Chapter

Accelerated Atherosclerosis in SLE: Mechanisms, Consequences, and Future Directions

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Abstract

The bimodal mortality rate in systemic lupus erythematosus (SLE) has been well documented, with atherosclerosis identified as a leading cause of late-stage death. Multiple mechanisms are responsible for accelerated atherosclerosis in SLE, ultimately resulting in endothelial dysfunction, arterial stiffness, arterial wall thickening, and plaque formation. This leads to an increased risk of coronary artery disease, cardiovascular events, cerebrovascular accidents, and peripheral arterial disease. SLE patients are not only impacted by traditional risk factors for cardiovascular disease (age, smoking, dyslipidemia, diabetes), but additionally nontraditional risk factors (prolonged corticosteroid use, disease activity and chronic inflammation). Identifying the impact of traditional risk factors and mediating nontraditional risk factors in SLE are vital to reduce morbidity and mortality related to atherosclerosis. SLE-specific screening methods should be established in the routine care of these patients, including the use of validated modified risk scores and imaging modalities. Furthermore, the utility of disease-specific biomarkers and anti-atherosclerotic therapies should be elicited. This chapter will provide an overview of considerations for the mechanisms, impact, and prevention of atherosclerosis in SLE patients.

Keywords: systemic lupus erythematosus, atherosclerosis, endothelial dysfunction, cardiovascular disease, coronary artery disease, cerebrovascular accident, peripheral arterial disease, risk stratification

1. Introduction

Survival in systemic lupus erythematosus (SLE) has dramatically improved over recent decades due to advancements in early diagnosis and therapies to prevent end-stage organ damage, particularly at the onset of disease [1, 2]. In 1976, Urowitz et al. reported a bimodal distribution of death in SLE, with atherosclerosis identified as a leading cause of late-stage mortality [3]. Although the prevalence and severity of the atherosclerotic cardiovascular events (CVEs) have been steadily decreasing over the last decades, the standardized mortality ratio (SMR) from atherosclerosis remains threefold higher compared with the general population [4].

Atherosclerosis is an inflammatory condition characterized by the storage of lipids and the accumulation of immune cells in the media layer of the arterial wall in medium- and large-sized arteries. Progressing disease will eventually lead to ischemia and hypoperfusion or complete obstruction of the blood flow in the affected organs, which manifests as CVEs, cerebrovascular accidents (CVA or stroke), and peripheral arterial disease (PAD) [5–8]. SLE patients have an earlier onset of atherosclerosis compared with the general population, which is not completely explained by traditional risk factors [9]. SLE-related disease factors are felt to contribute substantially to premature and accelerated atherosclerotic disease [10, 11]. The pathophysiology of accelerated atherosclerosis is not completely understood, but is a consequence of complex interactions between autoimmunity, chronic inflammation, vascular repair, traditional risk factors, and medications [12, 13].

Focused efforts by clinicians must incorporate preventative strategies to reduce the impact of traditional and nontraditional cardiovascular risk factors in SLE patients. This chapter provides an overview of considerations for the mechanisms, impact, and prevention of atherosclerosis in SLE.

2. Mechanisms

Traditional and nontraditional risk factors impact the risk of atherosclerotic disease in SLE patients [4, 14]. Traditional risk factors include: (a) non-modifiable risk factors (age, sex, and family history of atherosclerosis) and (b) modifiable risk factors (hypertension, diabetes, dyslipidemia, smoking, metabolic syndrome, elevated homocysteine levels, etc.). Lupus-related (nontraditional) risk factors include disease activity and related damage, disease duration, autoantibodies, soluble inflammatory mediators, disease-specific phenotypes, and comorbidities as well as select medications [4]. The aforementioned factors are shown in **Table 1**. In most cases, several of these factors act simultaneously to accelerate atherosclerosis; hence a comprehensive approach for cardiovascular risk reduction is warranted.

2.1 Traditional non-modifiable risk factors

Age: Age over 48 and postmenopausal status are independent risk factors of CVEs (HR 1.04–5.1) [15]. Subclinical markers of atherosclerosis (i.e., endothelial dysfunction, arterial stiffness, arterial wall thickening and/or plaque formation, coronary artery calcification, and angiographically defined plaques) are associated with increasing age [4].

Sex: Male sex is a predictor of CVEs (HR 1.56–6.2) and subclinical atherosclerosis [4].

Family history: A positive family history of coronary artery disease (CAD) is defined as the occurrence of a CVE in a first-degree male relative aged 55 years or younger, or a first-degree female relative aged 65 years or younger. Family history is associated with increased risk of CVEs, though this was not associated with subclinical disease [4].

