

An update on cardiovascular disorders in systemic lupus erythematosus

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Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2025

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Funding sources

None declared

Conflict of interest

None declared

Received on August 19, 2023

Reviewed on January 9, 2024

Accepted on February 21, 2024

Published online on March 12, 2024

Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a complex multifactorial etiology that develops as a result of autoimmune processes, leading to widespread inflammation and malfunction of multiple tissues and organs, and, as a consequence, triggers arterial hypertension, conduction disorders, valvular heart disease, pulmonary hypertension (PH), and venous thromboembolism events (VTE), contributing to increased mortality. Moreover, autoimmune abnormalities can accelerate atherogenesis and lead to many SLE manifestations, including coronary artery disease (CAD) and cerebrovascular events. The current review aimed to systematize existing data from the latest works and summarize published guidelines and recommendations. In particular, the prevalence of cardiovascular disorders in SLE patients, advances in diagnostics (including imaging methods and biomarker laboratory testing), the possible future direction of therapy, and the latest European Alliance of Associations for Rheumatology (EULAR) guidelines for optimal management of cardiovascular risk in SLE were overviewed.

Key words: risk, autoimmunity, cardiovascular, systemic lupus erythematosus, atherogenesis

Cite as

Pędzich E, Bednarek A, Młynarska J, et al. An update on cardiovascular disorders in systemic lupus erythematosus [published online as ahead of print on March 12, 2024]. *Adv Clin Exp Med*. 2025. doi:10.17219/acem/184868

DOI

10.17219/acem/184868

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease associated with widespread inflammation resulting in the malfunction of multiple tissues and organs. The pathophysiology of SLE includes the production of autoantibodies to nuclear and cytoplasmic antigens and the deposition of immune complexes in tissues. Systemic lupus erythematosus is one of the most common autoimmune diseases and affects approx. 3.4 million people worldwide, including around 18,500 cases in Poland. However, epidemiological data are lacking from some regions.^{1–3} In the context of this review, we consider cardiovascular complications of SLE (Fig. 1), which occur due to functional changes of the endothelium, oxidative stress increased by inflammation, and aberrations in the immune response.⁴

Systemic lupus erythematosus predominantly affects women, with a 9:1 female-to-male ratio, and patients tend to present symptoms during childbearing age.⁵ Cardiovascular mortality risk in SLE is about 3 times higher compared to the general population. Antiphospholipid antibodies (aPLs) are found in about 50% of SLE patients and are a significant independent risk factor for thrombotic events.⁶ Independent of aPLs, increased incidence of traditional cardiovascular and lupus-related thrombosis risk factors significantly increase the risk of premature atherosclerosis in SLE patients.⁷

Objectives

Due to the constantly expanding knowledge on the occurrence of cardiovascular complications, their pathomechanisms and their treatment methods in SLE, this review aimed to systematize data from the latest works and summarize the published guidelines and recommendations.

Materials and methods

The literature search used PubMed, Embase and Google Scholar databases, references from relevant articles, and internet sources, including the World Health Organization (WHO) and other reports. Search terms included “cardiovascular complications SLE,” “arrhythmias SLE,” “atherogenesis SLE,” “cardiovascular complications APS,” “pulmonary hypertension SLE,” “thromboembolic events SLE,” and “valvular disorders SLE,” using SLE and antiphospholipid syndrome (APS) as abbreviations and the full name – systemic lupus erythematosus. No publication date filters were applied, with the last literature search performed on July 29, 2023. Titles and abstracts were screened by the authors to identify relevant works, and the most appropriate sources that included data on epidemiology, complications, diagnostics, and suggested treatment were summarized.

Accelerated atherogenesis

Studies unambiguously show that SLE patients suffer atherosclerosis more often and, as a result, coronary artery disease (CAD), myocardial infarction (MI) and stroke, compared to the general population. Research suggests that chronic inflammation promotes accelerated atherogenesis. Although traditional risk factors are vital in accelerated atherogenesis pathophysiology in autoimmune diseases,^{8,9} the high incidence of cardiovascular disease (CVD) in SLE patients cannot be fully explained by traditional cardiovascular risk factors.¹⁰

Excessive immune system activity in SLE leads to oxidative stress, granulocyte activation, subsequent thrombin generation, and macrophage differentiation to foam cells, leading to accelerated lipoprotein accumulation and oxidation in the endothelium, which may stimulate plaque formation.¹¹ These processes are also mediated by aPLs,

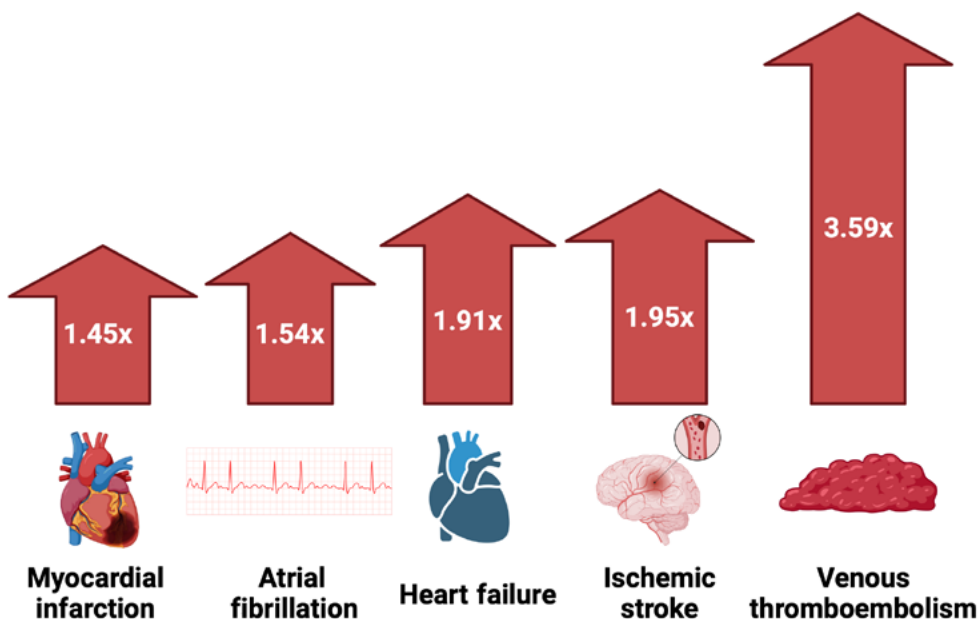


Fig. 1. Cardiovascular complications in systemic lupus erythematosus compared to a healthy population. Created with Biorender.com

