



HAL
open science

Expert opinion on managing chronic HCV in patients with cardiovascular disease

Cristina Vassalle, Salvatore Petta, Alessia Pepe, Antonio Craxi, Mark Bondin,
Patrice Cacoub

► **To cite this version:**

Cristina Vassalle, Salvatore Petta, Alessia Pepe, Antonio Craxi, Mark Bondin, et al.. Expert opinion on managing chronic HCV in patients with cardiovascular disease. *Antiviral Therapy*, 2018, 23 (Suppl 2), pp.35-46. 10.3851/IMP3248 . hal-01974544

HAL Id: hal-01974544

<https://hal.sorbonne-universite.fr/hal-01974544>

Submitted on 8 Jan 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Beyond the liver spotlight series: Cardiovascular disease

Expert opinion on managing chronic HCV in patients with cardiovascular disease

Cristina Vassalle^I, Salvatore Petta^{II}, Alessia Pepe^{III}, Antonio Craxi^{II}, Mark Bondin^{IV}, Patrice Cacoub^{V-VI}

[I] Laboratory Medicine Unit, Fondazione CNR-Regione Toscana G Monasterio, Pisa , Italy

[II] Department of Gastroenterology, Università di Palermo, Palermo, Italy

[III] MRI Unit, Fondazione CNR-Regione Toscana G Monasterio, Pisa , Italy

[IV] AbbVie, Inc. Chicago, IL, USA

[V] Sorbonne Universités, UPMC Univ Paris 06, UMR 7211, and Inflammation-Immunopathology-Biotherapy Department (DHU i2B), F-75005, Paris, France; [V] INSERM, UMR_S 959, F-75013, Paris, France; [VI] CNRS, FRE3632, F-75005, Paris, France;

[VII] AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, F-75013, Paris, France, E-mail: patrice.cacoub@aphp.fr.

Corresponding author: Patrice Cacoub

Abstract [heading level 1]

Extrahepatic manifestations of chronic HCV infection include cardiovascular diseases and an increase in cardiovascular mortality. The pathogenic mechanisms by which HCV contribute 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 [heading level 1]

Beyond the liver spotlight series: Cardiovascular disease

Chronic hepatitis C virus (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 e.g. 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 (e.g. 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, Petta S, *et al.* unpublished data]. These data, together with evidence of associations with atherosclerosis, stroke, myocardial infarction (MI), coronary artery disease, peripheral arterial disease, myocarditis [9-11], and heart failure [12,13] suggest that HCV infection increases the risk of CVD [3].

Many 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.

Beyond the liver spotlight series: Cardiovascular disease

HCV as a non-traditional risk factor for cardiovascular disease [heading level 1]

Carotid atherosclerosis [heading level 2]

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 two-fold higher risk of carotid plaques in HCV-infected individuals compared with uninfected controls [24]. Similar results were obtained when IMT 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 [heading level 2]

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

Beyond the liver spotlight series: Cardiovascular disease

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 [heading level 2]

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% vs. 2.0%; $P<0.05$), and the presence of HCV remained a significant predictor of CAD even after correction for cardiometabolic risk factors (OR 4.2; 95% CI 1.4–13.0) [30].

HCV infection was associated with a higher risk of CAD (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-naïve 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

Beyond the liver spotlight series: Cardiovascular disease

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-naïve 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% vs 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 plaque in HIV-positive patients than in HIV-mono-infected men [22].

Acute coronary syndromes [heading level 2]

The incidence of ACS was significantly higher in 13,983 treatment-naïve HCV-infected patients than in 55,932 HCV-negative individuals in a large cohort study; moreover, the presence

Beyond the liver spotlight series: Cardiovascular disease

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 (pegIFN) 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 pegIFN/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 [heading level 2]

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

Beyond the liver spotlight series: Cardiovascular disease

also independently associated with peripheral arterial stiffness (compliance index by photoplethysmography) [41].