2.2 Traditional modifiable risk factors

Hypertension: The prevalence of hypertension in SLE ranges from 25 to 74%, which is likely related to renal disease, chronic nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoid use [4]. Moreover, the activation of the

Traditional risk factors	
Non-modifiable	Age
	Male sex
	Family history
Modifiable	Arterial hypertension
	Diabetes
	Dyslipidemia
	Smoking
	Metabolic syndrome
	Elevated homocysteine
Nontraditional risk factors	
	Disease activity
	Cumulative disease-related damage
	Disease duration
	Disease phenotypes (e.g., neuropsychiatric disease, renal disease, leukopenia, lymphopenia)
	Autoantibodies (e.g., anticardiolipin, anti-dsDNA)
	Soluble inflammatory mediators (e.g., high-sensitivity C-reactive protein)
	Select therapies (e.g., high dose glucocorticoids, azathioprine)
	NSAID use
	Vitamin D deficiency

Table 1.
Risk factors for atherosclerotic disease in systemic lupus erythematosus.

renin-angiotensin system, increased levels of endothelin-1, and oxidative stress along with certain cytokines (IL-6, IL-17, TNFa) play a significant role [16]. Hypertension is an independent risk factor for CVEs (RR 1.05–3.5) [4]. Blood pressure in SLE has been found to fluctuate significantly, thus time-adjusted mean systolic and diastolic blood pressure may capture the cardiovascular risk in SLE patients more accurately than traditional definitions of blood pressure [17]. It was recently shown that levels of blood pressure between 130 and 139 mmHg (for systolic blood pressure) and between 80 and 89 mmHg (for diastolic blood pressure) confer a significantly higher risk for CVEs compared with blood pressure levels of <130/80 mmHg [18].

Diabetes: In SLE, diabetes is an independent risk factor for CVEs and subclinical disease detected by carotid intima-media thickness (IMT) and myocardial perfusion defects [4]. Insulin resistance in diabetic and non-diabetic SLE patients is less frequently related to glucocorticoid use, but is attributed to disease activity, elevated inflammatory markers, and increased oxidized LDL [19]. Impairment of glucose metabolism has been demonstrated by decreased sensitivity to insulin in non-diabetic lupus patients. Euglycemic state is achieved by a compensatory increase in insulin secretion [4].

Dyslipidemia: Dyslipidemia in SLE is believed to be secondary to autoantibody production against lipoprotein lipase (LPL), oxidized low-density lipoproteins (LDL), high-density lipoprotein (HDL), and apolipoprotein A1 [4]. There is also increased hepatic synthesis of very low-density lipoproteins (VLDL) related to cytokine release [20]. The first pattern of dyslipidemia in SLE is reflective of active or untreated disease, with increased triglycerides (TG) and VLDL as well as decreased HDL. The second pattern is related to renal disease, hypothyroidism, and glucocorticoid use and is characterized by elevated total cholesterol (TC), TGs, and LDL [4]. Decreased HDL, increased TGs and TC levels are independent risk factors for CVEs [4, 17, 20, 21].

Recently, the role of proinflammatory HDL in accelerated atherosclerosis in SLE was described. It is believed that chemically modified HDL molecules lose their antiatherogenic properties and induce vascular inflammation through immune-mediated mechanisms. Proinflammatory HDL was strongly associated with increased carotid IMT and plaque formation [22]. Dysfunctional proinflammatory HDL confers increased risk for atherosclerosis in women with SLE [22].

Smoking: Smoking is an independent predictor of CVEs (HR 2.2–3.7) and is associated with subclinical disease identified by carotid plaque and coronary artery calcification (CAC) [4].

Metabolic syndrome: Metabolic syndrome ("abnormal" waist circumference with elevated triglycerides, arterial hypertension, impaired glucose metabolism, and decreased HDL levels) is an independent risk factor for cardiovascular mortality and may better represent cardiovascular risk in females, rather than obesity [23]. Patients with SLE are three times more likely to have metabolic syndrome compared with the general population [24]. Metabolic syndrome has been associated with increased carotid IMT, arterial stiffness, and CAC [4]. Obesity seems to be the primary risk factor in such patients. Lupus patients with BMI > 30 demonstrated endothelial dysfunction, increased carotid IMT and plaque formation (HR 1.06–6.16), and CAC [4]. Obesity has also been recognized as the major driver of accelerated atherosclerosis in pediatric lupus patients, as assessed prospectively by IMT progression [25].

Elevated homocysteine: Elevated homocysteine levels are related to CAC and increased carotid IMT or plaques [4]. Elevated homocysteine levels increase oxidative stress and inhibition of endothelial derived nitric oxide synthetase, causing endothelial dysfunction. Homocysteine may also induce a prothrombotic state by impairing the function of platelets and soluble coagulation factors [26].

2.3 Nontraditional (lupus-related) risk factors

Disease-related factors: SLE is an independent predictor of CVEs due to various aspects of the disease. Disease-related factors independently associated with CVEs are disease activity (HR 1.05–1.2), as measured by the SLE Disease Activity Index (SLEDAI), disease-related damage, as measured by the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (HR 1.3–4.1), and disease duration (HR 1.10–1.45) [4].

SLE phenotypes and comorbidities: SLE patients with renal and neuropsychiatric disease are at increased risk of CVEs. Renal impairment (HR 1.2–6.8) and proteinuria (HR 2.4) are independent risk factors of CVEs. Renal impairment and lupus nephritis are also associated with Carotid IMT and plaque, and increased aortic stiffness. Neuropsychiatric disease is associated with CVEs (HR 2.2–5.2). Depression and bone mineral density were associated with increased CAC, while leukopenia was associated with increased aortic stiffness and lymphopenia with CVE and progression of carotid IMT [4].

