

Managing Cardiovascular Risk in Systemic Lupus Erythematosus: Considerations for the Clinician

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Abstract: A significant improvement in the survival of patients with systemic lupus erythematosus (SLE) over recent decades is largely attributed to the impact of disease-modifying therapies on end-organ damage. Thus, cardiovascular disease now represents the leading cause of mortality in SLE. Various disease-specific mechanisms are responsible for advanced atherosclerosis, as they lead to premature endothelial dysfunction, arterial stiffness, arterial wall thickening, and plaque formation. Consequently, in the assessment of cardiovascular risk in SLE, we must not only consider traditional risk factors (ie, age, gender, dyslipidemia) but also the additional role of non-traditional risk factors such as persistent disease activity and prolonged corticosteroid use. Cardiovascular risk assessment incorporates general cardiovascular screening, as existing risk prediction scores underestimate cardiovascular risk in this patient population. There is also an expanding role of imaging modalities in screening. Risk reduction strategies integrate unique considerations for the use of low-dose aspirin and more stringent hypertension targets. Hydroxychloroquine is the only disease-modifying therapy with known cardiovascular benefit in SLE, though this is a promising area of study.

Keywords: cardiovascular disease, atherosclerosis, endothelial dysfunction, coronary artery disease, risk stratification, prevention

Introduction

Systemic lupus erythematosus (SLE) is a complex multisystemic autoimmune disease that primarily impacts premenopausal women.¹ This heterogeneous disease has the potential to cause severe renal, central nervous system, and cardiac dysfunction. The bimodal distribution of mortality in SLE was recognized in 1976, with late-stage mortality primarily attributed to infections and atherosclerotic heart disease.² Increased survival rates in SLE over recent decades can be attributed to the prevention of end-organ damage through early diagnosis and prompt aggressive immunosuppressive management at disease onset.³ This has rendered cardiovascular disease (CVD) the leading cause of mortality in SLE.³

Advanced atherosclerosis in SLE occurs through various mechanisms related to autoimmunity and chronic inflammation, vascular injury, and disease-related factors.^{4,5} Thus, patients not only have premature atherosclerotic disease, but they are three times more likely to die from atherosclerotic disease compared to the general population.^{6,7} Traditional risk factors for CVD do not completely account for this increased risk, with disease activity and corticosteroids likely accelerating the development of atherosclerosis.⁸

Due to the multisystemic nature of SLE, these patients often require management from numerous generalists and specialists. Thus, it is essential for all clinicians to understand the nature of atherosclerosis in SLE. The objectives of this review are to describe the mechanisms of premature atherosclerosis in SLE and an approach to cardiovascular risk assessment and risk reduction in this high-risk population.

Cardiovascular Outcomes in SLE

SLE provides a similar risk for the development of cardiovascular disease as type 1 diabetes, thus it is considered an independent predictor of cardiovascular events (CVE).⁹ The prevalence of cardiovascular disease in SLE has been

estimated between 6% and 16% of patients, with one large population study identifying atherosclerotic CVD in 25.6% of hospitalized SLE patients.^{10–12} One study showed that people with SLE had almost 4 times higher odds of developing CVD within the first two years of diagnosis, compared to the general population.¹³ Compared to age-matched controls, premenopausal SLE patients are more likely to be hospitalized for acute myocardial infarction and congestive heart failure.¹⁴ These patients also have more prolonged hospitalizations compared to age-matched diabetic patients.¹⁵ Accelerated atherosclerosis also contributes to peripheral vascular disease, cerebrovascular disease, and their associated morbidity and mortality.

The impact of accelerated atherosclerosis on mortality in SLE was first recognized in 1976, when atherosclerosis was identified as a leading cause of late-stage mortality.² Survival has improved in SLE over recent decades, with 5-year and 10-year survival rates exceeding 90%, though much of this is related to advancements in therapies.^{3,16} Although we have also seen significant improvements in SLE mortality related to atherosclerotic disease, CVD remains a leading cause of death in SLE.^{17,18}

