Systemic Lupus Erythematosus and Cardiovascular Disease

Review began 01/26/2022
Review ended 02/06/2022
Published 02/08/2022

© Copyright 2022

Jha et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Surajkumar B. Jha¹, Ana P. Rivera², Gabriela Vanessa Flores Monar³, Hamza Islam⁴, Sri Madhurima Puttagunta⁵, Rabia Islam⁴, Sumana Kundu⁶, Ibrahim Sange^{7,8}

1. Research, Jinan University School of Medicine, Guangzhou, CHN 2. Research, Universidad Americana (UAM) Facultad de Medicina, Managua, NIC 3. Research, Universidad Central del Ecuador, Quito, ECU 4. Research, Faisalabad Medical University, Faisalabad, PAK 5. Research, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences, Chinoutpalli, IND 6. Research, R.G. Kar Medical College, Kolkata, IND 7. Research, California Institute of Behavioral Neurosciences & Psychology, Fairfield, USA 8. Research, K. J. Somaiya Medical College, Mumbai, IND

Corresponding author: Surajkumar B. Jha, drjhasuraj@gmail.com

Abstract

Systemic lupus erythematosus (SLE) is a condition in which autoimmune inflammation affects nearly every organ in the human body; it is characterized by a relapsing-remitting pattern. Systemic inflammation and tissue damage can arise from autoantibodies, the creation of immune complexes, and the deposition of autoantibodies, all defined as autoimmune diseases. Women of reproductive age are at a high risk of developing lupus, a chronic systemic condition. Among women between the ages of 15 and 44 years, the female-to-male ratio for the occurrence of lupus is as high as 13:1, while it is only 2:1 in children and in the elderly. In addition to accelerated atherosclerosis, SLE is associated with an increased risk of cardiovascular (CV) events such as coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular accident (CVA). Several SLE-specific processes, including impaired immunological regulation, impaired endothelial cell (EC) function, impaired vascular repair, hyperleptinemia, and traditional risk factors, contribute to early atherosclerosis in the disease. CAD can occur at any stage of the disease's progression, with younger individuals being much more at risk than their age-matched counterparts. This review article aims to provide a unique insight into the relationship between SLE and cardiovascular disease (CVD) by discussing the pathophysiological role of CVD in SLE, outlining screening criteria, and highlighting the treatment options for CVD in connection with SLE.

Categories: Cardiology, Internal Medicine, Rheumatology

Keywords: autoimmune heart disease, glucocorticoid-induced cardiomyopathy, pathogenesis of systemic lupus erythematosus, cvd & sle, cardiovascular disease, peripheral arterial diseases, women and heart disease, atherosclerotic cardiovascular disease, systemic lupus erythematosus disease, systemic lupus erythromatosus

Introduction And Background

Systemic lupus erythematosus (SLE) is a disease with a relapsing-remitting autoimmune course that may affect practically any organ in the body. It is characterized by the generation of autoantibodies, the formation of immune complexes, and the deposition of autoantibodies, resulting in systemic inflammation and tissue damage [1]. Throughout the Middle Ages, the Latin name lupus (meaning "wolf") was used to describe a variety of disorders that resulted in ulcerous lesions on the lower limbs. The name "lupus érythémateux" was used by French dermatologist Cazenave in the middle of the 18th century. The major turning point in the history of lupus occurred in the early 19th century when an understanding of the difference between cutaneous lupus and lupus vulgaris in the modern sense started to emerge progressively. Early 19th-century work by Kaposi, Sequiera and Baelean, and Osler contributed to the discovery of the disease's systemic nature. DNA was later identified as the primary target of antinuclear antibodies, and interferons (IFNs) have played a crucial role in modern research [2]. SLE has a prevalence of 9-241 cases per 100,000 people per year, and an incidence rate of 0.3-23.2 cases per 100,000 people per year, according to research done throughout the world over the previous 15 years [3].

Women of reproductive age have a strong predisposition to develop lupus. Among women between the ages of 15 and 44 years, the female-to-male ratio for the occurrence of lupus is as high as 13:1, while it is only 2:1 in children and in the elderly [4-6]. While it affects people of many races, it is more common among non-Caucasians. SLE is quite rare in Africa while being more common in Europe and the United States, especially among individuals of African origin [7,8]. It is thought that genetic factors interact with environmental exposures throughout the lifespan of an individual to influence susceptibility to develop SLE. The most substantial epidemiologic evidence for the increased risk of SLE is associated with exposure to crystalline silica, current cigarette smoking, use of oral contraceptives, and postmenopausal hormone replacement therapy, while there is an inverse association with alcohol use [9]. New research suggests a link between SLE risk and exposure to solvents, household and agricultural pesticides, heavy metals, and air pollution [9]. Ultraviolet light, vitamin D deficiency, certain infections, and vaccinations have also been hypothesized to be related to SLE risk [9]. Mechanisms that link environmental exposures with SLE include epigenetic modifications, increased oxidative stress, systemic inflammation, inflammatory cytokine upregulation, and

How to cite this article

Jha S B, Rivera A P, Flores Monar G, et al. (February 08, 2022) Systemic Lupus Erythematosus and Cardiovascular Disease. Cureus 14(2): e22027. DOI 10.7759/cureus.22027

hormonal effects [9].

There are many components to the SLE's complex pathogenesis: autoantibodies and immunocomplexes, involvement of the complement system, dysregulation of many cytokines including type I IFNs, and disturbance of the clearance of nucleic acids following cell death are only some of them [10]. Immunomodulators and immunosuppression can alter SLE's natural course [10]. In addition, SLE and treatment-related consequences such as accelerated coronary artery disease (CAD) and higher infection risk contribute significantly to both morbidity and mortality [10]. The 11-50% monozygotic twin concordance and significant risk observed within families reflect a genetic element [11]. Many genes, including HLA, IRF5, ITGAM, STAT4, BLK, and CTLA4, among others, have been associated with a propensity for lupus [11,12]. SLE diagnosis can be difficult, and while numerous categorization criteria have been proposed, their clinical value is still up for debate [13]. The management of SLE is determined based on organ system involvement, and despite the efficacy of various medications in the treatment of SLE, the disease still leads to significant morbidity and mortality among patients [13]. SLE is linked to an increased risk of accelerated atherosclerosis and cardiovascular (CV) events such as CAD, cerebrovascular accident (CVA), and peripheral artery disease (PAD). CV events occur both early and late in the course of the disease, with younger patients being substantially more at risk compared to their age-matched peers. By discussing the pathophysiological role of cardiovascular disease (CVD) in SLE and outlining screening criteria and treatment options for CVD in connection with SLE, this review article aims to provide distinct insight into the correlation between SLE and CVD.

