assessed the association between HCV infection and cardiovascular mortality. df, degrees of freedom; IV, instrumental variable.

myocardial perfusion (thallium-201 myocardial scintigraphy) defect was observed in 87% of the overall patients, and improvement in myocardial injury was observed in patients who achieved an SVR, transient improvement was observed in patients who relapsed, and no improvement was observed in non-responders after treatment with PEG-IFN/RBV [44]. Consistent with these data, a significant reduction in the occurrence of ACS and stroke was observed in patients receiving PEG-IFN-based antiviral therapy compared with those who did not receive treatment in a large Taiwanese cohort study [37]. Virological eradication was associated with a significant reduction in all-cause mortality ($P < 0.001$) and absolute risk reduction for CVD in a large Scottish cohort of HCV-infected patients who underwent PEG-IFN/RBV therapy (Figure 3); importantly the effect was considerably higher in individuals with non-mild liver disease, defined as an aspartate aminotransferase-to-platelet ratio index (APRI) ≥ 0.7 , than for individuals with mild liver disease [62]. Finally, the risk of all cardiovascular events or major adverse cardiovascular events was significantly reduced in patients who achieved SVR compared with non-responders in a large cohort of French patients with biopsy-proven HCV-related cirrhosis who received PEG-IFN/RBV or IFN-free antiviral therapy [17,18]. The protective effect of virological eradication was observed

for both IFN-based and IFN-free therapies. Of note, the severity of liver disease, together with classical cardiovascular risk factors, was an independent predictor of cardiovascular events [17].

Careful interpretation of these data is required because the majority of the conclusions are drawn from indirect evidence and from studies on patients healthy enough to be eligible for IFN-based therapies. Data on the effect of direct-acting antiviral (DAA) treatment on cardiovascular outcomes are still limited, as until now DAAs were only available in a small number of patients with compensated cirrhosis, and so longer follow-up and further validation is needed. A recent post hoc analysis of data across Phase III clinical trials showed that treatment of a cohort of 1,453 HCV-infected patients treated with glecaprevir and pibrentasvir resulted in statistically significant decreases in triglyceride levels compared with baseline by end of treatment regardless of treatment history or cirrhotic status, especially in patients with elevated baseline triglyceride levels [63]. Finally, a key clinical issue is to identify groups of patients in which virological eradication could have a minor or major impact on cardiovascular prognosis. It is in fact possible to expect the length and the severity of both liver disease and cardiovascular alterations, as well as the age and the comorbidity of patients, could strongly affect the impact of SVR on cardiovascular outcomes.

Figure 3. Absolute risk reduction of cardiovascular disease and all-cause mortality among patients who achieved SVR with interferon-based HCV therapy

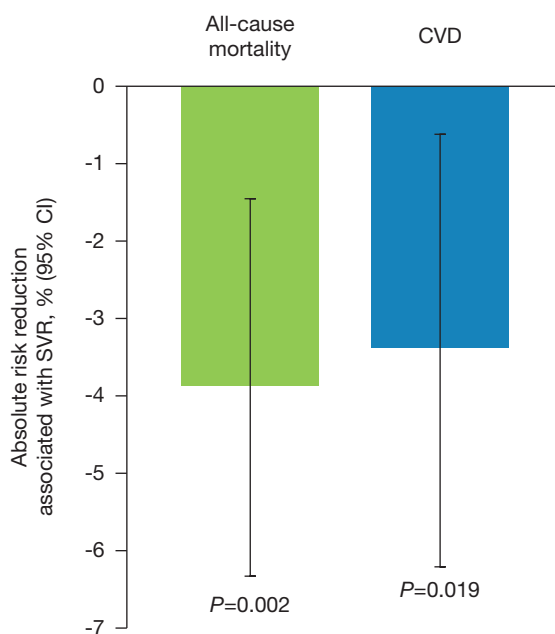


Figure adapted from Innes HA, et al. *Hepatology* 2015 [62]. CVD, cardiovascular disease; SVR, sustained virological response.

Management of patients with cardiovascular manifestations of chronic HCV infection

High efficacy and good safety of DAA regimens suggests that most patients with HCV infection and cardiovascular disorders should be treated with the goal of eradicating HCV, except in those patients with short life expectancy due to underlying CVD or other comorbidities [6].

