# Optimal Monitoring For Coronary Heart Disease Risk in Patients with Systemic Lupus Erythematosus: A Systematic Review

Konstantinos Tselios, Barry J. Sheane, Dafna D. Gladman, and Murray B. Urowitz

*ABSTRACT.* ***Objective.*** Premature coronary heart disease (CHD) significantly affects morbidity and mortality in systemic lupus erythematosus (SLE). Several studies have detected factors influencing the atherosclerotic process, as well as methods to quantify the atherosclerotic burden in subclinical stages. The aim of this systematic review was to identify the minimum investigations to optimally monitor CHD risk in SLE.

***Methods.*** English-restricted literature review was performed using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines through Ovid Medline, Embase, and Cochrane Central databases, from inception until May 2014 (Medline until October 2014). Specific search terms included, among others, "SLE," "atherosclerosis," "CHD," "myocardial ischemia," "acute coronary syndrome," "myocardial infarction," and "angina pectoris." We identified 101 eligible articles, 23 with cardiovascular events (CVE) as endpoints and 78 with measures of subclinical atherosclerosis. The Newcastle-Ottawa scale was used for quality assessment.

***Results.*** Certain traditional and disease-specific factors were identified as independent predictors for CHD. Among the former were age (particularly postmenopausal state), male sex, arterial hypertension, dyslipidemia, and smoking. Disease activity and duration, cumulative damage, antiphospholipid antibodies, high sensitivity C-reactive protein, and renal disease were the most consistent disease-related factors. Corticosteroids were linked to increased CHD risk whereas antimalarials were protective. Concerning imaging techniques, carotid ultrasonography (intima-media thickness and plaque) was shown to independently predict CVE.

***Conclusion.*** Premature CHD in SLE is multifactorial; modifiable variables should be monitored at frequent intervals to ensure prompt management. Disease-specific factors also affect the atherogenic process and should be evaluated regularly. Carotid ultrasonography may hold promise in predicting CVE in selected high-risk patients. (J Rheumatol First Release November 15 2015; doi:10.3899/jrheum.150460)

*Key Indexing Terms:*
SYSTEMIC LUPUS ERYTHEMATOSUS
CORONARY HEART DISEASE
ATHEROSCLEROSIS
RISK FACTORS

Accelerated atherosclerosis leading to coronary heart disease (CHD) represents one of the major causes of death in systemic lupus erythematosus (SLE); the standardized mortality ratio attributable to cardiovascular disease (CVD) was the only one that did not diminish over time[1]. Since the initial description of the bimodal pattern of mortality in SLE by Urowitz, *et al*[2], large epidemiological studies have demonstrated that atherosclerotic CHD significantly affects patients with SLE[3,4]. The relative risk for myocardial infarction (MI) in premenopausal female patients was estimated to exceed 50-fold that of age-matched healthy controls[5]. Patients with SLE aged 20–39 years had a 16-fold increase risk of death from CHD in a population-wide study from Sweden[6]. Increased morbidity for CHD has been confirmed even during the first year after diagnosis (relative risk for MI = 5)[7], as well as 2 years preceding diagnosis[8].

The pathophysiology of premature atherosclerosis in SLE is incompletely understood and involves a complex interplay between traditional and disease-related risk factors[9,10]. Among the latter, SLE itself confers the greater risk for premature CHD; and disease activity, cumulative damage,

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autoantibodies, soluble inflammatory factors, and medications seem to be involved as well[11]. Nevertheless, the importance of traditional risk factors cannot be underestimated because early detection and management may improve longterm prognosis.

Despite the incorporation of SLE in the "at risk" category for CVD by the American Heart Association[12], rheumatologists perform suboptimally in CV risk assessment in immune-mediated diseases[13,14].

The aim of our systematic review was to provide guidance for guide-practicing clinicians in using evidence-based investigations (predictive and/or diagnostic, laboratory, and imaging) in assessing CHD risk in SLE. The specific question addressed was: "What are the minimum investigations to optimally monitor the risk of atherosclerotic heart disease in an SLE patient?"

## MATERIALS AND METHODS

A systematic literature review was performed using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[15] through Ovid Medline, Embase, and the Cochrane Central databases from inception (1946) until the third week of May 2014 (Medline until the end of October 2014).

Specific search terms included, among others, "lupus," "systemic lupus erythematosus," "atherosclerosis," "arteriosclerosis," "atheroma," "coronary heart disease," "coronary artery disease," "myocardial ischemia," "acute coronary syndrome," "myocardial infarction," "angina pectoris," "myocardial perfusion," "congestive heart failure," "cardiac arrest," and "cardiac death".