Review

Pathophysiology

Vascular Endothelium Damage and Cardiovascular Disease in Systemic Lupus Erythematosus

One of the earliest signs of a developing CVD is the malfunction of the endothelial cells (ECs). In most cases, vascular injury is predicted to be accompanied by a faster rate of endothelium healing. The increased atherosclerotic load in SLE patients has been linked to decreased numbers of circulating endothelial progenitor cells (EPCs) and aberrant function of cells involved in vascular repair. As a result, lupus EPCs/myeloid circulating angiogenic cells (CACs) have a reduced ability to develop into mature ECs and produce lower levels of vascular endothelial growth factor (VEGF) and hepatic growth factor (HGF) [14-18]. Taraborelli et al. conducted a case-control study between 2014 and 2016 among a sample population of 40 females (20 cases with 20 matched controls) between the ages of 26-56 years with a disease duration of <5 years [19]. In this study, patients with a history of CVD or risk factors that could impair peripheral artery tonometry were excluded. Enrolled patients were matched to healthy controls with the same exclusion criteria for sex, age, body mass index (BMI), and blood pressure. Patients and controls received a transthoracic Doppler echocardiogram and an evaluation of endothelial function by peripheral artery tonometry. The study concluded that endothelial dysfunction and arterial stiffness are common in people with early lupus who have no known risk factors for CVD. A more extensive study is needed to compare the characteristics associated with the abnormalities [19].

Several soluble adhesion molecules, such as those released following EC injury and considered to be indicators of endothelial dysfunction, are upregulated in SLE and linked to higher coronary calcium scores [20]. Rho et al. conducted a study that evaluated the levels of cytokines like tumor necrosis factor-alpha (TNF- α), interleukin-1 alpha (IL-1 α), VEGF, and inflammatory enzymes such as myeloperoxidase (MPO), matrix metalloproteinases (MMP)-9, acute-phase reactants such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA), and adhesion molecules like vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and E-selectin in 109 patients with SLE and 78 healthy controls. In this study, in individuals with SLE, the connection between inflammatory indicators and calcified plaque revealed by electron beam CT was investigated. The study concluded that in SLE, concentrations of adhesion molecules and TNF- α are linked to CAD regardless of the Framingham Risk Score [20]. According to Nhek et al., SLE sera can activate platelets, leading to EC activation and proinflammatory mediators in an IL-1-dependent way [21]. In SLE, there is a significant imbalance between EC damage and healing [15]. As a result, people with SLE have defective ECs and poor repair of damaged ECs, encouraging vascular plaque formation.

Dysregulation of the Innate Immune Response

Due to the immensely essential function of type I IFNs in SLE, these cytokines have been studied extensively as a contributing factor to the development of lupus-related CVD. Endothelial function is impaired in lupus patients with a strong type I IFN signature (Table 1) [16]. Lee et al. conducted a study in 70 SLE patients and 31 healthy controls. EPCs in the blood of SLE patients and healthy controls were counted using a colony-forming assay. Real-time polymerase chain reaction (PCR) assessment of the IFN-I-inducible gene MX1 was used to determine serum IFN-I levels. Peripheral artery plethysmography was used to assess endothelial function. When compared to controls, SLE patients had significantly lower levels of EPC colony-forming units [median: 5.7/ml peripheral blood (interquartile range: 1.9-12.8) versus 28.5/ml peripheral blood (14.7-47.3); $p=0.0001$], and the loss of EPCs was more pronounced in patients with elevated concentrations of IFN-

I. These findings support the unique idea that endothelial dysfunction and higher CV risk are connected to EPC depletion produced by elevated IFN-I in SLE [16]. Increased serum IFN activity has been linked to a reduction in endothelial function, although serum levels of high-sensitivity CRP, adhesion molecules, and lupus disease activity have not. This shows that elevated type I IFN signaling may play a key role in increasing CV risk in SLE (Table 1) [22]. Tydén et al. recently showed that in SLE, activation of the type I IFN system could impair endothelial function, even in individuals with mild disease activity. The loss of nitric oxide production and decreased endothelial nitric oxide synthase (eNOS) activity are crucial in developing endothelial dysfunction [23]. According to a study published recently by King et al., type I IFNs have been shown to play a pathogenic function in myocardial infarction (MI) [24]. Ischemic cell death and ingestion of cell debris by macrophages in the heart drive a catastrophic response to MI by activating interferon regulatory factor 3 (IRF3) and type I IFN production via the cyclic GMP-AMP synthase-stimulator of IFN genes [24]. Furthermore, following an MI, animals who were given a type I IFN receptor-neutralizing antibody had their IFN response abated, which improved left ventricular dysfunction and survival [24].

Low-density granulocytes (LDGs), a subset of proinflammatory neutrophils seen in lupus patients, have been postulated to play pathogenic roles in lupus CVD through a variety of mechanisms, including their increased tendency to form neutrophil extracellular traps (NETs) [25]. Carlucci et al. found that SLE patients with overall mild-moderate disease activity have a substantial increase in aortic wall inflammation compared to healthy controls, as measured by 18F-fluorodeoxyglucose (18F-FDG) PET/CT scan. Noncalcified coronary plaque burden (NCB) and endothelial dysfunction were significantly higher in this SLE population [26]. The amount of LDGs was independently correlated with NCB when examining the correlations of lupus-related variables to these vascular abnormalities. Furthermore, an LDG gene profile established by RNA sequencing was linked to high vascular inflammation and high NCB in SLE [26]. An abnormality in neutrophil biology has been linked to an increased risk of early vascular disease in SLE.

Dysregulation of Adaptive Immune Response

In SLE patients, abnormal T cell subsets are a pivotal contributor to endothelial dysfunction and CVD. Tregs are anti-atherosclerotic T cells that suppress atherogenic T cell subsets and inflammation. In SLE, a Treg/Th17 imbalance is frequent, leading to atherosclerosis [27]. Plasmacytoid dendritic cells cause CD4+ CXC chemokine receptor 3 (CXCR3) cells to expand and migrate from the circulation into the artery wall in individuals with SLE, where they may have proatherogenic activities [28]. Baragetti et al. published a five-year prospective study in 2017, which showed that increased numbers of CD4+CXCR3 chemokine receptor (CCR)5+ T cells were linked to the development of carotid atherosclerosis in SLE patients (Table 1) [29]. According to these data, increased CD4+CCR5+ T cells in SLE may contribute to atherogenesis [29]. Smith et al. published a study in 2016, which proved that in SLE patients with asymptomatic atherosclerotic plaques, invariant natural killer T (iNKT) cells may produce an atheroprotective effect [30]. Healthy iNKT cells differentiated macrophages toward an anti-inflammatory M2 phenotype in the presence of healthy monocytes and serum from SLE patients with asymptomatic plaque. In contrast, SLE patients with clinical CVD had unresponsive iNKT cells and increased proinflammatory monocytes. Furthermore, the authors found that the anti-inflammatory iNKT cell phenotype was linked to dyslipidemia and was fueled by changes in monocyte phospholipid expression and CD1d-mediated iNKT-monocyte cross-talk [30].

