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REVIEW

A novel approach to cardiovascular events in patients with systemic lupus erythematosus: risk factor assessment and treatment analysis

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Abstract

Systemic lupus erythematosus (SLE) patients have a significantly increased risk of developing cardiovascular disease (CVD). Despite the implementation of preventive measures and treatment of lipid disorders, as well as reduced use of glucocorticoids, CVD remains one of the leading causes of death in this patient group. It is crucial to develop an appropriate CVD risk assessment strategy that considers the distinctive characteristics of this patient population. This paper provides a comprehensive analysis of the methods used to assess CVD risk in SLE patients. It also presents effective strategies for the reduction of the effects of traditional and non-traditional risk factors for atherosclerosis.

Keywords Atherosclerosis · Cardiovascular diseases · Cardiovascular risk · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a multi-organ, inflammatory autoimmune disease of unknown aetiology. The SLE is linked to an increased risk of accelerated atherosclerosis and cardiovascular events such as coronary artery disease, cerebrovascular accidents, and peripheral arterial disease [1]. This association is driven by both disease related factors (systemic inflammation, endothelial apoptosis, thrombosis and vasculitis) and traditional risk factors (dyslipidaemia, hypertension, smoking) [2]. The overall risk of cardiovascular disease (CVD) in SLE patients (pts) is twice that of the general population and increases significantly in younger patients and in the first year after diagnosis [1, 3]. Almost half a century ago, the bimodal pattern of mortality in SLE pts was first described. Early mortality was mainly attributed to infectious complications and organ damage caused by SLE. Late mortality was associated with CVD complications [4].

The aim of this study is to provide a comprehensive analysis of CVD events in SLE pts, with a special focus on the assessment method of CVD risk factors, their treatment, and prevention strategies.

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Search strategy

A comprehensive literature search was conducted in databases such as Medline/PubMed, Scopus and Directory of Open Access Journals (DOAJ) using a number of Medical Subject Headings (MeSH) search terms. The following keywords were used in the search: 'systemic lupus erythematosus', 'atherosclerosis', 'cardiovascular disease', 'risk factors', 'imaging studies'. Each article was rigorously assessed for relevance and the references cited in the article were examined to identify additional relevant sources. The review focused on peer-reviewed articles published in English, with no time limit on the search. Specific exclusion criteria were used. These criteria excluded articles without abstracts, conference proceedings, errata, retracted articles, studies that did not address the possible association between cardiovascular risk and SLE.

Epidemiology of CVD in SLE patients

Cardiovascular diseases affect 6–25% of SLE pts [5]. Studies have shown that SLE pts have at least a 2-3-fold higher risk of myocardial infarction, congestive heart failure, cerebrovascular disease, and overall mortality due to CVD compared to the general population [6, 7]. The cardiovascular risk in SLE pts has been estimated to be comparable to that of individuals with type 1 diabetes [8]. Approximately 30% of deaths in this group are attributed to coronary artery disease. Premenopausal women with SLE have been found to have a 50-fold increased risk of myocardial infarction compared with healthy women of the same age. Most cases of acute coronary syndrome in SLE are caused by atherosclerosis, with fewer cases resulting from thrombosis, vasculitis, or spontaneous coronary artery dissection [9, 10]. The risk of a major adverse cardiovascular event (MACE) is 2.4 times higher than in the general population, particularly among the youngest patients [11]. In addition, SLE patients are more frequently hospitalized for acute myocardial infarction and congestive heart failure, with significantly longer hospital stays than pts with diabetes.

