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Viral infections in cardiometabolic risk and disease between old acquaintances and new enemies

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Abstract

Atherosclerosis is a chronic disease, characterized by chronic inflammation, endothelial dysfunction, and lipid deposition in the vessel. Although many major, well-identified risk factors for atherosclerosis [e.g., hyperlipidemia, hypertension, type 2 diabetes (T2D), smoking habit, and obesity] explain a lot about the risk, there is a considerable number of patients who develop atherosclerotic damage and undergo adverse events without presenting any of these established modifiable risk factors. This observation has stimulated an urgent need to expand knowledge towards the identification of additional, less established risk factors that may help in the assessment of risk and fill the gap of knowledge in the cardiovascular (CV) setting. Among them, the hypothesis of a possible relationship between viral infectious agents and atherosclerosis has risen since the early 1900s. However, there is still a great deal of debate regarding the onset and progression of CV disease in relation to the roles of the pathogens (as active inducers or bystanders), host genomic counterparts, and environmental triggers, affecting both virus abundance and the composition of viral communities. Accordingly, the aim of this review is to discuss the current state of knowledge on infectious agents in the atherosclerotic process, with particular focus on two environmental-related viruses, as examples of familiar (influenza) and unfamiliar [severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)] disease triggers.

Keywords

Atherosclerosis, type 2 diabetes, viral infection, severe acute respiratory syndrome coronavirus-2, cardiometabolic risk, cardiometabolic disease, ischemic heart disease, non-traditional cardiovascular risk factors

Introduction

Atherosclerosis belongs to the group of chronic degenerative diseases, conditions that affect the subject for a long period or for a lifetime with a progressive deterioration over time, degenerating and causing multi-organ and multi-system damage, which may lead to death [1]. The atherosclerotic process is characterized

by chronic inflammation, endothelial dysfunction, and lipid deposition in the vessel [1]. Many major modifiable risk factors for atherosclerosis [e.g., hyperlipidemia, hypertension, type 2 diabetes (T2D), smoking habit, and obesity] explain a lot about the risk, and associated therapies adequately account for the significant reduction in cardiovascular (CV) disability and mortality in high-income countries [2]. Nonetheless, a considerable subset of patients remains, who develop atherosclerotic damage and undergo adverse events, exhibiting distinct risk profiles that either do not include any of these established modifiable risk factors or are poorly explained by traditional risk factors [3, 4]. This observation has stimulated an urgent need to expand our knowledge of less established risk determinants, whose identification may supplement the burden of the risk factors and/or evidence of special causal relevance in specific patient subsets [5, 6]. Among them, a possible relationship between viral infectious agents and atherosclerosis has been proposed since the early 1900s, when Osler included acute infection among the main factors that may cause atherosclerosis [acute infection, stress, intoxication (as T2D, obesity, or smoking habit)], while Frothingham identified the sclerosis of aging as a sum of lesions induced by infectious and metabolic toxins [7, 8]. However, it was in the late 1970s that the first convincing proof-of-concept was obtained, demonstrating that the Marek virus (an avian herpes virus) is able to induce fibroproliferative, lipid-laden atherosclerotic damage, and to generate a thrombus in normocholesterolemic chickens [9]. Since then, several seroepidemiological studies have shown that lasting infections (bacteria or viruses) may be linked to the onset and development of atherosclerotic lesion [10].

In general, the identification of direct and indirect mechanisms that microorganisms use to elicit chronic inflammation, the presence of an infectious agent in human atherosclerotic tissue, as well as the evidence of atherosclerosis quickening following infection in animal models of atherosclerosis, and the number of infectious agents found associated with CV disease (CVD; e.g., *Chlamydia pneumoniae* [11], periodontal disease infections [12], human immunodeficiency virus (HIV) [13], cytomegalovirus (CMV) [14], hepatitis C virus (HCV) [15], *Helicobacter pylori* [16], herpes simplex virus (HSV) types 1 and 2 [17] hepatitis A virus [18], hepatitis B virus (HBV) [19] and gut microbiota [20]) all suggest biological plausibility.

However, there is still a great debate regarding the onset and progression of CVD on the roles of the pathogens as active inducers or bystanders, host genomic counterparts, and environmental triggers affecting virus abundance and the composition of viral communities. Accordingly, this review aims to address the current state of knowledge about infectious agents and their role in atherosclerosis, including some examples and a special emphasis on two environmental-related viruses as examples of old acquaintances (influenza) and new enemies [severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)].

Action modes of infectious agents: differences and similarities

Microorganisms, in general, use a number of common direct or indirect strategies to trigger immunological and oxidative/inflammatory responses [e.g., increased expression of pro-inflammatory and prothrombotic cytokines including tumor necrosis factor (TNF)-α, interferon (INF)-γ, interleukin (IL)-6, IL-1β, proatherogenic factors as TLR2, TLR4, adhesion molecules, lectin-like oxidized low-density lipoprotein (oxLDL) receptor-1 (LOX-1), heat shock protein 60 (Hsp60) and monocyte chemoattractant protein-1 (MCP-1)], generate macrophage-derived foam cell generation, and increase proliferation while inhibiting apoptosis of smooth muscle cells (SMC) [21]. A direct effect of an infectious agent is represented by its ability to infect vascular cells, the detection of the organism within the plaque, and the acceleration of lesion formation following infection in experimental atherosclerosis models, as well as the demonstration of the efficacy of anti-infective therapies either in the reduction of atherosclerotic lesions or in the improvement of CV outcomes [21]. In contrast, an indirect action of infectious agents caused by infection and inflammation at a non-vascular site can accelerate atherosclerosis. Compliance with these criteria defines the degree of the individual infectious agent's function in the atherosclerotic process, ranging from stronger to weaker [21].

Moreover, each specific infectious agent may possess specific peculiar mechanisms for acting on the progression of atherosclerotic lesions. For example, *Helicobacter pylori* induced gastritis (with increased gastric juice pH and/or decreased ascorbic acid) and folate inadequate status [22], which in turn inhibits the methionine synthase with elevation of homocysteine, causing adverse effects on endothelial function and promoting atherosclerosis [22]. Specific inflammatory/atherogenic gene expression pathways in the aortic tissue of apolipoprotein E (apoE)$^{-/-}$ mice were induced by exposure to different pathogens, such as *C. pneumoniae* and *P. gingivalis* [23]. However, some differences were observed: *P. gingivalis* may reduce mitochondrial expression, glucose metabolism, and peroxisome proliferator-activated receptor (PPAR) pathways, whereas *C. pneumoniae* may, on the other hand, increase mitochondria expression, lipid metabolism, carbohydrate and aminoacid metabolism, and PPAR pathways [23].

Some examples of action modalities (direct and/or indirect effects and identification of the agent in the atherosclerotic plaque) of common viruses, which have been related to atherosclerosis onset and development, are discussed below and reported in Table 1.

HIV

The HIV was first isolated and identified in the early 1980s. It targets and damages especially the immune system: at the end of 2021, it has been estimated, indeed, that more than 38 million people were infected by HIV, which also induced the deaths of more than 40 million people around the world [24]. Although the development of therapies has contributed to longer life expectancy in patients who have benefited from them, however, there has been an increase in comorbidities, so that atherosclerotic CVD currently represents one of the major causes of morbidity and mortality for people living with HIV (PLWH) [25].