B cells primarily influence atherosclerosis by producing autoantibodies. B1 cells create harmful IgG antibodies, whereas B2 cells produce beneficial natural IgM and IgA antibodies. Overactive B cells' tendency to produce pathogenic IgG antibodies is also a risk factor for lupus-related atherosclerosis [31]. In particular, antiphospholipid antibodies (aPL) are independent indicators of atherosclerotic plaque development in SLE patients [32,33]. Atherosclerosis develops in SLE individuals with anti-high-density lipoprotein (anti-HDL)-IgG antibodies, allowing low-density lipoprotein (LDL) to enter ECs [34]. According to Kurien et al., anti-oxLDL antibodies are increased by SLE RNP and anti-Ro/LaRNP antibodies [34]. Anti-HDL antibody, anti-ApoA1 antibody, and anti-paraoxonase 1 (PON1) antibody are likely to share a common atherogenic pathway in that they disrupt the balance of PON1/MPO, which increases oxidative lipid modification and interferes with HDL's anti-inflammatory activity, all of which contribute to atherosclerosis [35-37]. Furthermore, anti-ApoA1-IgG induces atherosclerosis in a TLR2/TLR4/CD14-dependent manner through two pathways: it guides the expression of inflammatory factors by activating transcriptional nuclear factor-kappa B (NF- κ B); it provides an alternative (or concomitant) signal to phosphoinositide 3-kinase (PI3K) in an Src-dependent pathway, activating L-type Ca²⁺ channels and potassium/calcium exchangers, resulting in the depolarization of myocardial plasma membrane [38]. Anti-oxLDL-IgM, anti-ApoB100 antibodies, anti-choline phosphate (PC) antibodies, and anti-malondialdehyde (MDA) antibodies are all possible protective autoantibodies in SLE patients. The first three have a synergistic impact in that they lower oxLDL levels, oxLDL uptake, and foam cell formation [39-41]. Anti-PC-IgM boosts Tregs, lowers IL-17 and TNF- α in SLE and atherosclerosis, and renders dendritic cells (DCs) immature [42]. Anti-PC-IgM and anti-MDA-IgM used together have a double preventative effect on atherosclerosis [43]. On the other hand, SLE patients were shown to have a low level of protective autoantibodies [41]. By increasing pathogenic autoantibodies and blocking possible preventive autoantibodies, SLE raises CVD risk. Figure 1 presents a summary of endothelial damage in SLE leading to CVD.

FIGURE 1: Summary of endothelial damage in SLE leading to CVD

SLE: systemic lupus erythematosus; CVD: cardiovascular disease; TNF- α : tumor necrosis factor-alpha; VCAM: vascular cell adhesion molecule; ICAM: intercellular adhesion molecule; IL-1: interleukin-1; VEGF: vascular endothelial growth factor; eNOS: endothelial nitric oxide synthase; LDGs: low-density granulocytes; NETs: neutrophil extracellular traps; Treg: regulatory T cells; Th-17: T helper 17 cells; CD4+: cluster of differentiation 4+; CCR5+: cysteine-cysteine chemokine receptor 5+; iNKT: invariant natural killer T; aPL: antiphospholipid antibodies; anti-HDL: anti-high-density lipoprotein antibodies; Apo-A1: apolipoprotein A-I; PON1: paraoxonase 1; TLR: toll-like receptors; anti-PClgM: IgM antibodies against phosphorylcholine; MDA: malondialdehyde; anti-oxLDL: anti-oxidized LDL; Apo-B100: apolipoprotein B-100

Other Causes of CVD in SLE

Dyslipidemia is a predisposing factor for atherosclerosis and a well-established risk factor for CVD. Dyslipidemia is defined as an increase in total cholesterol, LDL, triglycerides, and apolipoprotein B and a decrease in HDL in SLE [44]. Patients with SLE have higher amounts of oxidized and malfunctioning HDL and reduced cholesterol efflux ability and atherosclerosis [45-47]. HDL protects the arteries by boosting the activation of transcription factor 3 (ATF3), which leads to a reduction in toll-like receptor (TLR)-induced inflammatory reactions [48]. In contrast, according to recent research, oxidized lupus HDL enhances proinflammatory responses in macrophages. Indeed, in patients with SLE, HDL stimulates NF- κ B, enhances the generation of inflammatory cytokines, and fails to prevent TLR-induced inflammation [49]. The inability of lupus HDL to suppress inflammatory responses is due to a reduced capacity to stimulate ATF3 production and nuclear translocation, which is triggered by oxidized LDL receptor signaling. Indeed, systemic administration of an HDL mimic to lupus-prone animals resulted in considerable ATF3 activation and reductions in proinflammatory cytokine levels, indicating therapeutic potential [49]. In recent studies, impaired cholesterol export capability was strongly linked with vascular inflammation and NCB in multivariate analysis, suggesting that improving HDL function may have considerable cardioprotective

implications in SLE [26].

Insulin resistance has been linked to CVD in SLE patients. Recent research has measured insulin sensitivity in SLE patients with a meal-tolerance test. Despite adequate glucose tolerance, intact β -cell function, and skeletal muscle glucose transporter 4 (GLUT4) translocation, SLE patients had a bi-hormone metabolic anomaly defined by enhanced insulin resistance and hyperglucagonemia. As a result, the authors believe that improving insulin sensitivity may involve more than just addressing insulin resistance [50].

Hyperleptinemia is linked to the progression of atherosclerosis by promoting inflammation through the release of proinflammatory cytokines such as IL-6, TNF- α , IL-17, and other cytokines [51]. In a cross-sectional study published in 2017, Versini et al. stated that there is a lack of data on the link between obesity and SLE. Although studies disagree on the connection between leptin and SLE, a rise in serum leptin levels may enhance systemic inflammation in SLE patients [52]. In contrast, investigations conducted in Egypt in 2018 found that SLE patients have significantly more amount of serum leptin [53].

In general, examining drugs and CVD risk is complex since there might be much confounding by indication. Patients with more severe SLE are more likely to be given glucocorticoids and other immunosuppressive drugs, whereas those with lesser illness may be given hydroxychloroquine alone [54]. Although rising glucocorticoid dosage is closely connected with more significant disease activity, the association between glucocorticoid usage and CVD risk among SLE patients is challenging to understand completely. While glucocorticoids reduce systemic inflammation, which may minimize atherogenesis, their usage is linked to an increase in several traditional risk variables, including total cholesterol, blood glucose, BMI, and systolic blood pressure [54]. More prolonged glucocorticoid usage was found to be independently related to incident CVD events, albeit the relative risk was not assessed in that study [55]. Nikpour et al. also reported that using glucocorticoids doubly increased the risk of MI, angina, and sudden cardiac death [RR: 2.01, 95% confidence interval (CI): 1.19-3.41] [56]. However, these effects have not been repeated in other studies. The difficulty of distinguishing disease activity from glucocorticoid usage, as well as the numerous ways in which glucocorticoid use has been assessed, such as duration of use and maximum, current, or total dosage, may contribute to the disparity among studies [56-59]. Two studies have found that azathioprine usage is an independent risk factor for CVD among SLE patients. One study published by Burgos et al. in 2009 predicted a three-fold higher risk of PAD [60]. And another study published by Haque et al. indicated a three-fold increased risk of MI and angina [61]. Table 1 presents a summary of studies about the pathogenesis of CVD in SLE.

