Generic and disease-adapted cardiovascular risk scores as predictors of atherosclerosis progression in SLE

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ABSTRACT

Objective Studies show that generic cardiovascular risk (CVR) prediction tools may underestimate CVR in SLE. We examined, for the first time to our knowledge, whether generic and disease-adapted CVR scores may predict subclinical atherosclerosis progression in SLE.

Methods We included all eligible patients with SLE without a history of cardiovascular events or diabetes mellitus, who had a 3-year carotid and femoral ultrasound follow-up examination. Five generic (Systematic Coronary Risk Evaluation (SCORE), Framingham Risk Score (FRS), Pooled Cohort Risk Equation, Globorisk, Prospective Cardiovascular Münster) and three 'SLE-adapted' CVR scores (modified Systematic Coronary Risk Evaluation (mSCORE), modified Framingham Risk Score (mFRS), QRESEARCH Risk Estimator V.3 (QRISK3)) were calculated at baseline. The performance of CVR scores to predict atherosclerosis progression (defined as new atherosclerotic plaque development) was tested with Brier Score (BS), area under the receiver operating characteristic curve (AUROC) and Matthews correlation coefficient (MCC), while rank correlation was tested with Harrell's *c*-index. Binary logistic regression was also applied to examine determinants of subclinical atherosclerosis progression.

Results Twenty-six (21%) of 124 included patients (90% female, mean age 44.4±11.7 years) developed new atherosclerotic plaques after a mean of 39.7±3.8 months' follow-up period. Performance analysis showed that plaque progression was better predicted by the mFRS (BS 0.14, AUROC 0.80, MCC 0.22) and QRISK3 (BS 0.16, AUROC 0.75, MCC 0.25). *c*-Index showed no superiority for discrimination between mFRS and QRISK3. In the multivariate analysis, QRISK3 (OR 4.24, 95% CI 1.30 to 13.78, p=0.016) among the CVR prediction scores and age (OR 1.13, 95% CI 1.06 to 1.21, p<0.001), cumulative glucocorticoid dose (OR 1.04, 95% CI 1.01 to 1.07, p=0.010) and antiphospholipid antibodies (OR 3.66, 95% CI 1.24 to 10.80, p=0.019) among disease-related CVR factors were independently associated with plaque progression.

Conclusions Application of SLE-adapted CVR scores such as QRISK3 or mFRS, as well as monitoring for glucocorticoid exposure and the presence of antiphospholipid antibodies, can help to improve CVR assessment and management in SLE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite accumulating data on the increased cardiovascular disease risk (CVR) in SLE compared with the general population, evidence about the performance of traditional (generic) CVR assessment tools versus those incorporating SLE diagnosis (SLE-adapted) is inconclusive. Subclinical atherosclerosis is frequent in SLE and predicts future cardiovascular events. This study examines for the first time the performance of multiple generic and 'SLE-adapted' cardiovascular risk (CVR) scores to predict vascular ultrasound-detected atherosclerosis progression in SLE.

WHAT THIS STUDY ADDS

⇒ SLE-adapted scores such as the modified Framingham Risk Score and QRESEARCH Risk Estimator V.3 (QRISK3) performed better than generic risk tools to predict atherosclerotic plaque progression in SLE. QRISK3 among CVR scores, and cumulative glucocorticoid exposure and antiphospholipid antibodies among disease-related risk factors were independently associated with new plaque development.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Generic risk scores compared with SLE-adapted tools are less efficient to predict the progression of subclinical atherosclerosis in SLE, which may lead to suboptimal management of CVR. Application of SLE-adapted risk scores, as well as strict monitoring of disease-specific features such as glucocorticoid exposure and antiphospholipid antibody (aPL) positivity, may improve CVR assessment and management in SLE. Validation of our findings in larger studies will help to improve cardiovascular health in these patients.

