COMPREHENSIVE LITERATURE REVIEW

Accelerated Atherosclerosis and Cardiovascular Mortality in Systemic Lupus Erythematosus: Mechanisms, Risk Stratification, and Emerging Therapeutic Targets

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ABSTRACT

Systemic lupus erythematosus (SLE) is a complex multisystem autoimmune disease that confers a substantially elevated risk of premature cardiovascular disease (CVD), representing one of the leading causes of morbidity and mortality in this patient population. The standardized mortality ratio for CVD in SLE patients aged 35–44 years is estimated at 50-fold above the general population — a striking disparity that cannot be explained by traditional Framingham risk factors alone. This review synthesizes current evidence on the immunopathological mechanisms driving accelerated atherosclerosis in SLE, with specific emphasis on type I interferon pathway dysregulation, neutrophil extracellular trap (NET) formation, endothelial dysfunction, and dyslipidemia driven by chronic inflammation. We critically evaluate established cardiovascular risk stratification tools and their limitations in the SLE population, review the cardiovascular safety and potential atheroprotective benefits of disease-modifying antirheumatic drugs (DMARDs) including hydroxychloroquine and belimumab, and highlight emerging therapeutic targets including the type I IFN receptor axis, NET inhibition, and lipid-modifying strategies.

Keywords: *systemic lupus erythematosus, cardiovascular disease, accelerated atherosclerosis, type I interferon, neutrophil extracellular traps, hydroxychloroquine, belimumab, endothelial dysfunction*

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypical systemic autoimmune disease characterized by polyclonal B-cell hyperactivation, pathogenic autoantibody production, immune complex deposition, and end-organ inflammation affecting the kidneys, skin, joints, hematologic system, and central nervous system. Beyond these well-recognized manifestations, a body of epidemiological evidence accumulated over three decades has established SLE as a powerful and independent risk factor for premature atherosclerotic cardiovascular disease, comparable in magnitude to established conditions such as diabetes mellitus and chronic kidney disease.

The landmark Manzi cohort study — now widely cited as establishing the paradigm of premature CVD in SLE — reported that women with SLE aged 35–44 years had a 50-fold higher rate of myocardial infarction compared with age-matched controls in the Framingham Heart Study. Subsequent population-based studies have consistently corroborated this finding, demonstrating elevated incidence of myocardial infarction, stroke, peripheral arterial disease, and heart failure across SLE cohorts, with the highest relative risk observed in younger patients. Despite advances in SLE management that have dramatically improved overall survival, CVD has emerged as the second leading cause of death in long-duration SLE, following only active disease and infection.

The mechanisms underlying this excess cardiovascular risk are multifactorial and incompletely understood. Traditional cardiovascular risk factors — including hypertension, dyslipidemia, insulin resistance, and smoking — which are more prevalent in SLE than in the general population, account for only a fraction of the observed excess risk. The residual risk is attributed to disease-specific pathological mechanisms including chronic type I interferon signaling, NET-mediated endothelial damage, defective clearance of apoptotic debris, and qualitative lipoprotein abnormalities induced by systemic inflammation.

2. EPIDEMIOLOGY AND RISK QUANTIFICATION

Population-based studies from multiple countries have consistently demonstrated significantly elevated cardiovascular event rates in SLE patients. A meta-analysis of 28 cohort studies encompassing over 100,000 person-years of follow-up reported pooled relative risks of 2.66 for myocardial infarction (95% CI: 2.11–3.35), 2.18 for stroke (95% CI: 1.78–2.66), and 3.53 for heart failure (95% CI: 2.64–4.70) in SLE patients compared with matched general population controls, after adjustment for traditional cardiovascular risk factors.

Subclinical atherosclerosis, detectable through carotid intima-media thickness (cIMT) measurement and coronary artery calcium (CAC) scoring, is also markedly elevated in SLE patients, including those without overt clinical cardiovascular events. A cross-sectional study from the Hopkins Lupus Cohort demonstrated that SLE patients had significantly greater cIMT and higher rates of carotid plaque than age- and sex-matched controls without SLE, independent of hypertension, smoking, and statin use.

Cardiovascular Outcome	Pooled RR (95% CI)	Adjusted for Risk Factors	I² (%)
Myocardial Infarction	2.66 (2.11–3.35)	Yes	54.2
Ischemic Stroke	2.18 (1.78–2.66)	Yes	48.7
Heart Failure	3.53 (2.64–4.70)	Yes	61.3
Peripheral Artery Disease	1.98 (1.44–2.72)	Partial	39.1
CVD Mortality	1.83 (1.51–2.21)	Yes	42.8

Table 1. Pooled relative risks for cardiovascular outcomes in SLE vs. general population.

3. IMMUNOPATHOLOGICAL MECHANISMS

3.1 Type I Interferon Pathway

Type I interferons (IFN-α and IFN-β) are the defining cytokines of SLE pathogenesis, with the 'interferon signature' — elevated expression of interferon-stimulated genes (ISGs) in peripheral blood mononuclear cells — present in approximately 75% of SLE patients and correlating with disease activity. Chronic type I IFN signaling promotes atherosclerosis through multiple convergent mechanisms: it impairs endothelial progenitor cell differentiation and mobilization, compromising vascular repair capacity; promotes a pro-inflammatory macrophage phenotype in subintimal spaces; upregulates expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin) on vascular endothelium; and amplifies production of oxidized LDL, a key driver of foam cell formation.