Literature search was restricted to English language, and 5775 relevant articles were identified. After duplicates were removed, 5178 articles remained. At a second stage, review articles, non-human studies, case reports and series, pathogenetic studies, and nonatherosclerotic CV manifestations in SLE (i.e., neonatal lupus, pericarditis, valvular disease, antiphospholipid syndrome, primary conduction disorders) were excluded. At a third stage, 262 articles were screened by abstract and/or full text, following predefined quality requirements. These included (1) variable evaluation for a clinical CV event (CVE) or a surrogate [endothelial dysfunction, arterial stiffness, arterial intima-media thickness (IMT), plaque formation, myocardial perfusion abnormalities, coronary artery calcification (CAC), coronary angiography] atherosclerotic endpoint, (2) at least 100 patients for CVE and 25 for surrogate markers, and (3) multivariate statistical analysis. Two independent reviewers assessed all articles; upon disagreement, final decision was reached through discussion with a third reviewer. The Newcastle-Ottawa scale was applied; studies with 6 or more stars were included.

Finally, 101 articles were considered eligible, 23 studies with clinical endpoints (CVE)[5,16–25,26–35,36,37] and 78 studies with subclinical atherosclerosis endpoints. Thirty studies used carotid or femoral artery Doppler ultrasound[38–47,48–57,58–67], 19 CAC computed tomography (CT)[57,68–77,78,79,80,81,82,83,84,85], 9 pulse wave velocity (PWV)-augmentation index[58,62,80,86,87,88,89,90,91], 9 brachial artery flow-mediated dilatation (FMD)[66,87,92,93,94,95,96,97,98], 6 myocardial scintigraphy[81,99,100,101,102,103], 2 cardiac magnetic resonance imaging (MRI)[104,105], and 3 coronary angiography[101,106,107]. Their reference lists were hand-searched, and no eligible article was further identified. Figure 1 depicts the article retrieval process.

## RESULTS

Since atherosclerosis is a multifactorial, time-dependent process, only variables proved to be independent predictors for clinical or surrogate endpoints after multivariate analysis are reported.

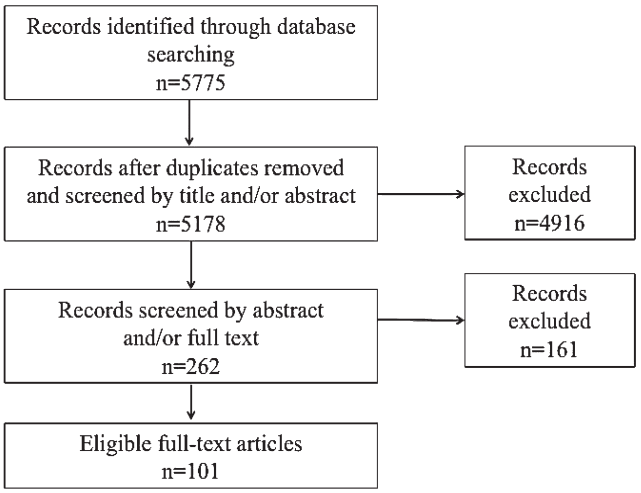


*Figure 1*. Flow chart of the article retrieval process.

### Traditional Risk Factors

*Nonmodifiable risk factors*. Age, particularly over 48 years or postmenopausal state, was a significant independent predictor for CHD events (HR 1.04–5.1 for all age groups)[4] and endothelial dysfunction[96,97], arterial stiffness (HR 1.13)[58,62,87,89,90], arterial wall thickening and/or plaque formation (HR 1.11–4.1)[38,39,40,41,42,44,45,46,48,50,52,53,55,56,58,59,60,62,63,64,65,66,67], CAC or noncalcified plaques (HR 1.08–8.5)[69,72,75,76,77,83,84,85], and angiographically defined plaques (HR 2.22)[106,107].

Positive family history, defined by the presence of a CVE in a first-degree relative under age 55 years for men or 65 years for women, was an independent risk factor for CVE (HR 3.6)[16,35], although it was not associated with increased carotid IMT and plaque formation[38,44,45,46,51,55,59,62,65], CAC[74,76,78,84], and angiographic findings[106].

Male sex was a strong predictor for CVE (HR 1.56–6.2)[16,23,27,28,29,35], as well as aortic stiffness[90], atherosclerotic plaques in the carotid and femoral arteries (HR 8.78)[48], CAC[69], and angiographic findings (HR 2.38)[106].

*Modifiable risk factors*. Obesity is a well-recognized risk factor for both CVE[35] and subclinical atherosclerosis in patients with SLE. Patients with SLE with body mass index (BMI) > 30 demonstrated endothelial dysfunction, assessed by brachial artery FMD[87], increased carotid IMT and plaque formation (HR 1.06–6.16)[41,53,61,65,66], and CAC[75,80]. Also, an abnormal waist-to-hip ratio was predictive of increased carotid IMT[64]. Obesity was among the major predictors of IMT progression over 3 years in pediatric patients with SLE[61].

Arterial hypertension (HTN), defined as systolic blood pressure (BP) > 140 mmHg and/or diastolic BP > 90 mmHg, was found to be independently (HR 1.05–3.5) associated with increased rates of CVE[16,17,18,27,32,34,35,36]. Further, it was related to impaired endothelial dysfunction[94,96] and arterial

stiffness[62,87,91], increased carotid IMT and plaque formation (HR 1.04–3.0)[41,46,50,56,62,66], CAC[76], and angiographically proven CHD[107]. HTN was an independent risk factor for myocardial perfusion defects (HR 2.11–2.53)[99,102].