INTRODUCTION

Cardiovascular disease is one of the most common causes of death, along with infections, in SLE,[1 2] a prototype rheumatic and musculoskeletal disorder (RMD) primarily affecting young adults. Cardiovascular risk (CVR) in patients with SLE is 2-fold to

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10-fold higher compared with the general population,[3 4] with higher relative risk of myocardial infarction and stroke reported in women of younger age.[5–7] Subclinical atherosclerosis, an early indicator of cardiovascular disease,[8] is also frequent in patients with SLE with a threefold to fourfold increased risk of carotid plaques compared with the general population[9–11] and a higher or comparable risk versus other diseases of increased CVR burden, such as rheumatoid arthritis and diabetes mellitus (DM).[12]

Measures for CVR assessment in SLE include generic CVR prediction tools and 'SLE-adapted' risk equations that incorporate the presence of SLE and/or disease features.[13 14] The validity of various generic CVR prediction tools is not fully elucidated, while evidence about the preferential use of disease-specific risk tools is inconclusive.[13–19] The recent 'EULAR Recommendations for CVR Management in RMDs Including SLE and Antiphospholipid Syndrome' did not endorse the use of any particular CVR assessment tool due to limitations of the current evidence.[12]

Aside from the established role of generic risk calculators to predict long-term cardiovascular events in the general population,[8] some studies have also shown their predictive value to assess atherosclerosis progression on vascular imaging.[20–22] Due to high atherosclerosis burden and the high risk of asymptomatic plaque progression in SLE associated with future cardiovascular events,[8–11] the evaluation of multiple generic and SLE-adapted scores as potential predictors of subclinical atherosclerosis progression in patients with SLE is of high clinical significance.

The aim of this study is to examine whether various generic and SLE-modified CVR scores can predict the development of new atherosclerotic plaques in a 3-year follow-up vascular ultrasound study in SLE.

METHODS
Study population
We included all eligible patients followed up in our academic centre who fulfilled the 2012 Systemic Lupus International Collaborating Clinics classification criteria for SLE[23] and had a vascular ultrasound examination at baseline and after 3 years of follow-up by the end of March 2020 (COVID-19 outbreak in Greece). Patients with SLE who concurrently fulfilled the criteria for antiphospholipid syndrome (APS) were also included.[24] We excluded from data analysis patients with a history of clinically established coronary artery disease (angina, myocardial infarction or coronary artery revascularisation procedure) or cerebrovascular disease (stroke, transient ischaemic attack or carotid artery revascularisation procedure) of atherosclerotic origin or atherosclerotic peripheral artery disease and patients with DM. Eight patients declined the follow-up ultrasound examination (flow chart, online supplemental figure S1).

Study design
All study participants underwent a baseline vascular ultrasound assessment for the detection of atherosclerotic plaques in the carotid and femoral arteries. The participants were re-evaluated by vascular ultrasound approximately 3 years after the baseline visit. The following baseline characteristics were recorded at the time of baseline and the 3-year follow-up vascular ultrasound: age, disease-related features (disease duration, disease activity assessed by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), disease damage assessed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI), antinuclear and anti-dsDNA antibodies, C3 and C4 levels, antiphospholipid antibodies including anticardiolipin and anti-β2GPI antibodies and lupus anticoagulant, which were measured and considered positive according to the laboratory classification criteria for APS,[24] lupus nephritis and chronic kidney disease (defined as the presence of glomerular filtration rate <60 mL/min), and medications: immunosuppressives, glucocorticoids use and their cumulative dose at the end of follow-up and during the 3-year follow-up period, while hydroxychloroquine, antihypertensives, statins and antiplatelets were recorded at baseline, at the end of follow-up, and during the follow-up period (reported as use over the 75% and 100% of time between the baseline and last follow-up visit). CVR factors included history of smoking (current or ever, pack-years), arterial hypertension (defined as use of antihypertensive treatment or blood pressure higher than 139/89 mm Hg as average of three sequential readings with 1 min interval in the supine position after at least 10 min of rest), hyperlipidaemia (defined as use of lipid-lowering medication and/or total cholesterol ≥240 mg/dL and/or low-density lipoprotein ≥130 mg/dL and/or triglycerides ≥160 mg/dL), obesity (body mass index ≥30 kg/m^2) and family history of coronary artery disease.