Pathogenesis of CVD in SLE patients

Accelerated atherosclerosis, which develops against a background of autoimmune inflammation, plays an important role in the pathogenesis of CVD in SLE pts. In the early stages of SLE, microcirculation damage and vascular endothelial dysfunction are observed, leading to a chronic inflammatory reaction response involving tumour necrosis factor alpha (TNF-α) and interleukin 1 (IL-1). These cytokines stimulate T lymphocytes and monocytes, which release adhesion molecules on contact with the endothelium: E-selectin, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), vascular endothelial growth factor (VEGF), pentraxin 3, thrombomodulin, interferon-inducible protein (IP-10) and monocyte chemotactic protein-1 (MCP-1). An increase in the concentration of these particles leads to vascular calcification and the production of reactive oxygen species, which interact with low-density lipoproteins (LDL), form oxidized LDL (oxLDL). In parallel, activation and apoptosis of endothelial cells occur. The presence of autoantibodies against endothelial cells and numerous apoptotic cells initiates an autoimmune response. Impaired ability to remove apoptotic cells and oxidized lipoprotein remnants causes loss of immunological tolerance to various autoantigens [12]. Regulatory T lymphocytes suppress atherogenic T lymphocytes. In SLE pts, Treg/Th17 balance is disturbed and interferon gamma (IFN-γ) is increased, which inhibits the growth of endothelial cells, smooth muscles and leads to atherosclerotic plaque instability. The participation of B lymphocytes and the autoantibodies produced by them is also important in the pathogenesis of atherosclerosis. Antiphospholipid antibodies (aPL) and anti-high-density lipoprotein (anti-HDL) are independent factors in the development of atherosclerotic plaque [13].

Risk factors for atherosclerosis and cardiovascular events in SLE patients

Atherosclerosis risk factors can be divided into traditional (non-modifiable and modifiable) and non-traditional risk factors.

Traditional non-modifiable risk factors include age, male sex and genetic factors. The SLE pts older than 48 years and/or postmenopausal have a 5-fold increased risk of CVD events. Similarly, male sex and a family history of coronary heart disease in a first-degree relative are associated with a significantly increased risk of CVD [8, 14]. Modifiable risk factors include smoking, hypertension, dyslipidaemia, hyperglycaemia and obesity. The SLE pts who smoke have a 4-fold increased risk of CVD compared to non-smokers. Previous studies have shown a higher risk of CVD in SLE pts with a systolic blood pressure of 130–139 mmHg and a diastolic blood pressure of 80–89 mmHg, compared to patients with blood pressure values below 130/80 mmHg [15]. This study showed that systolic blood pressure ≥ 132 mmHg is associated with a higher risk of cardiovascular events, and systolic blood pressure has a greater impact on this risk than diastolic blood pressure [16, 17]. 34–51% of SLE pts have hypercholesterolaemia and almost 30% can be diagnosed with metabolic syndrome [18, 19]. The

accompanying inflammation reduces HDL-C levels and increases the synthesis of phospholipid-rich low-density lipoproteins (VLDL), resulting in accelerated atherosclerosis [20]. One third of pts are diagnosed with dyslipidaemia at the onset of the disease, and this number doubles in the following three years [21]. The risk of dyslipidaemia is significantly increased in pts with lupus nephritis (LN), especially those with nephrotic syndrome and renal failure. Lipid abnormalities in SLE patients may lead to subclinical cardiovascular complications [22].

Non-traditional risk factors play an important role in the pathogenesis of CVD in SLE pts. Of particular note are chronic inflammation and corticosteroids (GCS) use [2]. The risk of CVD depends on SLE activity, disease duration and organ complications, especially renal damage [23].

The development of subclinical and overt clinical CVD is significantly influenced by antibodies. The aPLs and antibodies directed against endothelial cells play a special role. Some findings also confirm the negative effect of anti-dsDNA, anti-Ro and anti-Sm antibodies on CVD risk [24]. Among the drugs, GCS play a key role, doubling the risk of CVD. According to some authors, azathioprine may also increase this risk [8].