Mechanisms of Advanced Atherosclerosis

Accelerated atherosclerosis in SLE has been attributed to both the higher prevalence of traditional risk factors such as hypertension and dyslipidemia as well as disease-related risk factors and the deleterious effects of pharmaceutical agents that are used for disease management.⁷ Endothelial dysfunction is believed to be the initial event in the pathophysiologic cascade as demonstrated by the enhanced expression of adhesion molecules such as ICAM-1 (intercellular adhesion molecule-1), VCAM (vascular adhesion molecule-1), VEGF (vascular endothelial growth factor), pentraxin-3, thrombomodulin, IP-10 (interferon- γ -induced protein 10) and MCP-1 (monocyte chemoattractant protein-1).¹⁹ In parallel to the endothelial activation, there is increased endothelial apoptosis, mediated through Fas/FasL (CD95/CD95 ligand) and TNF/TNFRII (tumor necrosis factor/tumor necrosis factor receptor II) interactions. All these cytokines have been shown to be increased in patients with SLE, particularly during the active phases of the disease.²⁰ The increased rate of apoptosis of endothelial cells is not compensated by repair from the endothelial progenitors as IFN- α (interferon- α) induces dysregulation of these cells.²¹ The increased rate of endothelial apoptosis leads to insufficient apoptotic debris clearance from monocytes/macrophages and amplifies the autoimmune inflammation.

The proinflammatory cytokine milieu in SLE in tandem with the increased oxidative stress (as demonstrated by increased levels of reactive oxygen species, ROS) augments the oxidation of the low-density lipoprotein (LDL). Under normal circumstances, high-density lipoprotein (HDL) inhibits this pathway effectively. However, in SLE, a certain proportion of the HDL molecules are pro-inflammatory and do not regulate LDL oxidation. Oxidized LDL (oxLDL) further activates the endothelial cells to overexpress the aforementioned adhesion molecules. Consequently, circulating monocytes/macrophages are recruited in the subendothelial space and eventually phagocytose the oxLDL molecules and other lipids; this leads to the formation of “foam” cells that are considered to represent the earlier stages of the atherosclerotic plaque.²²

Atherosclerotic plaques have also been shown to contain abundant numbers of neutrophils and plasmacytoid dendritic cells (DCs). Under inflammatory conditions (such as in SLE), neutrophils release neutrophil extracellular traps (NETs) that induce endothelial damage and activate the macrophages towards the production of IL-1 β (interleukin-1 β), TNF α , and MCP-1. On the other hand, plasmacytoid DCs and low-density granulocytes secrete IFN- α , which induces platelet activation among other actions. 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 pro-inflammatory cytokines such as IL-17. This has been associated with increased vulnerability of the atherosclerotic plaques that may result in platelet aggregation and thrombosis. 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 down-regulate IFN- α 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 down-regulating CD36 and scavenger receptor A (SRA). This mechanism reduces the uptake of oxLDL, thus inhibiting foam cell formation.²³

OxLDL is highly immunogenic and stimulates the crosstalk between T and B cells for the production of antibodies against it (anti-oxLDL antibodies). The formed immune complexes will accelerate the rate of “foam” cell generation and enhance IFN- α secretion from the DCs. Similar actions have been demonstrated by immune complexes containing b2GPI, which is a potent anticoagulant protein and neutralized by these antibodies. Moreover, 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.²⁴

In parallel, various cytokines have been shown to affect other risk factors. TNF- α induces a dyslipidemic profile with increased triglycerides, decreased HDL, inhibition of lipoprotein lipase, and induction of very low-density lipoprotein (VLDL) synthesis. Serum levels of TNF- α are strongly correlated with 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- β) in SLE are associated with the breakdown of immune tolerance and have demonstrated a strong correlation with premature atherosclerosis.²⁵ Other cytokines that were shown to increase CV risk in lupus patients are tumor necrosis factor-like weak inducer of apoptosis (TWEAK), IL-6, VEGF, and type I interferons. Soluble CD40 ligand (sCD40L) is also 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 in tissue factor (TF) expression and is also related to plaque vulnerability.²⁰ The complexity of the pathophysiologic basis of atherosclerosis in SLE as well as its clinical impact warrants further investigation aiming to identify biomarkers for its early identification and prevention.