Heart dysfunction and failure [heading level 2]

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 interferon 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 subclinical 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

Beyond the liver spotlight series: Cardiovascular disease

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 2-fold 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 risk and with a different degrees of HCV-related liver damage.

Myocarditis [heading level 2]

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=59/1355) 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 Thalassemia major, HCV infection appears to be involved in the pathogenesis of myocardial fibrosis through direct and indirect mechanisms [9]. In an autopsy

Beyond the liver spotlight series: Cardiovascular disease

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, HLADQB1*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 [heading level 2]

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 between HCV infection and cardiovascular mortality in a large population-based cohort study of 29,571 patients on opioid substitution therapy, 14,048 of

Beyond the liver spotlight series: Cardiovascular disease

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 hemodialysis (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 **[heading level 1]**

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 cardiovascular disease, 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, 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 a SVR, transient improvement was observed in patients who relapsed, and no improvement was observed in nonresponders after treatment with pegIFN/RBV [44]. Consistent

Beyond the liver spotlight series: Cardiovascular disease

with these data, a significant reduction in the occurrence of ACS and stroke was observed in patients receiving pegIFN-based antiviral therapy compared with those who did not receive treatment 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 pegIFN/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 nonresponders in a large cohort of French patients with biopsy-proven HCV-related cirrhosis who received pegIFN/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 antivirals (DAAs) 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 3 clinical trials showed that treatment of a cohort of 1453 HCV-infected patients 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

Beyond the liver spotlight series: Cardiovascular disease

levels [63]. Finally, a key clinical issue, is to identify groups of patients in which virologic 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.

Management of patients with cardiovascular manifestations of chronic HCV infection [heading level 1]

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 the 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. Notwithstanding 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

Beyond the liver spotlight series: Cardiovascular disease

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 coronary artery disease, ACS, PAD, 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 etiologic factor for CVD, and consequently no advice with regard to HCV infection is provided. This implies a generally lack of consideration of HCV as a risk factor for CVD by cardiologists.

Treatment considerations for chronic HCV in patients with CVD [heading level 1]

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/parataprevir/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

Beyond the liver spotlight series: Cardiovascular disease

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 remodeling 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 [heading level 1]

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 interferon-free combinations that are more effective and better tolerated than interferon-based therapies. In this context, from a pathophysiological point of view, the observation that some

Beyond the liver spotlight series: Cardiovascular disease

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 (e.g. steatosis, diabetes), or biomarkers (e.g. 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.

Acknowledgements:

Medical Editing support was provided by Gillian Patman, funded by AbbVie.

Disclosure Statement (heading level 1)

Cristina Vassalle: No conflicts of interest to disclose

Salvatore Petta: Speaker and/or Advisor for Abbvie, Gilead, MSD, Intercept, Allergan, Polifarma

Beyond the liver spotlight series: Cardiovascular disease

Alessia Pepe: No conflicts of interest to disclose

Antonio Craxi: No conflicts of interest to disclose

Mark Bondin: Employee of AbbVie and may hold stock or options.

Patrice Cacoub: received consultancies, honoraria, advisory board, speakers' fees from Abbvie, Astra Zeneca, Bayer, Boehringer Ingelheim, Gilead, Glaxo Smith Kline, Janssen, Merck Sharp Dohme, Pfizer, Roche, Servier, and Vifor. Prof Patrice Cacoub 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.