Vascular ultrasound examination
All vascular ultrasound evaluations were performed by the same blinded assessor (GK). Subclinical atherosclerosis was assessed by the presence of plaques in a total of eight arterial beds (left and right, common and internal, carotid arteries and carotid bulb, and both common femoral arteries) by ultrasound. Atherosclerotic plaques were defined as the local increase of the intima–media thickness (IMT) of >50% compared with the surrounding vessel wall, an IMT of >1.5 mm or local thickening of >0.5 mm.[25] Progression of atherosclerosis was defined as either (1) new appearance of plaques in individuals without plaques at baseline or (2) increase in number of plaques in individuals who already had plaques at the same carotid or femoral artery. Measurements were performed using high-resolution B-mode ultrasound (Vivid 7 Pro, GE Healthcare) with a 12 MHz linear matrix array transducer.

Table 1   Demographics and clinical characteristics at baseline of 124 patients with SLE with or without vascular ultrasound-confirmed atherosclerosis and with or without progression of atherosclerosis

	All patients (N=124)	With plaques at baseline* (n=30)	No plaques at baseline (n=94)	P value†	With new plaques (n=26)	Without new plaques (n=98)	P value‡
Age (years), mean±SD	44.4±11.7	54.4±11.1	41.4±10.1	<0.001	52.8±8.7	42.3±11.5	0.001
Disease duration (years), mean±SD	8.8±7.5	9.6±7.5	8.6±7.5	0.556	11.0±7.3	8.2±7.5	0.090
SLEDAI-2K (points), mean±SD	2.4±3.0	2.5±2.8	2.4±3.2	0.923	2.5±2.6	2.4±3.2	0.937
SLICC/ACR DI (points), mean±SD	0.8±1.0	0.8±1.1	0.7±1.0	0.690	1.0±1.5	0.7±0.9	0.090
Antiphospholipid antibody positivity, n (%)	56 (47)	17 (57)	39 (41)	0.105	18 (69)	38 (39)	0.006
Lupus nephritis	26 (21)	7 (23)	19 (20)	0.715	5 (19)	21(21)	0.807
Chronic kidney disease	10 (8)	6 (20)	4 (4)	0.006	3 (12)	7 (7)	0.464
Family history of CAD, n (%)	14 (11)	3 (10)	11 (12)	0.798	1 (4)	13 (13)	0.177
Obesity, n (%)	27 (21)	8 (27)	19 (20)	0.456	10 (39)	17 (17)	0.020
Smoking							
Current, n (%)	46 (37)	12 (40)	34 (36)	0.658	11 (42)	35 (36)	0.536
Ever, n (%)	76 (61)	22 (73)	54 (57)	0.165	19 (73)	57 (58)	0.165
Pack-years	18.7±16.2	24.7±14.9	16.2±16.3	0.040	23.0±19.8	17.3±14.9	0.193
Hyperlipidaemia, n (%)	52 (42)	21 (70)	31 (33)	0.001	12 (46)	40 (41)	0.624
Total cholesterol (mg/dL), mean±SD	195±42	206±42	191±42	0.109	200±41	194±43	0.538
LDL (mg/dL), mean±SD	115±34	125±33	111±34	0.065	117±35	114±34	0.681
Hypertension, n (%)	44 (35)	15 (50)	29 (31)	0.056	11 (42)	33 (34)	0.413
Systolic BP (mm Hg), mean±SD	121±18	127±21	119±17	0.038	134±23	118±15	<0.001
Diastolic BP (mm Hg), mean±SD	73±9.	72±8	73±10	0.651	78±10	72±9	0.001
Glucocorticoids							
End of follow-up, n (%)	75 (60)	19 (63)	56 (60)	0.700	19 (73)	56 (57)	0.140
Cumulative dose, total (g)§	14.7±17.2	12.5±13.9	15.3±18.0	0.433	20.7±18.3	13±16.5	0.042
Cumulative dose (during follow-up period) (g)	3.5±5.3	3.0±3.1	3.8±5.8	0.523	4.4±4.5	3.4±5.5	0.405
Immunosuppressives, end of follow-up, n (%)	50 (40)	9 (30)	41 (44)	0.186	11 (42)	39 (40)	0.816
Hydroxychloroquine, n (%)							
Baseline	85 (69)	23 (77)	62 (66)	0.271	15 (58)	70 (72)	0.180
End of follow-up	98 (79)	25 (83)	73 (77)	0.500	19 (73)	79 (80)	0.401
Follow-up 75	98 (79)	26 (87)	72 (77)	0.238	19 (73)	79 (81)	0.401
Follow-up 100	92 (74)	25 (83)	67 (71)	0.189	19 (73)	73 (75)	0.884
Antiplatelets, n (%)							
Baseline	41 (33)	13 (43)	28 (30)	0.170	8 (31)	33 (34)	0.780
End of follow-up	44 (36)	14 (47)	30 (32)	0.141	11 (42)	33 (34)	0.413
Follow-up 75	43 (35)	14 (47)	29 (31)	0.113	10 (39)	33 (34)	0.648
Follow-up 100	40 (31)	14 (47)	26 (27)	0.041	9 (35)	30 (31)	0.696