Traditional and Non-Traditional Risk Factors for Atherosclerosis

Traditional non-modifiable and modifiable risk factors for atherosclerosis contribute to the development on CVD in SLE (Figure 1); however, SLE patients have elevated risk for CVDs even after controlling for traditional risk factors, therefore non-traditional risk factors (ie, chronic inflammation) must be taken into consideration in the assessment and management of CVD in SLE.⁶

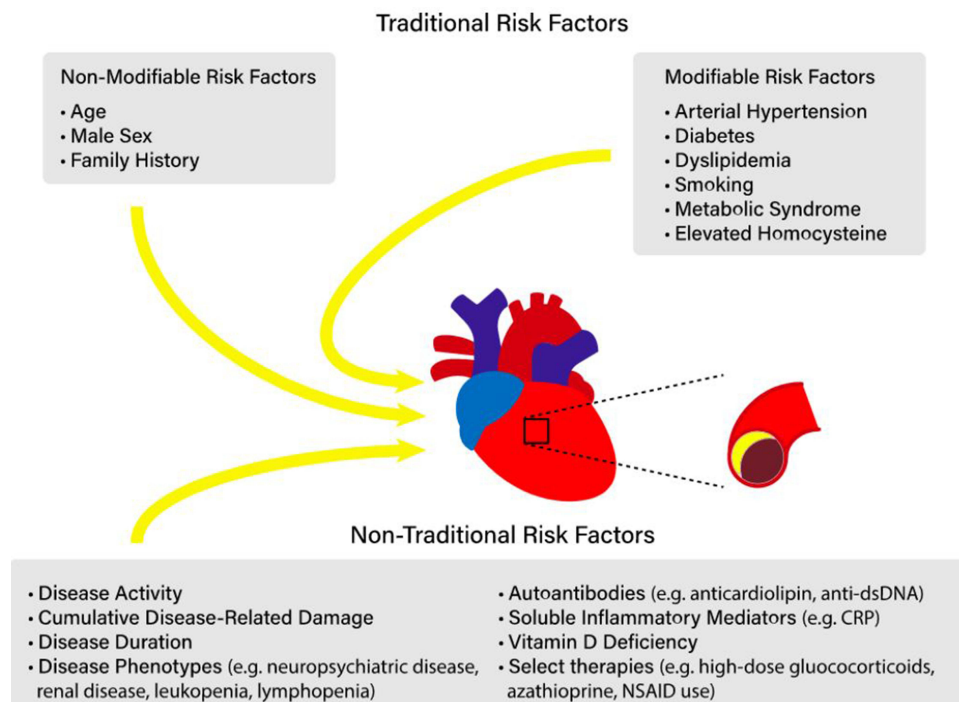


Figure 1 Risk factors for the development of atherosclerotic disease in systemic lupus erythematosus.

Traditional Risk Factors

Non-modifiable risk factors include age, male sex, and family history of premature coronary artery disease. SLE patients over the age of 48 and/or with postmenopausal status have a fivefold increased risk of cardiovascular events (CVEs).²⁶ These patients are also at increased risk of subclinical disease. Male sex also predicts subclinical atherosclerosis and CVEs. A family history of early coronary artery disease in a first-degree relative (male age less than 55 years or female age less than 65 years) is associated with increased risk of CVEs.⁷

Modifiable risk factors include smoking, hypertension, dyslipidemia, metabolic syndrome, obesity, and hyperglycemia. SLE patients who smoke have more subclinical disease and are at almost 4 times greater risk of CVEs relative to those who do not smoke.⁷ Multiple factors contribute to the development of hypertension in SLE, including renal disease and the use of non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids.^{7,27,28} General population targets for blood pressure (BP) may be inadequate for SLE patients, as studies have found a higher risk of CVEs in SLE patients with systolic BPs between 130 and 139 mmHg and diastolic pressures of 80–89 mmHg, compared to those with levels below 130/80 mmHg.²⁹

Autoantibody production against various lipoproteins and cytokine-related hepatic synthesis of very-low density lipoproteins (VLDLs) are the primary mechanisms by which SLE leads to dyslipidemia.^{7,30} The most common pattern of dyslipidemia in SLE consists of elevated triglycerides (TGs) and very low-density lipoproteins (VLDL), and decreased high-density lipoproteins (HDL).^{13,31} Furthermore, modified pro-inflammatory high-density lipoproteins (HDLs) accelerate atherosclerosis in SLE by inducing vascular inflammation.³²