References [level 1 heading]

- (1) Sebastiani G, Gkouvatsos K, Pantopoulos K. Chronic hepatitis C and liver fibrosis. *World J Gastroenterol.* 2014;20:11033-11053.
- (2) Younossi Z, Park H, Henry L, Adeyemi A, Stepanova M. Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. *Gastroenterology.* 2016;150:1599-1608.
- (3) Cacoub P, Gragnani L, Comarmond C, Zignego AL. Extrahepatic manifestations of chronic hepatitis C virus infection. *Dig Liver Dis.* 2014;46 Suppl 5:S165-73.
- (4) Antonelli A, Ferri C, Ferrari SM, et al. High levels of circulating N-terminal pro-brain natriuretic peptide in patients with hepatitis C. *J Viral Hepat.* 2010;17:851-853.
- (5) AASLD and IDSA. HCV Guidance: Recommendations for testing, managing, and treating hepatitis C. 2017; Available at: <http://www.hcvguidelines.org/>.
- (6) European Association for the Study of the Liver (EASL). EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol.* 2017;66:153-194.
- (7) Molnar MZ, Alhourani HM, Wall BM, et al. Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans. *Hepatology.* 2015;61:1495-1502.
- (8) Rein DB, Borton J, Liffmann DK, Wittenborn JS. The burden of hepatitis C to the United States Medicare system in 2009: Descriptive and economic characteristics. *Hepatology.* 2016;63:1135-1144.

Beyond the liver spotlight series: Cardiovascular disease

- (9) Pepe A, Meloni A, Borsellino Z, et al. Myocardial fibrosis by late gadolinium enhancement cardiac magnetic resonance and hepatitis C virus infection in thalassemia major patients. *J Cardiovasc Med (Hagerstown)*. 2015;16:689-695.
- (10) Omura T, Yoshiyama M, Hayashi T, et al. Core protein of hepatitis C virus induces cardiomyopathy. *Circ Res*. 2005;96:148-150.
- (11) Matsumori A, Shimada T, Chapman NM, Tracy SM, Mason JW. Myocarditis and heart failure associated with hepatitis C virus infection. *J Card Fail*. 2006;12:293-298.
- (12) Antonelli A, Ferri C, Ferrari SM, et al. N-terminal pro-brain natriuretic peptide and tumor necrosis factor-alpha both are increased in patients with Hepatitis C. *J Interferon Cytokine Res*. 2010;30:359-363.
- (13) Okada K, Furusyo N, Ogawa E, et al. Association between chronic hepatitis C virus infection and high levels of circulating N-terminal pro-brain natriuretic peptide. *Endocrine*. 2013;43:200-205.
- (14) Petta S, Macaluso FS, Craxi A. Cardiovascular diseases and HCV infection: a simple association or more? *Gut*. 2014;63:369-375.
- (15) Domont F, Cacoub P. Chronic hepatitis C virus infection, a new cardiovascular risk factor? *Liver Int*. 2016;36:621-627.
- (16) Jepsen P, Vilstrup H, Lash TL. Development and validation of a comorbidity scoring system for patients with cirrhosis. *Gastroenterology*. 2014;146:147-56; quiz e15-6.
- (17) Nahon P, Bourcier V, Layese R, et al. Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications. *Gastroenterology*. 2017;152:142-156.e2.
- (18) Cacoub P, Nahon P, Layese R, et al. HCV eradication reduces the occurrence of major adverse cardiovascular events in hepatitis C cirrhotic patients: data from the prospective ANRS CO12 CirVir cohort. *J Hepatol*. 2017;66:S20-S21.
- (19) Ishizaka Y, Ishizaka N, Takahashi E, et al. Association between hepatitis C virus core protein and carotid atherosclerosis. *Circ J*. 2003;67:26-30.
- (20) Petta S, Torres D, Fazio G, et al. Carotid atherosclerosis and chronic hepatitis C: a prospective study of risk associations. *Hepatology*. 2012;55:1317-1323.
- (21) Targher G, Bertolini L, Padovani R, Rodella S, Arcaro G, Day C. Differences and similarities in early atherosclerosis between patients with non-alcoholic steatohepatitis and chronic hepatitis B and C. *J Hepatol*. 2007;46:1126-1132.
- (22) McKibben RA, Haberlen SA, Post WS, et al. A Cross-sectional Study of the Association Between Chronic Hepatitis C Virus Infection and Subclinical Coronary Atherosclerosis Among Participants in the Multicenter AIDS Cohort Study. *J Infect Dis*. 2016;213:257-265.
- (23) Sosner P, Wangermez M, Chagneau-Derrode C, Le Moal G, Silvain C. Atherosclerosis risk in HIV-infected patients: the influence of hepatitis C virus co-infection. *Atherosclerosis*. 2012;222:274-277.

