



Review Article

Hepatitis C virus and cardiovascular disease: Current knowledge and unmet needs

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ABSTRACT

The relationship between hepatitis C virus (HCV) infection and cardiovascular disease (CVD) is increasingly recognized, with studies indicating elevated CVD prevalence and mortality among individuals with HCV. Chronic HCV patients exhibit a higher CVD risk, especially in the population of end-stage renal disease on hemodialysis. Pathogenic mechanisms may include oxidative stress, endothelial damage, metabolic dysregulation, and chronic inflammation. These factors enhance vascular damage, promoting plaque formation and instability. Direct-acting antivirals (DAAs), which have revolutionized HCV treatment by achieving sustained virologic response rates of over 95%, significantly mitigate CVD risk. DAA therapy improves endothelial function, reduces inflammatory biomarkers, and lowers the incidence of CVD events. However, lipid profiles may paradoxically increase following HCV clearance. In addition, the contrasting outcomes between DAA treatment and arrhythmia risk remain elusive. Potential epigenetic changes for CVD risk may persist after successful viral eradication. The elucidation of unmet needs is critical for solidifying screening guidelines for HCV patients with CVD and for exploration of the long-term CVD outcome in the DAA era.

KEYWORDS: Cardiovascular disease, Direct-acting antivirals, Hepatitis C virus

INTRODUCTION

Hepatitis C virus (HCV) infection is linked to a higher risk of cardiovascular disease (CVD). The global burden of CVD related to HCV infection has the greatest impact observed in low-income and middle-income countries [1]. Chronic hepatitis C (CHC) infection has been associated with both subclinical and clinical CVDs, including myocardial infarctions, congestive heart failure, cerebrovascular accidents, and peripheral arterial disease (PAD). Proposed mechanisms for this include chronic inflammation and immune activation caused by HCV infection, as well as direct invasion and dysfunction of the endothelium [2]. Direct-acting antivirals (DAAs) are highly effective and safe treatment options. Several studies have shown that clearing HCV with DAAs is linked to improvements in atherosclerosis and a reduced risk of cardiovascular events. In addition, HCV clearance is associated with enhancements in metabolic and immunological conditions that contribute to CVD [3].

COMPARATIVE ANALYSIS OF LIPID PROFILES AND INSULIN RESISTANCE IN CHRONIC HEPATITIS C

HCV infection disrupts lipid homeostasis, contributing to the development of hepatic steatosis. Lipids are critical for various stages of the HCV life cycle, and inhibition of cholesterol and fatty acid biosynthetic pathways has been shown to impair viral replication, maturation, and secretion. Moreover, HCV interferes with the synthesis and secretion of very low-density lipoproteins (VLDLs) [4]. Lipoprotein-associated HCV was exclusively present in the VLDL fraction, which was notably enriched in apolipoprotein E. One year after HCV eradication by DAAs, there was a significant reduction in the homeostatic model assessment index by 22% and in high-density lipoprotein (HDL)-associated triglycerides by 18% [5].

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HCV-infected patients had significantly lower lipid levels than their uninfected counterparts in terms of total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL cholesterol (HDL-C), and triglycerides [6]. In addition, insulin resistance (IR) is specifically associated with HCV infection, independent of traditional metabolic risk factors and the degree of liver disease severity [7,8]. HCV plays a direct pathogenic role in the emergence of diabetes even in the early stage of liver histological changes and the unique virus possesses the diabetogenic effect as one of the major extrahepatic manifestations [9]. The development of IR in turn could lead to other metabolic abnormalities, e.g., dyslipidemia, hyperglycemia, hyperinsulinemia, and obesity.

THE PREVALENCE OF CARDIOVASCULAR DISEASE IN CHRONIC HEPATITIS C

The prevalence of CVD in patients with CHC was reported 12.1% and the mortality rate was increased 1.5 times in Taiwan [10]. A study analyzing data from Canadian general population health surveys demonstrated that CHC patients had a significantly higher Framingham Risk Score (FRS) than their anti-HCV-negative counterparts. In addition, those CHC patients had a 1.6-fold higher prevalence of high CVD risk, defined as an FRS $\geq 20\%$, compared to uninfected individuals ($P = 0.038$) [11].