Diabetes mellitus (DM) was associated with adverse CVE in 1 study (HR 1.5)[27]. However, increased insulin and glucose levels, without a formal diagnosis of diabetes, have been related to increased arterial stiffness (HR 1.54)[62], and McMahon, *et al* recently reported a 60-fold increase for carotid IMT progression in patients with SLE with diabetes[55]. In addition, DM was independently related to CAC[75,82] and a 4-fold increased risk of myocardial perfusion defects[102].

Total cholesterol (TC) was an independent predictor for CVE (HR 3.9–6.9)[5,16,28,30,32], as well as subclinical atherosclerosis. In particular, an elevated TC was a risk factor for increased carotid IMT and plaque formation (HR 1.2–3)[41,42,62], CAC[76], angiographic CHD (HR 1.89)[106], and perfusion abnormalities (HR 2.51)[99]. Time-adjusted TC values may identify more precisely the increased CV risk of patients with SLE since lipid values may fluctuate over time, reflecting changes in disease activity and therapy[28]. Unexpectedly, low-density lipoprotein (LDL) was not an independent factor for CVE, CAC, or angiographic CHD. However, it was significantly related to increased carotid IMT and plaque (HR 7.6)[39,40,42,47]. Low levels of high-density lipoprotein (HDL) have been implicated in CVE[36], endothelial dysfunction[87], myocardial perfusion abnormalities (HR 3.86)[102], and carotid IMT and plaque (HR 4.8)[47], but not with coronary calcification. On the contrary, elevated triglycerides were an independent predictor for CVE (HR 1.15–8.00)[20,32], CAC[69], and arterial stiffness[58].

Proinflammatory HDL, not having the capacity of neutralizing LDL effects, was strongly associated (HR 9.1–12.8) with increased carotid IMT and plaque formation[55,56]. In addition, oxidized LDL was independently related to decreased small artery elasticity[97].

Metabolic syndrome was associated with increased carotid IMT, CAC (HR 3.11)[57,67], and arterial stiffness[90].

Elevated levels of homocysteine (HCY) were also related to CAC[69,85] and increased carotid IMT or plaque (HR 1.24)[42,59,60].

Smoking was associated with carotid plaque (HR 7.7)[48,56], CAC (HR 3.8)[72,76,78], and CVE (HR 2.2–3.7)[18,22,25,31,33,35]. Traditional risk factors, which may independently predict clinical or subclinical CHD, are presented in Table 1.

**Disease-related Risk Factors**

*Disease activity, cumulative damage, and disease duration*. Disease activity, assessed by composite indices such as the SLE Disease Activity Index (SLEDAI) and European Consensus Lupus Activity Measurement (ECLAM), was significantly associated with CVE (HR 1.05–1.2)[16,17,23,26,27,28,32], increased arterial stiffness[86,88], increased carotid IMT and plaque formation[52], and CAC (HR 12.3)[84]. Cumulative damage, assessed by the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index, was strongly related to CVE (HR 1.3–4.1)[16,22,29], endothelial dysfunction[89], carotid IMT and plaque (HR 1.7)[41,49,52,65,66], and CAC (HR 1.2)[83]. Likewise, disease duration was an independent predictor of CVE (HR 1.10–1.45)[23,31], arterial stiffness[90], small artery elasticity[97], increased carotid IMT and plaque (HR 1.7–3.2)[45,53,59,60,64,65,66,67], and CAC (HR 1.2–15.1)[83,84,85].

*Autoantibodies*. Anticardiolipin antibodies (aCL) were independent predictors of CVE (HR 3.1–5.8)[16,17,21,22,31]; likewise, they were associated with myocardial perfusion defects (HR 4.1)[81], carotid plaques (HR 5.2)[38], and coronary calcifications[81]. Anti-β2 glycoprotein I (GPI) antibodies were associated with CVE (HR 3.4)[21,22] and coronary calcifications[81], but not with carotid plaques or endothelial dysfunction. Lupus anticoagulant was related to CVE (HR 1.74)[27], carotid plaque (HR 5.2)[38], and coronary calcifications (HR 4.4)[81]. Other antiphospholipid epitopes, such as anti-oxPAPC (oxidized palmitoyl arachidonoyl phosphocholine), were identified as risk factors for carotid IMT and plaque formation (HR 1.06)[46]. Low levels of natural immunoglobulin M (IgM) antiphosphorylcholine antibodies were related to increased carotid IMT and plaque formation[39,108].

Anti-dsDNA autoantibodies were associated with CVE (HR 1.56)[27] and noncalcified coronary plaques[77].