Reference	Design	Cases	Controls	Population	Variables	Findings
Somers et al. (2012) [22]	Cohort study	95 SLE patients	38	<55 years, from Michigan Lupus Cohort	Real-time PCR was used to measure serum type I IFN activity. The impact of type I interferons on FMD, CIMT, and cardiac calcification was studied. Patients with CVD were not allowed to participate in the study	Type I IFNs are independently associated with atherosclerosis development in lupus patients without a history of overt CVD
Baragetti et al. (2017) [29]	Prospective study (2012-2017)	40 SLE patients	50 healthy age-matched controls	Mean age: 42 ± 9 years	Clinical history and details on the principal CVRFs were obtained at baseline and after five years. Carotid Doppler ultrasonography was employed to quantify the atherosclerotic burden at baseline and follow-up. The association between basal circulating T cell subsets and atherosclerosis development was evaluated	During the 5-year follow-up, 32% of SLE patients developed carotid atherosclerosis compared to 4% of controls. Increased levels of CD4+CCR5+ T cells were independently associated with the development of carotid atherosclerosis in SLE patients
Lee et al. (2007) [16]		70 SLE patients	31 healthy controls	University of Florida Center for Autoimmune Diseases; 27-45 years, females	EPCs in the blood of SLE patients and healthy controls were counted using a colony-forming assay. A real-time PCR quantified serum IFN-I levels. Endothelial function was determined by peripheral arterial plethysmography	When compared to controls, SLE patients had significantly fewer EPC colony-forming units. The loss of EPCs was more pronounced in patients with high IFN-I levels. In patients with SLE, high IFN-I levels were linked to poor endothelial function

TABLE 1: Summary of studies about the pathogenesis of CVD in SLE

SLE: systemic lupus erythematosus; CVD: cardiovascular disease; PCR: polymerase chain reaction; IFN: interferons; FMD: flow-mediated dilatation; CIMT: carotid intima-media thickness; EPC: endothelial progenitor cells; CVRFs: cardiovascular risk factors

Clinical implications

Evidence of an Increased CVD Risk in SLE Patients

Compared to healthy persons of the same age and gender, patients with SLE have a higher chance of having ischemic heart disease or stroke, referred to as CVD [62]. A population data-based study published by Aviña et al. in 2017, including all British Columbia and other Canadian residents, studied all patients with incident SLE with a healthy group from the general population as a matched cohort. Among 4,863 individuals with SLE (86% female, mean age: 48.9 years), the incidence rates (IRs) of MI, stroke, and CVD were 6.4, 4.4, and 9.9 events per 1,000 person-years, respectively, vs. 2.8, 2.3, and 4.7 events per 1,000 person-years in the comparison cohort. Compared with non-SLE individuals, the fully adjusted multivariable hazard ratios (HRs) among SLE patients were 2.61 (95% CI: 2.12-3.20) for MI, 2.14 (95% CI: 1.64-2.79) for stroke, and 2.28 (95% CI: 1.90-2.73) for CVD. The age, sex, and entry time-matched HRs for MI, stroke, and CVD were highest during the first year after SLE diagnosis: 5.63 (95% CI: 4.02-7.87), 6.47 (95% CI: 4.42-9.47), and 6.28 (95% CI: 4.83-8.17), respectively. Hence, CV events are more common in patients with SLE, especially in the first year after diagnosis. In this patient population, increased surveillance in tracking these potentially fatal outcomes and their modifiable risk factors is necessary (Table 2) [62].

A major international cohort study published in 2006 by Bernatsky et al. involving 9,547 individuals with SLE found 1,255 fatalities, 313 of them caused by CVD (Table 2) [63]. SLE raises the risk of CVD by 50 times in women between the ages of 35 and 44 years. However, the increased risk is more negligible at other ages (7-10 times) (Table 2) [64]. A recent meta-analysis discovered that the prevalence of asymptomatic atherosclerotic disease was higher in SLE patients than controls, with higher carotid intima-media thickness (CIMT) scores and a 2.5-fold increase in the prevalence of carotid plaques, both surrogate markers of subclinical atherosclerosis [65]. Aortic stiffness, a key predictor of early vascular aging measured by aortic pulse wave velocity (aPWV), was shown to be affected to a similar extent in SLE as it is in hypertensive patients, indicating that SLE has a similar impact on early vascular aging [66]. Increased PWV and proximal aorta arterial stiffness were seen in children and adolescents with active SLE, implying that inflammation could factor in the increased arterial stiffness seen in young patients [67]. According to epidemiologic research to date, traditional CVD risk variables, such as hyperlipidemia, cigarette smoking, advanced age, hypertension, male sex, and high CRP, appear to be related to increased CVD risk among SLE patients.

However, since previous studies did not look at all of these risk variables in the same populations simultaneously, comparisons of the relative risk associated with each are impossible [68]. According to one study, patients still had a 7-10-fold more significant risk of CVD after controlling for Framingham risk factors [69].

Reference	Design	Cases	Controls	Population	Variables	Findings
Bernatsky et al. (2006) [63]	Cohort study (1958-2001)	9,547 cases with SLE	--	>16 years from 7 countries (Canada, US, England, Scotland, Iceland, Sweden, South Korea)	Examined the mortality in SLE patients	1,255 fatalities, 313 of which were caused by CVD
Aviña-Zubieta et al. (2017) [62]	Cohort study (1996-2010)	4,863 cases with SLE (86% females)	10 healthy matched controls per case	Mean age: 48.9 years, from British Columbia and other parts of Canada	IRs of MI, stroke, and CVD were observed and compared	IRs of MI, stroke, and CVD were 6.4, 4.4, and 9.9 events per 1,000 person-years, vs. 2.8, 2.3, and 4.7 events per 1,000 person-years in the comparison cohort
Manzi et al. (1997) [64]	Cohort study (1980-1993)	498 women with SLE	2,208 women of similar age participating in the Framingham Offspring Study	University of Pittsburgh Medical Center	Risk factors associated with CV events occurring in SLE patients were determined	33 first events (11 MI, 10 angina pectoris, and 12 both angina pectoris and MI). Women with lupus in the 35-44-year age group were over 50 times more likely to have an MI vs. the control group

TABLE 2: Summary of studies about the evidence for CVD risk in SLE

SLE: systemic lupus erythematosus; CVD: cardiovascular disease; MI: myocardial infarction; IR: incidence rate

Cardiovascular Disease Screening and Assessment in Systemic Lupus Erythematosus

Recently, Mavrogeni et al. showed that CV MRI could detect silent cardiac illness overlooked by echocardiography. Indeed, 27.5% of SLE patients with regular echocardiograms but silent/past myocarditis, MI, or vasculitis had abnormalities discovered using CV MRI [70]. According to a recent study published by Seguro et al., SLE is linked to increased visceral adipose tissue and altered adiposity distribution [71]. Aortic perivascular adipose tissue density was also linked to aortic calcification in women with SLE, implying that adipose tissue malfunction may play an important role in CVD [72].

In the early stages of acute MI, cardiac troponin T (cTnT) has been postulated to measure myocyte necrosis and damage [73]. In the general population with a low CVD risk, high-sensitivity cTnT has shown promise in predicting CVD [74]. Divard et al. have observed that levels of high-sensitivity cTnT were independently related with subclinical atherosclerosis in asymptomatic SLE patients regarded as low risk for CVD based on conventional risk factors in a recent cross-sectional controlled study [75].

LDGs, as previously stated, have a pathogenic role in lupus CVD [26]. In an uncorrected linear regression analysis, LDG levels were substantially linked with NCB severity and reduced cholesterol efflux capability in SLE. Furthermore, the authors discovered that a neutrophil gene signature was related to vascular pathology in SLE patients. Indeed, some of the genes found to be elevated in high-NCB SLE groups were also shown to be increased in LDGs when compared to normal-density neutrophils. These data indicate that LDG levels in SLE patients might be used to predict CVD risk [26].