which account for a higher risk of cardiovascular events in APS patients.¹² The presence of aPLs is one of the SLE diagnostic criteria, and up to 40% of SLE patients have APS.¹³ Such patients are at a similar risk of new plaque formation as those with diabetes mellitus and have a 3.3 times higher risk than healthy controls.¹⁴ The prevalence of coronary artery plaques in SLE patients was assessed by multiple studies,^{15,16} and, depending on the study, plaques were found in 16.3%¹⁷ or 42.1%¹⁸ of patients. Patients with SLE also have a twofold higher prevalence of plaque compared to controls and a similar prevalence to patients with diabetes mellitus or rheumatoid arthritis.¹⁹ In addition, 32% of the SLE group had atherosclerotic plaques in their carotid arteries after a 5-year follow-up, while it was 4% in healthy control.²⁰ Moreover, a retrospective analysis revealed that the presence of either lupus anticoagulant or anti-cardiolipin antibodies was significantly associated with cardiovascular events, whereas the presence of anti-beta-2-glycoprotein I antibodies was not, which, after confirmation in other studies, may be used as a risk assessment factor in SLE patients.²¹

The high atherosclerosis incidence in women with SLE was first observed in autopsies in 1975, with many studies confirming the association between SLE and cardiovascular diseases.^{22–24} Atherosclerosis causes vessel narrowing through plaque buildup, and some plaques are prone to rupture, which may lead to MI or stroke. Generally, MI incidence is approx. 9 times greater in SLE patients than in the general population.²⁵ In the Framingham Offspring Study, women with SLE aged between 35 and 44 had an over 50 times higher risk of MI than similar-aged female participants.²⁶ A Dutch study analyzed 3,411 patients with SLE and matched control subjects and assessed their absolute 10-year MI risk at 2.17% (95% confidence intervals (95% CIs): 1.66–2.80) for SLE patients and 1.49% (95% CI: 1.26–1.75) in the healthy population. A meta-analysis by Ballocca et al. showed that 4.1% of 17,187 SLE patients presented with acute MI.²⁷ The cohort study published in 2021 showed that, among over 4,000 patients with SLE, the incidence of MI was 9.6 (95% CI: 8.9–10.5) events/1,000 person-year, contrary to the comparison cohort, where the incidence of MI was 4.9 (95% CI: 4.8–5.1) events/1,000 person-year.²⁸

Coronary artery disease, angina pectoris and MI were found significantly more frequently in SLE patients compared to age-matched controls (15.2% compared to 3.6%, $p = 0.0041$).²⁹ The rate of ischemic stroke and MI was also up to twice as high in SLE compared with the general population.³⁰ Such cerebrovascular events in SLE patients may be directly attributed to the disease, as a neuropsychiatric manifestation of SLE, or the result of impaired endothelial function or accelerated clot formation resulting in ischemic incidents.³¹ In a long-term follow-up study including over 17,000 patients, 3.75% (95% CI: 3.06–4.54%) of those in the SLE cohort developed ischemic stroke compared to 1.92% (95% CI: 1.66–2.20%) of control subjects.³² Another study showed a stroke in 7.4% of SLE patients after a 3-year follow-up.²⁴ Stroke is responsible for 15% of SLE

patient deaths.³³ Recent data from the Japan registry showed that the most common type of stroke is cerebral infarction (80%), and no significant differences were found in post-stroke prognosis and the degree of SLE activity.³⁴ In this regard, SLE not only influences stroke risk directly but also through the more frequent presence of comorbidities such as arterial hypertension.

Another concern is the recovery process after cardiovascular events, with analysis of patient medical history after acute MI showing that SLE subjects had higher inpatient mortality during the index hospitalization and higher 30-day hospital readmission compared to patients without SLE.³⁵

A recent cross-sectional study showed a higher prevalence of hypertension, dyslipidemia and carotid atherosclerosis in women with SLE. Moreover, CC homozygosity for the *GCKR rs1260326* gene (odds ratio (OR) = 0.111, 95% CI: 0.015–0.804, $p = 0.030$) and an increase of 1 mmol/L in triglyceride concentrations was associated with a greater risk of carotid plaque in women with SLE (OR = 7.576, 95% CI: 2.415–23.767, $p = 0.001$).³⁶ Studying *GCKR rs1260326* variants may be useful for adjusting lipid-lowering treatment or primary prevention by prescribing statins for these patients. However, current European Alliance of Associations for Rheumatology (EULAR) guidelines only recommend statin prescriptions accompanying estimation of CVD risk from the Systematic Coronary Risk Evaluation (SCORE), not considering SLE as a unique factor, probably due to the conflicting results, especially regarding atorvastatin.³⁷ Studies on atorvastatin, despite good drug tolerance, failed to prove beneficial on subclinical atherosclerosis progression or disease activity in children and adult populations with SLE.^{38,39} Data suggest that atorvastatin may normalize the T helper (Th)17/T regulatory (Treg) cell balance and apoptosis induction and may interact with C-reactive protein (CRP) and interleukin (IL)-6, which are elevated in SLE.⁴⁰ Thus, future studies should evaluate the direct effects in vitro and in SLE patients. Moreover, a recent study suggests that children with 2 or more copies of *C4b* genes may benefit more from atorvastatin therapy.⁴¹ However, current guidelines recommend guiding lipid treatment in line with the general population.⁴² To prevent CVD-related complications, low-aspirin treatment should be considered based on the patient's cardiovascular risk.⁴²