CHC had a higher prevalence of a higher prevalence of atherosclerosis and vice versa. In a large population-based study, investigated 1913 participants revealed that the overall prevalence of atherosclerosis in the study sample was 50.5%. This detection rate is similar to a previous large cohort study, the Multi-Ethnic Study of Atherosclerosis, showing a prevalence of 46.8% [12]. Out of these participants, 7.6% of individuals with atherosclerosis had HCV infection, compared to 3.2% of those without atherosclerosis [12].

Patients with drug abuse are at high risk for HCV infection, reaching an HCV positivity rate of $>90\%$ among injection drug users and nearly 70% among noninjection drug users [13]. Patients who are coinfecting with human immunodeficiency virus (HIV) and HCV experience a high incidence of cardiovascular events, highlighting the importance of managing cholesterol abnormalities and HCV treatment to reduce cardiovascular risk [14].

IMPACTS OF HEPATITIS C VIRUS RNA, LIVER FIBROSIS, AND STEATOSIS ON CARDIOVASCULAR DISEASE RISK

CHC carries an enormous impact on liver-related and all-cause mortality. A large-scale study with a long-term follow-up indicated that CHC patients with detectable serum HCV RNA levels had a 1.53-fold risk of death from circulatory diseases compared to anti-HCV-seronegative counterparts [15]. Our recent study aimed to assess calcification of the aorta by chest computed tomography (CT), and the Agatston score demonstrated that HCV infection with advanced liver fibrosis was significantly associated with atherosclerosis [12]. In addition, CHC patients without metabolic syndrome, HCV with metabolic syndrome, and metabolic syndrome without HCV were significantly associated with atherosclerosis

compared with those without metabolic syndrome and HCV infection [12].

However, the risk of atherosclerosis may differ across various populations and study designs. Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with metabolic syndrome and its components, including obesity, diabetes, and hyperlipidemia, all of which are known risk factors for CVD. A recent cross-sectional study involving patients with MASLD demonstrated that HCV infection was not significantly associated with an increased risk of carotid plaques in MASLD patients [16]. It implied that CHC patients with MASLD may face a higher risk of developing advanced liver fibrosis. Their risk of atherosclerotic CVD (ASCVD) appears to be comparable to MASLD patients.

IMPACT OF HEPATITIS C VIRUS ON CARDIOVASCULAR DISEASE IN PATIENTS UNDERGOING HEMODIALYSIS

The CVD risk in patients undergoing maintenance hemodialysis needs more attention. Patients with end-stage renal disease receiving long-term hemodialysis had a high risk of developing PAD [17]. The risk of PAD in CHC patients undergoing hemodialysis was measured by brachial-ankle pulse wave velocity (baPWV) method, defined as >2100 cm/s. In multivariate logistic regression analysis, HCV infection was significantly associated with an increasing baPWV. Furthermore, patients with a higher viral load exhibited a significant association with PAD risk compared to patients without HCV infection. In addition, CHC patients with genotype-1 infection showed a significant association with baPWV >2100 cm/s compared to non-HCV patients [18].

THE PATHOGENIC MECHANISMS OF HEPATITIS C VIRUS INFECTION LEADING TO CARDIOVASCULAR DISEASE

The mechanisms by which HCV infection contributes to cardiovascular injury are intricate.

Endothelial damage

CHC patients had elevated levels of soluble intercellular adhesion molecule-1 and soluble vascular cell adhesion molecule-1, surrogate markers of endothelial damage. It is particularly in those with advanced liver fibrosis and HCV genotype-1 infection. Successful treatment with interferon-alpha and ribavirin reduced these biomarkers, suggesting that achieving sustained virologic response (SVR) may lower cardiovascular risk in this population [19] [Figure 1].

Hypercoagulability

The pro-inflammatory environment associated with HCV infection promotes a hypercoagulable state. Inflammatory cytokines stimulate the production of clotting factors, increasing the risk of thrombosis. A study compared 3686 patients with newly diagnosed HCV infection to 14,744 individuals without HCV or hepatitis B virus infection. The incidence density rate of deep vein thrombosis in the HCV group was 2-fold higher than the non-HCV group. Nonetheless, no significant difference in the incidence