Reduced overall antioxidant capacity in SLE patients without typical CV risk factors is linked to subclinical coronary microvascular dysfunction [76]. PON1, an antioxidant enzyme that binds to HDL and protects LDL from oxidation, is lower in those with SLE, and it is linked to vascular damage [77,78]. Anti-PON1 and anti-HDL antibodies were studied as biomarkers for lupus CVD in recent research. It was discovered that anti-HDL antibodies were linked to a greater risk of CVD, while anti-PON1 antibodies were coupled to CIMT in SLE patients [36]. As a result, such antibodies might be used as early indicators for SLE-related premature atherosclerosis [36]. According to a recent study, biomarkers reflecting receptor-activated apoptosis and tissue degradation, such as Fas, TNF receptor 1, TNF-related apoptosis-inducing ligand receptor 2, MMP-1, and MMP-7, are significantly higher in SLE patients with CVD than those without CVD [79].

Management of CVD in SLE

SLE is a distinct CVD risk factor caused by traditional and illness-related risk factors, such as chronic condition activity, lupus nephritis (LN), aPL, and glucocorticoid usage [80]. The use of statins should be based on other conventional risk factors and cholesterol levels. Although the actual risk in people with SLE is overestimated, calculating the 10-year CVD risk using, for example, the systematic coronary risk evaluation (SCORE) is recommended [81]. Blood pressure should be kept at 140/90 mmHg; thus, this should be the general target for SLE patients [82]. Patients with blood pressure higher than 130/80 mmHg who have clinical CVD or a highly predicted CVD risk (>10%) should be treated to reach a goal of <130/80 mmHg [83,84]. SLE was independently associated with a high indicator of in-hospital mortality after percutaneous coronary angioplasty (PCI) and was linked to overall mortality, repeat revascularization, and major adverse CV events in a study based on Taiwan's National Health Insurance Research Database. The study showed the inherent risks of SLE in PCI patients and emphasized the need for better treatment and secondary preventive initiatives for these high-risk individuals [85].

Specific Treatment of SLE

Antimalarial's impact on CV risk in SLE has been analyzed in five studies: one meta-analysis, one cohort study, two case-control studies, and one cross-sectional study. In a meta-analysis, Ruiz-Irastorza et al. showed that hydroxychloroquine is effective in the primary prevention of thrombotic events in patients with SLE and cardiovascular risk factors (CVRFs) [86]. Antimalarials were also linked to a decreased incidence of thrombotic events in individual studies [87-89]. Penn et al. reviewed the medical records of 149 non-diabetic SLE patients, half of whom had received antimalarial therapy [90]. Over 16 years, the researchers measured glucose levels (mg/dL), homeostasis model assessment-estimated insulin resistance (HOMA-IR), and LDL. Compared to the control group, the antimalarial group had reduced fasting glucose levels (87.1 mg/dL against 91.5 mg/dL) and insulin resistance (HOMA-IR: 194 vs. 179). LDL levels were also lower in the treated group compared to the untreated group (LDL of 102 mg/dL vs. 118 mg/dL in the treated and untreated groups, respectively). Ultimately, hydroxychloroquine appears to be beneficial for the primary prevention of thrombotic events in patients with SLE and CVRFs, with a degree of scientific evidence and a grade of recommendation of SIGN 1+ B. Also, with a level of scientific evidence 1 for hydroxychloroquine, it appears to have a favorable effect on glucose levels, insulin resistance, and LDL levels. Still, the degree of SIGN recommendation could not be determined [90].

Limitations

This study does not address the traditional risk factors like smoking, obesity, age, hypertension, diabetes mellitus, menopause, and family history of CAD independently leading to CVD, as we focus specifically on SLE leading to CVD.

Conclusions

Based on the studies discussed in this article, SLE is linked to an elevated risk of accelerated atherosclerosis and CV events, including CAD, stroke, and vascular disease. CV events can occur both early and late in the course of the illness, with younger patients being substantially more at risk than their age-matched peers. In summary, the clinical implication of this article is to establish a strong link between several SLE-specific processes, including impaired immunological regulation, impaired EC function, impaired vascular repair, hyperleptinemia, and traditional risk factors that contribute to the development of early atherosclerosis in the disease. We believe this article can serve as a tool to overcome these challenges by providing a unique approach to the connection between the two entities, i.e., SLE and CVD, by highlighting the pathogenesis, clinical evidence, screening, and management options. We explicitly delineated the challenges faced by physicians while tackling the various association between SLE and CVD by enumerating the different mechanisms involved, specific treatment-related issues, and management of the disease altogether in this article. Despite considerable advances in understanding the mechanisms of such intricate interactions, more research is needed to evaluate the therapeutic value of treating those components in preventing SLE-related CVD. Also, in spite of the advances in treatment, standardized mortality rates in SLE remain three times higher than in the general population. The risk of mortality is significantly increased due to CVD, which is one of the main factors we covered in this article, others being renal involvement and infections. Continued efforts to perform research on alternative processes that contribute to accelerated CVD in SLE and more studies on screening modalities are required to identify better molecular possibilities, facilitate early diagnosis and primary prevention for therapeutic targeting, as well as an emphasis on secondary preventive initiatives for these high-risk individuals, in the long run, to improve the CV outcomes.