Methods for assessing CVD risk in SLE patients

Reliable CVD risk assessment is important for therapeutic decision making. Risk assessment should take into account the sensitivity and specificity of the method, as well as access to laboratory data and ease of use in clinical practice. Although CVD risk prediction tools consider similar parameters, they use different algorithms to determine risk. In addition, the same components are weighted differently in each tool [25]. Traditional CVD risk calculators such as the Framingham Risk Score (FRS) and Atherosclerotic Cardiovascular Disease (ASCVD) are widely used in the general population [26]. They do not take into account the specificity of inflammatory autoimmune diseases, including SLE, and some of them (such as the FRS) may even underestimate this risk [27]. Consequently, their use in the SLE pts population is widely debated. Urowitz et al. [28] showed that doubling the FRS improves CVD risk assessment in SLE pts and called this formula the modified Framingham Risk Score (mFRS). Another scale has also been developed - the PREDICTS (Predictors of Risk for Elevated Flares, Damage Progression and Increased Cardiovascular Disease in Patients with SLE), which assesses four inflammatory biomarkers: proinflammatory high-density lipoprotein (piHDL), leptin, soluble TNF-like weak inducer of apoptosis (sTWEAK), homocysteine and also two traditional biomarkers: age ≥ 48 years and diabetes. The SLE pts with a high-risk PREDICTS profile (≥ 3 positive biomarkers or ≥ 1 positive biomarker and history of diabetes) had a 28-fold increased risk of atherosclerosis and a 3.7-fold increased risk of MACE [29, 30]. In 2007, the QRISK calculator was published, which predicts 10-year CVD risk, followed a year later by QRISK2 which calculates the probability of MACE [31]. In 2017, a new version of this calculator, QRISK3, was created and applied to a younger group of patients (25–84 years old). In addition to the traditional risk factors, this calculator took into account chronic kidney disease (stage 3, 4 or 5), migraine, presence of SLE, severe mental illness, use of atypical antipsychotics, GCS, erectile dysfunction and changes in systolic blood pressure [32]. Both QRISK3 and PREDICTS showed higher predictive value compared to FRS and mFRS in predicting CVD risk in SLE pts [33, 34]. A new tool to assess the 10-year moderate/high risk of MACE in SLE pts is SLECRISK. It is an extension of the widely recommended American College of Cardiology/American Heart Association (ACC/AHA) risk assessment model. The SCLERISK takes gender and race into account, which is a significant advantage over other scales (the FRS assesses CVD risk in Caucasian pts). The increased CVD risk in SLE pts is mainly attributed to factors related to the disease itself, as reflected in the SLECRISK scale variables i.e. duration and activity of SLE, renal dysfunction, anti-dsDNA, anti-RNP, anti-Ro antibodies present, lupus anticoagulant and low levels of complement component C4. The SLECRISK was found to be more sensitive than the traditional ACC/AHA risk model (74% vs. 38%). It showed 3.4-fold more moderate/high CVD risk pts, especially among young SLE pts with severe, active disease, who typically have few traditional CVD risk factors. An important advantage of the SLECRISK is the inclusion of SLE symptoms and the ability to use this scale in daily clinical practice. It is worth considering the use of the SLECRISK scale in guidelines for the management of SLE patients, especially in decision making for primary CVD prevention [23]. The parameters considered in each CVD risk scale are listed in Table 1.

It is known that aPLs are an independent risk factor for CVD events [35]. The Global AntiPhospholipid Syndrome Score (GAPSS) is a risk scale that, among other things, includes the profile of aPLs. The first version of this scale was developed and validated in a cohort of SLE pts, and later in pts with primary antiphospholipid syndrome (APS). The GAPSS includes: hyperlipidaemia, hypertension, IgG/IgM anti-cardiolipin antibodies, IgG/IgM anti-β2-glycoprotein I (aβ2GPI), LAC and phosphatidylserine/prothrombin antibodies [34, 36]. The use of SLE-adapted CVD risk scales, i.e. QRISK3, mFRS, SLECRISK and also monitoring of gcs treatment may improve the results of CVD risk

Table 1 Parameters of selected cardiovascular risk assessment scales in SLE patients [10, 23, 26, 32, 34, 37]

FRS	mFRS	QRISK2	QRISK3	SLECRISK	ACC/AHA ASCVD
age sex treatment for HT diabetes smoking HDL total cholesterol SBP	FRS estimate multiplied by a 2.0 factor	age sex ethnicity Townsend score smoking type 2 diabetes family history of CVD (angina pectoris or heart attack in a first degree relative under 60 years) chronic kidney disease atrial fibrillation, treatment for HT RA HDL total cholesterol SBP BMI	QRISK2 and: migraine severe mental illness (schizophrenia, bipolar affective disorder, moderate/severe depression) treatment with atypical antipsychotic GCS erectile dysfunction SBP variability HIV/AIDS SLE	age sex SBP total cholesterol smoking diabetes SLEDAI≥2 low C3 history of LAC	Age sex race total cholesterol HDL LDL SBP DBP treatment for HT diabetes smoking