Among the underlying mechanisms linking HIV and atherosclerosis, it is well known that the activity of monocytes and macrophages, as well as macrophages cholesterol mechanisms, are dysregulated by HIV infection. These cells, which play a critical role in the development of the plaque in the subendothelial layer, support, indeed, HIV replication, and remain chronically infected [26]. Moreover, HIV Nef protein, which promotes viral replication and immune escape, may directly affect endothelial functions and gene expression in human pulmonary artery endothelial cells, reducing endothelium-dependent vasorelaxation in porcine pulmonary arteries [27]. Additionally, *in vitro* studies reveal a certain permissiveness for HIV by endothelial cells, which thus could serve as a viral reservoir [28].

Some viral proteins, such as Tat, Nef, Vpr, and glycoprotein 120 (gp120), are involved in indirect HIV effects, such as elevation of pro-inflammatory cytokines and oxidative stress [29, 30]. In particular, Tat, which controls HIV transcription, is able to induce not only oxidative stress [reactive oxygen species (ROS) generation, lipid peroxidation], but also the expression of vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule 1 (ICAM-1), as well as to lower antioxidants (e.g., glutathione-GSH) [30–34]. With regards to Nef protein, it increases superoxide release, also by decreasing endothelial nitric oxide (NO) synthase (eNOS) expression and NO release [25, 35–37], while Vpr protein promotes cell-cycle arrest, induces DNA damage and apoptosis, and modulates nuclear factor-kappa B (NF-κB) activity; Vpr is also able to reactivate viral production in latently infected cells by releasing ROS and the pro-inflammatory cytokine IL-6 [38–40]. Instead, gp120, a surface protein that facilitates HIV entry into the host cell, may promote apoptosis and induce the release of endothelin-1 (ET-1, endothelial vasoconstrictor peptide) [41–43]. Recent data also support the role of HIV-1 infection as an activator of the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome, which contributes to the risk of developing atherosclerosis [44]. Moreover, HIV-related immune dysregulation may also be proatherogenic [45], while HIV itself may affect the adipose tissue: adipocytes may, in fact, be involved in the immune response to HIV, act as HIV reservoirs, produce proinflammatory molecules and alter the lipid profile (e.g., enhancing the risk of hypertriglyceridemia); HIV can also be responsible for microbiota dysbiosis and microbial translocation from the intestinal tract into the blood (with chronic immune activation, hypercoagulability, and prothrombotic effects) [46–50]. Furthermore, HIV has been identified among diabetogenic viruses, as Nef protein inhibits glucose uptake after exposure in adipocytes [by interfering with glucose transport 4 (GLUT4)] and contributes to insulin

Table 1. Main common and specific virus mechanisms and complications related to the increased risk of atherosclerosis

Infectious agent	Main mechanisms and pathways involved	Main CV complications
HIV	- Presence in the atherosclerotic lesion	- AMI
	- Systemic inflammation/oxidative stress	- High prevalence of traditional CVD risk factors
	- Immunity ($CD4^+$ cell depletion)	- Carotid atherosclerosis
	- Opportunistic infections	- Carotid stiffness
		- HF
		- Myocardial fibrosis
		- T2D
		- cART-related adverse cardiometabolic effects
HSV-1 and -2	- Presence in the atherosclerotic lesion	- CV mortality
	- Systemic inflammation/oxidative stress	- CAD
	- Endothelial dysfunction	- AMI
	- Apoptosis	- Stroke
	- Procoagulant effects	- Carotid atherosclerosis
CMV	- Presence in the atherosclerotic lesion	- Carotid atherosclerosis
	- Systemic inflammation/oxidative stress	- CAD
	- Host immune response	- AMI
	- Endothelial dysfunction	- Stroke
	- Lipid dysregulation and lipid deposition, vascular SMC proliferation and migration	- T2D
	- Procoagulant effects and increased prothrombotic risk	
HCV	- Presence in the endothelial cells and atherosclerotic lesion	- CV mortality
	- Systemic and local arterial inflammation/oxidative stress	- Carotid atherosclerosis
	- Host immune response	- CAD
	- Liver iron deposition	- Dysrhythmias
	- Metabolic disarrangement	- HF
	- Cryoglobulinemia	- AMI
		- Cerebrovascular disease
		- Myocarditis and Cardiomyopathies
		- T2D
Influenza	- Presence in the endothelial cells and atherosclerotic lesions	- CV mortality
	- Systemic and local arterial inflammation/oxidative stress	- AMI
	- Hypercoagulability	- T2D
	- Fever, tachycardia, hypoxia-induced injury	
SARS-CoV-2	- Direct viral entry through ACE2 receptor (e.g., cardiomyocytes, fibroblasts, endothelial cells)	- HF
	- Systemic inflammation/cytokine storm	- Ventricular hypertrophy
	- Hypercoagulability, thrombosis	- Ventricular dilation
	- Local inflammation (myocardial inflammation-myocarditis, cardiac fibrosis, myocyte apoptosis)	- AMI
	- Plaque destabilization	- Fibrosis
	- Stress, anxiety, psycho-emotional status	- Myocarditis
	- Hypoxia-induced injury (myocardial oxygen demand/supply mismatch)	- T2D
	- Endothelial dysfunction	
	- Catecholamine stress response	

CAD: coronary artery disease; AMI: acute myocardial infarction; ACE: angiotensin-converting enzyme; cART: combined antiretroviral therapy; HF: heart failure

resistance (IR) [51]. Although PLWH can nowadays achieve a near-normal life expectancy, mainly thanks to the development of highly efficient cART, these pharmacological tools may, however, contribute to enhancing endothelial dysfunction and CV disease adverse events (e.g., exacerbation of CV risk factors, inflammation, and leptin-mediated reduction of NO bioavailability), although this applies more to the old drugs than to the new ones [52–54].

Subjects affected by HIV show a prevalence of CV risk factors, and higher risk and occurrence of CAD and heart failure (HF) [55]. In particular, AMI is the most common clinical complication in HIV patients, with a higher incidence compared to the general population [56, 57]. The pathogenesis of AMI during HIV infection is multifactorial and primarily influenced by the interaction between host CV risk factors, together with HIV infection and ART [57]. Male gender, viral load of HIV, low CD4 count, higher CD8 count, and types of ART are indeed among the risk factors linked to AMI in HIV patients [57]. Moreover, CV mortality, carotid artery atherosclerosis as well as increased carotid vessel wall stiffness, HF, and myocardial fibrosis have been associated with HIV [58, 59].

Experimental models also suggest that HIV may accelerate the atherosclerotic process, thus underlying the importance of caspase-1 and monocyte/macrophage activation and IL-18 elevation in HIV atherogenesis [60, 61]. Moreover, studies demonstrated that LOX-1 and VCAM-1 gene expression are increased in aorta as well as soluble ICAM-1(sICAM-1) blood levels in HIV-1 transgenic rats, suggesting HIV infection as a source and promoter of endothelial dysfunction and accelerated atherosclerosis [62].

HSV (human herpesvirus 1 and 2)

HSV is responsible for a very common infection affecting the mouth, genital area, or other parts of the body. The relationship between HSV and atherosclerosis has been reported since the beginning of the '90s, although it is still greatly debated [63]. Both types of HSV can be either present or absent in atherosclerotic plaques [64–66] and HSV-1 was not found in normal artery sites [67]. Moreover, HSV-infected endothelial cells express the adhesion molecule granule membrane protein-140 (GMP140), which may contribute to the recruitment and migration of blood cells to initiate and develop atherosclerotic lesions [68]. HSV infection may increase the expression of LOX-1 and the uptake of ox-LDL hence exacerbating cellular apoptosis [69, 70]. This infection also activates procoagulant changes, alters lipid metabolism, and promotes inflammation [71–75]: experimental data indicate that atheroma development is accelerated in infected apoE$^{-/-}$ mice compared to control uninfected apoE$^{-/-}$ mice (24-week period), effect that may be reduced by antiviral drugs [72].