In patients with chronic HCV infection, compensated liver disease and overt CVD, guidance should be provided on the control of risk factors such as diabetes [64], dyslipidaemia [65] and hypertension [66], and recommendations for drug therapy for the underlying cardiovascular disorder should be more carefully followed. The safe use of cardiovascular therapies is of particular interest, for example, consideration of the use of statins in patients with HCV infection. Despite a report that statins have beneficial effects on the risk of hepatocellular carcinoma (HR 0.42; 95% CI 0.27, 0.64), hepatic decompensation (HR 0.55; 95% CI 0.39, 0.77) and death (HR 0.56; 95% CI 0.46, 0.69) in HCV-infected patients [67], a recent report showed that statins are underused [68]. Application of risk criteria delineated by the Adult Treatment Panel III guidelines to a large cohort of HCV-infected US veterans (169,767) showed that 45.9% of subjects had indication for statin therapy, but only 30.5% of

patients were receiving them [68]. Therefore, correct management of cardiovascular risk factors in HCV-infected patients should include education aimed at reducing the underuse of drugs like statins. Similarly, a high proportion of HCV patients with diabetes are switched from metformin, the first-line therapy for type 2 diabetes, to insulin. However, metformin is safe in patients with compensated liver disease, has beneficial cardiometabolic effects and may improve liver-related prognosis [69–71].

After these general considerations for hepatologists, a key question is how to assess cardiovascular damage in HCV patients. A summary of current guidelines from scientific societies in the cardiovascular field is outlined in Table 1. Baseline assessments and follow-up evaluations are recommended for primary cardiovascular prevention (at any age for HCV-infected patients), and for patients with a history of stroke, stable CAD, ACS, peripheral arterial disease, myocarditis and heart failure. More in-depth details can be directly found in cited guidelines. Of note, no cardiovascular guidelines mention HCV as a possible aetiological factor for CVD, and consequently no advice with regard to HCV infection is provided. This implies a general lack of consideration of HCV as a risk factor for CVD by cardiologists.

Treatment considerations for chronic HCV in patients with CVD

Potential drug–drug interactions between HCV treatment and drugs used to manage CVD exist (Figure 4). In particular, care must be taken when prescribing certain DAAs with some statins and anti-arrhythmic drugs. Few combinations are contraindicated. In particular, amiodarone is contraindicated with sofosbuvir when used in combination with other DAAs (daclatasvir, simeprevir, ledipasvir) and with ombitasvir/paritaprevir/ritonavir with or without dasabuvir [72,73].

With regard to diuretics, the use of the maximum tolerated dosage of spironolactone should be encouraged in patients with heart failure. In particular, it should be taken into consideration that spironolactone antagonizes the action of aldosterone in the distal renal tubules, is a potassium sparing diuretic and protects against the consequences of uncontrolled fibrosis during myocardial remodelling induced by heart failure [74].

Finally, as available evidence suggests a comparable safety profile, there is no reason to prefer warfarin over novel oral anticoagulants unless the physician has a preference for vitamin K antagonists.

Conclusions

HCV has a complex role in the atherosclerotic process, although the association between HCV and CVD has

not been clearly defined. In particular, the biological significance of this association remains undefined. Thus, a pathogen resident in an atherosclerotic plaque may simply represent a ‘bystander’ rather than a ‘culprit’ or a diseased vessel may simply be more vulnerable to pathogens, including HCV. In any case, it would be superficial to consider as irrelevant a hypothesis that is reinforced by multiple lines of evidence, and by the involvement of systemic inflammation and the autoimmune response, which are both critical in HCV infection and atherosclerosis.

Currently, HCV-infected patients are not generally recognized as a high priority for cardiovascular assessment and/or treatment owing to the lack of definitive conclusions on the role of HCV in CVD. In view of present available evidence, it is important that clinicians begin to consider HCV as a non-traditional risk factor for CVD. Evidence of a beneficial effect of SVR after antiviral treatment on cardiovascular risk is encouraging, especially with the introduction of new IFN-free combinations that are more effective and better tolerated than IFN-based therapies. In this context, from a pathophysiological point of view, the observation that some patients with chronic HCV infection remained free of atherosclerosis, while others develop extensive disease, represents a challenging point that merits further investigation. Thus, it remains crucial for clinicians to consider their patients as a whole, and evaluate correlated factors and diseases that place the chronic HCV infection patient at risk for HCV-related extra-hepatic complications, including CVD. Specifically, it is critical for clinicians to recognize the multilevel dimensions of HCV disease and its natural history, in the attempt to optimize treatment, apply general guidelines, avoid adverse events and improve the quality of life for each patient. In this context, the assessment of additional factors and comorbidities (for example, steatosis, diabetes) or biomarkers (for example, inflammatory, lipids) might be helpful to eventually identify subgroups of patients at higher risk of developing atherosclerosis.