3.2 Neutrophil Extracellular Traps (NETs)

NETs — web-like extracellular structures released by activated neutrophils composed of chromatin decorated with antimicrobial proteins including myeloperoxidase and elastase — have emerged as critical mediators of vascular injury in SLE. Low-density granulocytes (LDGs), a pathogenic neutrophil subset markedly expanded in SLE, are particularly prone to NET formation (NETosis). NET components directly injure vascular endothelial cells, activate the complement cascade, and provide a scaffold for platelet aggregation and thrombus formation. In SLE patients, higher levels of circulating NET-derived DNA correlate with subclinical carotid intima-media thickness and incident cardiovascular events.

3.3 Dyslipidemia and Proatherogenic Lipoprotein Phenotype

SLE is associated with a qualitatively distinct dyslipidemia characterized by low HDL cholesterol with impaired cholesterol efflux capacity, elevated triglycerides, and the predominance of small, dense LDL particles — each individually proatherogenic. Paradoxically, some SLE patients develop anti-lipoprotein antibodies that alter LDL clearance kinetics. Hydroxychloroquine use is associated with a more favorable lipid profile, potentially contributing to its observed cardioprotective effects in SLE cohorts.

3.4 Antiphospholipid Antibodies and Thrombotic Risk

Antiphospholipid antibodies (aPL) — including lupus anticoagulant, anti-cardiolipin, and anti-β2 glycoprotein I antibodies — are present in approximately 40% of SLE patients and confer an independent prothrombotic risk that amplifies atherosclerosis-driven cardiovascular events. Triple aPL positivity (all three antibody types) identifies patients at highest thrombotic risk, in whom long-term anticoagulation is recommended alongside aggressive atherosclerosis risk factor management.

4. RISK STRATIFICATION AND MANAGEMENT

4.1 Limitations of Traditional Risk Calculators

The Framingham Risk Score (FRS) and Pooled Cohort Equations — the dominant cardiovascular risk stratification tools in general clinical practice — substantially underestimate cardiovascular risk in SLE patients by failing to capture the disease-specific inflammatory burden. The QRISK3 algorithm, which includes rheumatoid arthritis as a risk modifier but not SLE specifically, partially addresses this gap. SLE-specific risk modifiers — including SLEDAI score, complement levels, anti-dsDNA titer, cumulative corticosteroid exposure, and renal involvement — should be integrated into clinical risk assessment.

4.2 Hydroxychloroquine (HCQ)

Hydroxychloroquine remains the cornerstone of SLE pharmacotherapy and has demonstrated pleiotropic cardiovascular benefits. Multiple observational studies and a meta-analysis of 19 studies have documented lower rates of arterial thrombotic events, reduced lipid levels, lower platelet aggregation, and improved insulin sensitivity in HCQ users compared with non-users. The proposed mechanisms include TLR7/9 inhibition (dampening type I IFN production), interference with platelet activation via lysosomal alkalinization, and direct anti-inflammatory effects on vascular endothelium.

4.3 Belimumab and Anifrolumab

Belimumab, a monoclonal antibody targeting B-lymphocyte stimulator (BLyS/BAFF), is the first biologic approved for SLE. Post-hoc analyses of the BLISS-52 and BLISS-76 trials have suggested a trend toward reduced cardiovascular events in belimumab-treated patients. Anifrolumab, which blocks the type I IFN receptor (IFNAR), has shown promising disease-activity

reduction in phase III trials; its potential to ameliorate the interferon-driven component of SLE-associated atherosclerosis is an active area of investigation.

5. EMERGING THERAPEUTIC TARGETS

Several novel therapeutic strategies targeting the SLE-CVD interface are under investigation. NET inhibition — through DNase I supplementation, PAD4 inhibitors, and gasdermin D blockade — may attenuate NET-mediated endothelial injury. Anti-type I IFN strategies including JAK inhibitors (baricitinib, upadacitinib) with established anti-IFN activity represent another promising avenue. Lipid-lowering strategies using PCSK9 inhibitors are being evaluated in SLE-specific trials given the suboptimal response to statins in the context of ongoing inflammatory dyslipidemia.

6. CONCLUSIONS

Accelerated atherosclerosis in SLE results from the complex interplay of traditional cardiovascular risk factors amplified by SLE-specific immunopathological processes, particularly chronic type I interferon signaling, NET-mediated vascular injury, and proatherogenic dyslipidemia. Current cardiovascular risk stratification tools substantially underestimate risk in SLE patients, and the development of SLE-specific risk calculators incorporating disease activity indices (SLEDAI), complement levels, anti-dsDNA titers, and biomarkers of vascular inflammation is a critical unmet need. Aggressive management of modifiable risk factors, universal use of hydroxychloroquine in eligible patients, and emerging targeted therapies addressing the type I IFN axis represent the most promising strategies for reducing premature cardiovascular mortality in SLE.

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