A meta-analysis (17 studies) also suggests that HSV-1 and HSV-2 infection could increase the risk of atherosclerosis (considering myocardial ischemia, and other types of atherosclerosis as stroke and carotid atherosclerosis) [17], while, in another study based on 14,415 subjects, HSV-2, rather than HSV-1, was associated with premature CVD [76].

CMV (human CMV, human herpesvirus 5)

CMV, part of the herpesvirus family, causes a widespread and very common infection, characterized by a wide range of severity (from no symptoms to fever and fatigue to severe complications in the eye, brain, or other organs). This virus was found to be expressed in carotid plaques and it may contribute to the inflammatory response in plaques via enhanced infiltration of CD68 and CD3 cells [77]. CMV infection elicits inflammatory and immune responses [e.g., IL-6, high-sensitivity C-reactive protein (CRP), fibrinogen, and secretory phospholipase A2, increase in memory T-cells]. It also triggers endothelial dysfunction, lipid dysregulation and deposition, proliferation, and migration of vascular SMC (e.g., through modulation of metalloproteinase 9), coagulation, and increased prothrombotic risk (e.g., increasing the production of thrombin and making endothelial cells more responsive to thrombin stimulation), upregulation of adhesion molecules [78–85]. Interestingly, murine CMV infection increases aortic expression of proatherosclerotic genes [p38, extracellular signal-regulated kinase1/2 mitogen-activated protein kinase (ERK 1/2 MAPK), VCAM-1, ICAM-1, and MCP-1], whereas inhibition of p38 (SB203580) decreases pro-atherogenic molecules and CMV viral load in aortas of infected mice [85]. The virus has also been associated with endothelial dysfunction, AMI, coronary and peripheral atherosclerosis, and stroke [86–88].

Different evidence showed increased antibody positivity in patients at risk of atherosclerosis, as well as the number of plasma virus-DNA copies in patients with acute coronary syndrome compared to controls [89–92]. Moreover, the presence of CMV-DNA in atherosclerotic plaques has been commonly found [93, 94]. However, negative data are also available, showing the lack of association between antibody titers and atherosclerosis, and highlighting the presence of the virus in non-atherosclerotic sites [65, 95–97].

HCV

HCV remains one of the major causes of chronic liver disease, with 58 million HCV infections worldwide, about 1.5 million new HCV infections/year, and 290,000 deaths from HCV infection in 2019 [World Health Organization (WHO) data] [98]. HCV is also associated with several extrahepatic conditions, so the definition of liver-localized disease is superseded by the concept of systemic disease, which can involve a variety of extrahepatic complications [99]. In particular, emerging results highlight the relationship between HCV infection and CV risk factors, subclinical and clinical atherosclerosis (e.g., T2D, alterations of the lipid profile, carotid atherosclerosis, cerebrovascular events, stable coronary heart disease, and acute coronary events), as well as the biological plausibility of this association (especially when considering inflammatory and immune-related responses and metabolic alterations elicited by the virus) [100]. However, data are often contradictory and still widely discussed [101] as reported in the following paragraphs.

Potential mechanisms linking HCV to atherosclerosis

Endothelial cells are permissive to HCV infection in culture, an event that may lead to endothelial dysfunction and trigger the early atherogenesis process [102]. As a result, HCV clearance improved not only liver function, but also endothelial dysfunction and subclinical atherosclerosis (improvement of the ankle-brachial index, decrease in VCAM, e-selectin, endothelial and platelet apoptotic microparticles, and cell-free DNA) [103]. In fact, in addition to the identification of HCV in the carotid lesion, an indicator of the direct replication of the virus within the arterial wall, HCV^+ was associated with intima-media thickness (IMT), strengthening the concept of a local pro-atherogenic effect of the virus at the atherosclerotic lesion level [104].

Actually, the virus may contribute to atherosclerosis through different mechanisms, including the enhancement of inflammation and oxidative stress (e.g., by increasing TNF-α and IL-6, activation of toll-like receptors associated with pro-inflammatory cytokines, endoplasmic reticulum stress), both at liver and systemic levels [105–110]. Chronic HCV infection may significantly trigger alterations in biomarkers of inflammation (e.g., CRP, IL-6, and TNF-α) and endothelial function (e.g., sICAM-1, sVCAM-1), but also cardiac dysfunction [e.g., on the N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponins]; HCV therapy may improve some of these alterations [111].

Furthermore, HCV has been related to IR and T2D, mainly through mechanisms that include direct viral effects, elevation of proinflammatory cytokines, and immune-mediated responses [112]. In particular, HCV core protein expression induces hepatic IR by altering the signaling pathway of the insulin receptor substrate (IRS)-1 and -2 through direct and indirect effects (respectively, proteasomal degradation and increased levels of proinflammatory cytokines, such as TNF-α) [113]. Moreover, in HCV patients, IR is correlated with inflammatory markers like ferritin [114]. Increased levels of hepatic iron and copper, which are associated with chronic HCV, are hepatotoxic and contribute to increased oxidative stress, while zinc reduction (as zinc inhibits viral replication) may, in turn, increase the systemic inflammatory response [115]. In this context, different data demonstrate that Zn, thanks to its several properties (e.g., immune, antioxidant, anti-inflammatory, and antiviral capacities), may be beneficial for HCV patients [115–119].

HCV core protein induces changes in the cellular redox state [decreasing the oxidized and reduced forms of nicotinamide adenine dinucleotide (NAD^+/NADH ratio)] and affects the sirtuin-1/AMP-activated protein kinase (SIRT1/AMPK) pathway, thus modifying the expression of glucose and lipid metabolism-related genes, and, as a consequence, inducing metabolic dysregulation at liver level [120]. In particular, this lipids disarrangement [e.g., increase in lipid biosynthesis, hepatic levels of triglycerides, cholesterol

esters, and sphingolipids, but also reduction of mitochondrial oxidation, lipid degradation, and apolipoproteins export, in particular very-low-density lipoproteins (VLDL)] lead to circulatory hypo-cholesterolemia and hypo-lipoproteinemia, steatosis and lipotoxicity [121, 122]. Steatosis is in turns a well recognized CV risk factor, as it promotes IR, adiponectin elevation, metabolic syndrome, oxidative stress, hyperhomocysteinemia, and TNF-α [122–125]. Clearly, alteration in the lipid asset may also be secondary to worsened liver function induced by HCV, in addition to direct HCV effects.

Cryoglobulinemia (reversible precipitation of mixed-immunoglobulin at body temperatures lower than 37°C) has been strongly associated with HCV infection, and may exacerbate systemic inflammation and organ damage at different levels (e.g., kidney, liver, vasculitis) [126].