Continued

Table 1 Continued

	All patients (N=124)	With plaques at baseline* (n=30)	No plaques at baseline (n=94)	P value†	With new plaques (n=26)	Without new plaques (n=98)	P value‡
Statins, n (%)							
Baseline	13 (10)	8 (27)	5 (5)	0.001	3 (12)	10 (10)	0.843
End of follow-up	28 (22)	13 (43)	15 (16)	0.002	9 (35)	19 (20)	0.099
Follow-up 75	28 (22)	13 (43)	15 (16)	0.002	9 (35)	19 (20)	0.099
Follow-up 100	28 (22)	13 (43)	15 (16)	0.002	9 (35)	19 (20)	0.099
Antihypertensives, n (%)	45 (36)						
Baseline	42 (34)	14 (47)	28 (30)	0.089	9 (35)	33 (34)	0.928
End of follow-up	45 (36)	15 (50)	30 (31)	0.073	11 (42)	34 (35)	0.473
Follow-up 75	40 (32)	15 (50)	25 (27)	0.017	10 (39)	30 (31)	0.447
Follow-up 100	38 (31)	13 (43)	25 (27)	0.083	9 (35)	29 (30)	0.621

*Carotid plaques in 25 patients, femoral plaques in 19 patients and plaques at both arterial sites in 14 patients.
†Comparison between patients with or without atherosclerotic plaques at baseline.
‡Comparison between patients with or without new atherosclerotic plaques at follow-up.
§Glucocorticoid cumulative dose total: dose between glucocorticoids first (ever) administration and the end of follow-up.
BP, blood pressure; CAD, coronary artery disease; SLICC/ACR DI, Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index; follow-up 75, duration of continuous treatment ≥75% of follow-up period; follow-up 100, continuous treatment during the entire follow-up period; LDL, low-density lipoprotein; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

CVR scores

The following five generic CVR scores were calculated for all study participants: the Systematic Coronary Risk Evaluation (SCORE) score[26]; the Framingham 10-year risk score for coronary heart disease (Framingham Risk Score (FRS))[27]; the Pooled Cohort Risk Equation (PCRE) score[28]; the Globorisk score[29]; and the Prospective Cardiovascular Münster (PROCAM) score.[30] Additionally, three SLE-adapted scores were calculated for all participants: the modified Systematic Coronary Risk Evaluation (mSCORE) (a 1.5-times multiplier to SCORE is applied),[8] the modified Framingham Risk Score (mFRS) (a 2.0-times multiplier to FRS is applied)[31] and the QRESEARCH Risk Estimator V.3 (QRISK3), which includes SLE as an independent CVR factor.[32] Details about each score are presented in online supplemental table 1.

Table 2 Mean values of generic and SLE-adapted cardiovascular risk scores at baseline of 124 patients with SLE with or without vascular ultrasound-confirmed atherosclerosis and with or without progression of atherosclerosis