*Soluble inflammatory mediators*. High-sensitivity C-reactive protein (hsCRP)[22,29,31], as well as specific alleles[18], confer an increased risk for CVE (HR 1.6–3.4). In addition, it was an independent predictor of endothelial dysfunction[95] and increased arterial stiffness[90], carotid IMT and plaque (HR 3)[40,51,53,62,66], and coronary calcification presence and severity (HR 1.65–4.15)[74,76,82]. Complement fragment C3 was associated with increased risk for arterial stiffness[62], increased carotid IMT[40,60], and CAC[78].

Tumor necrosis factor (TNF)-like weak inducer of apoptosis increased risk for carotid IMT and plaque by 29-fold (levels > 373 pg/ml)[55]; interleukin 6 was related to CAC (HR 1.07)[68]; vascular endothelial growth factor to increased carotid IMT[43] and coronary calcification[82]. TNF-α, vascular cell adhesion molecule, E-selectin, and intercellular adhesion molecule 1 were associated with coronary calcifications[74,82]. In contrast, low transforming growth factor-β1 was related to increased IMT[109]. Type I interferons were independently associated with increased carotid IMT and severity of coronary calcification[73].

Adipocytokines were introduced as potential atherosclerosis risk factors; leptin (particularly > 34 ng/dl) conferred an increased risk for carotid IMT and plaque[55,56]. Finally, uric acid was an independent predictor of coronary calcification[72].

*Specific disease phenotypes and comorbidities*. Renal disease was implicated in increasing CVD risk; renal impairment was

*Table 1*. Studies identifying traditional (modifiable and nonmodifiable) risk factors with an independent predictive ability for CVE or surrogate atherosclerosis measures in patients with SLE. For each endpoint, the respective HR range is shown. Values shown for atherosclerosis variables indicate reference numbers.

| Variable | FMD | HR | PWV | HR | CP, IMT | HR | CAC | HR | SPECT | HR | CA | HR | CVE | HR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age, yrs | 96, 97 | | 58, 62, 87, 89, 90 | 1.13 | 38, 39, 41, 42, 44–46, 48, 50, 52, 53, 55, 56, 58–60, 62–67 | 1.11–4.1 | 69, 72, 75–77, 83–85 | 1.08–8.5 | | | 106, 107 | 2.22 | Reviewed in reference 4 | 1.04–5.1 |
| Positive family history | | | | | | | | | | | | | 16, 35 | 3.6 |
| Male | | | 90 | | 48 | 8.78 | 69 | | | | 106 | 2.38 | 16, 23, 27–29, 35 | 1.56–6.2 |
| BMI > 30 | 87 | | 18 | | 41, 53, 61, 65, 66 | 1.06–6.16 | 75, 80 | | | | | | 35 | |
| Waist-to-hip ratio | | | | | 61, 64 | | | | | | | | | |
| Arterial HTN | 94, 96 | | 62, 87, 91 | | 41, 46, 50, 56, 62, 66 | 1.04–3 | 76 | | 99, 102 | 2.11–2.53 | 107 | | 16–18, 27, 32, 34–36 | 1.05–3.5 |
| DM | | | 62 | 1.54 | 55 | 60 | 75, 82 | | 102 | 4 | | | 27 | 1.5 |
| TC | | | | | 41, 42, 62 | 1.2–3 | 76 | | 99 | 2.51 | 106 | 1.89 | 5, 16, 28, 30, 32 | 3.9–6.9 |
| LDL | | | | | 39, 40, 42, 47 | 7.6 | | | | | | | | |
| HDL | 87 | | | | 47 | 4.8 | | | 102 | 3.86 | | | 36 | |
| piHDL | | | | | 55, 56 | 9.1–12.8 | | | | | | | | |
| TG | | | 58 | | | | 69 | | | | | | 20, 32 | 1.15–8 |
| oxLDL | 97 | | | | | | | | | | | | | |
| Metabolic syndrome | | | 90 | | 57 | | 67 | 3.11 | | | | | | |
| HYC | | | | | 42, 59, 60 | 1.24 | 69, 85 | | | | | | 71 | |
| Smoking | | | | | 48, 56 | 7.7 | 72, 76, 78 | 3.8 | | | | | 18, 22, 25, 31, 33, 35 | 2.2–3.7 |

CVE: cardiovascular events; SLE: systemic lupus erythematosus; FMD: flow-mediated dilatation; PWV: pulse wave velocity; CP: carotid plaque; IMT: intima-media thickness; CAC: coronary artery calcification; SPECT: single photon emission computed tomography; CA: coronary angiography; BMI: body mass index; HTN: hypertension; TC: total cholesterol; DM: diabetes mellitus; LDL: low-density lipoprotein; HDL: high-density lipoprotein; piHDL: proinflammatory HDL; TG: triglycerides; oxLDL: oxidized LDL; HYC: homocysteine.

an independent predictor of CVE (HR 1.2–6.8)[19,27,36,37], increased aortic stiffness (HR 7.5)[62], and increased carotid IMT and plaque[40,50], even in pediatric patients with SLE[61]. Creatinine levels > 110 mmol/l were associated with a 16.4-fold increase of coronary calcification[78,85]. Proteinuria was related to CVE (HR 2.4)[36,37] and increased carotid IMT and plaque[50,63,64]. Neuropsychiatric involvement was associated with CVE (HR 2.2–5.2)[16,18,24,33]. Leukopenia was related to increased aortic stiffness[62], while lymphopenia predicted CVE[24] and was related to the presence and progression of carotid IMT[51]. Comorbidities, such as low bone mineral density and depression (HR 3.85), conferred increased risk for CAC[83,110].