Autoantibodies: Several autoantibodies are associated with clinical and subclinical cardiovascular disease, including anticardiolipin antibodies (aCL), anti-β2 glycoprotein 1 (GPI) antibodies, lupus anticoagulant, and anti-dsDNA antibodies. Presence of aCL (HR 3.1–5.8), GPI (HR 5.2), lupus anticoagulant (HR 1.74), and anti-dsDNA (HR 1.56) are independent predictors of CVEs.

Both aCL and lupus anticoagulant are associated with carotid plaques and coronary calcifications, anti-b2GPI antibodies are associated with coronary calcifications, and anti-dsDNA antibodies with non-calcified coronary plaques. Other phospholipid

epitopes, such as anti-oxPAPC (oxidized palmitoyl arachidonoyl phosphocholine), are risk factors for carotid IMT and plaque formation (HR 1.06). Anti-Sm antibodies are protective against carotid plaques [4].

Soluble inflammatory mediators: High-sensitivity C-reactive protein (hsCRP) independently predicts CVEs (HR 1.6–3.4), endothelial dysfunction, arterial stiffness, carotid IMT, and plaque, as well as CAC scores. Complement fragment C3 is associated with increased arterial stiffness, carotid IMT, and CAC [4]. Tumor necrosis factor (TNF)-like inducer of apoptosis increased the risk of carotid IMT and plaque by almost 30-fold, while TNF-α, vascular cell adhesion molecule (VCAM), E-selectin, and intercellular adhesion molecule 1 (ICAM-1) were associated with CAC. Additional inflammatory mediators found to be associated with clinical and subclinical atherosclerotic disease include low transforming growth factor-β (TGF-b), type I interferons, adipocytokines, leptin, and uric acid [4].

Select therapies: The use of high-dose glucocorticoids independently predicts CVEs (HR 2.5), carotid IMT and plaque formation, CAC, and arterial stiffness. Azathioprine (HR 1.45) and the general use of immunosuppressive agents (HR 1.7) were associated with CVEs, while hydroxychloroquine is protective (HR 0.77) [4].

Other risk factors for atherosclerosis that have been identified, including NSAID use and vitamin D deficiency [14].

2.4 Immunopathophysiology of atherosclerosis in SLE

The interplay of the traditional and disease-related risk factors results in the activation of the endothelial cells that express high levels of adhesion molecules such as ICAM-1, VCAM, and E-selectin. In parallel, there is increased apoptosis of the endothelial cells that is mediated through Fas/FasL and TNF/TNFRII interactions, while its potency leads to insufficient apoptotic debris clearance from monocytes/macrophages. At the same time, IFN-a, a major pathogenetic cytokine in SLE, induces dysregulation of the endothelial progenitor cells that leads to impaired endothelial repair [27].

The proinflammatory cytokine milieu in SLE as well as the increased oxidative stress (expressed with increased levels of reactive oxygen species, ROS) augments the oxidation of LDL. Under normal circumstances, HDL inhibits this pathway effectively. However, in SLE, a certain proportion of the HDL molecules are proinflammatory. At the tissue level (atherosclerotic plaque), oxidized LDL (oxLDL) activates the endothelial cells. This, along with the overexpression of adhesion molecules, induces the subepithelial recruitment of monocytes/macrophages that will eventually phagocytose the oxLDL molecules and other lipids and will transform to "foam" cells [27].

Abundant numbers of neutrophils and plasmacytoid dendritic cells (DCs) have also been detected within the plaque. Neutrophils release neutrophil extracellular traps (NETs) that induce endothelial damage and activate the macrophages toward the production of IL-1β, TNFα, and MCP-1. Plasmacytoid DCs and low-density granulocytes secrete IFN-a, which induces platelet activation. Moreover, B cells are producing antibodies against oxLDL and b2GPI, a potent anticoagulant protein; the formed immune complexes will accelerate the rate of "foam" cell generation and enhance IFNa secretion from the DCs. Simultaneously, the immune complexes containing oxLDL and/or anti-b2GPI and other phospholipid epitopes bind to the C1q receptor of the endothelial cells and induce the expression of VCAM-1, resulting in an auto-amplification loop [27].

Certain T cell subpopulations are also involved in the atherogenic process, mainly Th17 and Th1, while T regulatory cells (Tregs) are found in reduced numbers in the periphery and in the vessel wall. Both Th1 and Th17 cells contribute to the perpetuation of inflammation by secreting proinflammatory cytokines such as Il-17. This has been associated to increased vulnerability of the atherosclerotic plaques that may result in platelet aggregation and thrombosis. All these mechanisms are poorly regulated by Tregs, which are quantitatively and qualitatively impaired in SLE. Tregs may suppress the principal effectors of arterial wall inflammation, namely Th1 and Th17 cells, and downregulate IFN-a and TNF-α. This action is mediated by IL-10 and TGF-β, by cell-to-cell contact mechanisms (including CTLA-4, cytotoxic T cell antigen 4), and by modulation of DC function. Tregs are also able to steer macrophage differentiation toward the M2 anti-inflammatory phenotype by downregulating CD36 and scavenger receptor A (SRA). This mechanism reduces the uptake of oxLDL, thus inhibiting foam cell formation [27].