Carotid atherosclerosis, CAD, cerebrovascular disease, myocarditis, and cardiomyopathies related to HCV

In the early 2000s, HCV-seropositivity was identified to be correlated to an increased risk of carotid plaque and carotid intima-media thickening (4,784 subjects enrolled, 2.2% HCV^+) providing the first evidence of the atherogenic potential of this virus [127]. The same authors also demonstrated that circulating HCV core protein is a strong, independent predictor of carotid plaques in a large general population (1,992 subjects) [128]: since then, several attempts have also been performed in other large populations, but with results that alternately support or debunk the link between HCV infection and CVD, indicating a higher, null, or even lower risk in HCV patients [129–131]. In this context, a meta-analysis was performed to better define this relationship: the obtained results showed a higher risk of carotid plaques in HCV-infected patients compared to controls (OR, 2.27; 95% CI, 1.76–2.94; $P < 0.001$), without significant heterogeneity between studies [15]. Similar results were obtained when IMT, instead of carotid plaques, was considered as the outcome [15]. Interestingly, the significance of HCV infection on the presence of carotid plaques was influenced by smoking habits and was particularly strong in groups with a high prevalence of smokers [15]. A different meta-analysis study (5 studies) shows that the risk of developing carotid intimal media thickening or a carotid plaque in a subject with chronic hepatitis C is approximately four times higher than in an uninfected person [132]. Another recent meta-analysis (consisting of 341,739 people with HCV infection included in 36 studies from 51 countries) showed that HCV infection is associated with an increased risk of myocardial infarction, stroke, and vascular mortality, with values corresponding to 1.13 [95% confidence intervals (CI) 1.00–1.28], 1.38 (1.19–1.60), and 1.39 (1.24–1.55), respectively [133]. The authors also showed that the global burden of CVD associated with HCV infection is responsible for 1.5 million disability-adjusted life-year (DALYs; due to ischaemic heart disease and stroke), with the highest burden in low- and middle-income countries (regions in South Asia, Eastern Europe, North Africa, and the Middle East account for two-thirds of all HCV-associated CV DALYs) [133]. In fact, beyond carotids, many studies suggest that HCV infection can also increase CAD (as well as cerebrovascular disease and stroke). This effect was hypothesized when HCV^+ was found to be associated with the presence of CAD, which remained significant even after correction for cardiometabolic risk factors, and which was associated with the severity of disease (number of diseased vessels) [134]. Many further investigations have confirmed this link, whereas others have found no significant relationship [135–137]. As a result, the balance of these data ranges widely from no correlation to a favorable relationship. However, when analyzed in aggregate form in a meta-analysis (297,613 HCV patients, 557,814 uninfected controls), these results indicate an increased risk of CAD associated with HCV infection (20 studies, OR: 1.382; 95% CI: 1.103, 1.732) [138]. Similar results were confirmed in a meta-analysis of 10 studies, which showed a tripled risk of developing coronary atherosclerosis for HCV-positive patients when compared to non-infected subjects [139].

Notably, HCV-related damage to the kidney may impact CV diseases and outcomes, as an increased risk of kidney disease has been observed in various groups of HCV^+ patients [140, 141]. Several studies have also considered the potential association between HCV infection and cerebrovascular events, finding contradictory results, ranging from HCV infection as a risk factor to HCV infection as a protective factor [142–144]. Despite the heterogeneity found among the studies included in a meta-analysis (made up of six studies, five retrospective and one prospective) published in 2013, results suggested that HCV infection increases the risk of stroke; with a random-effects model, the outcome was 1.58 (0.86, 2.30), which was

improved after excluding the study that caused the heterogeneity, with a pooled odds ratio (OR) with a 95% CI equating to 1.97 (1.64, 2.30) [145]. A second meta-analysis, which included 8 studies, found that HCV-infected subjects kept an increased risk of cerebro-CV events (OR, 1.30; 95% CI, 1.10–1.55; $P < 0.01$) than uninfected subjects, with a stronger impact in those with higher CV risk (e.g., high incidence of T2D or hypertension) [15]. This trend was confirmed in a further meta-analysis (13 studies) where a higher risk of cerebrovascular disease was reported in HCV patients than in uninfected controls (OR: 1.485; 95% CI: 1.079, 2.044) [138]. Actually, a link between chronic HCV infection and altered cerebrovascular reactivity, measured by transcranial color Doppler for measurement of blood flow velocity, has been found, which may have adverse consequences on cerebrovascular hemodynamics and may also lead to increased risk of cerebrovascular diseases [146]. Interestingly, recent data have shown that HCV infection increases the risk of developing CAD or cerebrovascular disease in patients with hepatocellular carcinoma, pointing to the importance of atherosclerosis prevention in this specific group of patients [147].

Myocarditis and subsequent cardiomyopathy can be triggered by several viruses, including HCV, which has been associated with both dilated cardiomyopathy (DCM; characterized by ventricular dilation and impaired contraction) and hypertrophic cardiomyopathy (HCM; characterized by increased ventricular wall mass not due to volume overload) [100]. Indeed, the virus genome has been detected within heart tissue biopsies from patients with myocarditis and DCM or HCM, suggesting a causal link [148, 149]. Among the possible mechanisms underlying this relationship, immune system activation, cardiac inflammation, and viraemia have been identified as the main HCV-related indirect factors associated with inflammatory myocarditis [150].

CV mortality and HCV

Interestingly, a higher mortality due to CV diseases was observed in more than 10,000 HCV-positive blood donors [151]. However, this relationship was not confirmed by other studies, such as in the analysis of a very large Australian population (30,000 subjects; although the particular enrolled population, which consisted of subjects with opioid dependence) [152]. Thus, these controversial results still make the association of HCV with mortality widely discussed and not sure yet. However, when the data are considered as aggregate in meta-analysis approaches, evidence of increased CV mortality due to HCV infection emerges. In fact, a meta-analysis including three cohort studies (68,365 patients, 735 deaths) showed an increased risks of CV-related mortality (OR: 1.65, 95% CI: 1.07–2.56; $P = 0.02$) in HCV infected patients, despite showing significant heterogeneity ($I^2 = 76\%$; $P < 0.05$) and the lack of consideration of important covariates (e.g., CV risk factors) [15]. Moreover, another meta-analysis including 574,081 patients on long-term dialysis confirmed an increased risk of CV mortality in HCV^+ individuals compared with HCV^- controls [153].

Interestingly, chronic HCV patients treated with direct-acting antivirals (DAA) experienced lower rates of CV events and all-cause mortality than those without treatment [154]. This finding is of particular interest, especially in view of the development of new DAA, which has profoundly simplified and improved HCV treatment for many more patients, and may lower CVD morbidity and mortality in chronic HCV patients.

HCV relevance in specific subset of patients: the case of thalassemia major

HCV infection may be more critical in subsets of patients at high risk of infection, such as thalassemic patients (due to frequent transfusions), where the virus may represent a strong accelerator of thalassemia major (TM) complications [155]. In fact, even though donor screening control reduces the likelihood of new infections, especially in Western nations where the risk of new cases is actually minimized, the elderly remain more vulnerable to the long-term consequences of previous chronic infection [156]. Nonetheless, in many other less-developed countries, patients with TM continue to contract HCV, often as children [156–158]. Similar to other patient populations, chronic HCV infection is associated with a significantly higher risk of T2D and CV complications in TM patients, where it should be managed as a systemic disease in which extrahepatic complications exacerbate the weight of its pathological burden [159]. At the CV level,

HCV infection can be involved in the pathogenesis of myocardial fibrosis through both myocarditis directly, and the pancreatic and liver damage with the development of diabetes indirectly in TM patients [160]. In this context, HCV infection represents one additional risk factor for low bone mass and reduced osteocalcin blood levels in TM patients [161].

Interestingly, YKL-4 (inflammatory glycoprotein and a marker of endothelial dysfunction, name based on the one letter code for the first three N-terminal amino acids, tyrosine (Y), lysine (K), and leucine (L) as well as the molecular weight of YKL-40) is higher in patients with CVD or HCV, and it is also linked to liver stiffness and hepatic fibrosis degree in TM patients with liver disease [162]. Moreover, the fact that YKL-40 was also positively associated with the transfusion index, alanine aminotransferase, lactate dehydrogenase, ferritin, and liver iron concentrations (LIC), and negatively correlated with cardiac magnetic resonance imaging (T2*; biomarker to assess iron deposition and guide chelation therapy indicating properties of the tissue, and encoded in the pixels of the map) identified this protein as one potential key factor in the relationship between liver disease and CV complications [162].