It is conceivable that all patients with chronic HCV infection would benefit from a detailed assessment of their cardiovascular status, whereas patients with CVD would benefit from the screening for HCV and other HCV-related parameters. In this scenario, a close collaboration between hepatologists and cardiologists is also desirable to correctly interpret patient-specific data and make the best recommendation for each patient.

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Table 1. Management of patients with chronic HCV infection and CV disease

Extrahepatic manifestation	Patient history	Investigations	Follow-up
Primary cardiovascular prevention (at any age) [75]	Traditional CV risk factors	Assessment of risk as per current risk score calculators (keeping in mind that HCV infection is a non-traditional risk factor) ECG Echocardiography Carotid ultrasound General laboratory assessment	Check for correction of risk factors ECG Echocardiography Carotid ultrasound Specific laboratory assessment for associated comorbidity and risk factors
Stroke [76]	Central nervous system deficit	Brain MRI with diffusion Carotid ultra-sounds Echocardiography Holter	Central nervous system deficit Brain MRI Check for risk factors correction
Stable CAD	Angina on effort Dyspnea Arrhythmias	Assess for clinical pretest probability for CAD According to current guidelines [77,78] (keeping in mind that HCV infection is a non-traditional risk factor) Coronary CT or stress imaging (echo MRI or scintigraphy) as per pretest probability	Coronary CT or stress imaging (echo MRI or scintigraphy) according to pretest probability
Acute coronary syndrome [79,80]	Acute chest pain Dyspnea Arrhythmias	ECG hsTroponin Echocardiography Coronary angiography	Secondary prevention and scheduled follow-up visit In symptomatic pts, stress imaging is indicated rather than stress ECG In asymptomatic pts late stress imaging test may be considered based on CV risk profile
PAD [81]	Claudication Acute limb ischaemia	Clinical assessment Based on ABI (basal and/or exercise) and TBI Duplex ultrasound, CTA or MRA, or invasive angiography	Check for correction of risk factors Based on ABI (basal and/or exercise) and TBI Duplex ultrasound, CTA or MRA, or invasive angiography
Myocarditis [82]	Acute chest pain HF symptoms Arrhythmias	ECG hsTroponin Inflammatory biomarkers Echocardiography Cardiac MRI Exclude CAD Endomyocardial biopsy in unstable pts or pts with persistent heart dysfunction	Echocardiography Cardiac MRI hsTroponin Inflammatory biomarkers
HF [83]	Breathlessness Orthopnea Paroxysmal nocturnal dyspnea Reduced exercise tolerance Fatigue Dyspnea Ankle swelling	Assessment of HF probability (clinical history, physical examination, ECG; keeping in mind that HCV infection is a non-traditional risk factor) NTproBNP Echocardiography	Check for correction of risk factors NTproBNP ECG Echocardiography Cardiopulmonary exercise testing or 6 min walk test

ABI, ankle-brachial index; CAD, coronary artery disease; CT, computer tomography; CTA, CT angiography; CV, cardiovascular; ECG, electrocardiogram; GFR, glomerular filtration rate; HF, heart failure; hsTroponin, high sensitivity troponin; MRA, mineralocorticoid receptor antagonists; MRI, magnetic resonance imaging; NTproBNP, N-terminal pro-brain natriuretic peptide; PAD, peripheral arterial disease; pts, patients; TBI, toe-brachial index.

Table 1. Continued

Extrahepatic manifestation	Patient history	Investigations	Follow-up
	Elevated jugular venous pressure Hepatojugular reflux	Cardiac MRI CT or coronary angiography to rule out CAD (based on pretest probability)	Cardiac MRI
Cardiorenal syndrome	See HF section	See HF section, with particular attention to: GFR, albuminuria Renal Doppler to exclude renal artery stenosis	See HF section Keep in mind effectiveness of certain drugs with reduced renal function Keep in mind renal toxicity for drugs and contrast medium