Apart from the local effects, various cytokines have been shown to affect other risk factors. TNF-α induces a dyslipidemic profile with increased TG, decreased HDL, inhibition of lipoprotein lipase, and induction of VLDL synthesis. Serum levels of TNF-α are strongly related to disease activity and drive the activation of endothelial cells, smooth muscle cells, and macrophages, thus augmenting the atherogenic process. TNF-α is also implicated in endothelial cell apoptosis (through p55 receptor) and vulnerability of the atherosclerotic plaque. Low levels of the transforming growth factor β (TGF-b) in SLE are associated with the breakdown of immune tolerance and have demonstrated a strong correlation with premature atherosclerosis. Other cytokines that were shown to increase CV risk in lupus patients are tumor necrosis factor-like weak inducer of apoptosis (TWEAK), IL-6, vascular endothelial growth factor (VEGF), and type I interferons. Soluble CD40 ligand (sCD40L) is overexpressed in SLE and associated with increased activation of the endothelial cells through CD40 binding on their surface. It induces the coagulation cascade through the increase of tissue factor (TF) expression and is also related to plaque vulnerability. Increased sCD40L is associated with increased risk for recurrence after an acute coronary syndrome [27].

3. Consequences

Accelerated atherosclerosis has a significant impact on long-term morbidity and mortality in SLE. Resultant endothelial dysfunction, increased arterial wall thickening and stiffness, and plaque formation increase the risk of CVD, which is the most common cause of death in SLE [4, 28–31]. Additional consequences include increased PAD, CVA, and premature mortality [8, 32]. From 1970 to 2004, the University of Toronto Lupus Clinic documented a 10.9% (95% CI 9.0%–12.3%) prevalence of atherosclerotic vascular events (i.e., myocardial infarct [MI], angina, TIA, stroke, peripheral vascular disease, and sudden death presumed to be of cardiac etiology) among patients within the first 9 years of SLE diagnosis [33].

3.1 Cardiovascular disease

SLE is an independent risk factor for the development of CVD, providing similar cardiovascular risk as type 1 diabetes [34]. Numerous studies have demonstrated an increased risk of CVEs in SLE patients, which disproportionately impacts

premenopausal women [35–38]. Women (aged 35–44) with SLE followed at the University of Pittsburg Medical Center were 52 times more likely to have an MI (rate ratio 52.43, 95% CI 21.6–98.5), compared with healthy controls from the Framingham Offspring Heart Study [35]. Premenopausal women with SLE were two times as likely to be hospitalized from acute MI (proportionate morbidity ratio [PMR] 2.27, 95% CI 1.08–3.46) and almost four times more likely to be hospitalized for congestive heart failure (CHF) (PMR 3.80, 95% CI 2.41–5.19) [36], compared with age-matched controls. In a retrospective population-based study, SLE patients had an almost four times higher odds (OR 3.8, 95% CI 1.8–8.0) of being diagnosed with CVD within 2 years of their SLE diagnosis [37].

The increased burden of premature CVD is paired with worse overall outcomes. In a nationwide American study of almost 700,000 patients from 1993 to 2002, SLE patients had a higher probability of prolonged hospitalization following an acute MI (OR 1.46, 95% CI 1.31–1.61) compared with diabetic patients (OR 1.17, CI 1.16–1.19) and controls, when adjusted for age, sex, race/ethnicity, income, and CHF [39]. Adjusted in-hospital mortality was also greater for SLE patients (OR 1.68, 95% CI 1.43–2.04) compared with diabetic patients (OR 1.00, 95% CI 0.97–1.02) [39]. CVD remains the leading cause of mortality in SLE [28–30, 40].

3.2 Cerebrovascular accident

The prevalence of CVA in SLE has been reported as between 2 and 19% [41]. The risk of CVA in SLE is approximately 2–3-fold higher than the general population [42–46]. In a meta-analysis of stroke in SLE, 10 studies identified a 2.5-fold higher risk of stroke from all causes (RR 2.53, 95% CI 1.96–3.26), ischemic stroke (2.10, 95% CI 1.68–2.62), intracerebral hemorrhage (2.72, 95% CI 2.15–3.44), and subarachnoid hemorrhage (3.58, 95%CI 3.20–4.64). The greatest risk was among those aged 50 years or younger [43]. Standardized incidence ratios (SIRs) were 2.02 (95% CI 1.30–3.81) among SLE patients in a Chinese study [44]. Younger patients were disproportionately impacted, with the highest incidence ratios among ages 30–40 (SIR 21.0, 95% CI 7.84–56.5) and less than 30 years (SIR 22.8, 95% CI 5.67–91.7). Patients less than 30 years had a 54 times higher incidence of ischemic stroke (SIR 53.9, 95% CI 7.47–389), the highest among all age groups [44]. SLE patients are at highest risk of ischemic stroke and intracerebral hemorrhage [43, 44, 47]; this risk does not appear to be impacted by the development of end-stage renal disease in the context of lupus nephritis [48].