	All patients (N=124)	With plaques at baseline* (n=30)	No plaques at baseline (n=94)	P value†	With new plaques (n=26)	Without new plaques (n=98)	P value‡
SCORE (%)	0.67±0.8	0.98±0.7	0.54±0.8	0.022	1.01±0.9	0.52±0.7	0.014
mSCORE (%)	1±1.2	1.46±1.1	0.8±1.2	0.022	1.52±1.4	0.8±0.9	0.014
FRS (%)	5.2±4.5	8.2±5.4	4.2±3.7	<0.001	9±5.8	4.2±3.5	<0.001
mFRS (%)	10.5±9.1	10.8±2.0	8.5±7.4	<0.001	18±11.6	8.4±7.0	<0.001
QRISK3 (%)	9.1±7.1	14±7.8	7.5±6.0	<0.001	13.5±7.6	7.9±6.4	<0.001
PCRE (%)	3.7±5.0	6.1±7.2	2.6±3	0.002	5±6.8	3.2±4	0.114
Globorisk (%)	6.7±5.6	9.0±6.5	5.8±4.9	0.014	9.9±7.8	5.3±3.5	<0.001
PROCAM score (points)	23.3±13.0	33.8±10	19.9±12	<0.001	30±10.2	21.5±13.0	0.003

*Carotid plaques in 25 patients, femoral plaques in 19 patients and plaques at both arterial sites in 14 patients.
†Comparison between patients with or without atherosclerotic plaques at baseline.
‡Comparison between patients with or without new atherosclerotic plaques at follow-up.
FRS, Framingham Risk Score; mFRS, modified Framingham Risk Score; mSCORE, modified Systematic Coronary Risk Evaluation; PCRE, Pooled Cohort Risk Equation; PROCAM, Prospective Cardiovascular Münster; QRISK3, QRESEARCH Risk Estimator V.3; SCORE, Systematic Coronary Risk Evaluation.

Table 3 Performance of cardiovascular risk prediction models for plaque progression in 124 patients with SLE
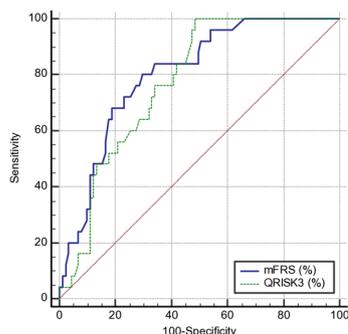
	Brier score	Area under the curve	Matthews correlation coefficient
SCORE	0.19	0.701	0.001
mSCORE	0.19	0.701	0.04
FRS	0.14	0.802	0.13
mFRS	0.14	0.802	0.22
QRISK3	0.16	0.754	0.25
PCRE	0.20	0.657	0.07
Globorisk	0.18	0.709	0.22
PROCAM score	0.15	0.698	0.10

FRS, Framingham Risk Score; mFRS, modified Framingham Risk Score; mSCORE, modified Systematic Coronary Risk Evaluation; PCRE, Pooled Cohort Risk Equation; PROCAM, Prospective Cardiovascular Münster; QRISK3, QRESEARCH Risk Estimator V.3; SCORE, Systematic Coronary Risk Evaluation.

Statistical analysis

All data were assessed for normal distribution. Categorical variables were presented as frequencies and percentages and compared with the χ^2 test. Continuous variables were presented as mean±SD or median with IQR; subgroup comparison was made with Student's t-test or Mann-Whitney U test, as appropriate. The performance of each of eight CVR scores to predict the progression of subclinical atherosclerosis was assessed with Brier Score (BS), Matthews correlation coefficient (MCC) and receiver operating characteristic (ROC) curves, while rank correlation was tested with Harrell's c-index.

Logistic regression models were used to assess determinants of atherosclerotic plaque progression. Demographic, clinical, laboratory and treatment parameters (including baseline and end of follow-up medication use, use for at least 75% of the follow-up period or the entire follow-up period (100%), and cumulative dose (in gram) for corticosteroids) were included in the univariate analysis and those found statistically significant (p<0.1), along with clinical considerations, were entered in the multivariate model. We additionally performed a second model (model 2) including only the variables with a p value of <0.05 in the univariate analysis. At a second step, one generic or SLE-adapted risk score was added each time in the logistic regression model to examine their potential role as independent predictors for plaque progression. A cut-off value of p<0.05 was set to denote statistical significance except for the univariate analysis where the cut-off p value was <0.1. Statistical analysis was performed using SPSS V.25.0 and MedCalc analysis V.14.2.