*The role of commonly used medications*. High doses of steroids, either as cumulative or current dose, were independent predictors for CVE (HR 2.5)[26,27,36], increased carotid IMT and plaque formation (HR 1.1)[46,53,61], coronary calcifications (HR 2.3)[78,82], and increased arterial stiffness[91]. Azathioprine use was also associated with CVE (HR 1.45)[31] and increased carotid IMT and plaque (HR 3.8)[38,61]. In general, use of immunosuppressives was related to increased rate of CVE (HR 1.7)[32]. In contrast, hydroxychloroquine was protective against CVE (HR 0.77)[27,28,37].

Disease-related risk factors with independent predictive ability for clinical and subclinical atherosclerotic vascular disease are shown in Table 2.

## Imaging Studies

*FMD of the brachial artery*. Impaired FMD was shown to be an independent predictor for future CVE in the general population[111]. Most studies in SLE have assessed FMD using widely accepted guidelines[112,113], although measurement reproducibility has been questioned[114].

A recent metaanalysis of 22 relevant studies demonstrated that FMD was significantly reduced in SLE in comparison with healthy controls[115]. FMD was inversely correlated to carotid IMT[66,94] and associated with traditional and disease-related CV risk factors[87,94,95,96,97]. However, other investigators have not found significant correlations, except for the presence of SLE[92,98]. Its predictive ability for clinical CHD has not been investigated in patients with SLE.

*Pulse wave velocity*. PVW analysis and the derivative variable augmentation index quantify arterial stiffness and independently predict future CVE in the general population[116]; technique details for carotid-femoral PWV have been published elsewhere[117]. Most studies in patients with SLE were cross-sectional in design and confirmed the association of increased PWV with traditional and disease-related risk

*Table 2*. Studies identifying SLE-related risk factors with an independent predictive ability for CVE or surrogate atherosclerosis measures. For each endpoint, the respective HR range is shown. Values shown for atherosclerosis variables indicate reference numbers.

| Variable | FMD | HR | PWV | HR | CP, IMT | HR | CAC | HR | SPECT | HR | CA | HR | CVE | HR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Disease activity | | | 86, 88 | | 52 | | 84 | 12.3 | | | | | 16, 17, 23, 26–28, 32 | 1.05–1.2 |
| Cumulative damage | 89 | | | | 41, 49, 52, 65, 66 | 1.7 | 83 | 1.2 | | | | | 16, 22, 29 | 1.3–4.1 |
| Disease duration | 97 | | 90 | | 45, 53, 59, 60, 64–67 | 1.7–3.2 | 83–85 | 1.2–15.1 | | | | | 23, 31 | 1.1–1.45 |
| aCL | | | | | 38 | 5.2 | 81 | | 81 | 4.1 | | | 16, 17, 21, 22, 31 | 3.1–5.8 |
| Anti-β2GPI | | | | | | | 81 | | | | | | 21, 22 | 3.4 |
| LA | | | | | 38 | 5.2 | 81 | 4.4 | | | | | 27 | 1.74 |
| Anti-oxPAPC | | | | | 46 | 1.06 | | | | | | | | |
| Anti-dsDNA | | | | | | | 77* | | | | | | 27 | 1.56 |
| hsCRP | 95 | | 90 | | 40, 51, 53, 62, 66 | 3 | 74, 76, 82 | 1.65–4.15 | | | | | 22, 29, 31 | 1.6–3.4 |
| C3 | | | 62 | | 60 | | 78 | | | | | | | |
| TWEAK | | | | | 55 | 29 | | | | | | | | |
| IL-6 | | | | | | | 68 | 1.07 | | | | | | |
| VEGF | | | | | 43 | | 82 | | | | | | | |
| TNF-α | | | | | | | 82 | | | | | | | |
| VCAM-1 | | | | | | | 82 | | | | | | | |
| ICAM-1 | | | | | | | 74, 82 | | | | | | | |
| E-selectin | | | | | | | 82 | | | | | | | |
| TGF-β1 | | | | | 109 | | | | | | | | | |
| Type I IFN | 73 | | | | 73 | | 73 | | | | | | | |
| Leptin | | | | | 55, 56 | | | | | | | | | |
| Uric acid | | | | | | | 72 | | | | | | | |
| Renal disease | | | 62 | 7.5 | 50, 61 | | 78, 85 | 16.4 | | | | | 19, 27, 36, 37 | 1.2–6.8 |
| Proteinuria | | | | | 50, 63, 64 | | | | | | | | 36, 37 | 2.4 |
| Neuropsychiatric SLE | | | | | | | | | | | | | 16, 18, 24, 33 | 2.2–5.2 |
| Leukopenia | | | 62 | | | | | | | | | | | |