Arterial hypertension is a frequent complication of SLE and APS, which may result from the presence of renal disease or as an unwanted treatment effect.⁴³ Up to 77% of SLE patients can have arterial hypertension, compared to 7.7% in the healthy population aged 22–44 years.⁴⁴ Hypertension is related to increased CVD incidence in such patients and may be associated with up to a 2 times higher risk of cognitive dysfunction or stroke.^{45,46} Current guidelines suggest that a blood pressure (BP) target of <130/80 mmHg should be considered in this group of patients.⁴² Moreover, patients with SLE may have a different circadian BP pattern, with the non-dipper pattern frequently presented,⁴⁷ so 24-h ambulatory BP monitoring is suggested.

Valvular disorders

Inflammation, initiated by deposits of antibodies and complement components, leads to fibrotic processes that result in valve damage. Multiple studies have shown a strong link between the presence of aPLs and valvular disorders,^{48–53} which are common lupus manifestations – including leaflet thickening, vegetations, regurgitation, and stenosis (Fig. 1). Such abnormalities are reported in over 30% of SLE patients,^{49,50} though most cases display no clinical symptoms concomitant to valvular disorder.^{51,54} Therefore, there is a risk of overlooking this condition in a significant group of patients, which may lead to more advanced defects requiring surgical treatment.

The most affected valve is the mitral valve, followed, in order of prevalence, by tricuspid, aortic and pulmonary valves. Mitral valve abnormalities are found in over 30% of patients, and the most common valvular dysfunction

is regurgitation.^{48,55,56} According to a 2016 meta-analysis, patients with SLE tend to have an 11-fold increased risk of combined valvular alterations, and a 10-fold increase in mitral valve thickening, aortic valve thickening, mitral valve regurgitation, and mitral valve vegetation in comparison to healthy controls. Furthermore, SLE patients have a 5 times higher risk of tricuspid and aortic valve regurgitation and mitral valve stenosis (Fig. 2). However, there were no differences in tricuspid valve thickening or aortic valve stenosis.⁵⁷

Valvular disorders are also associated with aPLs. After analyzing 23 studies with 1,656 SLE patients, valvular disease was found in 43% (95% CI: 40–47) of aPL-positive individuals and 22% (95% CI: 19–25) of aPL-negative patients (OR = 3.13, 95% CI: 2.31–4.24, $p < 0.00001$).⁴⁹ Meanwhile, the likelihood of developing valvular disease is estimated to be 8% for APS patients.⁵⁸ High aPL levels, defined as titers over 20, were associated with the presence of valve abnormality after adjusting for disease duration and patient