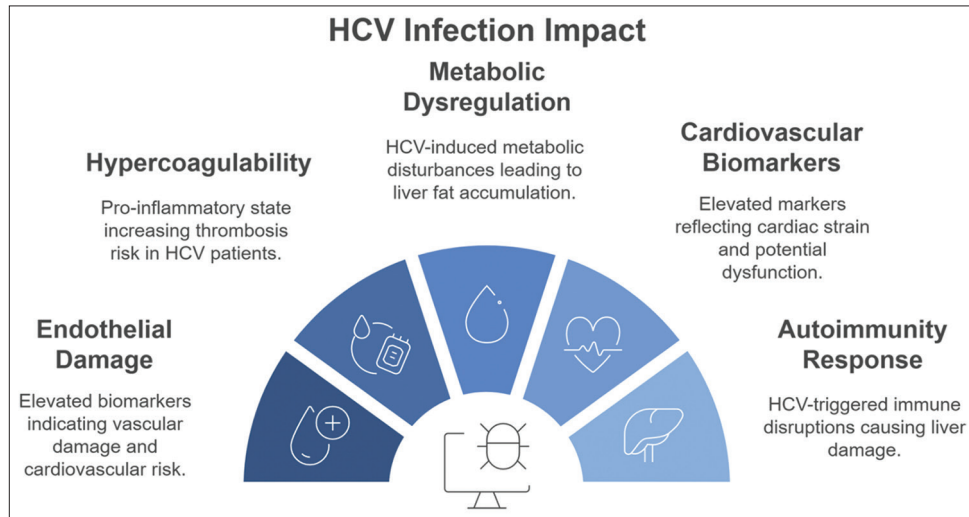


Figure 1: Indirect mechanisms such as endothelial damage, hypercoagulability, metabolic dysregulation, elevated inflammatory and cardiovascular biomarkers, immune response alterations, and hormonal regulation changes contribute to cardiovascular risk in patients with hepatitis C virus infection. HCV: Hepatitis C virus

of pulmonary embolism was observed between the two groups [20] [Figure 1].

Metabolic dysregulation

HCV infection is associated with various metabolic disturbances, including IR, hyperglycemia, and hepatic steatosis [21]. It exerts a significant impact on both hepatic and systemic metabolism through direct interactions of viral proteins as well as indirect metabolic disruptions. Notably, HCV proteins, especially those of genotype 3, promote *de novo* lipogenesis, hinder mitochondrial fatty acid oxidation, and alter the VLDL secretion pathway, ultimately resulting in fat accumulation in the liver. HCV infection indirectly contributes to IR and diabetes, aggravating metabolic dysfunction and promoting hepatic steatosis, inflammation, and fibrosis. These metabolic alterations, further exacerbated by obesity and metabolic syndrome, increase the risk of hepatocellular carcinoma [22]. The combination of these metabolic factors with endothelial dysfunction and inflammation might generate a milieu that favors vascular damage, plaque formation, and plaque instability [22] [Figure 1].

Elevated inflammatory biomarkers

CHC patients had consistently elevated levels of pro-inflammatory biomarkers, such as interleukin-6 and tumor necrosis factor- α . This chronic inflammatory state is believed to play a significant role in the development of atherosclerosis and CVD. Interestingly, levels of C-reactive protein, a common inflammatory marker used to assess cardiovascular risk, often appear paradoxically lower than anticipated in CHC patients. Beyond inflammatory and endothelial markers, CHC patients frequently exhibit elevated levels of cardiac biomarkers, including brain natriuretic peptide, N-terminal pro-BNP, and troponins T and I. These elevated biomarkers of cardiac strain and injury suggested that HCV infection may compromise cardiac function even in the absence of overt symptoms, thereby increasing the risk of CVD. The interplay of these direct and indirect mechanisms, influenced by

both genetic and environmental factors, highlights the complexity of cardiovascular injury associated with HCV infection [2] [Figure 1].

THE PROMISE OF DIRECT-ACTING ANTIVIRALS: A NEW ERA IN HEPATITIS C VIRUS AND CARDIOVASCULAR DISEASE MANAGEMENT

The novel invention of DAAs has enormously changed the landscape of HCV treatment. This shift has redefined HCV management from chronic disease maintenance to a preventative approach focused on mitigating its long-term sequelae, especially CVD.