ACC/AHA ASCVD - American College of Cardiology/ American Heart Association Atherosclerotic Cardiovascular Disease; BMI - body mass index; CVD - cardiovascular diseases; DBP - diastole blood pressure; FRS - Framingham Risk Score; GCS- glucocorticoids; HDL-high density lipoproteins; HIV/AIDS - human immunodeficiency virus/acquired immunodeficiency syndrome; HT - hypertension, LAC- lupus anticoagulant; LDL-low density lipoproteins; mFRS - EULAR modified FRS; SLECRISK - SLE Cardiovascular Risk Equation; RA - rheumatoid arthritis; SBP-systole blood pressure; SLE- systemic lupus erythematosus; SLEDAI - Systemic Lupus Erythematosus Disease Activity Index

assessment in SLE pts [37]. However, there is still no ideal tool. Both PREDICTS and GAPSS include markers that are not routinely measured, which hinders their use in daily practice [30, 38]. Sivakumaran et al. [10] in an analysis of 1887 SLE pts showed that none of the CVD risk assessment scales used to date: QRISK2, QRISK3, FRS, mFRS or SLECRISK have sufficient sensitivity and specificity, hence further research is needed [10]. The latest recommendations from the European Alliance of Associations for Rheumatology (EULAR) recognise the limitations and lack of validation of existing tools for predicting cardiovascular risk in SLE and therefore do not endorse any particular calculator. Instead, they recommend a comprehensive assessment of the patient and the use of prophylaxis to reduce the impact of traditional and non-traditional atherosclerotic risk factors [17, 39].

Use of imaging studies to assess cardiovascular risk in SLE patients

Imaging studies are widely used in the diagnosis of CVD. Some of them are used in the diagnosis of vascular lesions in SLE. Flow-mediated dilatation (FMD) of the brachial artery is a reliable, non-invasive and relevant index of early atherosclerosis. FMD of the brachial artery indirectly provides information on vascular endothelial dysfunction and can be used to assess the risk of progression to ischaemic heart disease and other CVDs in SLE [40–42]. Pulse wave velocity (PWV) measures the stiffness of the carotid and femoral arteries, and increased PWV may be a marker of early atherosclerosis. A meta-analysis in SLE pts showed significantly higher PWV values compared to controls, which correlated with BMI and disease duration [43–45]. A useful and readily available test is ultrasound assessment of the thickness of the intima-media thickness (IMT) and carotid artery plaque. In the general population, an IMT > 0.83 mm is considered abnormal, in SLE pts > 0.9 mm. On ultrasound, carotid artery atherosclerotic plaques are detected in 7–50% of SLE pts and are associated with a 4-fold increased risk of CVD. The presence of atherosclerotic plaques in the carotid and femoral arteries has a higher predictive value compared with isolated atherosclerosis of the carotid arteries only [46, 47]. Another diagnostic method is the assessment of coronary artery calcification (CAC) by computed tomography. The degree of CAC is significantly higher in SLE pts than in the general population [48]. Measurement of CAC may help to estimate the risk of CVD in the SLE population, particularly in pts with high disease activity and LN [13]. Some researchers recommend using this imaging modality early in the diagnosis of SLE to detect subclinical CVD. It is believed that non-calcified atherosclerotic plaques are more metabolically active and their presence is associated with a higher risk of CVD compared to calcified plaques. More than half of SLE pts have been shown to have non-calcified atherosclerotic plaques [49]. Coronary angiography remains the 'gold standard' for the diagnosis of ischemic heart disease [50]. According to a study by Kaul et al. [51], SLE pts showed similar severity of coronary lesions to non-SLE pts, although the SLE group was 20 years younger and had

significantly fewer diabetic pts. Assessment of myocardial perfusion by a single-photon emission computerized tomography (SPECT) is a sensitive test that detects significant defects in myocardial perfusion. SPECT examination is a strong predictor of cardiovascular mortality. The SLE pts have been shown to have a high rate of myocardial perfusion defects despite the absence of clinical signs of CVD [52, 53]. More than half of SLE pts have myocardial perfusion abnormalities on SPECT, in the absence of significant changes on coronary angiography [14]. Cardiac magnetic resonance (CMR) is also used in the diagnosis of vascular complications. The CMR lesions have been demonstrated in approximately 40% of SLE pts, and in the group with normal echocardiography, CMR lesions were present in approximately 25% of pts [54, 55]. It is worth considering the use of the imaging modalities presented in the diagnosis of vascular lesions in SLE, especially those that predict the occurrence of CVD at the subclinical stage [8].