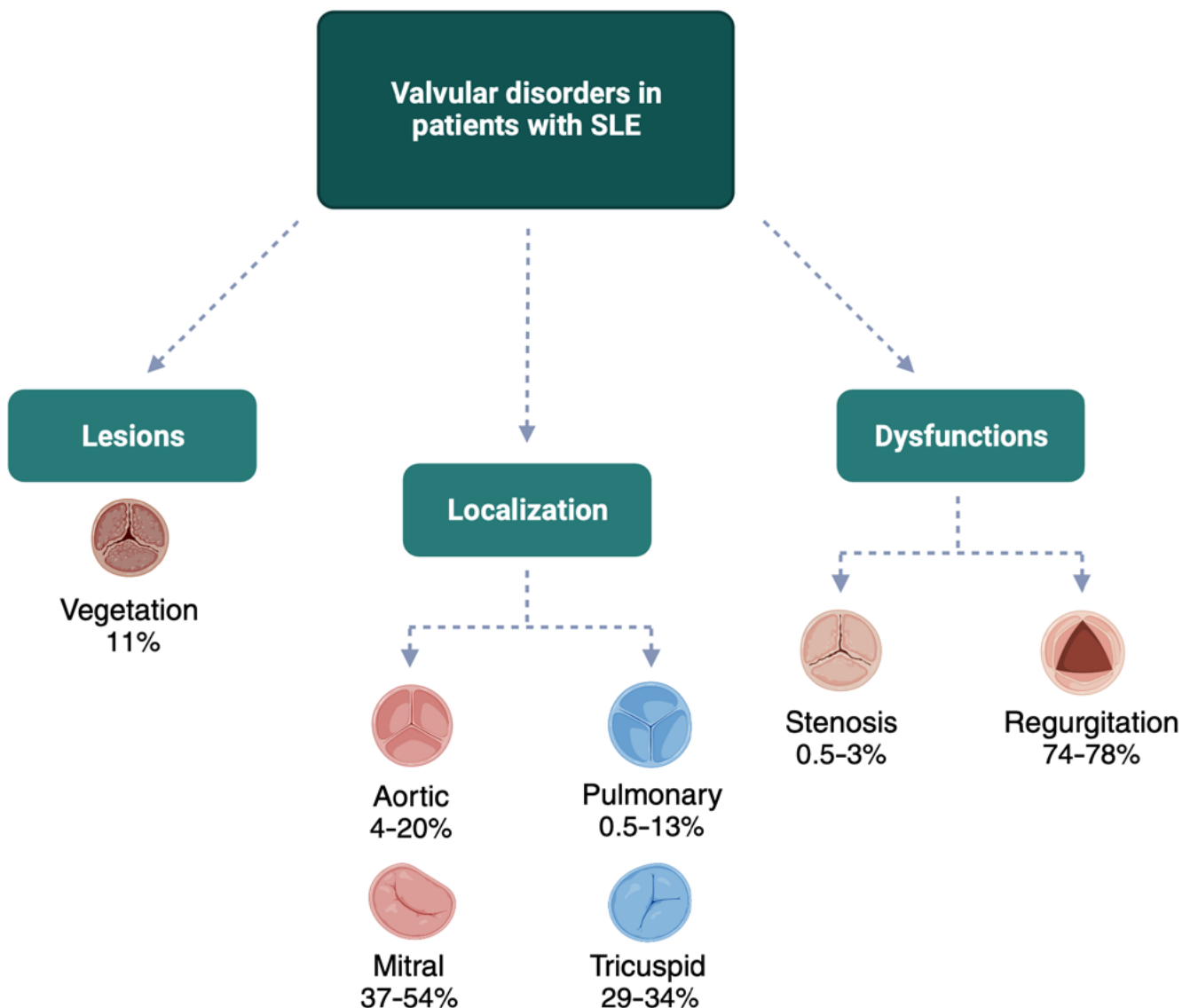


Fig. 2. Valvular disorders in patients with SLE

age.⁴⁸ Furthermore, there was a significant association between valvular heart disease in SLE and immunoglobulin G (IgG) anti-cardiolipin antibody positivity, suggesting that IgG anticardiolipin-positive SLE patients may profit from echocardiography screening.⁵⁹

After discovering a valvular disorder, adequate personalized treatment should be considered. The latest reports indicate that the socio-demographic index (SDI) may be a useful predictor of cardiovascular outcomes after cardiac valve surgery.⁶⁰ However, results should be interpreted carefully due to the limited patients number. Furthermore, xenograft should be the preferred option for patients with SLE or APS, but more data should be obtained to confirm these observations.⁶¹ Guidelines do not indicate special treatment for patients with SLE.⁶²

Libman–Sacks (LS) endocarditis is a nonbacterial thrombotic endocarditis found in approx. 1 in 10 SLE patients.⁵¹ The vegetation on valves may develop as a result of fibrin and platelet aggregation without bacterial infection present.⁶³ Rarely, LS is associated with valve dysfunction – usually left side valves – mitral and aortic, but the involvement of other valves is not excluded. The endothelial damage is caused by hypercoagulability, typical for SLE, APS and neoplasms,⁶⁴ so anticoagulant treatment should be considered in all patients with LS endocarditis. There is a significant association between APS and LS endocarditis. In one of the latest retrospective cohort studies, patients with LS endocarditis were more likely to have β 2GP1 IgG antibodies and lupus anticoagulant.⁵² In another study, after comparing SLE patients with and without LS endocarditis, the SLE group had a significantly higher prevalence of aPL and a lower prevalence of SLE-specific antibodies.⁵³ However, the direct mechanism of endocarditis in these patients is unknown and may be associated with immunosuppressive therapy. In practice, performing transthoracic echocardiography in SLE patients with triple aPL positivity can be useful for screening and can be confirmed by transesophageal echocardiography. Anticoagulant treatment should be considered alongside SLE treatment.⁶⁵

Electrophysiologic dysfunctions

SLE-linked structural changes can affect the conduction system. As previously stated, patients with SLE are more likely to develop atherogenesis and, due to that, commonly suffer from ischemic cardiac events that can damage conduction pathways and lead to arrhythmogenesis.⁶⁶ The prevalence of sinus node dysfunction was reported as 4.3%.⁶⁷ Of these patients, only 3.6% had a pacemaker implanted over a 5-year period.⁶⁷ As inflammation processes progress, myocardial cells are replaced by connective tissue, disturbing repolarization and conduction.⁶⁸ Patients with SLE develop atrial fibrillation (AF) more frequently than the general population,³² with the most common arrhythmias being tachyarrhythmias, specifically, sinus tachycardia, AF and atrial ectopies.⁶⁹

An association exists between anti-Ro/SSA antibodies and QT prolongation.⁷⁰ Myung et al. reviewed 12-lead electrocardiogram (ECG) records of 235 SLE patients and assessed 53 patients with abnormalities that included sinus tachycardia (18% of patients), sinus bradycardia (14%), QT prolongation (17%), and tachyarrhythmias (6%) such as AF, atrial flutter, atrial tachycardia, and atrioventricular nodal reentrant tachycardia (AVNRT)/atrioventricular re-entrant tachycardia (AVRT).⁷¹ Electrocardiography findings correlated positively with age, disease duration, anti-nuclear antibody (ANA) titer, and disease activity (systemic lupus erythematosus disease activity index (SLEDAI)-2K), and were associated with hypertension, positive anti-SSA and secondary Sjögren syndrome.⁷² A 2018 study confirmed the independent association between SLE and AF, even after adjusting for age, sex, race, and CAD.⁷³ Furthermore, SLE patients have almost twice the increased risk of hospitalization due to AF.⁷⁴

Corticosteroids and anti-malarial drugs, standard SLE treatments, may cause tachyarrhythmias and QRS prolongation, but chloroquine may have a protective effect on the conduction system.^{75,76} Furthermore, hydroxychloroquine might induce QTc prolongation in SLE patients,⁷⁷ though the findings of the study published in 2022 did not confirm clinically consequential QTc prolongation in SLE patients treated with hydroxychloroquine.^{78,79} Tachycardia can also be induced by other SLE therapeutics, including mycophenolate mofetil, tacrolimus and rituximab, while AF can be caused by rituximab. In the opinion of the Federal Drug Administration (FDA), azathioprine and belimumab do not affect conduction processes.⁸⁰

Pulmonary hypertension

The link between pulmonary hypertension (PH) and SLE was first observed over 30 years ago.^{81,82} However, studies assessing the prevalence of PH in SLE patients gave ambiguous results. Pulmonary hypertension is a rare but severe condition in SLE patients, and some papers report PH as the first clinical lupus manifestation,^{83–85} with the prevalence of PH in SLE patients estimated at between 0.5% and 17.5%.⁸⁶ A meta-analysis of 23 cross-sectional studies showed that PH may be present in 8% of patients with SLE, though the prevalence differed depending on patient age, gender, geographical region, and the year of the study.⁸⁷ Patients with SLE may present with different types of PH resulting from interstitial lung disease, left heart disease, pulmonary arterial hypertension (PAH), and chronic thrombo-embolic complications.