Additional Information**Disclosures**

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might

have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

- Gustafsson JT, Svenungsson E: Definitions of and contributions to cardiovascular disease in systemic lupus erythematosus. *Autoimmunity*. 2014, 47:67-76. [10.3109/08916934.2013.856005](#)
- Felten R, Lipsker D, Sibilia J, Chasset F, Arnaud L: The history of lupus throughout the ages [Epub ahead of print]. *J Am Acad Dermatol*. 2020, [10.1016/j.jaad.2020.04.150](#)
- Rees F, Doherty M, Grainge M, Davenport G, Lanyon P, Zhang W: The incidence and prevalence of systemic lupus erythematosus in the UK, 1999-2012. *Ann Rheum Dis*. 2016, 75:136-41. [10.1136/annrheumdis-2014-206334](#)
- Petri M: Epidemiology of systemic lupus erythematosus. *Best Pract Res Clin Rheumatol*. 2002, 16:847-58. [10.1053/berh.2002.0259](#)
- Johnson AE, Gordon C, Palmer RG, Bacon PA: The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Relationship to ethnicity and country of birth. *Arthritis Rheum*. 1995, 38:551-8. [10.1002/art.1780380415](#)
- Danchenko N, Satia JA, Anthony MS: Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. *Lupus*. 2006, 15:308-18. [10.1191/0961203306lu2305xx](#)
- Symmons DP: Frequency of lupus in people of African origin. *Lupus*. 1995, 4:176-8. [10.1177/096120339500400303](#)
- Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS: Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum*. 2010, 39:257-68. [10.1016/j.semarthrit.2008.10.007](#)
- Parks CG, de Souza Espindola Santos A, Barbhaiya M, Costenbader KH: Understanding the role of environmental factors in the development of systemic lupus erythematosus. *Best Pract Res Clin Rheumatol*. 2017, 31:306-20. [10.1016/j.berh.2017.09.005](#)
- Fava A, Petri M: Systemic lupus erythematosus: diagnosis and clinical management. *J Autoimmun*. 2019, 96:1-13. [10.1016/j.jaut.2018.11.001](#)
- Generali E, Ceribelli A, Stazi MA, Selmi C: Lessons learned from twins in autoimmune and chronic inflammatory diseases. *J Autoimmun*. 2017, 83:51-61. [10.1016/j.jaut.2017.04.005](#)
- Ghodke-Puranik Y, Niewold TB: Immunogenetics of systemic lupus erythematosus: a comprehensive review. *J Autoimmun*. 2015, 64:125-36. [10.1016/j.jaut.2015.08.004](#)
- Justiz Vaillant AA, Goyal A, Bansal P, Varacallo M: Systemic Lupus Erythematosus. *StatPearls*, Treasure Island, FL; 2021.
- Denny MF, Thacker S, Mehta H, et al.: Interferon-alpha promotes abnormal vasculogenesis in lupus: a potential pathway for premature atherosclerosis. *Blood*. 2007, 110:2907-15. [10.1182/blood-2007-05-089086](#)
- Rajagopalan S, Somers EC, Brook RD, et al.: Endothelial cell apoptosis in systemic lupus erythematosus: a common pathway for abnormal vascular function and thrombosis propensity. *Blood*. 2004, 103:3677-83. [10.1182/blood-2003-09-3198](#)
- Lee PY, Li Y, Richards HB, et al.: Type I interferon as a novel risk factor for endothelial progenitor cell depletion and endothelial dysfunction in systemic lupus erythematosus. *Arthritis Rheum*. 2007, 56:3759-69. [10.1002/art.23035](#)
- Moonen JR, de Leeuw K, van Seijen XJ, Kallenberg CG, van Luyn MJ, Bijl M, Harmsen MC: Reduced number and impaired function of circulating progenitor cells in patients with systemic lupus erythematosus. *Arthritis Res Ther*. 2007, 9:R84. [10.1186/ar2283](#)
- Westerweel PE, Luijten RK, Hoefer IE, Koomans HA, Derksen RH, Verhaar MC: Haematopoietic and endothelial progenitor cells are deficient in quiescent systemic lupus erythematosus. *Ann Rheum Dis*. 2007, 66:865-70. [10.1136/ard.2006.065631](#)
- Taraborelli M, Sciatti E, Bonadei I, et al.: Endothelial dysfunction in early systemic lupus erythematosus patients and controls without previous cardiovascular events. *Arthritis Care Res (Hoboken)*. 2018, 70:1277-83. [10.1002/acr.23495](#)
- Rho YH, Chung CP, Oeser A, et al.: Novel cardiovascular risk factors in premature coronary atherosclerosis associated with systemic lupus erythematosus. *J Rheumatol*. 2008, 35:1789-94.
- Nhek S, Clancy R, Lee KA, et al.: Activated platelets induce endothelial cell activation via an interleukin-1 β pathway in systemic lupus erythematosus. *Arterioscler Thromb Vasc Biol*. 2017, 37:707-16. [10.1161/ATVBAHA.116.308126](#)
- Somers EC, Zhao W, Lewis EE, et al.: Type I interferons are associated with subclinical markers of cardiovascular disease in a cohort of systemic lupus erythematosus patients. *PLoS One*. 2012, 7:e37000. [10.1371/journal.pone.0037000](#)
- Tydén H, Lood C, Gullstrand B, et al.: Endothelial dysfunction is associated with activation of the type I interferon system and platelets in patients with systemic lupus erythematosus. *RMD Open*. 2017, 3:e000508. [10.1136/rmdopen-2017-000508](#)
- King KR, Aguirre AD, Ye YX, et al.: IRF3 and type I interferons fuel a fatal response to myocardial infarction. *Nat Med*. 2017, 23:1481-7. [10.1038/nm.4428](#)
- Knight JS, Kaplan MJ: Lupus neutrophils: 'NET' gain in understanding lupus pathogenesis. *Curr Opin Rheumatol*. 2012, 24:441-50. [10.1097/BOR.0b013e3283546703](#)
- Carlucci PM, Purmalek MM, Dey AK, et al.: Neutrophil subsets and their gene signature associate with vascular inflammation and coronary atherosclerosis in lupus. *JCI Insight*. 2018, 3:276. [10.1172/jci.insight.99276](#)
- Wilhelm AJ, Rhoads JP, Wade NS, Major AS: Dysregulated CD4⁺ T cells from SLE-susceptible mice are sufficient to accelerate atherosclerosis in LDLr^{-/-} mice. *Ann Rheum Dis*. 2015, 74:778-85. [10.1136/annrheumdis-2013-203759](#)
- Clement M, Charles N, Escoubet B, et al.: CD4⁺CXCR3⁺ T cells and plasmacytoid dendritic cells drive