Metabolic syndrome is associated with subclinical cardiovascular disease and cardiovascular mortality in SLE and is three times more common in SLE patients compared to the general population.^{7,28,33,34} SLE patients are known to have impaired glucose homeostasis.³⁵ Hyperglycemia appears to modulate the risk of cardiovascular events and disease.^{36,37} Pre-diabetes is associated with arterial stiffness.³⁸ Diabetes is associated with subclinical CVD and CVEs.^{39–41}

Non-Traditional Risk Factors

Non-traditional risk factors are not only attributed to disease-related processes but also therapies, namely prolonged corticosteroid use.⁷ Disease-related processes that contribute to increased cardiovascular risk in SLE include ongoing disease-related activity, more disease-related damage, and longer duration of disease. Select organ manifestations, such as renal disease and neuropsychiatric diseases, have been associated with increased subclinical and clinical CVEs. Laboratory markers associated with subclinical and clinical cardiovascular disease include lupus anticoagulant, anti-cardiolipin antibodies (aCL), anti- β_2 glycoprotein 1 (b2GPI) antibodies, and anti-dsDNA antibodies, high-sensitivity C-reactive protein (hsCRP), C3 complement fragment, and uric acid. Associations with additional inflammatory mediators have been described (eg, vascular cell adhesion molecule (VCAM), E-selectin, type 1 interferons, adipocytokines, leptin), though their clinical utility is unclear.⁷ High-dose glucocorticoids are associated with greater than two times increased risk of CVEs, and exacerbate many traditional risk factors such as hypertension, dyslipidemia, and hyperglycemia. Azathioprine has also been associated with increased CVEs.⁷

Management of Cardiovascular Disease in SLE

Multiple considerations are required for the appropriate management of cardiovascular disease in SLE. Clinicians must recognize the limitations of risk assessment tools, adjust their screening compared to the general population, consider the role of imaging modalities, and the use of SLE-specific anti-atherosclerotic therapies.

Risk Assessment

Screening

Cardiovascular risk in SLE not only begins at an earlier age compared to the general population, but these patients also experience accelerated atherosclerosis due to chronic inflammation and prolonged glucocorticoid use.^{8,42} Existing cardiovascular risk scores have not been validated in this patient population, which makes accurate risk assessment challenging. The Framingham risk score (FRS) underestimates cardiovascular risk in SLE, with a modified score shown to more accurately predict risk by multiplying each item by 2.⁶ The Predictors of Risk for Elevated Flares, Damage

Progression, and Increased Cardiovascular Disease in Patients with SLE (PREDICTS) score was developed with these limitations in mind, as it incorporates certain biomarkers (proinflammatory high-density lipoprotein [pHDL], leptin, soluble TNF-like weak inducer of apoptosis [sTWEAK] and homocysteine levels) in the risk calculation.⁴³ Although the PREDICTS score has been shown to predict subclinical atherosclerosis and major adverse CVDs (MACEs), its use is likely limited by clinical availability of the incorporated biomarkers.^{43,44}

The European Alliance of Associations for Rheumatology (EULAR) previously recommended using the Systemic Coronary Risk Evaluation (SCORE) for CV risk assessment in SLE patients.⁴⁵ Although this score has been shown to predict subclinical disease, it has also been shown to underestimate cardiovascular risk in SLE patients.^{7,8,46} Other CV risk prediction tools were assessed in the setting of SLE; however, the more recent EULAR recommendations recognize the limitations and lack of validation of existing cardiovascular risk prediction tools in SLE and, thus, do not endorse any particular risk calculator.^{47,48} Rather, they recommend comprehensive assessments and initiation of preventative strategies to reduce the impact of the traditional and non-traditional atherosclerotic risk factors.⁴⁷

More recent studies have identified promising risk prediction tools for future consideration, including the QRESEARCH risk estimator version 3 (QRISK3) calculator, which was shown to have a greater discriminating capacity for the presence of carotid plaque compared to SCORE.⁴⁹ Additionally, an updated SCORE prediction model, SCORE2, was developed using more recent CVD rates and by accounting for fatal and non-fatal CVD events, and demonstrated a higher ability to predict the presence of subclinical atherosclerosis in a cross-sectional study, compared to SCORE.⁵⁰