Direct-acting antivirals reduce cardiovascular disease risk

Numerous studies have demonstrated that treatment with DAAs significantly reduces the risk of CVD events in individuals with HCV infection [23-30]. For example, research by Butt *et al.* reported a 43% reduction in the risk of new-onset CVD events among patients treated with DAAs compared to those untreated counterparts [Table 1]. Another study of 2204 patients with HCV found that achieving viral clearance through DAA therapy significantly reduced the annual incidence of CVD events by 0.68% [28]. A meta-analysis found that antiviral therapy for HCV was linked to a reduced risk of several cardiovascular outcomes, including overall CVD, coronary artery disease, and stroke [31]. Furthermore, attaining SVR was associated with a significantly reduced risk of CVD compared to those who did not achieve SVR (hazard ratio= 0.74, 95% confidence interval: 0.60–0.92) [31]. Another systematic review revealed that, although total cholesterol and LDL-C levels tend to rise following viral eradication, cardiovascular markers such as carotid plaques and intima-media thickness demonstrate improvement. However, changes in liver steatosis, glucose homeostasis, and body weight seem to be closely linked to preexisting metabolic disorders at baseline [32].

Table 1: Summary of key epidemiological and clinical studies investigating the association between hepatitis C virus and cardiovascular disease risk

| Study (Author, year) | Population | Sample size and demographics | Key prognostic factors examined | Study design and follow-up duration | CVD outcomes | Effect estimates (95% CI) |
|-------------------------------------|--------------------------------------|--|---|-------------------------------------|---|---|
| Lee <i>et al.</i> , 2012 [15] | General population | <i>n</i> =19,636; mean age 47.6 years.; Taiwan | HCV RNA detectability | Prospective; long-term (1991–2008) | Circulatory disease mortality | HR=1.53 (1.05–2.23) |
| Wang <i>et al.</i> , 2024 [12] | General population | <i>n</i> =1913; mean age 57.5 years; male (39.3%); Taiwan | Metabolic syndrome; liver fibrosis (FIB4; APRI) | Cross-sectional (2016–2018) | Aortic atherosclerosis (CT calcification, Agatston score) | OR=2.75 (1.48–5.30) |
| Tsai <i>et al.</i> , 2023 [16] | MASLD patients; Taiwan bio-bank | <i>n</i> =154 (with HCV) versus <i>n</i> =7225 (without HCV) | Concomitant HCV infection | Cross-sectional (2008–2022) | Carotid plaque presence | No significant association |
| Wang <i>et al.</i> , 2024 [18] | ESRD on hemodialysis; Taiwan | <i>n</i> =36 (with HCV) versus <i>n</i> =174 (without HCV) | HCV RNA >60,000 IU/mL, genotype-1 | Cross-sectional (2016) | PAD (baPWV >2100 cm/s) | OR=2.67 (1.07–6.68) |
| Butt <i>et al.</i> , 2019 [23] | Veterans with HCV; US | <i>n</i> =17,103 treated/17,103 untreated | DAA treatment | Retrospective cohort | CVD events | HR=0.87 (0.77–0.98) |
| Petta <i>et al.</i> , 2018 [24] | CHC with advanced fibrosis; European | <i>n</i> =182; all treated | DAA treatment | Prospective; 9–12 months | IMT | ↓ IMT from 0.94 mm to 0.81 mm (<i>P</i> <0.001) |
| Wang <i>et al.</i> , 2023 [25] | US-insured HCV patients | <i>n</i> =11,106 treated/39,405 untreated | DAA treatment | Retrospective; 2.3 years | Multiple CVD outcomes | HR=0.76 (0.76–0.87) |
| McGlynn <i>et al.</i> , 2019 [26] | US health system HCV patients | <i>n</i> =15,524 treated/18,284 untreated | DAA treatment | Retrospective (2012–2017) | Arrhythmia, AMI | OR=0.47 (0.25–0.88); OR=0.81 95% CI (0.30–2.20) |
| Lam <i>et al.</i> , 2023 [27] | French cohort HCV patients | <i>n</i> =7037 treated/7081 untreated | DAA treatment | Retrospective; 4.3 years | PAD, arrhythmia | HR=0.54 (0.33–0.89); HR=1.46 (1.04–2.04) |
| Casas-Deza <i>et al.</i> , 2023 [5] | HCV-infected, DAA-naive | 83; Spain | HOMA-IR, TG/HDL-TG, lipoprotein profile | Prospective; 1 year | Surrogate: IR, TG | ↓ HOMA (22%), ↓ HDL-TG (18%) |
| Butt <i>et al.</i> , 2017 [6] | HCV+and HCV–men | 85,863; USA | Lipid levels, HCV status | Retrospective; not stated | AMI | HRs ↑ with LDL/TC; lipid-lowering ↓ AMI risk (HR from 1.82 to 1.19 in HCV+) |
| Adinolfi <i>et al.</i> , 2020 [28] | HCV patients pre/post-DAA | 2204; Italy; median age 68 | Fibrosis, HTN, DM, lipids | Prospective; median 28 months | IHD, ICS | ↓ CV events: RR 0.379; HR 3.671; OR 4.716 |
| Huang <i>et al.</i> , 2017 [29] | CHC patients receiving DAAs | 65; Taiwan; mean age 59.8; 29% male | HOMA-IR, beta-cell function | Prospective; end-of-follow-up | Surrogate: HOMA-IR, beta-cell function | HOMA-IR unchanged; β-cell function improved (<i>P</i> =0.05); 60% prediabetics normalized |
| Huang <i>et al.</i> , 2020 [30] | CHC patients achieving SVR | 617; Taiwan; mean age 62.1 | LDL-C, total cholesterol, smoking | Prospective; mean 26.8 months | Cardio-cerebral disease (e.g., stroke, cardiac events) | LDL-C ↑ post-SVR; LDL-C surge >40% → HR 15.44 (95% CI: 1.73–138.20, <i>P</i> =0.014); age and smoking predicted ↑ cholesterol |