Premenopausal SLE patients are two times more likely to be hospitalized due to stroke (PMR 2.05, 95% CI 1.17–2.93), though a difference in hospitalization has not been consistently identified [44]. Moreover, lupus patients are at a higher risk of death from CVA compared with the general population, with strokes accounting for up to 15% of deaths in SLE [42, 49, 50].

3.3 Peripheral arterial disease

Peripheral arterial disease is often asymptomatic, and the ankle-brachial index (ABI) is typically used to assess for subclinical disease [51]. The prevalence of PAD in SLE has been reported between 21 and 33% [52–54]. SLE patients are four times more likely to have PAD (OR 3.9, 95% CI 1.8–7.9), compared with controls [54]. A retrospective review of the Taiwan National Health Insurance program data identified a ninefold higher risk of PAD (HR 9.39, 95% CI 7.70–11.5) in SLE patients, compared with controls [32]. Among this cohort, the greatest risk of PAD was within

the first year following diagnosis of SLE. Females had a higher risk compared with sex-matched controls (HR 9.90, 95% CI 7.98–12.3), than males (HR 5.96, 95% CI 3.50–10.2). Like other forms of vascular disease, the risk was highest among young patients (HR [for age < 34] 43.4, 95% CI 24.5–76.9) and declined over time [32].

Morbidity from symptomatic PAD can be substantial, as it may lead to disability and ischemic-related complications [55, 56]. Fortunately, the prevalence of symptomatic PAD seems to be substantially lower (1–2%) than asymptomatic disease in SLE [52, 57]. PAD is a predictor of all-cause mortality, cardiovascular disease, cardiovascular mortality, and stroke [57, 58].

3.4 Mortality

The bimodal distribution of death in lupus was first identified by Urowitz et al. in 1976, with atherosclerotic heart disease and infection most responsible for late-stage mortality [3]. Survival has significantly improved since the 1950s, as the 5-year and 10-year survival rates are greater than 92% in SLE, primarily due to advancements in therapy [2, 59]. Data from the Toronto Lupus Clinic, from 1971 to 2013, showed an improvement in mortality related to atherosclerosis from 1980–1989 (SMR 8.3, 95% CI 3.8–12.8) to 2010–2013 (SMR 3.2, 95% CI 0.1–6.3) [1]. The next leading causes of death were malignancy (SMR 1.4, 95% CI 0.2–2.7) and infection (SMR 0.9, 95% CI 0–1.9) [1]. Atherosclerosis has persistently been identified as the leading cause of death in SLE [1, 60].

4. The role of imaging modalities in atherosclerosis in SLE

Vascular imaging has been used in the general population to assess for atherosclerotic burden [26]. Carotid ultrasound with IMT and carotid plaque has been shown to independently predict CVEs. Various other imaging modalities have shown benefit in the general population, with yet unclear clinical value in the setting of SLE [26].

Flow-mediated dilation (FMD) of brachial artery: The initial stage of atherosclerosis is endothelial dysfunction, which can be assessed by FMD [61]. Impaired FMD has been shown to independently predict future CVE in the general population [62]. The generalizability of these findings is unclear in SLE [63]. A meta-analysis of 22 studies found a reduction in FMD in SLE patients, compared with controls [64]. FMD was also associated with traditional and disease-related cardiovascular risk factors and inversely related to carotid IMT. SLE was identified as a risk factor for impaired FMD [4].

Pulse-wave velocity (PWV): PWV analysis and the derivative variable augmentation index are surrogate measure of arterial stiffness, which occurs in the next stage of atherosclerosis [26, 65]. These are independent predictors of CVEs in the general population. Cross-sectional studies in SLE have found increased PWV to be related to traditional and disease-related risk factors, though the predictive value of PWV for future CVEs has not yet been tested in SLE [26].

Carotid intima-media thickness (IMT) and carotid plaque: During later stages of atherosclerosis, increased carotid IMT and plaque formation occur [4, 66]. This is characterized by limited reversibility potential. Mean carotid IMT measurements in asymptomatic SLE patients range from 0.37 mm to 0.89 mm, with increased carotid IMT independently associated with future CVEs (HR 1.35 after 8 years) [67–69]. Carotid IMT is also strongly associated with traditional and disease-related risk factors for cardiovascular disease in SLE [4].

Plaque detection in SLE ranges from 7 to 50%. Carotid plaque was found to more accurately predict CVEs in the general population, with the presence of both carotid and femoral plaques as a better predictor of CVEs than carotid plaques alone [26]. SLE patients with carotid plaques have more than a fourfold increased risk of CVE. One study showed that total plaque area was more strongly associated with clinical CAD than carotid IMT (HR 9.55 vs. 2.02, respectively) [69].