Imaging Modalities

Flow-Mediated Dilation

Various modalities can be used to assess cardiovascular risk in SLE. Flow-mediated dilation (FMD) of the brachial artery can provide clinicians with information regarding endothelial dysfunction and can therefore be used as a surrogate in the assessment of early atherosclerosis. It can also monitor the risk of progression to coronary heart disease in SLE.^{51,52} A meta-analysis of 22 studies found that the FMD in SLE was significantly lower when compared to the general population. Similar to findings from other high cardiovascular risk populations; however, there have been no studies assessing the ability of FMD to predict clinically significant CVD in SLE.^{22,52}

Pulse Wave Velocity

Pulse wave velocity (PWV) measures the stiffness of the carotid and femoral arteries and increased PWV can be a marker of early atherosclerotic disease.^{53,54} In a meta-analysis of 14 studies, patients with SLE had a significantly greater PWV when compared to the general population.⁵³

Intima Media Thickness and Carotid Plaque

Intima media thickness (IMT) of the carotid artery as assessed by ultrasound is inversely related to FMD, with an increase in IMT acting as a predictor for vascular events including CHD.⁵¹ Studies have identified an IMT of >0.83 mm as abnormal in the general population, with an IMT >1.0 mm corresponding to plaque formation; conversely, in SLE an IMT >0.9 mm is considered to be abnormal with plaque formation corresponding to an IMT >1.3 mm.⁵⁵ IMT progression is associated with a number of traditional and disease-related risk factors as noted in [Table 1](#).

In SLE, the presence of carotid plaque, as assessed by ultrasound, has a detection rate of 7% to 50% and is associated with a four-fold increased risk for cardiovascular events, furthermore, progression of carotid plaques occurs more frequently in SLE when compared to the general population.^{56–58} When compared to IMT of the carotid artery, the total plaque area has a stronger association with clinically significant CAD.⁵⁸ As well, the combined presence of carotid plaques and femoral plaques has a higher predictive value when compared to isolated carotid plaques.⁵⁸

Coronary Artery Calcification

Coronary artery calcification (CAC) is predictive of atherosclerotic disease in the general population, and in SLE, it is associated with various traditional and non-traditional risk factors as seen in [Table 1](#). However, even with optimal

Table 1 Overview of Cardiac Imaging Modalities in SLE and Associated Risk Factors

	Atherosclerotic Assessment	Associated Risk Factors
FMD	Non-invasive High-frequency ultrasound Measures endothelial dysfunction through assessment of flow-mediated dilatation that is endothelium dependent	Age BMI >30 Arterial hypertension Low HDL Oxidative LDL
Pulse wave velocity (PWV)	Non-invasive Assesses vascular stiffness as a surrogate for atherosclerosis	Age BMI >30 Arterial hypertension Male sex Elevated triglycerides Metabolic syndrome Diabetes mellitus Hypertension
Intima media thickness (IMT) and Carotid plaque	Non-invasive High-frequency ultrasound IMT inversely related to PWV	Age BMI >30 Arterial hypertension Male sex Smoking Family history Waist circumference Metabolic syndrome Diabetes mellitus Diastolic blood pressure Total cholesterol and triglyceride level Low HDL or pro-inflammatory HDL Increased serum C3 SLE duration Elevated homocysteine
Coronary artery calcification	Non-invasive Coronary CT angiography Described by the Agatston score	AGE BMI >30 Arterial hypertension Male sex Smoking Metabolic syndrome Diabetes mellitus Elevated total cholesterol and triglycerides Elevated homocysteine
Coronary Angiogram	Invasive “Gold standard” Assesses obstructive disease	Age Arterial hypertension Male sex Elevated total cholesterol and HDL
Myocardial SPECT	Non-invasive Percentage of patient with perfusion deficits without associated disease seen on angiogram	Arterial hypertension Diabetes Elevated total cholesterol and HDL Anti-phospholipid antibodies

(Continued)

Table 1 (Continued).