CKD: Chronic kidney disease, CHC: Chronic hepatitis C, CVD: Cardiovascular disease, ESRD: End-stage renal disease, HR: Hazard ratio, HOMA-IR: Homeostatic model assessment-insulin resistance, IMT: Intima media thickness, LDL-C: Low-density lipoprotein cholesterol, PAD: Peripheral artery disease, SVR: Sustained viral response, CI: Confidence interval, HCV: Hepatitis C Virus, DAAs: Direct-acting antivirals, HTN: Hypertension, DM: Diabetes mellitus, TG: Triglycerides, OR: Odds ratio, AMI: Acute myocardial infarction, RR: Risk ratio, baPWV: Brachial-ankle pulse wave velocity, IHD: Ischemic heart disease, ICS: Ischemic coronary syndrome, FIB: Fibrosis, ↑: increase; ↓: decrease

Direct-acting antivirals improve endothelial function

A previous study assessed intima-media thickness, carotid thickening, and the presence of carotid plaques through ultrasonography at baseline and 9 months after DAA therapy. A significant reduction in mean intima-media thickness was noted from baseline to follow-up, indicating that HCV eradication had a beneficial impact on carotid atherosclerosis,

independent of other metabolic risk factors [24] [Table 1]. Flow-mediated dilation, a recognized CVD risk marker, serves as an accurate and noninvasive method for assessing endothelial function. Flow-mediated dilation and postischemic hyperemia significantly improved after successful HCV eradication, suggesting a sustained enhancement in endothelial function. However, it is noteworthy that changes

in flow-mediated dilation were not statistically significant among patients with cirrhosis [33]. There were significant reductions in endothelium-derived adhesion molecules, including E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1. These findings suggest that DAA treatment enhances endothelial function by reversing HCV-induced endothelial damage [34].

In vitro studies on HCV replicon-carrying cells treated with sofosbuvir for HCV clearance demonstrated that sofosbuvir treatment significantly improved insulin sensitivity. The observation in HCV-infected hepatocytes was evidenced by enhanced phosphorylation of Akt and its downstream targets, Foxo1 and GSK3 β [35]. This effectively reversed IR, as demonstrated by the reduction in gluconeogenic gene expression, decreased glucose production, and improved glycogen synthesis that had been impaired by HCV infection [35].

However, several other large cohort studies have somewhat discordant results regarding cardiovascular outcomes. The discordant findings regarding arrhythmia risk post-DAA therapy underscore the importance of considering methodological variability when interpreting cardiovascular outcomes. Differences in follow-up duration, population selection, baseline cardiovascular risk, and data sources may significantly influence the observed associations. These findings highlight the need for further prospective, mechanistic studies to better characterize arrhythmia risk in HCV patients undergoing antiviral therapy and to guide appropriate cardiovascular surveillance strategies.