* Noncalcified coronary plaques. SLE: systemic lupus erythematosus; CVE: cardiovascular events; FMD: flow-mediated dilatation; PWV: pulse wave velocity; CP: carotid plaque; IMT: intima-media thickness; CAC: coronary artery calcification; SPECT: single photon emission computed tomography; CA: coronary angiography; aCL: anticardiolipin antibodies; anti-β2GPI: anti-β2 glycoprotein I; LA: lupus anticoagulant; anti-oxPAPC: antioxidised palmitoyl arachinodoyl phosphocholine; hsCRP: high sensitivity C-reactive protein; C3: complement factor 3; TWEAK: tumor necrosis factor-related weak inducer of apoptosis; IL-6: interleukin 6; VEGF: vascular endothelial growth factor; TNF-α: tumor necrosis factor-α; VCAM-1: vascular cell adhesion molecule 1; ICAM-1: intercellular adhesion molecule 1; TGF-β1: transforming growth factor-β1; IFN: interferon.

factors[58,62,80,86,87,88,89,90,91]. Its predictive value for future CVE has not been tested in SLE.

*Carotid IMT and carotid plaque*. Increased carotid IMT and plaque formation occur at a later stage of the atherosclerotic process and are characterized by restricted reversibility potential. Ultrasonography assessment improved the predictive ability for CVD risk[118,119]; however, precise standardization was still lacking, leading to significant discrepancies[120]. Nevertheless, carotid IMT and plaque evaluation was considered less expensive, easy to perform by trained physicians, and well tolerated by patients[121].

Carotid IMT was strongly associated with traditional as well as disease-related risk factors in SLE[38–47,48–57,58–67]. The precise mean IMT in patients with asymptomatic SLE ranged from 0.37 mm[60] to 0.89 mm[40], raising questions as to the definition of a "normal" IMT threshold. In longitudinal studies, IMT progressed in 28% to 40% of the patients in 20–34 months[45,59,60,61]. Further, increased carotid IMT was an independent predictor of future CVE (HR 1.35 after 8 yrs of followup)[54].

The assessment of carotid plaque was shown to be a more accurate predictor of CVE in the general population[122]; in patients with SLE, plaque detection rate ranged from 7% to 50%[38,40,41,43,44,45,46,59,60,62,65,67]. In 1 longitudinal study, carotid plaque frequency was increased from 20% to 24% of the patients in 2 years[60]. Regarding its predictive ability, Eder, *et al* showed that total plaque area was more strongly associated with clinical CHD than carotid IMT (HR 9.55 vs 2.02, respectively) in 103 patients[47]. Further, Kao, *et al* demonstrated a 4.26-fold increased risk for CVE in 392

patients with SLE with carotid plaque[54]. In addition, the concurrent presence of carotid and femoral plaques was a better predictor for CVE than carotid plaque alone (HR 5.92)[48].

*CAC evaluation*. CAC evaluation, quantified with the Agatston score, achieved further risk stratification[123,124]. Potential pitfalls, besides radiation, were the technique's inability to evaluate noncalcified plaques or plaque stability.

Several reports evaluating CAC in patients with SLE showed significant correlations with traditional and disease-related risk factors[57,68–77,78,79,80,81,82,83,84,85]. The prevalence of CAC ranged from 7% to 48%[74,84]. The disease itself conferred a significant risk for CAC presence (HR 7.7–9.8)[69,84]. Most of those studies were cross-sectional and not designed to assess the method's predictive ability; nevertheless, in 1 prospective study, 20% of the patients demonstrated an increase of CAC scores after 2 years[76]. In addition, Kiani, *et al* showed that noncalcified coronary plaques, considered to be more prone to rupture, could be detected in nearly all patients with CAC and in half the patients without CAC; their presence was related to age and anti-dsDNA antibodies[77].

*Myocardial perfusion evaluation with single photon emission computed tomography (SPECT)*. Myocardial SPECT is a reliable method for assessing myocardial perfusion in the general population; when appropriately selected, perfusion defects confer a 3.7-fold increased risk for MI and cardiac death[125]. In SLE, limited studies have revealed significant associations between perfusion defects and traditional and disease-related risk factors, including age (postmenopausal status), arterial HTN, dyslipidemia, disease activity, cumulative damage, and the presence of antiphospholipid antibodies[81,99,100,102]. The prevalence of perfusion defects ranged from 28–58%, while the pattern of abnormalities included reversible, permanent, and combined defects[81,99,100,101,102,103]. Nikpour, *et al* showed that perfusion abnormalities confer a significant (HR 13) risk for CVE after a followup of 8.7 years[100], whereas in a smaller study, no minor or major CVE development was reported after 40 months[103]. However, later studies showed that there was poor agreement between SPECT and coronary angiography, since about two-thirds of patients with perfusion defects had normal angiograms[101].