Coinfection

In nature, viral coinfection is as common as viral infection alone, worsening things. In fact, coinfection may affect mutual viral pathogenicity, synergistically attack of host defense, and mix-up clinical symptoms, making diagnosis and treatment more difficult [163].

The study of coinfection dynamics still represents an emerging field in virology, which may indeed improve diagnoses, the development of vaccines, and antiviral therapy in the future. HCV and HIV coinfection patients may be of particular interest because they show a higher risk of subclinical atherosclerosis (prevalence of carotid plaque) than those with HIV mono-infection, presenting an elevated blood proinflammatory milieu [164, 165]. Moreover, a meta-analysis including 33,723 participants evidenced a pooled adjusted HRs for the association between HIV/HCV coinfection and CVD (CAD, congestive HF, and stroke) of 1.24 (95% CI: 1.07–1.40) when compared with HIV mono-infection [166]. Co-infection of HIV and HCV also increases the risk of significant QT prolongation in HIV patients because the viruses may independently facilitate the development of torsade-de-pointes arrhythmia and death [167].

Respiratory viruses

Many viral infections show a seasonal trend, generally related to colder seasons (e.g., influenza), although some respiratory virus infections peak in the spring or summer (e.g., some parainfluenza virus), events whose underlying factors are not fully defined yet [168]. However, it is known that temperature and humidity are important factors affecting respiratory virus stability and transmission rates, as well as the modulation of host immune responses to viral respiratory infections [168]. In particular, it is known that influenza seasonality is significantly affected by temperature and humidity, with cool and dry conditions enhancing the virus's survival and transmissibility in temperate climates [169]. These meteorological variables were found to be important factors also in the transmissibility and mortality of coronavirus disease 2019 (COVID-19), similar to what was observed for influenza [170–174]. Nonetheless, other studies have shown that changes in meteorological variables (increase in temperature and humidity) may not necessarily lead to a decline in COVID-19 cases [175, 176]. Thus, to establish this association with greater certainty, future studies should evaluate other exposure measurements and important cofactors, such as immunological and socio-economic factors and inter-human contacts, population density, pollution, appropriate lag times, and non-linear associations [174, 177–181].

In view of their common dependency on environmental factors, in many temperate areas of the world a substantial overlap between human seasonal coronaviruses (e.g., alpha-coronaviruses NL63 and 229E and beta-coronaviruses OC43 and HKU1) and influenza virus has been observed, a fact that may increase misdiagnosis and represent a substantial additional burden on health systems [182]. As a result, SARS-CoV-2 and influenza coinfection are quite common (taking into account the underestimation due to the rate of those not detected, especially in those cases with milder symptoms that do not require healthcare services),

in particular in patients with comorbidities (e.g., obesity, T2D, hypertension, cancer, and CAD), where exacerbation of symptoms (e.g., fever, cough, dyspnea, diarrhea, and fatigue), and complications (e.g., acute ischemic cardiac disease, kidney injury, and acute HF) can occur [183]. Thus, considering that SARS-CoV-2 and influenza viruses infect a common subgroup of high-risk patients, more knowledge is needed to assess how coinfection may affect a patient's clinical response and prognosis.

Atherosclerosis and influenza (between the old acquaintances)

Influenza is a very common infection, responsible for an estimated 1 billion cases, and 3 to 5 million severe cases, with up to 650,000 leading to influenza-related respiratory deaths each year worldwide [184, 185].

The close epidemiological link between atherosclerosis, CVD, and influenza infection has been recognized since the beginning of the 20th century, coinciding with the great flu epidemic of 1918–1920 [186].

Pathogenic mechanisms

It has been shown that the virus can infect and localize directly in the atherosclerotic arteries and that infection is associated with the pro-inflammatory response at both systemic and arterial levels [187]. As a result, endothelial cells are permissive to virus infection, which generates a strong increase of cytokines and adhesion molecules locally [188]. Moreover, the virus can induce apoptosis of epithelial cells and increase endothelial permeability through the hyperactivation of cytokines and chemokines, inducing endothelial dysfunction [189]. Another possible mechanism linking the virus to atherosclerosis is the effect observed on the high-density lipoprotein (HDL) antiinflammatory capacity by increasing arterial macrophage traffic in mice, an event that appeared preventable by the administration of D-4F, an apolipoprotein A-I mimetic peptide [190].

Furthermore, influenza virus infection and AMI resulted in being closely cross-linked, as influenza virus infection can destabilize atherosclerotic plaques and induce platelet activation and inflammatory responses, hence causing a thrombogenic milieu [191–195]. One of the main mechanisms the virus can use to exert its effects is the induction of inflammatory cytokines, which may take part in the development of atherosclerosis and trigger the occurrence of AMI [196]. Moreover, influenza A virus infection increases p38 MAPK-mediated matrix metalloproteinase-13 (MMP-13) expression, which may lead to destabilization of vulnerable atherosclerotic plaques in the artery [197]. Type 2 AMI may also indirectly occur due to the increased metabolic demands of myocardial tissue for tachycardia, fever, and hypoxia [198].

Clinical evidences

Available data on the relationship between influenza and CAD reported controversial results, ranging from a positive to null relationship [198–201]. Nonetheless, a temporal relationship between influenza infection and AMI has also been found using patients self-reported data to classify respiratory symptoms, finding a significant risk due to respiratory tract infections in the week prior to the onset of AMI, and suggesting an inflammatory response associated with the precipitation of the acute CV event [202, 203]. A more recent study that used laboratory-confirmed influenza infection data corroborated these findings by showing a six-fold incidence ratio for AMI hospitalization during the risk interval (one week after respiratory specimen collection); the incidence of AMI was also high after infection with non-influenza respiratory viruses (although to a lesser extent than influenza, corresponding to 3.51 for respiratory syncytial virus; 95% CI: 1.11–11.12, and 2.77 for other viruses; 95% CI: 1.23–6.24) [204]. AMI patients with concomitant influenza infection also exhibited higher rates of in-hospital mortality, 30-day readmission, and in-hospital complications, as well as higher health-system resource utilization compared to those without influenza [205].

Influenza vaccine

An interesting experimental study evaluated the effect of vaccination (45 μg/0.5 mL Vaxigrip®, the same dose used to immunize human adults against influenza) on atherosclerotic plaque development in hyperlipidemic mice [apoE$^{-/-}$ mice] [206]. Results showed that vaccinated animals developed smaller

lesions with lower lipid but higher SMC content and collagen deposition than control animals, in parallel with decreased levels of pro-inflammatory cytokines (IFN-γ, TNF-α, IL10) and increased levels of the anti-inflammatory cytokine IL-4 [206]. Thus, influenza vaccination seems to exert a beneficial effect by promoting smaller and stable atherosclerotic plaques and eliciting atheroprotective immune responses.