- accelerated atherosclerosis associated with systemic lupus erythematosus. *J Autoimmun.* 2015, 63:59-67. [10.1016/j.jaut.2015.07.001](#)
29. Baragetti A, Ramirez GA, Magnoni M, et al.: Disease trends over time and CD4+CCR5+ T-cells expansion predict carotid atherosclerosis development in patients with systemic lupus erythematosus. *Nutr Metab Cardiovasc Dis.* 2018, 28:53-63. [10.1016/j.numecd.2017.09.001](#)
30. Smith E, Croca S, Waddington KE, et al.: Cross-talk between iNKT cells and monocytes triggers an atheroprotective immune response in SLE patients with asymptomatic plaque. *Sci Immunol.* 2016, 1:4081. [10.1126/sciimmunol.aah4081](#)
31. Theodorou E, Nezos A, Antypa E, et al.: B-cell activating factor and related genetic variants in lupus related atherosclerosis. *J Autoimmun.* 2018, 92:87-92. [10.1016/j.jaut.2018.05.002](#)
32. Kravvariti E, Konstantonis G, Sfrikakis PP, Tektonidou MG: Progression of subclinical atherosclerosis in systemic lupus erythematosus versus rheumatoid arthritis: the impact of low disease activity. *Rheumatology (Oxford).* 2018, 57:2158-66. [10.1093/rheumatology/key233](#)
33. Perez-Sanchez C, Barbarroja N, Messineo S, et al.: Gene profiling reveals specific molecular pathways in the pathogenesis of atherosclerosis and cardiovascular disease in antiphospholipid syndrome, systemic lupus erythematosus and antiphospholipid syndrome with lupus. *Ann Rheum Dis.* 2015, 74:1441-9. [10.1136/annrheumdis-2013-204600](#)
34. Kurien BT, Fesmire J, Anderson CJ, Scofield RH: Anti-Ro and concomitant anti-La autoantibodies strongly associated with anti-oxLDL or anti-phospholipid antibody in systemic lupus erythematosus. *J Clin Rheumatol.* 2016, 22:418-25. [10.1097/RHU.0000000000000429](#)
35. Kiss E, Seres I, Tarr T, Kocsis Z, Szegedi G, Paragh G: Reduced paraoxonase1 activity is a risk for atherosclerosis in patients with systemic lupus erythematosus. *Ann N Y Acad Sci.* 2007, 1108:83-91. [10.1196/annals.1422.009](#)
36. López P, Rodríguez-Carrio J, Martínez-Zapico A, et al.: Serum levels of anti-PON1 and anti-HDL antibodies as potential biomarkers of premature atherosclerosis in systemic lupus erythematosus. *Thromb Haemost.* 2017, 117:2194-206. [10.1160/TH17-03-0221](#)
37. Batuca JR, Ames PR, Isenberg DA, Alves JD: Antibodies toward high-density lipoprotein components inhibit paraoxonase activity in patients with systemic lupus erythematosus. *Ann N Y Acad Sci.* 2007, 1108:137-46. [10.1196/annals.1422.016](#)
38. Chistiakov DA, Orekhov AN, Bobryshev YV: ApoA1 and ApoA1-specific self-antibodies in cardiovascular disease. *Lab Invest.* 2016, 96:708-18. [10.1038/labinvest.2016.56](#)
39. de Faire U, Frostegård J: Natural antibodies against phosphorylcholine in cardiovascular disease. *Ann N Y Acad Sci.* 2009, 1173:292-300. [10.1111/j.1749-6632.2009.04748.x](#)
40. Caligiuri G, Khallou-Laschet J, Vandaele M, et al.: Phosphorylcholine-targeting immunization reduces atherosclerosis. *J Am Coll Cardiol.* 2007, 50:540-6. [10.1016/j.jacc.2006.11.054](#)
41. Svenungsson E, Engelbertsen D, Wigren M, et al.: Decreased levels of autoantibodies against apolipoprotein B-100 antigens are associated with cardiovascular disease in systemic lupus erythematosus. *Clin Exp Immunol.* 2015, 181:417-26. [10.1111/cei.12651](#)
42. Sun J, Lundström SL, Zhang B, et al.: IgM antibodies against phosphorylcholine promote polarization of T regulatory cells from patients with atherosclerotic plaques, systemic lupus erythematosus and healthy donors. *Atherosclerosis.* 2018, 268:36-48. [10.1016/j.atherosclerosis.2017.11.010](#)
43. Rahman M, Sing S, Golabkesh Z, et al.: IgM antibodies against malondialdehyde and phosphorylcholine are together strong protection markers for atherosclerosis in systemic lupus erythematosus: Regulation and underlying mechanisms. *Clin Immunol.* 2016, 166:27-37. [10.1016/j.clim.2016.04.007](#)
44. Szabó MZ, Szodoray P, Kiss E: Dyslipidemia in systemic lupus erythematosus. *Immunol Res.* 2017, 65:543-50. [10.1007/s12026-016-8892-9](#)
45. Smith CK, Vivekanandan-Giri A, Tang C, et al.: Neutrophil extracellular trap-derived enzymes oxidize high-density lipoprotein: an additional proatherogenic mechanism in systemic lupus erythematosus. *Arthritis Rheumatol.* 2014, 66:2532-44. [10.1002/art.38703](#)
46. Ronda N, Favari E, Borghi MO, et al.: Impaired serum cholesterol efflux capacity in rheumatoid arthritis and systemic lupus erythematosus. *Ann Rheum Dis.* 2014, 73:609-15. [10.1136/annrheumdis-2012-202914](#)
47. McMahon M, Grossman J, FitzGerald J, et al.: Proinflammatory high-density lipoprotein as a biomarker for atherosclerosis in patients with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum.* 2006, 54:2541-9. [10.1002/art.21976](#)
48. De Nardo D, Labzin LI, Kono H, et al.: High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. *Nat Immunol.* 2014, 15:152-60. [10.1038/ni.2784](#)
49. Smith CK, Seto NL, Vivekanandan-Giri A, et al.: Lupus high-density lipoprotein induces proinflammatory responses in macrophages by binding lectin-like oxidized low-density lipoprotein receptor 1 and failing to promote activating transcription factor 3 activity. *Ann Rheum Dis.* 2017, 76:602-11. [10.1136/annrheumdis-2016-209683](#)
50. Miyake CN, Gualano B, Dantas WS, et al.: Increased insulin resistance and glucagon levels in mild/inactive systemic lupus erythematosus patients despite normal glucose tolerance. *Arthritis Care Res (Hoboken).* 2018, 70:114-24. [10.1002/acr.23237](#)
51. Dessie G, Ayelign B, Akalu Y, Shibabaw T, Molla MD: Effect of leptin on chronic inflammatory disorders: insights to therapeutic target to prevent further cardiovascular complication. *Diabetes Metab Syndr Obes.* 2021, 14:3307-22. [10.2147/DMSO.S321311](#)
52. Versini M, Tiosano S, Comaneshter D, Shoenfeld Y, Cohen AD, Amital H: Smoking and obesity in systemic lupus erythematosus: a cross-sectional study. *Eur J Clin Invest.* 2017, 47:422-7. [10.1111/eci.12757](#)
53. Mohammed SF, Abdalla MA, Ismaeil WM, Sheta MM: Serum leptin in systemic lupus erythematosus patients: its correlation with disease activity and some disease parameters. *Egypt Rheumatol.* 2018, 40:23-7. [10.1016/j.ejr.2017.06.005](#)
54. Karp I, Abrahamowicz M, Fortin PR, Pilote L, Neville C, Pineau CA, Esdaile JM: Recent corticosteroid use and recent disease activity: independent determinants of coronary heart disease risk factors in systemic lupus erythematosus?. *Arthritis Rheum.* 2008, 59:169-75. [10.1002/art.23352](#)