According to Sun et al., 2 clinical types of PAH can be distinguished in SLE, including vasculopathic, characterized by low lupus activity, and vasculitic, with broad clinical manifestations including pericarditis, rash, arthritis, nephritis, and neuropsychiatric lupus.⁸⁸ Kaplan–Meier survival analysis showed that patients with the vasculitic type had a higher 3-year mortality rate than those

with the vasculopathic type (34.5–40.2% compared to 13.0–18.6%, $p < 0.05$; hazard ratio (HR) 2.84–3.15) after adjusting for treatment variations.⁸⁸ The authors suggest that 2 distinct phenotypes of PAH in SLE may have different pathophysiological processes. Moreover, the vasculitic PAH type seems more sensitive to immunosuppressive therapy. There are 2 independent predictive factors of the vasculitic subtype, which include the time interval between the diagnosis of SLE and PAH (<2 years) and an SLEDAI > 9. A weighted score ≥ 2 , combining these 2 factors (time interval <2 years and ≥ 2 years were 1 and 0 points, respectively, while SLEDAI >9, 5–9 and <5 were 2, 1 and 0 points, respectively), was further developed as a prediction model of vasculitic subtype.^{88–90}

The mechanism of PAH secondary to SLE was studied employing genetic analysis due to the shared and unique gene signatures of these diseases. The shared interferon (IFN)-induced genes might be crucial for identifying new biomarkers and potential therapeutic targets.⁹¹ Meta-analysis showed that modern therapy provides a similar reduction in morbidity/mortality risk in patients with connective tissue disease-PAH compared to the PAH population overall and revealed that survival rates of SLE-PAH patients are higher than those with systemic sclerosis-PAH.⁷⁸ D-dimer levels are a known predictive factor for PAH and may act as a mediator of reduced low-density lipoprotein (LDL), although optimal cutoff points and estimations of individual pressure ranges are unknown.⁹²

Patients with SLE may benefit from PH screening using transthoracic ECG, lung function tests (forced vital capacity and diffusion lung capacity for carbon monoxide) and an N-terminal pro-B-type natriuretic peptide (NT-proBNP) test, particularly in combination.⁹³ Moreover, genetic phenotyping may be a standard beneficial option in the future. The latest work revealed *HLA-DQA1*03:02* as a genetic variant associated with PAH in SLE patients.⁹⁴ The study included 172 patients with SLE and PAH confirmed by right heart catheterization and over 11,000 controls. Patients with PAH and the presence of *HLA-DQA1*03:02* had significantly lower rates of target role achievement ($p = 0.005$) and survival ($p = 0.04$). Therefore, genetic typing may open the way for individualized patient care, which may be particularly beneficial in autoimmune diseases since they have different patterns and manifestations in each patient.⁹⁴ Current guidelines recommend the same algorithm for treating PAH associated with connective tissue disease and idiopathic PAH, including treatment of the underlying condition.⁹⁵

Heart failure

Pathomechanisms of heart failure (HF) include CAD, but there are also many other causes, highlighting the complexity of its development. Myocarditis and pericarditis, which are relatively common cardiac complications in SLE, may lead to HF.^{96,97} Patients with SLE have

up to a twofold higher risk of developing HF compared to the healthy population,³² and the coexistence of SLE and HF contributes to increased mortality. Current HF classification based on ejection fraction includes HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF),⁹⁸ which is the most common type in these patients, probably due to the multifactorial nature of the disease and widespread inflammation. Complications of HF in SLE patients are similar to those in patients without autoimmune disorders and may contribute to hospitalization or death. Diagnostic pathways to confirm HF in SLE patients do not differ from those for the general population,⁹⁹ and include symptoms, laboratory and echocardiographic assessments. Interestingly, the high prevalence of subclinical HF confirmed with cardiac magnetic resonance (CMR) is observed in SLE patients.¹⁰⁰ A prognostic tool was developed based on CMR to enable stratification of SLE HFpEF risk, which may contribute to a more accurate diagnosis and better treatment approach. Nevertheless, this solution should be validated in future trials.¹⁰¹ Current guidelines do not recommend special treatment for this group.⁹⁹

Venous thromboembolism

The latest meta-analysis indicates a significantly higher risk of venous thromboembolism (VTE) events, including deep vein thrombosis and pulmonary embolism (risk ratio (RR) = 4.38, 95% CI: 2.63–7.29), in SLE patients compared to the general population.⁷ Moreover, the absolute risk of VTE in younger patients with SLE (<40 years) is higher than in patients with SLE at the age of 41–64.⁷ A retrospective study with a median follow-up period of 13 years revealed that VTE was the most frequent cardiovascular event, accounting for 50% of the total.²¹

The absolute risk of VTE events is higher in SLE patients with APS or aPL.⁷ Similar to healthy populations, SLE patients with normal D-dimer levels are at low risk for thrombosis, and those with elevated D-dimer levels, without other influencing comorbidities, are at high risk for thrombosis.¹⁰² Higher risks of VTEs and the associated risk factors among patients with SLE should be considered when optimizing treatment to balance the risks and benefits of the chosen therapy.⁷