Beyond the liver spotlight series: Cardiovascular disease

- (24) Petta S, Maida M, Macaluso FS, et al. Hepatitis C Virus Infection Is Associated With Increased Cardiovascular Mortality: A Meta-Analysis of Observational Studies. *Gastroenterology*. 2016;150:145-155.e4; quiz e15-6.
- (25) Enger C, Forssen UM, Bennett D, Theodore D, Shantakumar S, McAfee A. Thromboembolic events among patients with hepatitis C virus infection and cirrhosis: a matched-cohort study. *Adv Ther*. 2014;31:891-903.
- (26) Liao CC, Su TC, Sung FC, Chou WH, Chen TL. Does hepatitis C virus infection increase risk for stroke? A population-based cohort study. *PLoS One*. 2012;7:e31527.
- (27) Adinolfi LE, Restivo L, Guerrera B, et al. Chronic HCV infection is a risk factor of ischemic stroke. *Atherosclerosis*. 2013;231:22-26.
- (28) Lee MH, Yang HI, Wang CH, et al. Hepatitis C virus infection and increased risk of cerebrovascular disease. *Stroke*. 2010;41:2894-2900.
- (29) Butt AA, Khan UA, McGinnis KA, Skanderson M, Kent Kwoh C. Co-morbid medical and psychiatric illness and substance abuse in HCV-infected and uninfected veterans. *J Viral Hepat*. 2007;14:890-896.
- (30) Vassalle C, Masini S, Bianchi F, Zucchelli GC. Evidence for association between hepatitis C virus seropositivity and coronary artery disease. *Heart*. 2004;90:565-566.
- (31) Butt AA, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. *Clin Infect Dis*. 2009;49:225-232.
- (32) Butt AA, Yan P, Chew KW, et al. Risk of Acute Myocardial Infarction Among HCV+ and HCV- Men at Various Lipid Levels: Results from ERCHIVES. *Clin Infect Dis*. 2017.
- (33) Hsu YC, Lin JT, Ho HJ, et al. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. *Hepatology*. 2014;59:1293-1302.
- (34) Oliveira CP, Kappel CR, Siqueira ER, et al. Effects of hepatitis C virus on cardiovascular risk in infected patients: a comparative study. *Int J Cardiol*. 2013;164:221-226.
- (35) Pothineni NV, DeLongchamp R, Vallurupalli S, et al. Impact of hepatitis C seropositivity on the risk of coronary heart disease events. *Am J Cardiol*. 2014;114:1841-1845.
- (36) Tsai MS, Hsu YC, Yu PC, Lin CL, Kao CH. Long-term risk of acute coronary syndrome in hepatitis C virus infected patients without antiviral treatment: A cohort study from an endemic area. *Int J Cardiol*. 2015;181:27-29.
- (37) Hsu YC, Ho HJ, Huang YT, et al. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut*. 2015;64:495-503.
- (38) Forde KA, Haynes K, Troxel AB, et al. Risk of myocardial infarction associated with chronic hepatitis C virus infection: a population-based cohort study. *J Viral Hepat*. 2012;19:271-277.