Moreover, as effective vaccination prophylaxis is possible for influenza, several clinical studies have focused on the effects of influenza vaccination on CV events, overall supporting a correlation between influenza vaccination and a reduction in CV events, although some studies remain controversial [207–209]. Notably, the Influenza Vaccination in Prevention From Acute Coronary Events in Coronary Artery Disease study (FLUCAD) study, carried out in CAD patients, reported a lack of significance for the composite outcome estimated at 12-month event rate (including CV death, myocardial infarction, coronary revascularization), and slight significance for the composite outcome (including the previous endpoints and rehospitalization for myocardial ischaemia) [209]. A meta-analysis of case-control studies (8 on influenza vaccination, 10 on influenza infection and AMI) found a significant association between recent respiratory infection and AMI, with a pooled OR 2.01 (95% CI 1.47 to 2.76) [210]. Moreover, influenza vaccination was found to be significantly associated with protection from AMI, with an estimated vaccine effectiveness of 29% (95% CI 9% to 44%) [210]. Recent results from the Influenza Vaccination After Myocardial Infarction (IAMI) study also showed that early influenza vaccination after an AMI (within 72 h of hospitalization) result in a significant 28% reduction in major adverse CV events (MACE; as AMI, or stent thrombosis) and a 41% reduction in CV mortality, with no excess in serious adverse complications [211]. The updated meta-analysis of 8 randomized clinical trials, including IAMI and the recent influenza vaccine to prevent adverse vascular events trials (4,420 patients), showed that influenza vaccine, compared with control/placebo, was associated with a significantly lower risk of MACE at follow-up [risk ratio (RR) 0.75, 95% CI 0.57–0.97] [212]. Moreover, a very recent meta-analysis (5 randomized trials, 4,187 patients, 2 studies included patients with acute coronary syndrome, 3 patients with stable CAD and acute coronary syndrome) reported that influenza vaccine may represent a cheap and reliable tool to reduce the risk for all-cause mortality (by by 44%), CV mortality (by 46%), major acute CV events (by 34%), and acute coronary syndrome among CAD patients (by 36%) [213]. Another very recent meta-analysis (22,634,643 hospitalizations) assessed the role of influenza vaccination in protecting the CV system, revealing that those patients vaccinated against influenza were associated with a lower incidence of AMI (RR = 0.84, 95% CI: 0.82–0.87, $P < 0.001$), transient ischemic attack (TIA; RR = 0.93, 95% CI: 0.9–0.96, $P < 0.001$), cardiac arrest (RR = 0.36, 95% CI: 0.33–0.39, $P < 0.001$), stroke (RR = 0.94, 95% CI: 0.91, 0.97, $P < 0.001$), and mortality (RR = 0.38, 95% CI: 0.36–0.4, $P < 0.001$) [214].

Taken altogether, these results support the hypothesis that the influenza vaccine may be a cheap and effective intervention to reduce the risk for all-cause mortality, CV mortality, major acute CV events, and acute coronary syndrome. This information may be of critical public health significance, because of the number of unvaccinated subjects, the high number of CV complications associated with respiratory tract infection, and the beneficial effect of vaccination in terms of risk reduction on patients with high CV risk. Accordingly, the 2019 European Society of Cardiology-ESC guidelines for the diagnosis and management of chronic coronary syndromes recommended influenza vaccination (class I, level of evidence B) [215]. However, these recommendations have not yet been fully implemented in the cardiology clinical practice. As a matter of fact, a US survey (2016–2019) reported that only 50% of patients with CVD had received influenza vaccination, pointing to socio-economic disparities as a critical determinant associated with the inadequate delivery of this important preventive tool [216].

Atherosclerosis and SARS-CoV-2: a new enemy?

Since its first appearance at the end of 2019, SARS-CoV-2 virus, responsible for COVID-19, has infected more than 766,440,796 people and caused about 6,932,591 deaths until now [184]. Its link to CVD has emerged since the beginning of the pandemic, with an increased incidence of myocarditis, pericarditis, arrhythmias, HF, and thromboembolism, not only in the acute phase but also beyond the first 30 days of the infection [217, 218]. Moreover, preexisting CVD risk factors (such as obesity, hypertension, and T2D)

increase susceptibility to COVID-19 [219]. In particular, hypertension was found to be closely related to disease severity and higher mortality [220]. To date, COVID-19 represents one of the most critical health and economic issues, as this infection is posing new diagnostic, clinical, and therapeutic challenges as well as long-lasting direct and indirect effects whose recognition and containment are critical to addressing the negative collateral consequences, which are likely to be seen in currently infected patients in the near future but also for decades to come.

Pathogenic mechanisms

The ability of SARS-CoV-2 to bind to ACE2 receptors for entry into cells allows direct access to the circulatory and CV systems, disseminating the virus towards major organs and leading to major health complications; SARS-CoV-2 may directly enter endothelial cells (triggering the inflammatory response and causing apoptosis and disruption of intercellular junctions) and cardiac cells (causing myocarditis through direct cardiac damage) [221].

Although every viral infection triggers an increase in certain inflammatory biomarkers, SARS-CoV-2 is mainly associated with the activation of an even greater number of different cytokines (e.g., TNF-α, IL-1β, IL-2, IL-6, CRP, and ferritin) at very high levels, which likely contribute to the more severe symptoms and health complications observed in many COVID-19 patients compared with other respiratory infections [222, 223]. In addition, SARS-CoV-2 also works as a complement activator (C3, C5), exacerbating symptoms and inducing acute respiratory distress syndrome [224]. The hypercoagulable state associated with COVID-19 is reflected in the increased concentration of coagulation and inflammatory biomarkers (e.g., CRP, D-dimer, fibrinogen, and fibrin degradation products) [225]. Moreover, other mechanisms, including hypoxia-induced injury and endothelial dysfunction, may play a pathogenetic role in the SARS-CoV-2-related CV manifestations [226, 227].

T2D and COVID have already shown a bidirectional relationship; in fact, if T2D is a risk factor for the development of severe and critical forms of COVID-19, the virus can also induce new-onset T2D in nondiabetic patients. Mechanisms likely involve ACE2 (entry factor) and ketoacidosis precipitation in infected patients (characterized by decreased insulin blood levels, decreased glucose utilization, and uncontrolled lipolysis, but also an excessive increase in ketone bodies and acidosis) [228, 229]. Moreover, the virus may increase IR through enhanced expression of the RE1-silencing transcription factor (REST), which in turn modulates the expression of metabolic factors (e.g., myeloperoxidase, apelin, and myostatin), thus altering glucose and lipid metabolism [229]. The reduction of adiponectin, a hormone involved in glycemic and lipid homeostasis, may be an additional mechanism linking SARS-CoV-2 to IR [230].

An interesting recent development in this field concerns sphingolipids, bioactive molecules that play important roles in many crucial cellular pathways, including inflammatory and oxidative stress, as well as in all processes related to membrane dynamics [231, 232]. The properties of these molecule make them potential regulators of the life cycle of several viruses (e.g., HCV, HIV, influenza, and SARS-CoV-2) and, indeed, evidence of the interaction has been found at different steps of viral replication cycle (entry into the plasma membrane or endosomal membranes, relationship leading to sphingolipid-mediated signal transduction, relationship with internal membranes and lipids during replication, virus assembly and budding) [233]. Remarkably, recent data evaluated the antiviral activity of two specific inhibitors of uracil-diphosphate glucose (UDP)-glucose:ceramide glucosyl-transferase [glucosylceramide synthase (GCS)], which catalyzes the biosynthesis of glucosylceramide (GlcCer; backbone of more than 300 structurally different glycosphingolipids), blocking the conversion of ceramide to GlcCer [234]. Both inhibitors hamper the replication of SARS-CoV-2 and influenza virus, suggesting that synthesis of glycosphingolipids is needed to sustain viral life cycles and that GCS inhibitors might be used as antiviral tools, likely effective also in case of coinfections [234].

Thus, as some sphingolipids inhibitors are already in use or being studied in different clinical settings, targeted modulation of sphingolipid metabolism may really open new possibilities for additive pharmacological strategies to reinforce current available antiviral therapies [235].