Antiphospholipid syndrome is the primary determinant for the recurrence risk of a first SLE-associated VTE, meaning that indefinite anticoagulant therapy may be warranted in SLE patients with secondary APS. In the absence of APS treatment, decisions on SLE-associated VTE may be approached similarly to the general population. However, studies on the bleeding risk of anticoagulant therapy are needed to make an adequate benefit–risk assessment. Furthermore, active SLE at the time of a VTE may act as a transient provoking factor, but this finding needs to be confirmed in future research.¹⁰³

Advances in diagnostics

Accurate tools can detect and monitor even subclinical changes in the cardiovascular system to prevent future cardiovascular events (Fig. 3). The detection of CAD and perfusion deficits may be supported with computed tomography (CT), single photon emission tomography (SPECT), CMR, and invasive angiography, though there are no specific recommendations for patients with SLE in the current guidelines.¹⁰⁴ The CAD diagnostic algorithm should be primarily based on non-invasive assessments if there are no severe symptoms refractory to medical therapy.¹⁰⁴ Multidetector CT (MDCT) is used for non-invasive assessment of calcium score, which reflects the extent, severity and distribution of atherosclerotic plaques in arteries.^{105,106} The specificity of this method is high, so it can exclude clinically relevant stenosis, though the disease should be confirmed using coronary angiography.

CT-fractional flow reserve (FFR) can be used to coronary flow physiology, while single photon emission tomography (SPECT) is a sensitive method to evaluate myocardial perfusion defects. The extent, severity and reversibility of myocardial perfusion abnormalities can be identified at rest and under stress.^{106–108} As myocardial perfusion defects are predictors of CAD in SLE patients,¹⁰⁹ SPECT may be used for risk stratifying purposes. Myocardial blood flow can also be measured using PET (positron emission tomography) to reflect coronary flow reserve and may be an early predictor of CAD in SLE patients.¹¹⁰ Moreover, it can assess coronary microvascular dysfunction in this group.¹¹¹

The presence of diffuse contrast enhancement in vessel walls visualized with CMR indicates inflammation and atherosclerosis in SLE patients.¹¹² However, such patterns of enhancement can also be found in asymptomatic

patients.¹¹³ Other pathological findings include late gadolinium enhancement (LGE) and signs of stress-perfusion deficit observed in over 40% of SLE patients without known CAD.¹¹⁴ Moreover, CMR is commonly used to assess myocardial edema and ischemia and may be used to confirm myocarditis. Patients with evidence of LGE on CMR are more likely to develop CAD, atrial tachycardia, myocarditis, pericarditis, HF, and myopericarditis, suggesting that CMR should be considered as part of routine surveillance in patients with SLE for prognostic value and to guide management. Cardiac magnetic resonance can help answer the question of the substrate behind cardiac hypertrophy in SLE and what will guide the final decision for patients' risk stratification and further treatment (mainly to differentiate hypertrophic cardiomyopathy from CAD). Cardiac magnetic resonance can also identify the underlying pathophysiology of myocardial injury, such as inflammation, fibrosis, microvascular damage, or sub-epicardial ischemia,^{115,116} which contribute to individualized treatment management. Cardiac magnetic resonance is widely used in the diagnostic pathway in patients with SLE in early and even preclinical stages of autoimmune diseases.^{98,117} However, besides these benefits and general use, there are no specific recommendations for the usage of this method in SLE, probably due to poor availability and high cost.

Future perspectives include the use of artificial intelligence in accelerating the process of imaging, scar analysis with prediction of major arrhythmic events, and obtaining global circumferential strain, which may have prognostic value in patients with normal CMR.^{118,119} However, it should be highlighted that, before considering introducing these solutions in patients with SLE, the algorithm ought to be optimized for this group, which is often under-represented in the trials.

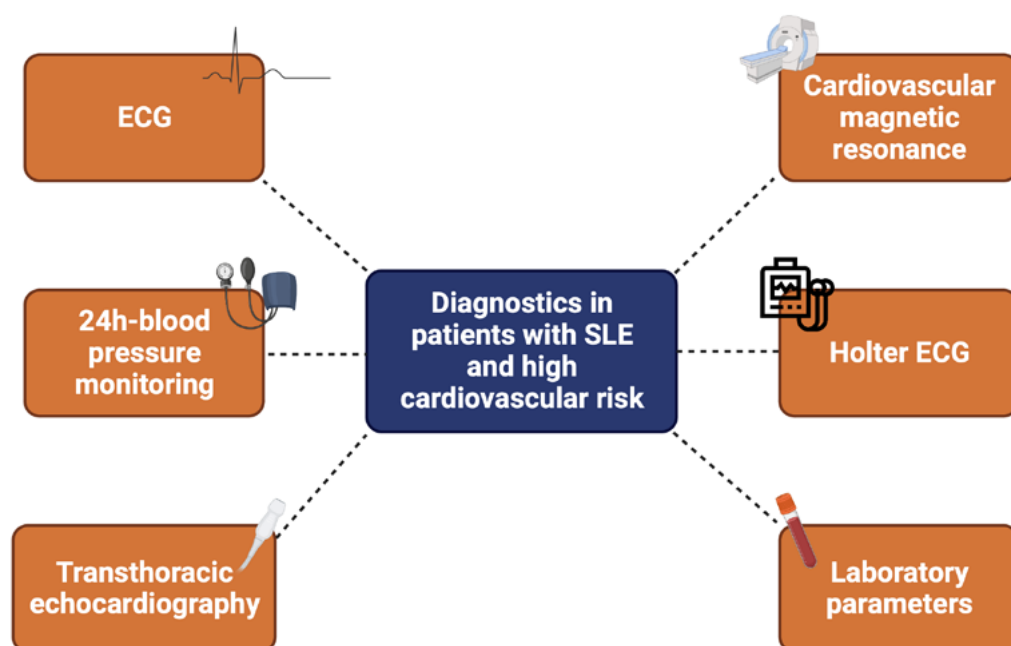


Fig. 3. Suggested diagnostic methods for patients with SLE and high cardiovascular risk

ECG – electrocardiography; SLE – systemic lupus erythematosus. Created with Biorender.com.