Beyond the liver spotlight series: Cardiovascular disease

- (39) Arcari CM, Nelson KE, Netski DM, Nieto FJ, Gaydos CA. No association between hepatitis C virus seropositivity and acute myocardial infarction. *Clin Infect Dis*. 2006;43:e53-6.
- (40) Hsu YH, Muo CH, Liu CY, et al. Hepatitis C virus infection increases the risk of developing peripheral arterial disease: a 9-year population-based cohort study. *J Hepatol*. 2015;62:519-525.
- (41) Chou CH, Ho CS, Tsai WC, Wang MC, Tsai YS, Chen JY. Effects of chronic hepatitis C infection on arterial stiffness. *J Am Soc Hypertens*. 2017;11:716-723.
- (42) Che W, Liu W, Wei Y, et al. Increased serum N-terminal pro-B-type natriuretic peptide and left ventricle diastolic dysfunction in patients with hepatitis C virus infection. *J Viral Hepat*. 2012;19:327-331.
- (43) Demir M, Demir C. Effect of hepatitis C virus infection on the left ventricular systolic and diastolic functions. *South Med J*. 2011;104:543-546.
- (44) Maruyama S, Koda M, Oyake N, et al. Myocardial injury in patients with chronic hepatitis C infection. *J Hepatol*. 2013;58:11-15.
- (45) Perticone M, Miceli S, Maio R, et al. Chronic HCV infection increases cardiac left ventricular mass index in normotensive patients. *J Hepatol*. 2014;61:755-760.
- (46) Ngu PJ, Butler M, Pham A, Roberts SK, Taylor AJ. Cardiac remodelling identified by cardiovascular magnetic resonance in patients with hepatitis C infection and liver disease. *Int J Cardiovasc Imaging*. 2016;32:629-636.
- (47) Tsui JI, Whooley MA, Monto A, Seal K, Tien PC, Shlipak M. Association of hepatitis C virus seropositivity with inflammatory markers and heart failure in persons with coronary heart disease: data from the Heart and Soul study. *J Card Fail*. 2009;15:451-456.
- (48) Younossi ZM, Stepanova M, Nader F, Younossi Z, Elsheikh E. Associations of chronic hepatitis C with metabolic and cardiac outcomes. *Aliment Pharmacol Ther*. 2013;37:647-652.
- (49) Matsumori A, Matoba Y, Sasayama S. Dilated cardiomyopathy associated with hepatitis C virus infection. *Circulation*. 1995;92:2519-2525.
- (50) Okabe M, Fukuda K, Arakawa K, Kikuchi M. Chronic variant of myocarditis associated with hepatitis C virus infection. *Circulation*. 1997;96:22-24.
- (51) Grumbach IM, Heermann K, Figulla HR. Low prevalence of hepatitis C virus antibodies and RNA in patients with myocarditis and dilated cardiomyopathy. *Cardiology*. 1998;90:75-78.
- (52) Matsumori A, Yutani C, Ikeda Y, Kawai S, Sasayama S. Hepatitis C virus from the hearts of patients with myocarditis and cardiomyopathy. *Lab Invest*. 2000;80:1137-1142.
- (53) Sato Y, Takatsu Y, Yamada T, et al. Interferon treatment for dilated cardiomyopathy and striated myopathy associated with hepatitis C virus infection based on serial measurements of serum concentrations of cardiac troponin T. *Jpn Circ J*. 2000;64:321-324.