Coronary artery calcification (CAC): CAC measures atherosclerotic calcification [70]. Cardiac risk stratification can be accomplished by evaluating CAC, measured by the Agatston score. The prevalence of CAC has been reported between 7 and 48%, and CAC has been correlated with traditional and disease-related risk factors [4, 71, 72]. SLE is an independent predictor of CAC presence (RR 7.7–7.9) [71, 72]. One study demonstrated that non-calcified coronary plaques, which are prone to rupture, were detected in essentially all patients with CAC (45/47, 96%) and more than half of those without CAC (52/99, 53%). The presence of these plaques was related to age and anti-dsDNA antibodies [4].

Coronary angiography: A large prospective cohort study assessing the burden of atherosclerotic disease among SLE and non-SLE patients used coronary angiogram, the "gold standard" to assess flow limiting disease [26]. The rates of obstructive CAD were similar among SLE patients and controls (52% vs. 62%, $p = 0.11$), and SLE was an independent predictor of CAD (OR 2.24, 95% CI 1.08–4.67) [73]. However, SLE patients were younger than controls (mean age 49 vs. 70 years, $p < 0.001$), were less likely to have diabetes (14 vs. 35, $p < 0.001$) and/or hyperlipidemia (30 vs. 50, $p = 0.001$), and more likely to be on glucocorticoids (50 vs. 11, $p < 0.001$) [73]. Another study found postmenopausal state, hypertension, and the number of traditional cardiovascular risk factors to be associated with more severe angiographic abnormalities [74].

Myocardial perfusion evaluation with single-photon emission computed tomography (SPECT): Myocardial evaluation with SPECT is a reliable assessment of myocardial perfusion in the general population, with perfusion defects associated with an almost fourfold increased risk of MI and cardiac death [75]. An association between perfusion defects with traditional and disease-related risk factors has been identified in SLE studies. Myocardial perfusion defects are predictive of CAD (HR 12.0, 95% CI 2.8–60.1) [76]. However, SPECT may overestimate the burden of atherosclerotic disease in SLE, when compared with coronary angiogram [77].

Cardiac magnetic resonance imaging (MRI): Cardiac MRI has known predictive ability in the general population, with an increased incidence of MI and cardiovascular death [26]. Allowing visualization of microvascular disease, limited data suggest that perfusion defects may be relatively frequent in SLE patients in the absence of obstructive CAD [78]. Ventricular wall abnormalities may be better identified with cardiac MRI compared with conventional transthoracic echocardiogram [79]. A diffuse pattern of coronary artery wall contrast enhancement, reflective of vascular inflammation, is seen in SLE patients, compared with the patchy distribution seen in traditional CAD [4, 80].

Refer to **Table 2** for an overview of surrogate atherosclerotic measures in SLE.

5. Management of cardiovascular risk in SLE

Considerations for cardiovascular risk reduction in patients with SLE include the management of traditional and nontraditional atherosclerotic risk factors through

Imaging modality	Purpose	Associated traditional and disease-related cardiovascular risk factors
Flow-mediated dilatation (FMD)	Noninvasive assessment of endothelial dysfunction	Age, BMI > 30 Arterial hypertension Low HDL oxLDL
Pulse-wave velocity (PWV)	Noninvasive assessment of arterial stiffness	Age Male sex, BMI > 30 Arterial hypertension Diabetes, Elevated triglyceride Metabolic syndrome
Carotid intima-media thickness (IMT) and carotid plaque	Noninvasive measure of the presence of carotid plaques	Age Family history Male BMI > 30 Waist-to-hip ratio Arterial hypertension Diabetes Elevated total cholesterol Elevated LDL Low HDL or proin-inflammatory HDL Metabolic syndrome Elevated homocysteine, smoking
Coronary artery calcification (CAC)	Noninvasive measure of atherosclerotic calcification, as per Agatston score	Age Male sex BMI > 30 Arterial hypertension Diabetes Elevated total cholesterol Elevated triglycerides Metabolic syndrome Elevated homocysteine Smoking
Coronary angiography	Invasive "gold standard" assessment of flow limiting disease	Age Male sex Arterial hypertension Elevated total cholesterol Elevated HDL
Myocardial perfusion evaluation with single photon emission computed tomography (SPECT).	Noninvasive assessment of myocardial perfusion	Arterial hypertension Diabetes Elevated total cholesterol Elevated HDL
Cardiac Magnetic Resonance Imaging (MRI)	Noninvasive measurement of microvascular disease	-

Adapted from Tselios K, Sheane BJ, Gladman DD, Urowitz MB. Optimal monitoring for coronary heart disease risk in patients with systemic lupus Erythematosus: A systematic review. J Rheumatol. 2016;43(1):54–65.

Table 2.
Surrogate atherosclerosis measures in systemic lupus erythematosus.

screening and preventative strategies. The management of traditional risk factors and disease activity has been shown to significantly reduce atherosclerotic vascular events (HR 0.40, 95% CI 0.23–0.70), including angina, MI, TIAs, stroke, and CHF [81]. Given the lack of SLE-specific risk reduction approaches, the identification and management of modifiable risk factors remain the most effective means of reducing cardiovascular risk in lupus patients [59].