Clinical evidences

High levels of cardiac biomarkers (e.g., NT-proBNP, troponin), common in COVID-19 patients, are indicative of myocardial injury and can be used to predict short- and long-term outcome of COVID-19 infection [236]. In this regard, a meta-analysis (3,044 confirmed COVID-19 cases from 12 studies) reported that the most common CV complications in COVID-19 patients were myocardial injury (21.2%, 95% CI 12.3–30.0%), arrhythmia (15.3%, 95% CI 8.4–22.3%), HF (14.4%, 95% CI 5.7–23.1%), and acute coronary syndrome (1.0%, 95% CI 0.5–1.5%) [237]. Moreover, the pooled incidence of HF, arrhythmia, and myocardial injury in non-survivors was 47.8% (95% CI 41.4–54.2%), 40.3% (95% CI 1.6–78.9%) and 61.7% (95% CI 46.8–76.6%), respectively [237]. In another meta-analysis (20,875,843 patients, follow-up of 8.5 months), COVID-19 patients resulted at high risk of AMI (HR: 1.93, 95% CI: 1.65–2.26, $P < 0.0001$, $I^2 = 83.5\%$) [238]. Acute event precipitation in COVID patients is likely triggered by high levels of inflammation and hypercoagulability, as suggested by proteomic analysis [239]. Moreover, several studies reported an increased risk of mortality and complications in COVID-19 patients with preexisting CVD [240, 241].

Myocarditis may also occur during COVID-19, with variable severity and generally characterized by high lymphocytic inflammatory infiltrates [242]. It has been estimated that the incidence of myocarditis pre-COVID ranged from 1 to 10 cases/100,000 subjects, increasing after the SARS-CoV-2 pandemic from 150 to 4,000 cases/100,000 individuals [243]. Five years after the onset of the pandemic, long-term outcome data indicate a significant burden of CVD after recovery from acute COVID-19 illness [243]. In particular, late complications following acute SARS-CoV-2 infection may occur, including disturbances in vascular hemostasis and blood coagulation, CAD, myocardial fibrosis, AMI, and cardiac hypertrophy [244–246]. Interestingly, also asymptomatic SARS-CoV-2 infection may present CV complications, as shown in a study that enrolled 139 healthcare workers with confirmed prior SARS-CoV-2 infection [serological or reverse transcriptase-polymerase chain reaction (RT-PCR)], in which signs of myocarditis were observed on cardiac magnetic resonance in 37% of the participants (median of 10 weeks after infection) [247]. Among the participants, only half had symptoms of COVID-19, suggesting that even asymptomatic patients may present important CV complications quite sometime after SARS-CoV-2 infection. Notably, following SARS-CoV-2 infection and inflammatory burst, autoimmune reactions may complicate post-COVID recovery, contributing to the post-acute complications of COVID-19 (long COVID) [248].

Some CV drugs [including ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), statins, anticoagulants, and aspirin] seem to have a role in preventing COVID-19 complications, although current recommendations from leading Cardiovascular Scientific Societies are to maintain patient's current regimens, unless clinically indicated (e.g., hemodynamic instability) [249]. In contrast, pharmacological agents used for COVID-19 (e.g., remdesivir, ribavirin, lopinavir, chloroquine, methylprednisolone, and tocilizumab) may have significant CV side effects and, by interacting with CV agents, cause potential adverse effects on the CV system [250].

Although vaccination against SARS-CoV-2 is generally safe and effective, a certain rate of complications is observed. In particular, compared to the influenza vaccine, COVID-19 mRNA vaccines showed a significantly higher risk for hypertensive crisis (adjusted OR 12.72; 95% CI 2.47–65.54), and supraventricular tachycardia (7.94; 2.62–24.00) [251]. The overall risk of myopericarditis after receiving the COVID-19 vaccine is low; however, cases of myocarditis and pericarditis may occur, with an overall incidence of about 10/100,000, a range that may increase when considering the subgroup of young males (about 50/100,000; most cases occurring some days after the second dose) [244, 252–255]. Autopsies performed on 25 people who died unexpectedly and within 20 days after anti-SARS-CoV-2 vaccination revealed acute (epi-)myocarditis in four patients without detection of any other significant disease that may have caused an unexpected death [256]. Histological analysis showed patchy interstitial myocardial T-lymphocytic infiltration (predominantly of the CD4-positive subset), associated with mild myocyte damage. Taken together, autopsy findings suggested death due to acute arrhythmogenic cardiac failure, and indicated myocarditis as a life-threatening complication following mRNA-based anti-SARS-CoV-2 vaccination. One origin of this damage is that, despite differences in their composition (amount of lipid nanoparticles and excipients), all vaccines elicit a strong release of pro-inflammatory cytokines (e.g., IL-18),

and NFκB activation, which may increase immune-mediated responses, cardiotoxicity, and myocarditis risk [257]. Moreover, spike protein impairs mitochondrial function in human cardiomyocytes and alters endothelial function, immune response, and renin-angiotensin-system balance, with negative consequences for the pathophysiology of the CV system [258, 259]. A "hyper-catecholaminergic" status has also been identified as one of the key triggers of SARS-CoV-2 mRNA vaccine-induced myocarditis and related outcomes (whether triggered by SARS-CoV-2 mRNA, SARS-CoV-2 spike protein, or both remains unclear) [260]. Noteworthy, the psycho-emotional repercussions and decreased well-being perception in Italian adolescents in response to the COVID-19 pandemic are significant, with gender-related differences (concerning psychological and physical well-being, mood/emotion, and self-perception), whereas combined stress (psychological and physical) could exacerbate CV responses in young males, contributing to adverse consequences after vaccination in this particular population segment [261, 262].

The primary concern on the difficulties associated with managing the negative consequences of the COVID-19 pandemic, which has strained the health care system globally, has decreased attention towards psychological effects in the general population and people with chronic diseases. In particular, a significant drop in AMI hospitalizations was observed worldwide during the COVID-19 outbreak. One possible explanation for this outcome is that the pandemic may have generated fear and adverse psychological consequences in AMI patients, delaying hospital access [263]. Hence, there was a significant delay in the elapsed time "from symptom onset to first medical contact" when considering "total ischemic time" (definition denoting the elapsed time from the onset of chest pain to the first medical contact, arrival at the hospital, and balloon inflation during primary percutaneous coronary intervention) [263, 264]. This behavior denotes patients' hesitation to contact healthcare personnel and go to the hospital or even not seek care at all, which is also confirmed by the higher levels of emotional and symptomatic fear expressions [fear of COVID-19 scale (FCV-19S) questionnaire] found in AMI patients during the pandemic compared to the general population [265, 266]. Noteworthy, "door-to-hospital-arrival-time" and "hospital-arrival-to-insufflation-time" did not differ significantly during the pandemic with respect to the pre-COVID period, suggesting an effective organization of the healthcare system and leaving a major role to the patient's fear and reluctance [263, 264].

Moreover, health workers, potentially exposed to the pathogen and subjected to high workload and job stress, generally did not receive mental health assistance during the pandemic (e.g., mindfulness-based stress reduction courses to reduce distress during emergency periods), and this may indirectly affect care quality [267]. Thus, it is crucial to focus on the psycho-emotional aspects of the current sanitary crisis and to understand how people relate to the pandemic, providing assistance also for these aspects and giving correct information about the pandemic course and the risks of delayed access to the hospital in case of acute events, supporting at the same time caregivers as well as patients and the general population with appropriate and targeted coping strategies when needed.