The role of echocardiography cannot be ignored since, as in other populations, it can assess cardiac systolic and diastolic functions, valve abnormalities and contractility disorders and estimate the pulmonary hypertension probability. There are no specific guidelines for using this method in SLE patients, though it is commonly used due to its wide availability, low cost and minimal complication risk. Libman–Sacks endocarditis is routinely detected and monitored using transthoracic echocardiography and transesophageal echocardiography, though studies reporting successful use of magnetic resonance imaging (MRI), MDCT, PET-CT, and SPECT in endocarditis diagnostics have also been published.^{120,121}

Therapeutic options and future directions

EULAR recommendations were formulated for the optimal management of cardiovascular risk in SLE patients (Fig. 2). They include hyperlipidemia treatment in line with the general population and BP control with a target BP of less than 130/80 mm Hg, especially in concomitant lupus nephritis. In this case, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blocker (ARB) therapy should be used. In SLE patients with no history of thrombosis or pregnancy complications, a prophylactic dose of aspirin (75–100 mg daily) should be

recommended for those with high aPL levels and may be considered in those with low aPL.⁴²

High lupus activity is associated with increased cardiovascular risk, so lupus activity should be carefully controlled.^{42,122} In lupus pharmacotherapy, glucocorticoids, immunosuppressants and anti-malarials are used, though most studies suggest that a high mean daily and cumulative dose of glucocorticoid increases cardiovascular risk.^{122,123} Therefore, EULAR recommends the lowest possible glucocorticoid dose.⁴² In turn, hydroxychloroquine is recommended for all SLE patients without contraindications. Hydroxychloroquine use is associated with lower lupus activity, risk of atherothrombotic events and CAD.⁴² Moreover, the latest meta-analysis showed that anti-malarial agents, of which the most popular was hydroxychloroquine, were associated with reduced risk of diabetes mellitus type 2 and reduced diastolic BP.¹²⁴

There are no specific immunosuppressant recommendations, though there was no association between cardiovascular risk and the use of methotrexate, mycophenolate, cyclosporine, or rituximab, while studies testing cyclophosphamide and azathioprine gave incompatible results⁴² (Fig. 4). Immunosuppressants and glucocorticoids are non-specific therapeutics with various systemic adverse effects.

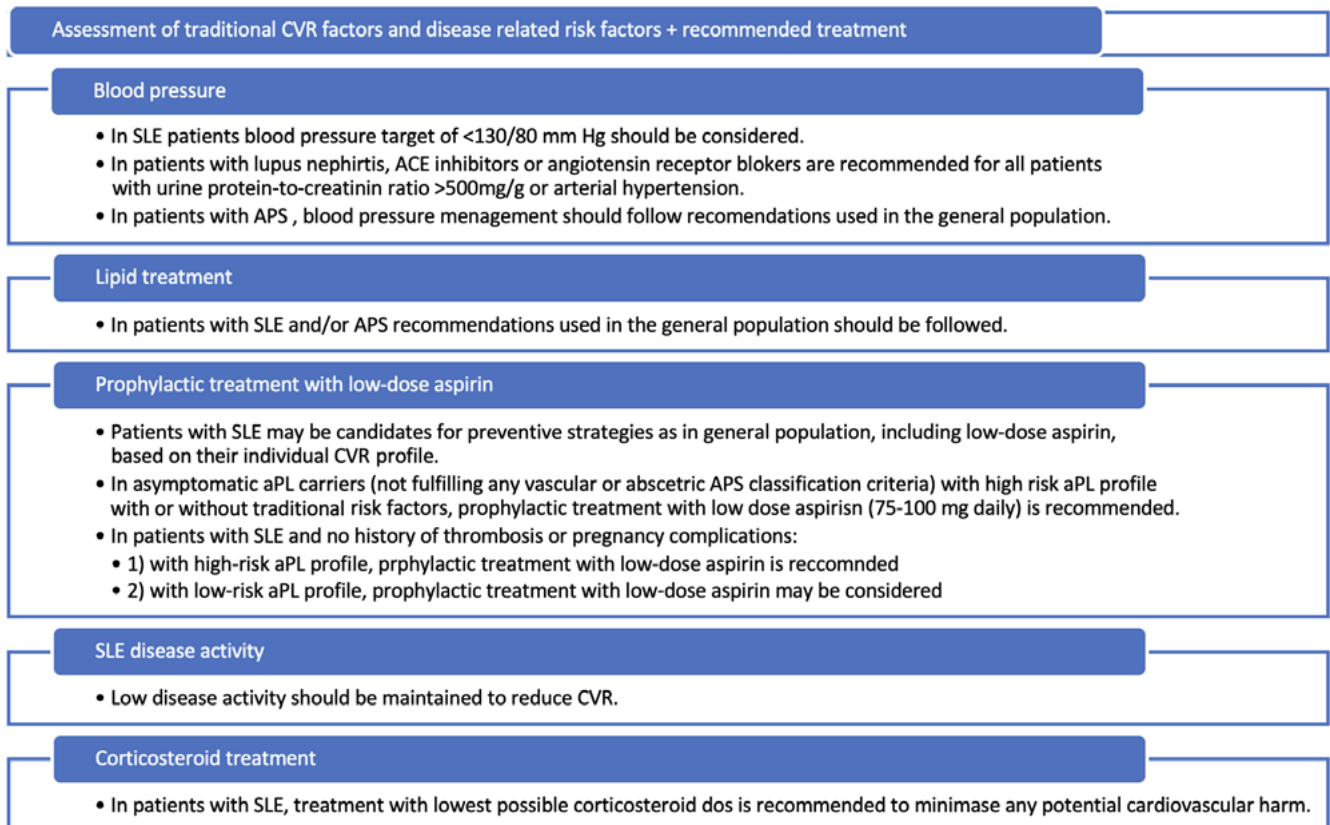


Fig. 4. European Alliance of Associations for Rheumatology Recommendations for CVR management in SLE and APS