RESULTS

In total, 124 Caucasian patients with SLE (90% female, mean age 44.4±11.7 years, mean disease duration 8.8±7.5 years) were included in the study. The mean follow-up period was 39.7±3.8 months, and the range of the time span between the two ultrasound examinations was 30–47 months. The mean SLEDAI-2K was 2.4±3.0, and the SLICC/ACR DI was 0.8±1.0. Thirty-eight patients fulfilled also the classification criteria for APS.[24]

At baseline, atherosclerotic plaques were evident in 30 patients, and more specifically carotid plaques were detected in 25 patients, femoral plaques in 19, and at both sites in 14 patients. After a mean of 39.7±3.8 months' follow-up, progression of subclinical atherosclerosis (new atherosclerotic plaques) was observed in 26 patients: 9 with and 17 without the presence of plaques at baseline. Characteristics of study participants and risk estimates by the different generic and SLE-adapted CVR scores at baseline are shown in tables 1 and 2, respectively.

The performance of five generic and three SLE-adapted CVR scores to predict the progression of subclinical atherosclerosis, according to BS, ROC analysis and MCC, is depicted in table 3 and figure 1 and in online supplemental file 1. As presented, mFRS and QRISK3 showed the best overall performance (BS 0.14 and 0.16, respectively) and classification ability (MCC 0.22 and 0.25, respectively). Additionally, ROC analysis displayed a fair-to-good discriminatory capacity for all risk models (area under the curve (AUC) values from 0.66 to 0.80), while both mFRS and QRISK3 presented the highest AUC among examined scores. The c-index showed no superiority for discrimination between mFRS and QRISK3 (figure 1).

Multivariate analysis of plaque progression showed that age (OR 1.13, 95% CI 1.06 to 1.21, p<0.001), cumulative glucocorticoid dose (OR 1.04, 95% CI 1.01 to 1.07, p=0.010) and antiphospholipid antibodies (OR 3.66, 95% CI 1.24 to 10.80, p=0.019) were independently associated with plaque progression (model 1, table 4). Among the different risk scores, QRISK3 (OR 4.24, 95% CI 1.30 to 13.78, p=0.016) was the only independent predictor for plaque progression, after adjustment of potential

Figure 1 Receiver operating characteristic analysis evaluating the performance of mFRS and QRISK3 to predict the progression of subclinical atherosclerosis in patients with SLE (discriminatory difference in area under the curve compared by c-index: 0.80 vs 0.75, p=0.37). mFRS, modified Framingham Risk Score; QRISK3: QRESEARCH Risk Estimator V.3.

Table 4 Multivariate regression analysis of atherosclerotic plaque progression in 124 patients with SLE

Variable	OR (95% CI)	P value
Model 1		
Age, years (per 1 year increase)	1.13 (1.06 to 1.21)	<0.001
Disease duration, years (per 1 year increase)	0.99 (0.93 to 1.07)	0.963
Smoking (pack-years)	1.02 (0.99 to 1.05)	0.292
BMI (kg/m^2) (per 1 unit increase)	1.05 (0.95 to 1.15)	0.341
Antiphospholipid antibody positivity	3.66 (1.24 to 10.80)	0.019
SLICC/ACR DI (points per 1 point increase)	1.07 (0.67 to 1.70)	0.781
Presence of plaques at baseline	0.38 (0.10 to 1.46)	0.158
Glucocorticoids, cumulative dose (g) (per 1 g increase)	1.04 (1.01 to 1.07)	0.010
Statin, current use	0.68 (0.20 to 2.32)	0.538
Model 2		
Age, years (per 1 year increase)	1.10 (1.05 to 1.16)	<0.001
Antiphospholipid antibody positivity	3.51 (1.25 to 9.89)	0.017
Glucocorticoids, cumulative dose (g) (per 1 g increase)	1.04 (1.01 to 1.07)	0.011

Model 1 adjusted for age, disease duration, smoking, BMI, antiphospholipid antibody positivity, SLICC/ACR DI, presence of plaques at baseline, glucocorticoid cumulative dose and statin current use.
Model 2 adjusted for age, antiphospholipid antibody positivity and glucocorticoid cumulative dose.
BMI, body mass index; SLICC/ACR DI, Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index.

confounders (model 1, table 5). The aforementioned associations were confirmed in the additional multiple regression models (model 2, table 4, and model 2, table 5, respectively) including only the variables with a p value less than 0.05 (age, cumulative glucocorticoid dose and antiphospholipid antibodies) in the univariate analysis (online supplemental table 2).