55. Petri M, Perez-Gutthann S, Spence D, Hochberg MC: Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med.* 1992, 93:513-9. [10.1016/0002-9343\(92\)90578-y](#)
56. Nikpour M, Urowitz MB, Ibanez D, Harvey PJ, Gladman DD: Importance of cumulative exposure to elevated cholesterol and blood pressure in development of atherosclerotic coronary artery disease in systemic lupus erythematosus: a prospective proof-of-concept cohort study. *Arthritis Res Ther.* 2011, 13:R156. [10.1186/ar3473](#)
57. Urowitz MB, Gladman D, Ibanez D, et al.: Atherosclerotic vascular events in a multinational inception cohort of systemic lupus erythematosus. *Arthritis Care Res (Hoboken).* 2010, 62:881-7. [10.1002/acr.20122](#)
58. Urowitz MB, Gladman D, Ibanez D, et al.: Clinical manifestations and coronary artery disease risk factors at diagnosis of systemic lupus erythematosus: data from an international inception cohort. *Lupus.* 2007, 16:731-5. [10.1177/0961203307081113](#)
59. Pons-Estel GJ, González LA, Zhang J, Burgos PI, Reveille JD, Vilá LM, Alarcón GS: Predictors of cardiovascular damage in patients with systemic lupus erythematosus: data from LUMINA (LXVIII), a multiethnic US cohort. *Rheumatology (Oxford).* 2009, 48:817-22. [10.1093/rheumatology/kep102](#)
60. Burgos PI, Vilá LM, Reveille JD, Alarcón GS: Peripheral vascular damage in systemic lupus erythematosus: data from LUMINA, a large multi-ethnic U.S. cohort (LXIX). *Lupus.* 2009, 18:1303-8. [10.1177/0961203309105877](#)
61. Haque S, Gordon C, Isenberg D, et al.: Risk factors for clinical coronary heart disease in systemic lupus erythematosus: the lupus and atherosclerosis evaluation of risk (LASER) study. *J Rheumatol.* 2010, 37:322-9. [10.3899/jrheum.090306](#)
62. Aviña-Zubieta JA, To F, Vostretsova K, De Vera M, Sayre EC, Esdaile JM: Risk of myocardial infarction and stroke in newly diagnosed systemic lupus erythematosus: a general population-based study. *Arthritis Care Res (Hoboken).* 2017, 69:849-56. [10.1002/acr.23018](#)
63. Bernatsky S, Boivin JF, Joseph L, et al.: Mortality in systemic lupus erythematosus. *Arthritis Rheum.* 2006, 54:2550-7. [10.1002/art.21955](#)
64. Manzi S, Meilahn EN, Rairie JE, et al.: Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol.* 1997, 145:408-15. [10.1093/oxfordjournals.aje.a009122](#)
65. Wu GC, Liu HR, Leng RX, Li XP, Li XM, Pan HF, Ye DQ: Subclinical atherosclerosis in patients with systemic lupus erythematosus: a systematic review and meta-analysis. *Autoimmun Rev.* 2016, 15:22-37. [10.1016/j.autrev.2015.10.002](#)
66. Morreale M, Mulè G, Ferrante A, D'ignoto F, Cottone S: Early vascular aging in normotensive patients with systemic lupus erythematosus: comparison with young patients having hypertension. *Angiology.* 2016, 67:676-82. [10.1177/0003319715613917](#)
67. El Gamal YM, Elmasry OA, El Hadidi IS, Soliman OK: Proximal aortic stiffness is increased in systemic lupus erythematosus activity in children and adolescents. *ISRN Pediatr.* 2013, 2013:765253. [10.1155/2013/765253](#)
68. Schoenfeld SR, Kasturi S, Costenbader KH: The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: a systematic review. *Semin Arthritis Rheum.* 2013, 43:77-95. [10.1016/j.semarthrit.2012.12.002](#)
69. Esdaile JM, Abrahamowicz M, Grodzicky T, et al.: Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum.* 2001, 44:2331-7. [10.1002/1529-0131\(200110\)44:10<2331::aid-art395>3.0.co;2-i](#)
70. Mavrogeni S, Koutsogeorgopoulou L, Markousis-Mavrogenis G, et al.: Cardiovascular magnetic resonance detects silent heart disease missed by echocardiography in systemic lupus erythematosus. *Lupus.* 2018, 27:564-71. [10.1177/0961203317731533](#)
71. Seguro LP, Paupitz JA, Caparbo VF, Bonfa E, Pereira RM: Increased visceral adipose tissue and altered adiposity distribution in premenopausal lupus patients: correlation with cardiovascular risk factors. *Lupus.* 2018, 27:1001-6. [10.1177/0961203318758504](#)
72. Shields KJ, El Khoudary SR, Ahearn JM, Manzi S: Association of aortic perivascular adipose tissue density with aortic calcification in women with systemic lupus erythematosus. *Atherosclerosis.* 2017, 262:55-61. [10.1016/j.atherosclerosis.2017.04.021](#)
73. Katus HA, Remppis A, Neumann FJ, et al.: Diagnostic efficiency of troponin T measurements in acute myocardial infarction. *Circulation.* 1991, 83:902-12. [10.1161/01.cir.83.3.902](#)
74. Saunders JT, Nambi V, de Lemos JA, et al.: Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation.* 2011, 123:1367-76. [10.1161/CIRCULATIONAHA.110.005264](#)
75. Divard G, Abbas R, Chenevier-Gobeaux C, et al.: High-sensitivity cardiac troponin T is a biomarker for atherosclerosis in systemic lupus erythematosus patients: a cross-sectional controlled study. *Arthritis Res Ther.* 2017, 19:132. [10.1186/s13075-017-1352-7](#)
76. Yilmaz S, Caliskan M, Kulaksizoglu S, et al.: Association between serum total antioxidant status and coronary microvascular functions in patients with SLE. *Echocardiography.* 2012, 29:1218-23. [10.1111/j.1540-8175.2012.01797.x](#)
77. Soran H, Schofield JD, Liu Y, Durrington PN: How HDL protects LDL against atherogenic modification: paraoxonase 1 and other dramatis personae. *Curr Opin Lipidol.* 2015, 26:247-56. [10.1097/MOL.0000000000000194](#)
78. Delgado Alves J, Ames PR, Donohue S, Stanyer L, Nourooz-Zadeh J, Ravirajan C, Isenberg DA: Antibodies to high-density lipoprotein and beta2-glycoprotein I are inversely correlated with paraoxonase activity in systemic lupus erythematosus and primary antiphospholipid syndrome. *Arthritis Rheum.* 2002, 46:2686-94. [10.1002/art.10542](#)
79. Wigren M, Svenungsson E, Mattisson IY, et al.: Cardiovascular disease in systemic lupus erythematosus is associated with increased levels of biomarkers reflecting receptor-activated apoptosis. *Atherosclerosis.* 2018, 270:1-7. [10.1016/j.atherosclerosis.2018.01.022](#)
80. Kostopoulou M, Nikolopoulos D, Parodis I, Bertsias G: Cardiovascular disease in systemic lupus erythematosus: recent data on epidemiology, risk factors and prevention. *Curr Vasc Pharmacol.* 2020,

- 18:549-65. [10.2174/1570161118666191227101636](https://doi.org/10.2174/1570161118666191227101636)
81. Piepoli MF, Hoes AW, Agewall S, et al.: 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016, 37:2315-81. [10.1093/eurheartj/ehw106](https://doi.org/10.1093/eurheartj/ehw106)
 82. Tselios K, Gladman DD, Su J, Urowitz M: Impact of the new American College of Cardiology/American Heart Association definition of hypertension on atherosclerotic vascular events in systemic lupus erythematosus. *Ann Rheum Dis*. 2020, 79:612-7. [10.1136/annrheumdis-2019-216764](https://doi.org/10.1136/annrheumdis-2019-216764)
 83. Whelton PK, Carey RM, Aronow WS, et al.: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018, 71:e127-248. [10.1016/j.jacc.2017.11.006](https://doi.org/10.1016/j.jacc.2017.11.006)
 84. Williams B, Mancia G, Spiering W, et al.: 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018, 39:3021-104. [10.1093/eurheartj/ehy339](https://doi.org/10.1093/eurheartj/ehy339)
 85. Lai CH, Lai WW, Chiou MJ, Lin WC, Yang YJ, Li CY, Tsai LM: Outcomes of percutaneous coronary intervention in patients with rheumatoid arthritis and systemic lupus erythematosus: an 11-year nationwide cohort study. *Ann Rheum Dis*. 2016, 75:1350-6. [10.1136/annrheumdis-2015-207719](https://doi.org/10.1136/annrheumdis-2015-207719)
 86. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA: Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis*. 2010, 69:20-8. [10.1136/ard.2008.101766](https://doi.org/10.1136/ard.2008.101766)
 87. Kaiser R, Cleveland CM, Criswell LA: Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. *Ann Rheum Dis*. 2009, 68:238-41. [10.1136/ard.2008.093013](https://doi.org/10.1136/ard.2008.093013)
 88. Jung H, Bobba R, Su J, et al.: The protective effect of antimalarial drugs on thrombovascular events in systemic lupus erythematosus. *Arthritis Rheum*. 2010, 62:863-8. [10.1002/art.27289](https://doi.org/10.1002/art.27289)
 89. Ruiz-Irastorza G, Egurbide MV, Pijoan JI, et al.: Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. *Lupus*. 2006, 15:577-83. [10.1177/0961203306071872](https://doi.org/10.1177/0961203306071872)
 90. Penn SK, Kao AH, Schott LL, et al.: Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. *J Rheumatol*. 2010, 37:1136-42. [10.3899/jrheum.090994](https://doi.org/10.3899/jrheum.090994)