Discussion

It is still very difficult to establish whether infection and CV risk and disease are actually related through direct or indirect underlying pathogenic mechanisms, or whether they simply coexist in an association, as both diseases are common occurrences that can be observed in a significant portion of the general population. Moreover, the available results are often controversial and limited by different design and patient cohorts, the definition of CV outcomes, confounding factors, and small sample size, thus lacking adequate statistical power to demonstrate significant differences.

Despite extensive efforts, there is still weak proof of infections of some viruses in the atherosclerotic lesions [65, 268]. Even the presence of a virus in an atherosclerotic artery doesn't constitute a conclusive finding since it might be a bystander rather than an active inducer of the illness, which has to be verified by additional evidence at the cellular and molecular levels. Moreover, a diseased vessel may simply be more vulnerable to an infectious agent. Noteworthy, an extensive reviewed literature places greater correlations in chronic infections, in agreement with several physiopathogenetic mechanisms. In particular, it appears that chronic infections may induce structural and proinflammatory modification related to the

development of the atherosclerotic lesion, as in the case of latent and persistent infection from CMV [269]. However, things in this area are much more complex; in fact, influenza A infection appears to accelerate the early stage of atherosclerosis [270, 271]. Thus, a specific virus would play a more important role in specific steps of the atherosclerotic process (e.g., at the beginning of the injury *vs.* following phases during the development of the plaque) acting more in specific subgroups of patients (e.g., patients with subclinical atherosclerosis *vs.* those with an established disease). Moreover, the presence of infected individuals without atherosclerosis, together with others who develop extensive damage in the context of a multifactorial disease such as CVD, implies that a single factor cannot be considered a necessary and sufficient causal factor, and that the contribution of other factors (e.g., host genomics and environmental factors) is also required. Anyway, for example considering influenza, the effect of meteorological variables is still under evaluation, due to the complex mechanisms underlying disease dynamics (e.g., peculiarities of the population, demographic dispersion, spatial diffusion, and climatic characteristics) [272, 273].

Viruses are not studied in the same way since they act through some common mechanisms but also present peculiarities; in the future, it will be important to define the strength of each agent in terms of the onset and development of atherosclerosis, also considering the role of coinfection and the interaction of other factors (e.g., diseases such as steatosis and T2D; biomarkers like CRP, TNF-α, and ILs; host susceptibility, and host genetic asset). In addition, as more evidence has reported the presence of more than one pathogen in atherosclerotic plaques [274, 275], the study of coinfection, which is now an emerging discipline in virology, will be important to define subgroups of patients at higher risk (as simultaneous infection with multiple agents seems to increase the risk of CVD and its complications), where combined anti-infectious and anti-inflammatory strategies might be useful and more efficient [166, 276, 277]. Nonetheless, antiviral pharmacological agents may also alternatively benefit or exacerbate CVD risk, as in the case of antiretroviral therapy, which may reduce inflammation and other markers of CV risk but induce lipid abnormalities (e.g., hypertriglyceridemia) [50].

For it concerns vaccinations, data from different meta-analyses testify for a protective role of influenza vaccination on the CV system [213, 214], although the fact remains that influenza vaccination as a preventive measure for CV disease remains low and is not yet considered an additional and reliable CV preventive strategy in clinical settings, although recommended by many guidelines for different subgroups of patients at risk [208, 215, 278, 279]. In particular, the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes recommended annual influenza vaccination in patients with CAD, especially in the elderly [215]. Similar advice from the AHA/ACC for patients with coronary and other atherosclerotic vascular disease (class I, level B) [278]. Awareness of the general population, patients, and cardiologists surely needs to be improved with targeted campaigns, and alternatives to vaccination must be applied in patients with contraindication to vaccine (e.g., severe allergic reaction to any vaccine component or to a previous dose of vaccine, immune compromisation) recommending protective behaviors, always considering that key barriers to influenza vaccination (e.g., socioeconomic status, racial disparities) are not completely eliminated, and not all the causes have been completely identified, thus needing further careful evaluation in future [278, 280].

In contrast, COVID-19 mRNA vaccines may induce a range of CV complications (e.g., thrombosis, stroke, myocarditis, myocardial infarction, pulmonary embolism, and arrhythmias) [281]. Moreover, the long-term outcomes following CV complications (e.g., myocarditis) related to SARS-CoV-2 vaccination are yet to be clarified. Therefore, it may be crucial to monitor more, and with appropriate diagnostic and therapeutic tools, subgroups of vaccinated patients at risk to minimize serious adverse events.

The COVID-19 pandemic has led to new indirect effects on atherosclerosis for the general population, patients, and healthcare workers, including delayed presentation of acute illness (e.g., AMI) and the burden of social distancing and quarantine on socialization, decreased psycho-emotional well-being, and reduced physical activity. Hence, it will be particularly important to assess the role of social and psychological issues and adopt measures to assist vulnerable and CV high-risk patients, as well as distressed healthcare professionals.

Conclusions

Despite the amount of evidence and strong biological plausibility (particularly in terms of inducing inflammatory and immunological responses), the causal relationship between viral infection and atherosclerosis has not been confirmed without any doubt, due to the complexity in the relation between viruses and atherosclerosis, and the persistence of many aspects still unsolved. At present, the importance of viral infection as risk factors has not been fully recognized in clinical practice. Nonetheless, monitoring, targeting, and treating conditions that predispose to CVD in infected subjects as well as considering infection as a risk factor for cardiometabolic disease are concerns gaining more and more attention among cardiologists. So, further research in this field, increased information for patients and physicians together with the development of improved tools (e.g., vaccine strategies and therapeutic agents reliable to prevent and/or treat the acute and long-term effects of viruses in terms of atherosclerosis) may have important implications for CV patient health, especially for those belonging to more vulnerable subgroups.

Key points requiring further deepening in the future:

(a) Although the amount of evidence and biological plausibility strongly suggest a pathogenic relationship between virus infection and CVD, a definitive proof of evidence has not yet been clearly reached.

(b) Not all viruses have been studied equally, and even for the most studied heterogeneity between studies exists.

(c) Coinfection may exacerbate the pro-atherogenic effects.

(d) The relationship between viruses and atherosclerosis is likely to be more important in subgroups of patients with specific risk profiles.

(e) Viruses may have peculiar mechanisms of action, in addition to common effects (such as the enhancement of inflammation and oxidative stress), which may affect their acute and long-term effects on the atherosclerotic process.

(f) Anti-/pro-atherogenic effects of antiviral drugs may be taken into consideration.

(g) SARS-CoV-2 has evidenced new additive mechanisms related to fear and social reactions, which may involve the social and psycho-emotional status of the individual and affect management and prognosis in the CV setting.

Abbreviations

ACE: angiotensin-converting enzyme

AMI: acute myocardial infarction

apoE: apolipoprotein E

CAD: coronary artery disease

COVID-19: coronavirus disease 2019

CMV: cytomegalovirus

CRP: C-reactive protein

CV: cardiovascular

CVD: cardiovascular disease

CI: confidence intervals

HCV: hepatitis C virus

HIV: human immunodeficiency virus

HSV: herpes simplex virus

HF: heart failure

ICAM-1: intercellular adhesion molecule 1

IL: interleukin

IMT: intima-media thickness

IR: insulin resistance

LOX-1: lectin-like oxidized low-density lipoprotein receptor-1

NO: nitric oxide

OR: odds ratio

RR: risk ratio

SARS-CoV-2: severe acute respiratory syndrome coronavirus-2

SMC: smooth muscle cells

T2D: type 2 diabetes

TM: thalassemia major

TNF: tumor necrosis factor

VCAM: vascular cell adhesion molecule

Declarations

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