Beyond the liver spotlight series: Cardiovascular disease

- (54) Matsumori A. Hepatitis C virus and cardiomyopathy. *Herz*. 2000;25:249-254.
- (55) Frustaci A, Calabrese F, Chimenti C, Pieroni M, Thiene G, Maseri A. Lone hepatitis C virus myocarditis responsive to immunosuppressive therapy. *Chest*. 2002;122:1348-1356.
- (56) Frustaci A, Chimenti C, Calabrese F, Pieroni M, Thiene G, Maseri A. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. *Circulation*. 2003;107:857-863.
- (57) Matsumori A, Ohashi O, Ito H, Furukawa Y, Hasegawa K, Sasayama S, et al. Genes of the major histocompatibility complex class II influence the phenotype of cardiomyopathies associated with hepatitis C virus infection. In: Matsumori A, editor. *Cardiomyopathies and Heart Failure* Boston: Kluwer Academic; 2003. p. 515-521.
- (58) Guiltinan AM, Kaidarova Z, Custer B, et al. Increased all-cause, liver, and cardiac mortality among hepatitis C virus-seropositive blood donors. *Am J Epidemiol*. 2008;167:743-750.
- (59) Lee MH, Yang HI, Lu SN, et al. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis*. 2012;206:469-477.
- (60) Vajdic CM, Marashi Pour S, Olivier J, et al. The impact of blood-borne viruses on cause-specific mortality among opioid dependent people: An Australian population-based cohort study. *Drug Alcohol Depend*. 2015;152:264-271.
- (61) Ohsawa M, Kato K, Tanno K, et al. Seropositivity for anti-HCV core antigen is independently associated with increased all-cause, cardiovascular, and liver disease-related mortality in hemodialysis patients. *J Epidemiol*. 2011;21:491-499.
- (62) Innes HA, McDonald SA, Dillon JF, et al. Toward a more complete understanding of the association between a hepatitis C sustained viral response and cause-specific outcomes. *Hepatology*. 2015;62:355-364.
- (63) Tran T, Mehta D, Mensa F, Park C, Sanchez Y. Pan-genotypic hepatitis C treatment with glecaprevir + pibrentasvir resulted in improvement in cardiovascular and metabolic extrahepatic manifestations and stable renal function: Results from phase 3 clinical trials. *Hepatology*. 2017;66:633A.
- (64) **Standards of medical care in diabetes 2017**. *Diabetes Care*. 2017;40:S1-S135.
- (65) Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J*. 2016;37:2999-3058.
- (66) Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159-2219.
- (67) Mohanty A, Tate JP, Garcia-Tsao G. Statins Are Associated With a Decreased Risk of Decompensation and Death in Veterans With Hepatitis C-Related Compensated Cirrhosis. *Gastroenterology*. 2016;150:430-40.e1.

Beyond the liver spotlight series: Cardiovascular disease

- (68) Clement ME, Park LP, Navar AM, et al. Statin Utilization and Recommendations Among HIV- and HCV-infected Veterans: A Cohort Study. *Clin Infect Dis*. 2016;63:407-413.
- (69) Zhang X, Harmsen WS, Mettler TA, et al. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. *Hepatology*. 2014;60:2008-2016.
- (70) Marchesini G, Forlani G. Diabetes and hepatocellular cancer risk: not only a matter of hyperglycemia. *Hepatology*. 2012;55:1298-1300.
- (71) Lavine JE, Schwimmer JB, Van Natta ML, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA*. 2011;305:1659-1668.
- (72) Gilead Sciences. Sovaldi Summary of Product Characteristics. 2017; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf. Accessed August, 2017.
- (73) AbbVie. Viekirax Summary of Product Characteristics. 2017; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003839/WC500183997.pdf. Accessed August, 2017.
- (74) Cezar MD, Damatto RL, Pagan LU, et al. Early Spironolactone Treatment Attenuates Heart Failure Development by Improving Myocardial Function and Reducing Fibrosis in Spontaneously Hypertensive Rats. *Cell Physiol Biochem*. 2015;36:1453-1466.
- (75) Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315-2381.
- (76) Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160-2236.
- (77) Genders TS, Steyerberg EW, Alkadhi H, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J*. 2011;32:1316-1330.
- (78) Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949-3003.
- (79) Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569-2619.
- (80) Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267-315.

Beyond the liver spotlight series: Cardiovascular disease

(81) Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e726-e779.

(82) Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;34:2636-48, 2648a-2648d.

(83) Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129-2200.