Clinical implications of metabolic shifts following hepatitis C virus eradication

Following SVR after DAA therapy, patients often experience notable metabolic shifts. These include increases in LDL-C and total cholesterol [30], alongside improvements in glucose metabolism [29]. The rise in LDL-C post-SVR may theoretically elevate cardiovascular risk, especially in patients with preexisting metabolic syndrome or atherosclerotic disease. A recent prospective multicenter study demonstrated an annual reduction in the incidence of cardiovascular events by 0.68% following HCV eradication. These findings suggest that HCV clearance through DAA therapy is associated with a decreased risk of cardiovascular events [28]. These divergent metabolic effects necessitate a nuanced approach to post-SVR care. Clinicians should consider reassessing cardiovascular risk profiles in patients who achieve SVR, incorporating lipid and glycemic parameters into long-term follow-up. This may warrant the initiation or adjustment of lipid-lowering therapies, lifestyle interventions, or glucose-lowering agents, tailored to the individual's overall cardiovascular risk.

Assessment of atherosclerosis in chronic hepatitis C

Coronary artery calcification (CAC) and aortic calcification, typically evaluated through CT [36], provide quantitative and reproducible assessments of calcified plaque burden in the coronary and aortic arteries. These imaging modalities are considered reliable indicators of subclinical atherosclerosis, with CAC scoring being widely validated. Several studies have demonstrated an association between HCV infection and increased CAC, suggesting a potential link to subclinical

atherosclerotic disease. Carotid intima-media thickness assessment with plaque detection by carotid ultrasound offers additional insights into atherosclerotic burden. Emerging evidence from prospective cohort studies supports the presence of carotid plaques as a robust, independent predictor of ASCVD, offering incremental value when added to conventional risk prediction models [37].

It is important to note that the studies cited in this review employed varied methodologies to assess atherosclerosis – including coronary and aortic calcification via CT, carotid intima-media thickness and plaque detection via ultrasound, and clinical cardiovascular endpoints – each with differing sensitivities and specificities. This variability may influence the comparability and interpretation of the reported associations between HCV and atherosclerotic disease.

Challenges remain after hepatitis C virus eradication and cardiovascular disease management

While DAAs improve most CVD risk factors, they have been associated with an increase in LDL-C levels, potentially increasing the risk of CVD development [30]. HCV-induced epigenetic signaling and gene expression changes may persist even after viral eradication, potentially contributing to a continued risk of liver disease progression and hepatocellular carcinoma [38]. CHC patients are prone to develop SLD and express cardiometabolic risk factors (CMRFs). Whether HCV eradication mitigates MASLD status is elusive. Despite the decrease in glycated hemoglobin (HbA1C) and body mass index (BMI) and the increase in HDL-C and triglycerides after HCV eradication, the proportion of MASLD did not alter significantly. A lower BMI was the factor associated with MASLD resolution. In contrast, unfavorable CMRFs including a higher BMI, LDL-C, and HbA1C level were independently associated with MASLD emergence after HCV cure. CMRF surveillance is mandatory for CHC patients with metabolic alterations, which are altered after HCV cure and predict the evolution of MASLD [21].

CONCLUSION

HCV infection is closely linked to IR and various metabolic disturbances, contributing significantly to both hepatic and extrahepatic disease burden. The advent of DAAs has markedly improved liver-related outcomes and reduced cardiovascular risk, marking a new era in the integrated management of HCV and CVD. While current screening recommendations advocate for universal HCV testing in adults, most major cardiology and hepatology societies have yet to identify patients with CVD as a priority population for HCV screening. Recent guidelines from major society of hepatology indicated that post-SVR care should include an assessment of cardiovascular risk factors, accompanied by appropriate counseling, ideally delivered by general practitioners [39]. Meanwhile, the 2024 Guidelines of the Taiwan Society of Cardiology on the Primary Prevention of Atherosclerotic Cardiovascular Disease highlight that certain inflammatory and infectious conditions relevant to ASCVD are preventable. These include hyperuricemia with gouty arthritis, periodontitis, HCV infection, and HIV infection, all of which should be managed in accordance with the respective guidelines issued by relevant medical societies [37].

In light of accumulating evidence linking HCV infection to CVD, future consensus guidelines should consider categorizing patients with CVD as a high-risk group warranting targeted HCV screening. Further prospective studies are essential to assess the long-term cardiovascular benefits following SVR and to promote equitable access to DAA therapy among all at-risk populations.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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