	Atherosclerotic Assessment	Associated Risk Factors
Cardiac MR	Non-invasive Adenosine-stress perfusion deficits indicate CHD Late gadolinium enhancement confers increased risk of future events	Arterial hypertension Dyslipidemia Anti-phospholipid antibodies
PET Scan	Non-invasive Assess systemic and vascular inflammation Assesses inflammation and micro-calcification	

management of traditional risk factors, the degree of CAC, as described by the Agatston score, has been shown to be higher in SLE when compared to the general population.⁵⁹ Since they are often more metabolically active, non-calcified coronary plaques carry a higher risk for acute coronary events when compared to calcified plaques; it has previously been shown that up to 54% of SLE patients had non-calcified coronary plaques.⁶⁰

Coronary Angiogram

Coronary angiogram is the “gold standard” modality for diagnosing CVD in the general population.⁶¹ In a retrospective cohort, SLE was associated with angiographic CVD.⁶² This study also found that although the traditional risk factors were associated with CVD in patients with SLE, certain factors, specifically hypercholesterolemia and diabetes mellitus, were seen less in the SLE group compared to non-SLE sex-matched controls. As well, patients with SLE were noted to be 20 years younger than controls with similar severity of CVD.⁶² Of note, studies have shown that up to two-thirds of SLE patients with perfusion defects did not have disease on coronary angiogram.⁷

Myocardial Perfusion Evaluation with Single-Photon Emission Computed Tomography (SPECT)

Perfusion abnormalities found in SPECT are a strong predictor of mortality, with general population studies showing the risk of myocardial infarction and cardiac death is almost four times greater among those with myocardial perfusion defects compared to those without.^{63,64} In patients with SLE, a high rate of myocardial perfusion defects in SPECT analysis has been seen, despite a lack of clinical symptoms suggestive of CVD.^{63,64} Up to two-thirds of SLE patients may have perfusion defects without associated disease on coronary angiogram, indicating that SPECT analysis may detect CVD earlier.⁷

Cardiac Magnetic Resonance Imaging (CMR)

One study demonstrated that greater than 40% of SLE patients had abnormalities noted by cardiac MR and the majority of abnormal findings included late gadolinium enhancement (LGE) in non-ischemic patterns, pericardial effusions, and at least 20% had adenosine-stress perfusion deficits indicating underlying CHD.⁶⁵ Another study showed that in patients with connective tissue diseases with normal echocardiograms, 25.2% of them were found to have myocardial fibrosis; also, in patients where the LGE within the left ventricle was greater than 5%, the risk of future events occurring was increased.⁶⁶

Positron Emission Tomography (PET)

Combined use of PET with other non-invasive modalities mentioned above is an emergent method of assessing CVD in patients with chronic inflammatory diseases, including SLE.⁶⁷ PET assesses both systemic and vascular inflammation, and as prior studies have found a direct association with increased inflammation with both plaque burden and coronary obstruction, PET can act as a surrogate marker indicating CVD.^{67,68}

See Table 1 for an overview of cardiac imaging modalities in SLE and associated risk factors. The only modalities that have proven to be predictive for coronary vascular events in SLE are IMT of the carotid and plaque assessment by ultrasound.⁵⁸

Risk Reduction

Anti-Atherosclerotic Therapies

The initiation of anti-atherosclerotic therapies in SLE is directed by general population guidelines, with a few important considerations highlighted in the EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal disease, including systemic lupus erythematosus and antiphospholipid syndrome.⁴⁷ There is no additional benefit of the use of low-dose aspirin for primary prevention, thus low-dose aspirin use should generally be reserved for secondary prevention in SLE. However, low dose ASA should be recommended in SLE patients with high-risk antiphospholipid (aPL) risk profiles regardless of the occurrence of previous thromboembolic events, based on 2a level of evidence (LoE) on the Oxford Centre for Evidence-Based Medicine system. ASA should also be considered in patients with low aPL risk profiles. Blood pressure targets also differ from the general population targets of less than 140/90. Clinicians should target a BP of less than 130/80 to prevent increased CVEs.^{69,70} Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) should be used for hypertension management in lupus nephritis.^{47,70} Additional unique considerations for reducing cardiovascular risk in SLE include maintaining low disease activity and the use of the lowest possible dose of corticosteroids. Statins use is guided by general population recommendations, as there is insufficient evidence to show benefit with use of statins for primary prevention in SLE.^{45,47}