5.1 Risk reduction

5.1.1 Risk scores

Cardiovascular risk scores are used in the general population to estimate future risk of a cardiovascular event [82]. These scores are not completely generalizable to SLE patients, as they are generally validated in older patient populations than those affected by SLE, and do not take into account the impact of chronic systemic inflammation, which plays a major role in increasing atherosclerotic risk in these patients [4, 83]. In fact, the Framingham risk score (FRS) has been shown to largely underestimate cardiovascular risk in SLE [9]. After controlling for traditional risk factors in 296 SLE patients, there was a significantly higher risk of nonfatal MI (RR 10.1, 95% CI 5.8–15.6), death due to CVD (RR 17.0, 95% CI 8.1–29.7), overall CVD (RR 7.5, 95% CI 5.1–10.4), and stroke (RR 7.9, 95% CI 4.0–13.6) [84]. Urowitz et al. determined that the use of a modified FRS, which multiplies each item by 2, can more accurately predict cardiovascular risk in SLE [85].

The Systemic Coronary Risk Evaluation (SCORE) has been recommended by EULAR to calculate 10-year CVD risk in SLE [86]. Although SCORE has been shown to predict increased carotid IMT, its use in SLE is unclear as it likely also underestimates cardiovascular risk in SLE patients [4, 11, 86]. The Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular Disease in Patients with SLE (PREDICTS) score incorporates biomarkers in risk calculations and has previously been proposed as an alternative risk prediction score [83, 87].

5.1.2 Screening guidelines

As part of best practices, the Canadian Rheumatology Association (CRA) states that a cardiovascular risk assessment should be performed in newly diagnosed adult SLE patients [88]. A strong recommendation was made to initially and periodically assess for traditional risk factors (i.e., obesity, arterial hypertension, diabetes, dyslipidemia, and smoking) according to recommendations in the general population. There is also a conditional recommendation against the use of carotid ultrasonography for cardiovascular risk assessment except in select circumstances where expertise is available, since there is a high risk of false-positive results outside of the appropriate setting [88].

The *EULAR* recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases proposed several recommendations for the management of cardiovascular risk in SLE patients [89]. Cardiovascular risk modification should be guided by traditional and disease related risk factors. A blood pressure target of <130/80 should be considered, and ACE inhibitors or ARBs are recommended in lupus nephritis in patients with arterial hypertension or a urine protein-to-creatinine ratio > 500 mg/g [4]. Low disease activity, the lowest possible glucocorticoid dose and the use of hydroxychloroquine are recommended to reduce cardiovascular

risk. Aspirin should be used based on individual cardiovascular risk profile, and no immunosuppressive medications are recommended to lower risk of CVEs. Lipid management should be guided by general recommendations.

Others have also proposed annual assessments of smoking status and body mass index, routine diabetes screening, possible annual homocysteine levels, and hsCRP at each visit [4, 59]. Additional recommendations include carotid IMT and plaque assessments in patients with more than one traditional risk factor, postmenopausal status, or renal impairment [4].

5.1.3 Pharmacologic intervention

To date, hydroxychloroquine (HCQ) is the only immunomodulatory therapy recommended for cardioprotective benefit in SLE [89]. HCQ is an antimalarial with multiple mechanisms of action resulting in immunomodulatory and cardioprotective effects [59, 90]. It modifies the intracellular pH to block T-cell proliferation, inhibits toll-like receptor (TLR) activation, and reduces the production of select cytokines (i.e., TNF-alpha, IL-17, IL-6, IFNα, and IFNγ) [90]. HCQ also modifies antibody and self-antigen presentation and reduces oxidative stress. Furthermore, HCQ effectively reduces platelet aggregation, lipid levels, and insulin resistance, all mechanisms that are cardioprotective [90].

HCQ has been shown to consistently reduce SLE disease activity and flares [79, 80] as well as protect against damage accrual using SLICC Damage Index in the Lupus in Minorities: nature versus nurture (LUMINA) study (HR 0.55, 95% CI 0.34–0.87). There is also evidence of mortality benefit (HR 0.62, 95% CI 0.39–0.99) in a multinational Latin American inception cohort [91].

A multivariate analysis showed benefit in reducing plaque burden (adjusted OR 0.49, 95% CI 0.21–1.12). Use of HCQ has also been associated with lower aortic stiffness in premenopausal women (partial R2 0.025, p = 0.032) and a significant reduction of thromboembolic events (OR 0.32, 95% CI 0.14–0.74) [92].

6. Future directions

6.1 Screening

To mediate the impact of accelerated atherosclerosis in SLE, it is essential to establish effective screening mechanisms to detect early disease. Validated risk prediction tools will enhance the accuracy by which clinical risk of cardiovascular disease is predicted among lupus patients [12]. Longitudinal studies are warranted to determine the utility of biomarkers and various imaging modalities (**Table 2**) to predict CVEs and subclinical cardiovascular disease in SLE [4, 59]. Other potential biomarkers that have proven association with atherosclerotic risk include IL-1, adipocytokines, and peroxidase [83, 93]. Focusing research efforts in these areas will allow for successful cardiovascular risk stratification and ideally intervention at reversible stages of disease [4, 59].