Novel methods, such as 13N-ammonia positron emission tomography, may detect myocardial ischemia earlier; however, given their cost, results should be confirmed in larger trials[126].

*MRI*. Cardiac MRI primarily aims to visualize microvascular disease. The method's predictive ability has been confirmed in the general population with an increased incidence of MI (HR 7.7) and CV death (HR 7)[127]. Limited data in SLE suggested that there may be a considerable frequency of perfusion defects in the absence of obstructive CHD[104]. Cardiac MRI findings suggested CHD in patients with SLE and the method could detect more ventricular wall abnormalities than conventional transthoracic echocardiogram[105]. Patients with SLE demonstrated a diffuse pattern of coronary artery wall contrast enhancement (reflecting generalized vascular inflammation), while patients with conventional CHD had a patchy distribution of the lesions[128].

*Coronary angiography*. Coronary angiography is considered the "gold standard" for diagnosis of flow-restricting CHD. Kaul, *et al*, in a retrospective study of 86 patients, demonstrated that patients with SLE had comparable coronary atherosclerotic burden with controls, although they were 20 years younger and had half the incidence of DM and dyslipidemia[106]. Even though 10% of the patients were receiving hemodialysis at the time of catheterization, SLE was an independent predictor of symptomatic CHD (HR 2.24). Additional predictive factors were age (HR 2.22), male sex (HR 2.38), and dyslipidemia (HR 1.89). Previously, Sella, *et al* had shown that postmenopausal status, HTN, and the mean number of traditional CHD risk factors were associated with more severe angiographic findings[107].

### Composite CV risk scores

Composite scores, such as the Framingham risk score (FRS) and the Systematic Coronary Risk Evaluation (SCORE), have been used to predict longterm CV risk in the general population; however, their value in SLE is questionable. In a cross-sectional study, using CAC as an endpoint, FRS and PDAY (Pathobiological Determinants for Atherosclerosis in the Youth, a modified score for younger patients) did not differ between patients with SLE and controls[129]. Urowitz, *et al* showed that a multiplication of FRS by 2 more accurately predicts CV risk in patients with SLE[130]. On the other hand, SCORE was shown to independently predict increased carotid IMT[44].

## DISCUSSION

Several traditional and disease-related risk factors were identified to decisively affect CV risk in patients with SLE; moreover, certain imaging techniques hold promise in further improving risk stratification.

Traditional risk factors included age (in particular postmenopausal status), male sex, positive family history for premature CHD, obesity, arterial HTN, DM, dyslipidemia, metabolic syndrome, hyperhomocysteinemia, and smoking. The majority of these factors have been reported with increased frequency in patients with SLE[131]. Further, disease characteristics, such as activity and medications used, can substantially affect their severity[132]. Concerning HCY, its high serum levels are thought to be an important predictor for CVE in the general population. In addition, hyperhomocysteinemia correction with folic acid is protective against cerebrovascular disease[133]. In the context of SLE, in which many factors may contribute to elevated HCY levels (renal impairment, various medications), its assessment and

treatment seems reasonable. However, no studies have shown HCY to be an independent predictor for CVE in patients with SLE.

Identified disease-related risk factors included overall disease activity, cumulative damage, disease duration, antiphospholipid (lupus anticoagulant, aCL, anti-β2GPI) and anti-dsDNA antibodies, hsCRP, the presence of renal disease, neuropsychiatric involvement, corticosteroids, and the use of immunosuppressives. Overall disease activity was evaluated, in most studies, with the use of composite indices, such as SLEDAI or ECLAM; cumulative damage, on the other hand, was assessed by the SLICC Damage Index. Certain other factors, such as renal and neuropsychiatric involvement, hsCRP, and anti-dsDNA antibodies, as well as corticosteroids and immunosuppressives, are thought to reflect disease activity. These complex interactions lead to a cumulative inflammatory load, consisting of several soluble mediators of the inflammatory cascade, which (along with corticosteroids) naturally affect the severity of traditional risk factors, such as HTN, dyslipidemia, and glucose metabolism. However, existing evidence for these soluble mediators comes from solitary studies; restrictions in measurement standardization and commercial availability do not allow their evaluation for CHD risk in routine practice.

Concerning imaging techniques, only carotid artery Doppler ultrasound, with IMT and total plaque assessment, was shown to independently predict CVE[47,54]. From the other imaging modalities, none has been tested against CVE. In this context, FMD of the brachial artery and PWV analysis should not be evaluated routinely; further studies to investigate their predictive ability for CVE in the longterm are warranted, since both methods assess a relatively reversible stage of the atherosclerotic process. As for myocardial perfusion evaluation with SPECT or MRI, existing evidence is scarce and inconclusive; routine performance of both tests seems unjustified. Several studies have investigated CAC in patients with SLE; none assessed its predictive ability for CVE. Given the technique's pitfalls, other CT-based methods, such as coronary CT angiography, may be more reliable in assessing CHD severity. However, it could be used in selected patients to further clarify the need for more aggressive investigations. Finally, invasive coronary angiography should not be performed in the absence of typical signs and symptoms of CHD.