Reducing CVD risk in SLE patients

Appropriate diet, physical activity and pharmacological treatment are recommended for CVD prevention in patients with SLE. Lipid disorders in SLE pts should be treated according to the recommendations of the Polish Cardiac Society and the European Society of Cardiology. In 2022, EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including SLE and APS, were published. According to EULAR, there is no additional benefit of low-dose acetylsalicylic acid (ASA) for primary prevention of CVD, but only for secondary prevention. Low doses of ASA are recommended in SLE pts with aPL with a high risk profile for thromboembolic complications and should be considered in pts with aPL with a low risk profile. Blood pressure targets should be below 130/80 mmHg. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are recommended for the treatment of hypertension in pts with LN [14, 17, 56]. It is very important to maintain low disease activity and use the lowest possible dose of GCS. The antimalarials - chloroquine (HQ) and hydroxychloroquine (HCQ) - have been shown to be cardioprotective in SLE pts. These drugs inhibit T-lymphocyte proliferation, Toll-like receptor (TLR) activation and reduce the production of the cytokines TNF-a, IL-17, IL-6, IFNα and IFNγ. Antimalarial drugs reduce total cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides and increase HDL cholesterol. They show similar effects to statins after by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase and reducing the hepatic synthesis of LDL cholesterol in GCS-treated pts. The hypolipemic effect of these drugs becomes apparent after at least 12 months of use [57, 58]. Antimalarials reduce the risk of venous and arterial thrombosis by inhibiting platelet aggregation, arachidonic acid secretion and aPL binding [59, 60]. In addition, they significantly reduce the risk of thrombosis in pts with other cardiovascular risk factors, such as diabetes and CVD [61]. A meta-analysis of 19 observational studies showed that antimalarials reduce cardiovascular risk in pts with rheumatic disease by approximately 30% due to their hypoglycaemic, hypolipemic, vasodilator and antiplatelet effects [62, 63]. Concerns have long been raised around the potential toxicity of antimalarials. A review of the literature revealed an increased incidence of cardiac toxicity (QTc prolongation, torsades de pointes, ventricular arrhythmias, cardiomyopathy) and ocular toxicity (corneal deposits, posterior subcapsular lens opacity, ciliary body dysfunction, retinopathy, vision loss). It is of the utmost importance that the application of these pharmaceutical agents be subjected to exhaustive and continuous observation and evaluation in order to ensure the safety of pts [64, 65].

There are few data confirming the cardioprotective effects of other immunosuppressive drugs used in SLE patients. Mycophenolate mofetil (MMF) has been shown to reduce cardiovascular mortality in diabetic patients after renal transplantation [66]. MMF used in mouse models of SLE showed cardioprotective effects, but no improvement in subclinical CVD was observed in a small prospective cohort study of SLE patients [67, 68].

Despite the lack of conclusive evidence for the cardioprotective effect of immunosuppressive drugs other than antimalarials, their use in SLE patients is recommended. Immunosuppressive drugs lead to remission of SLE and reduce the need for gks, which reduces cardiovascular risk.

Conclusions

Despite significant improvements in the survival of SLE pts, CVD remain a significant cause of death, especially in the youngest group of pts. Dyslipidaemia in the SLE population may lead to subclinical cardiovascular complications. The risk of CVD is underestimated by standard assessment methods. Most CVD risk calculators used in the general population are not appropriate for SLE pts and available imaging techniques do not always detect vascular changes. More sensitive and specific diagnostic methods should be sought. The basis of CVD prevention is lifestyle modification, control of disease activity and use of antimalarials.

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All authors reviewed the results and approved the final version of the manuscript DS. All authors take full responsibility for the integrity and accuracy of all aspects of the work.

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Declarations

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Conflict of interest Authors: Dorota Suszek, Magdalena Popławska, Jakub Prośniak, Katarzyna Siemieniec, Karolina Przeniosło, Weronika Wallach, Monika Żybowska-Męczyńska, Klaudia Ostrowicz, Anna Rzewuska-Fijałkowska, Bożena Targońska - Stępniak declare that they have no conflict of interest.

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