Beyond the liver spotlight series: Cardiovascular disease

Table 1: Management of patients with chronic HCV infection and cardiovascular disease

Extrahepatic manifestation	Clinic	Investigations	Follow-up
Primary cardiovascular prevention (at any age)[75]	<ul style="list-style-type: none"> • Traditional CV risk factors 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Check for correction of risk factors • ECG • Echocardiography • Carotid ultrasound • Specific laboratory assessment for associated comorbidity and risk factors
Stroke[76]	<ul style="list-style-type: none"> • Central nervous system deficit 	<ul style="list-style-type: none"> • Brain MRI with diffusion • Carotid ultra-sounds • Echocardiography • Holter 	<ul style="list-style-type: none"> • Central nervous system deficit • Brain MRI • Check for risk factors correction
Stable coronary artery disease	<ul style="list-style-type: none"> • Angina on effort • Dyspnea • Arrhythmias 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Coronary CT or stress imaging (echo MRI or scintigraphy) according to pretest probability
Acute coronary syndrome[79,80]	<ul style="list-style-type: none"> • Acute chest pain • Dyspnea • Arrhythmias 	<ul style="list-style-type: none"> • ECG • hs Troponin • Echocardiography • Coronary angiography 	<ul style="list-style-type: none"> • 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]	<ul style="list-style-type: none"> • Claudication • Acute limb ischemia 	<ul style="list-style-type: none"> • Clinical assessment • Based on ABI (basal and/or exercise) and TBI • Duplex ultrasound, CTA 	<ul style="list-style-type: none"> • Check for correction of risk factors • Based on ABI (basal and/or exercise) and

Beyond the liver spotlight series: Cardiovascular disease

		or MRA, or invasive angiography	TBI <ul style="list-style-type: none"> • Duplex ultrasound, CTA or MRA, or invasive angiography
Myocarditis[82]	<ul style="list-style-type: none"> • Acute chest pain • HF symptoms • Arrhythmias 	<ul style="list-style-type: none"> • ECG • hsTroponin • Inflammatory biomarkers • Echocardiography • Cardiac MRI • Exclude CAD • Endomyocardial biopsy in unstable pts or pts with persistent heart dysfunction 	<ul style="list-style-type: none"> • Echocardiography • Cardiac MRI • hsTroponin • Inflammatory biomarkers
Heart failure[83]	<ul style="list-style-type: none"> • Breathlessness • Orthopnea • Paroxysmal nocturnal dyspnea • Reduced exercise tolerance • Fatigue • Dyspnea • Ankle swelling • Elevated jugular venous pressure • Hepatojugular reflux 	<ul style="list-style-type: none"> • Assessment of HF probability (clinical history, physical examination, ECG) (keeping in mind that HCV infection is a non-traditional risk factor) • NTproBNP • Echocardiography • Cardiac MRI • CT or coronary angiography to rule out CAD (based on pretest probability) 	<ul style="list-style-type: none"> • Check for correction of risk factors • NTproBNP • ECG • Echocardiography • Cardiopulmonary exercise testing or 6 min walk test • Cardiac MRI
Cardiorenal syndrome	<ul style="list-style-type: none"> • See HF section 	<ul style="list-style-type: none"> • See HF section, with particular attention to: <ul style="list-style-type: none"> • GFR, albuminuria • Renal Doppler to exclude renal artery stenosis 	<ul style="list-style-type: none"> • See HF section • Keep in mind effectiveness of certain drugs with reduced renal function • Keep in mind renal toxicity for drugs and contrast medium
<p>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-branchial index.</p>			

Beyond the liver spotlight series: Cardiovascular disease

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

Abbreviations: 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; PCR, polymerase chain reaction.

Figure 2: Association between HCV infection and cardiovascular mortality

Meta-analysis of three studies that assessed the association between HCV infection and cardiovascular mortality. Adapted from Petta S, *et al. Gastroenterology* 2016 [24].

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]. Abbreviation: CVD, cardiovascular disease.

Figure 4: Potential DDIs between HCV therapies and lipid lowering (A) or cardiovascular drugs

(B)

Abbreviations: 3D, ombitasvir/paritaprevir/ritonavir plus dasabuvir; DCV, daclatasvir; EBR, elbasvir, GZR, grazoprevir; LDV, ledipasvir; SIM, simeprevir; SOF, sofosbuvir; VEL, velpatasvir.