Immunomodulatory Therapies

To date, hydroxychloroquine (HCQ) is the only immunomodulatory therapy recommended for cardioprotective benefit in SLE.⁴⁷ HCQ is an antimalarial agent with multiple immunomodulatory and cardioprotective effects.⁷¹ It modifies the intracellular pH to block T-cell proliferation, inhibits Toll-like receptor (TLR) activation, and reduces the production of select cytokines (ie, TNF- α , IL-17, IL-6, IFN α and IFN γ). 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 counteract the inflammatory effects on traditional risk factors. A multivariate analysis showed benefit in reducing plaque burden (adjusted OR 0.49, 95% CI 0.21–1.12).⁷² Use of HCQ has also been associated with lower aortic stiffness in premenopausal women and a significant reduction of thromboembolic events (OR 0.32, 95% CI 0.14–0.74).⁷³

In vivo studies with mycophenolate mofetil (MMF) have shown promising results in mouse models with lupus.⁷⁴ 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.⁷⁵ However, there was no improvement in subclinical cardiovascular disease in a small prospective cohort study of SLE patients.⁷⁶

Apart from HCQ and MMF, canakinumab was the first commercially available drug to demonstrate efficacy in reducing cardiovascular risk in patients with a recent acute coronary syndrome and residual inflammation.⁷⁷

Canakinumab is a monoclonal antibody against IL-1 β and disrupts the IL-6 signaling pathway. Canakinumab-treated patients showed a significant decrease of the C-reactive protein without any effect on the levels of LDL and HDL, implying that targeting of inflammation alone may be adequate to decrease the atherosclerotic burden in selected patients. Colchicine affects the activation of the NLRP3 inflammasome and disrupts lymphocyte activation. Several studies have shown modest benefit in chronic atherosclerotic coronary disease as well as acute coronary syndromes.⁷⁸ On the contrary, methotrexate, a potent suppressor of certain pro-inflammatory cytokines (IL-6, IL-12, TNF α), did not reduce the rate of cardiovascular events in CAD patients with residual inflammation.⁷⁹

Harnessing other inflammatory mediators such as IFN α may prove beneficial in reducing the atherosclerotic burden in SLE. The recent development of anifrolumab, an IFN receptor antagonist, may achieve this goal not only by regulating the IFN-induced autoimmune phenomena but also by reducing disease activity and the need for glucocorticoids.

Strengths and Limitations

The major strength of this review is that we have highlighted essential considerations for the management of CVD in SLE, allowing all clinicians managing patients with SLE to participate in this important aspect of this patient populations care. Given that practice patterns among rheumatologists and cardiologists may vary, a systematic review or meta-analysis might provide further insight for those requiring more in-depth knowledge about this aspect of care.

Future Directions

Optimizing screening strategies will enable early intervention to reduce the risk of cardiovascular disease among SLE patients. This may include the development of CV risk prediction tools validated in this population and identifying the role of biomarkers and imaging modalities in pre-clinical disease screening.⁴ Also, the development of anti-atherosclerotic therapies in SLE, including recognizing the role of novel immunomodulatory therapies in mediating atherosclerotic risk in these patients.⁸⁰ As ongoing advancements continue to reduce the impact of CVD in SLE, we must address poorer outcomes seen in certain subsets of the population, related to socioeconomic, racial, and ethnic disparities.^{15,81} These should be explored further to reduce disparate CV risk.

Conclusion

We have highlighted the significant impact of cardiovascular disease on morbidity and mortality in SLE. Disease-related processes directly contribute to the development of premature atherosclerosis among the patient population. This is further compounded by traditional cardiovascular risk factors and non-traditional risk factors, such as disease activity and prolonged glucocorticoid use. Cardiovascular risk calculators are not generalizable to this predominantly young and female patient population, and they have consistently been shown to underestimate risk. Carotid IMT assessed via ultrasound independently predicts CVEs. The utility of other forms of vascular imaging to assess atherosclerotic burden in SLE is unclear.

EULAR recommends comprehensive monitoring and management of cardiovascular risk factors based on general population guidelines. Unique considerations include the use of low dose ASA based on aPL risk profile and tighter BP control (targeting a BP of less than 130/80). Also, the use of hydroxychloroquine in all SLE patients without contraindications, as this therapy has additional cardioprotective effects (ie, lipid lowering, insulin tolerance). Previous studies have failed to identify additional immunomodulatory therapies with anti-atherosclerotic effect. Advancements in therapy are promising, as they relate to direct anti-atherosclerotic effects (ie, canakinumab) or perhaps by improving disease activity and reducing the need for prolonged glucocorticoid use.

Disclosure

The authors report no conflicts of interest in this work.

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