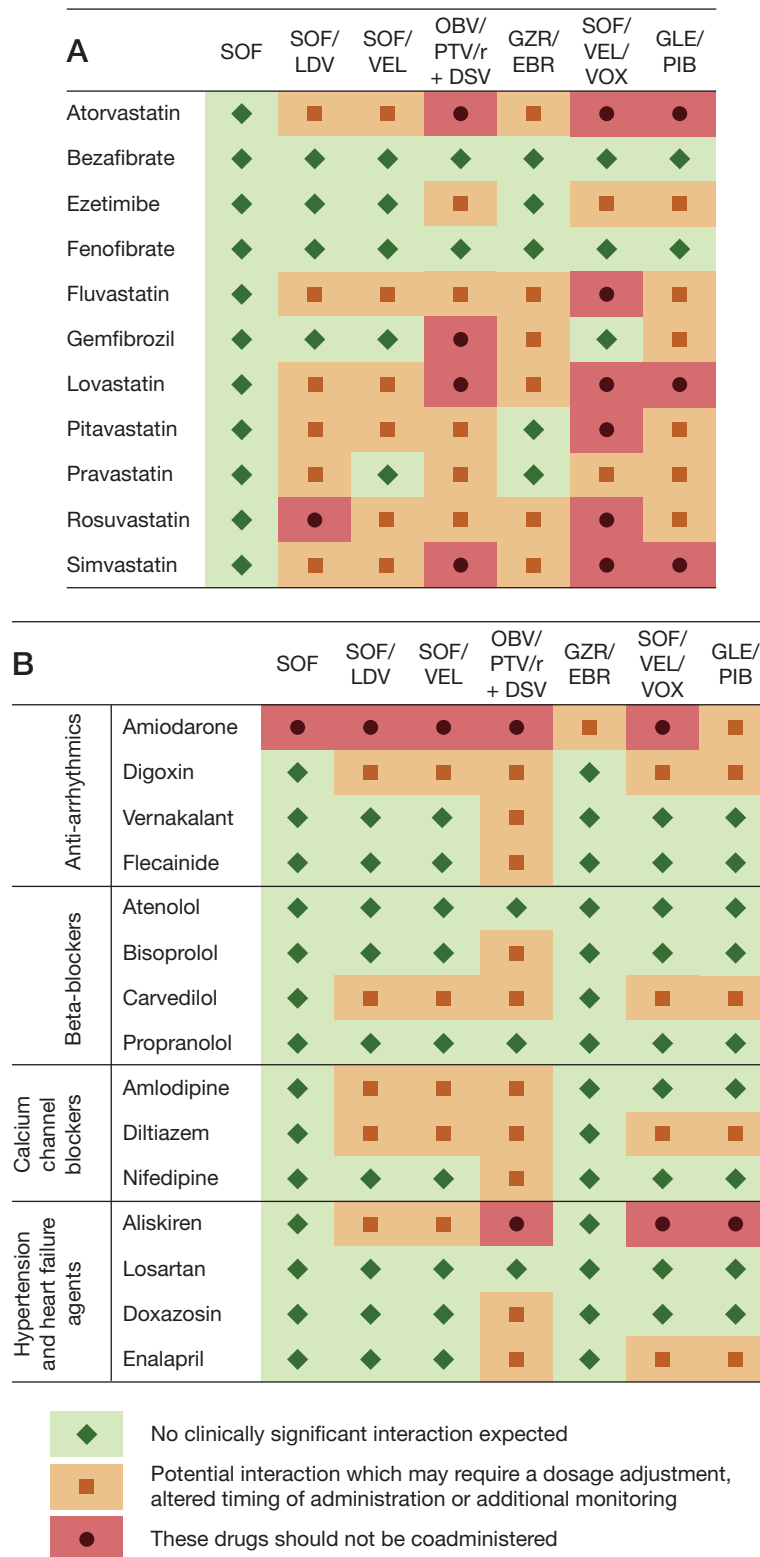
Disclosure statement

SP: speaker and/or advisor for AbbVie, Gilead, MSD, Intercept, Allergan, Polifarma. MB: employee of AbbVie and may hold stock or options. PC: received consultancies, honoraria, advisory board, speakers' fees from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Pfizer, Roche, Servier and Vifor. PC is an inventor of a patent application owned by his academic institution and licensed to ILTOO Pharma, a biotechnology company developing low dose IL-2 in autoimmune diseases, in which PC holds shares. The remaining authors declare no competing interests.

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Figure 4. Potential DDIs between HCV therapies and lipid-lowering or cardiovascular drugs



Reprinted with permission from EASL recommendations on treatment of hepatitis C 2018 by European Association for the Study of the Liver (2018) in *J Hepatol* 69:461–511 [6]. Potential drug–drug interactions (DDIs) between HCV therapies and (A) lipid lowering or (B) cardiovascular drugs. DCV, daclatasvir; EBR, elbasvir, GLE, glecaprevir; GZR, grazoprevir; LDV, ledipasvir; OBV/PTV/r+DSV, ombitasvir/paritaprevir/ritonavir plus dasabuvir; PIB, pibrentasvir; SIM, simeprevir; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

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