Composite indices have not proven their ability to identify CVD risk in patients with SLE. Therefore, their routine use is not justified. However, modification of these scores (to include the peculiar characteristics of SLE) may lead to improvement in the longterm.

Based on the aforementioned evidence, Table 3 summarizes the minimum investigations for CHD risk monitoring in patients in SLE.

Initial CV risk assessment should include all traditional risk factors, such as demographic data, BMI, lipid profile, BP assessment, fasting glucose, smoking habits, and HCY. The frequency of reassessment has not been clarified precisely, but given the variability of these variables (reflecting alterations in disease activity and medications used)[131], a frequent

*Table 3*. Recommended investigations and followup for optimal monitoring CHD risk in patients with SLE.

| Variable | Frequency of Assessment | Followup |
|---|---|---|
| Demographic data (age, sex, family history, BMI, smoking habits) | Initial evaluation | As needed |
| Blood pressure | At each clinic visit | 3–6 mos, more stringently if arterial HTN |
| Fasting glucose | At each clinic visit | 3–6 mos, more stringently if DM (add HbA1c) |
| Lipid profile (TC, HDL, LDL, TG) | At each clinic visit | 3–6 mos |
| Homocysteine | Annually? | |
| Disease activity | At each clinic visit | 3–6 mos, use of an accepted composite index is recommended. Anti-dsDNA antibodies and complement C3 and C4 levels should be included |
| Cumulative damage | Annually | Use of an accepted index, like SLICC, is recommended |
| Antiphospholipid antibodies | Initially | If positive, annual reevaluation. Anticardiolipin, anti-β2GPI, and LA should be included |
| hsCRP | At each clinical visit | |
| Renal disease | Serum creatinine and urinalysis at each clinic visit | 24-h urine protein and other investigations, if indicated |
| Medications | Review at each clinic visit | HCQ should be encouraged, corticosteroid usage to be minimized accordingly to disease activity control |
| Carotid IMT and plaque assessment | In patients with > 1 classic risk factor, or postmenopausal status or renal impairment | Assessment of total plaque area is recommended |
| Other imaging techniques | As needed | |

CHD: coronary heart disease; SLE: systemic lupus erythematosus; BMI: body mass index; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; hsCRP: high sensitivity C-reactive protein; IMT: intima-media thickness; HTN: hypertension; DM: diabetes mellitus HbA1c: glycosylated hemoglobin A1c; C3: complement factor 3; C4: complement factor 4; SLICC: Systemic Lupus International Collaborating Clinics; anti-β2GPI: anti-β2 glycoprotein I; LA: lupus anticoagulant; HCQ: hydroxychloroquine.

assessment (i.e., BP at every clinical visit, lipid profile every 3–6 mos) seems justified.

Disease-related risk factors, such as hsCRP, add prognostic value and should be assessed frequently (every 3–6 mos). Laboratory investigations, necessary for the assessment of disease activity (such as C3, C4, and anti-dsDNA antibodies), should be performed at each clinic visit. Renal impairment and proteinuria should be assessed at each clinic visit; in cases of impaired renal function, patients should be monitored more strictly.

Antiphospholipid antibodies, mainly lupus anticoagulant, aCL, and anti-β2GPI antibodies, should be assessed at baseline and managed accordingly. The frequency of reassessment has not been addressed yet; it seems reasonable that yearly reevaluation (or more frequently in case of positivity) would add to better risk stratification.

Carotid artery ultrasonography, assessing both IMT and total plaque area, should be performed by trained personnel in selected patients (i.e., those who have > 1 classic risk factor and/or renal impairment).

Limitations of our present study include the inevitable publication bias since positive (demonstrating a statistically significant effect) studies are more likely to be published than negative (showing little or no association) ones. Another weakness is that studies in SLE and atherosclerosis usually enroll a relatively small number of patients; in this context, the importance of certain risk factors, such as DM, may be underestimated. Lastly, since our study is not a metaanalysis, only positive associations (derived after multivariable analysis) are reported, without discretion for small and large studies. In this context, negative associations might affect the overall significance of a given variable. The restriction of literature search in English language might have precluded important studies; however, it has been reported that the exclusion of non-English studies is unlikely to significantly affect the results[134].

Future work needs to be done in certain areas of accelerated atherosclerosis in SLE. Longitudinal studies for the assessment of the predictive ability of the various imaging techniques, preferably those addressing the initial and potentially reversible stages of atherosclerosis, are clearly warranted. Further, the development of more accurate and specific composite scores for CVE prediction in SLE would be more than welcomed.

Traditional and disease-related atherosclerotic risk factors are important predictors for CVE in patients in SLE. Their documentation and frequent monitoring will facilitate risk stratification and proper management, aiming to reduce CV morbidity and mortality in SLE.

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