6.2 Antiatherosclerotic therapies in SLE

No immunomodulatory medications have been found to have a favorable impact on atherosclerotic disease processes in SLE, aside from hydroxychloroquine [89, 90].

In vivo studies with mycophenolate mofetil (MMF) have shown promising results in mouse models with atherosclerosis [94]. MMF may reduce cardiovascular mortality in renal transplant patients with diabetes and has been shown to reduce the development of carotid artery plaques in non-SLE patients, by decreasing T cell activation and increasing regulatory T cells [95, 96]. However, there was no improvement in subclinical cardiovascular disease in a small prospective cohort study [97]. Larger studies may be warranted to explore the utility of MMF for this indication [59]. Celastrol, an anti-neoplastic drug with anti-inflammatory properties, is another promising drug that has been shown to inhibit atherosclerotic pathways and reduce plaque in animal models [93].

Biologic disease-modifying therapies (bDMARDs) should be further investigated. Hu et al. found a reduced risk of MI (OR 0.74, 95% CI 0.63–0.87), cardiovascular death (OR 0.62, 95% CI 0.40–0.95), and a composite endpoint of MI, stroke, and cardiovascular death (OR 0.69, 95% CI 0.53–0.89) in those on bDMARDs, compared with those not on bDMARDs [98]. These finding were mostly driven by the reduction of risk in rheumatoid arthritis patients, thus the role in SLE is unclear.

Interleukin-1β is a potent inflammatory cytokine that induces the production of IL-6, which is known to be associated with vascular events [91]. Canakinumab is an anti-IL-Iβ therapy that has been investigated as a potential antiatherosclerotic intervention in the general population. The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) is a randomized, double-blind, placebo-controlled trail that examined the impact of Canakinumab on adverse CVEs in patients with a previous history of MI and persistently elevated CRP (greater than 2 mg/L) [99]. Participants receiving Canakinumab 150 mg subcutaneously every 2 weeks had significantly less adverse CVEs (HR 0.86, 95% CI 0.75–0.99, p = 0.031) and hospitalization due to urgent revascularization for unstable angina (HR 0.83, 95% CI 0.73–0.95, p = 0.005). These results were all independent of lipid lowering effects. Post hoc analysis found that patients with less inflammation (defined as IL-6 below 1.65 ng/L) had a reduction in major adverse CVEs (HR 0.68, 95% CI 0.56–0.82) and cardiovascular mortality (HR 0.48, 95% CI 0.34–0.68) [100]. This study may not be generalizable to SLE patients since patients with known immunocompromised states or those already on systemic anti-inflammatory treatments were excluded. Moreover, Canakinumab may be cost prohibitive in this setting. Regardless, the mechanistic implications of reducing cardiovascular risk in the absence of lipid lowering effects are encouraging.

We also wonder whether new biologics, such a Belimumab and Anifrolumab, may reduce CVEs by reducing nontraditional risk factors, specifically glucocorticoid use and disease-related damage. The role of additional therapies in mediating atherosclerotic pathways, such as type 1 interferons, seems promising [59, 101]. Future research should explore the impact of harnessing other inflammatory mediators or enhancing regulatory mechanisms.

6.3 Addressing disparities

Socioeconomic and racial and ethnic disparities in cardiovascular risk, outcomes, and mortality remain persistent, despite advancements in SLE morbidity and mortality over several decades. Low socioeconomic status has been associated with increased cardiovascular risk factors [102, 103]. Racial disparities in CVD, stroke, and CV mortality have been identified [39, 104, 105], though findings vary [103, 106, 107]. One study found African American SLE patients to be on average 10 years younger

than their Caucasian peers at the time of first hospital admission for cardiovascular disease [108]. The same conclusions were also made for Hispanic SLE populations (as compared with Caucasians). It should be mentioned that socioeconomic variables were not taken into account in this study [108]. In another relevant study of the LUMINA cohort, this difference could not be reproduced [109]. These disparities should be explored further, with an aim to mediate disproportionate risk among affected groups.

7. Conclusions

Atherosclerosis is the leading cause of death in SLE and is responsible for substantial morbidity related to cardiovascular events, cerebrovascular accidents, and peripheral arterial disease. SLE patients are at increased risk of atherosclerotic disease due to traditional and nontraditional risk factors (e.g., disease activity and long-term glucocorticoid use). Clinicians should be aware of the need to limit the impact of nontraditional risk factors in order to reduce the burden of atherosclerotic disease in SLE. Current risk prediction tools likely underestimate cardiovascular risk in this population, thus further studies are needed to validate their use in SLE. The utility of imaging modalities for the routine assessment of subclinical cardiovascular disease has not yet been established and should remain a research priority. Hydroxychloroquine remains a mainstay in SLE management, as it provides additional cardioprotective benefit. Significant improvements in SLE survival over recent decades were largely due to disease-modifying therapies. With morbidity and mortality now largely related to accelerated atherosclerosis, evidence-based preventative strategies should be implemented to establish further gains in survival moving forward.

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