CVR – cardiovascular risk; SLE – systemic lupus erythematosus; APS – antiphospholipid syndrome; ACE – angiotensin-converting enzyme; aPL – antiphospholipid antibody. Based on Drosos et al.⁴²

Currently, we face the challenge of developing biological molecular target-specific drugs.¹²⁵ Belimumab, an antibody against B cell-activating factor (BAFF) used since 2011, was the first biologic approved for SLE patients. Studies found that belimumab modifies the course of the disease and enables the gradual lowering of glucocorticoid doses.¹²⁶ Anifrolumab, an anti-type I IFN receptor antibody, was approved in the USA in 2021.¹²⁷ Ustekinumab targets IL-12/23 (p40) and is currently in clinical trials. In a randomized study, 37 (62%) of 60 patients in the ustekinumab group and 14 (33%) of 42 patients in the placebo group achieved a SLEDAI-2K responder index-4 (SRI-4) response (percentage difference 28%, 95% CI: 10–47, $p = 0.006$), which meant more pronounced improvements in clinical parameters, including global SLE disease activity responder index, joint counts, mucocutaneous disease, disease flares, and laboratory parameters (C3 complement concentrations and anti-double stranded deoxyribonucleic acid (dsDNA) autoantibodies) at week 24.¹²⁸ Another drug, baricitinib, a Janus kinase 1/2 (JAK 1/2) inhibitor, mediates signal transduction for IL-6, IL-12, IL-23, and IFN.¹²⁹ Biological treatment seems to be a promising strategy in SLE treatment and may lead to the reduction of cardiovascular risk.

So far, we know that blood biomarkers such as IgG against high-density lipoprotein (HDL) and paraoxonase 1 (PON1) are increased in SLE patients (Table 1). Anti-PON1 is an indicator of decreased PON1 activity in rheumatoid arthritis and is associated with carotid intima-media thickness in SLE, while anti-HDL poses a higher risk of CVD and lower HDL serum levels at disease onset.^{130,131} A study from 2020 found an elevated monocyte-to-HDL cholesterol ratio and a low-density

granulocytes-to-HDL cholesterol ratio in SLE patients with traditional risk factors or subclinical atheromatosis but not in those who were CVD-free.¹³² The level of dysfunctional HDLs in atherosclerosis in SLE was found to be affected by lupus therapy, which may be promising for monitoring lupus treatment.^{131,133,134}

Asymmetric dimethyl arginine (ADMA) is an acute-phase plasma protein, an endogenous nitric oxide inhibitor that rises through the activation of inducible endothelial nitric oxide synthase (eNOS), and is a reliable marker of endothelial dysfunction in APS patients. High serum ADMA levels may represent a risk factor for disease activity and poor prognosis among SLE patients.^{135,136} Other potentially useful biomarkers are presented in Table 1.^{121,131,137–139}

Biomarkers may help to detect SLE patients at high cardiovascular risk and need further investigation to develop personalized treatment.¹⁴⁰ Assessing biomarker levels and genomic profiles may be the standard future strategy for early detection of CVD or estimating cardiovascular risk and monitoring therapies.

Limitations

Due to the complex characteristics of SLE, little is known about the pathomechanisms affecting the development of cardiovascular complications. As such, an explanation for their presence has not been described in full. Furthermore, the autoimmune nature of SLE means the disease course can vary greatly between patients. The studies referenced primarily refer to whole populations, though there are subgroups in which the frequency of complications may differ from those described in this work.

Table 1. Biomarkers in SLE patients related to increased CVD risk


Biomarker	Sample type	Level in patients with SLE	Clinical application
Ig-G against HDL and PON1	serum	elevated	Associated with accelerated atherosclerosis; can indicate early endothelial damage or premature atherosclerosis in SLE patients; therapeutic targets for preventing CVD in SLE patients.
LHR; MHR	serum	elevated	Indicative of CVD risk in SLE patients even at the onset of disease.
hs-cTnT	serum	elevated	Independently associated with cardiovascular events in SLE patients.
IgG-anticardiolipin antibodies; E-selectin	serum	elevated	Associated with CVD and disease activity.
Dysfunctional HDLs	serum	modified by pharmacotherapy	Useful in monitoring the treatment of SLE.
Adiponectin	serum	elevated	Useful for CVD risk stratification in accelerated carotid atherosclerosis in SLE young women.
s-LOX-1	serum	elevated	Associated with increased CVD risk in SLE patients; potential therapeutic target.
ADMA	serum	elevated	Independently associated with endothelial dysfunction in APS patients.

SLE – systemic lupus erythematosus; CVD – cardiovascular disease; PON1 – paraoxonase 1; HDL – high-density lipoprotein; MHR – monocyte-to-high-density lipoprotein cholesterol ratio; LHR – low-density granulocytes-to-high-density lipoprotein cholesterol ratio; hs-cTnT – high-sensitivity cardiac troponin; ADMA – asymmetric dimethyl arginine.

Conclusions

Systemic lupus erythematosus is associated with an increased risk of cardiovascular disorders, so its management should involve early diagnosis and treatment of such complications. At present, there are no specific guidelines for cardiovascular risk prevention in SLE patients, and further research on the topic is warranted. In the treatment process of SLE patients, a personalized adaptation of EULAR and European Society of Cardiology (ESC) guidelines should be implemented to maintain low disease activity and use the lowest possible glucocorticoid dosage to avoid complications.

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