DISCUSSION

In the present study, we examined for the first time to our knowledge the performance of various generic and SLE-adapted CVR scores to predict the development of new atherosclerotic plaques in patients with SLE over a 3-year follow-up period. SLE-adapted risk scores such as QRISK3 and mFRS performed better than the generic tools.

The results of the present study further support previous observations from our group and others demonstrating that generic CVR scores inadequately identify high CVR as defined by the presence of atherosclerotic plaques.[15–17] Their low performance to predict future progression of atherosclerosis is also consistent with evidence from some prospective studies reporting underperformance of several generic scores to predict future cardiovascular events in SLE,[15 18] limiting their role to guide CVR management in these patients.

Studies in the general population have shown a significant association between several generic risk scores and the incidence of subclinical atherosclerosis in healthy individuals and a good performance to predict the formation of new atherosclerotic plaques in prospective studies in asymptomatic populations.[20–22] A large multicentre study in young adults examined the performance of the FRS, Reynolds, SCORE, PROCAM and Finrisk CVR scores to predict a 6-year subclinical atherosclerosis progression assessed by carotid IMT and plaques, carotid artery distensibility and brachial artery flow-mediated dilatation, concluding that preclinical CVR as measured by these modalities can be assessed with any of the aforementioned scores.[20] Inadequate performance of the same generic CVR scores to predict progression of plaque formation in the present study supports the need for further investigation about their routine use for CVR management in SLE.[13 16] Lack of weighting for disease-specific features with a potential inadequate weighting also for traditional CVR factors which are often more prevalent in SLE in comparison to the general population[33] may explain the underperformance of generic CVR scores in this group of patients.[13 34 35]

Among the disease-specific risk scores, both QRISK3 and mFRS showed good overall performance for the progression of subclinical atherosclerosis, while the multivariate analysis confirmed that QRISK3 was an independent predictor for future development of new plaques. Conversely, mSCORE failed both as a discriminator and a predictor of the progression of atherosclerosis, indicating that a multiplication by 1.5 may not accurately reflect the impact of SLE as additional risk factor. Indeed, evidence from the general population suggests that multipliers, although seemingly practical to employ in the clinical setting, may not accurately incorporate the critical impact of risk factor prevalence.[36]

In our study, the progression of subclinical atherosclerosis was twice as much prevalent in patients with no plaques (n=17) versus those with plaque presence (n=9)

Table 5 OR for each cardiovascular risk score to predict the progression of subclinical atherosclerosis in 124 patients with SLE

Risk score	OR (95% CI)	P value
Model 1		
SCORE	1.41 (0.21 to 9.58)	0.725
mSCORE	1.87 (0.37 to 9.36)	0.446
FRS	3.64 (0.33 to 39.75)	0.289
mFRS	3.81 (1.00 to 14.49)	0.050
QRISK3	4.24 (1.30 to 13.78)	0.016
PCRE	1.85 (0.08 to 45.23)	0.706
Globorisk	2.67 (0.72 to 9.85)	0.140
PROCAM	2.56 (0.29 to 22.87)	0.396
Model 2		
SCORE	1.26 (0.20 to 7.97)	0.803
mSCORE	1.77 (0.36 to 8.67)	0.480
FRS	4.19 (0.48 to 36.32)	0.193
mFRS	4.31 (1.36 to 13.64)	0.013
QRISK3	4.33 (1.58 to 11.85)	0.004
PCRE	2.11 (0.10 to 42.89)	0.628
Globorisk	2.52 (0.79 to 8.15)	0.123
PROCAM	3.50 (0.46 to 26.72)	0.227

Model 1 adjusted for: disease duration, SLICC/ACR DI, cumulative glucocorticoid dose, BMI, antiphospholipid antibody positivity, presence of plaque at baseline, statin treatment and one single risk score each time.

Model 2 adjusted for: age, antiphospholipid antibody positivity, glucocorticoids cumulative dose and one single risk score each time.

BMI, body mass index; FRS, Framingham Risk Score; mFRS, modified Framingham Risk Score; mSCORE, modified Systematic Coronary Risk Evaluation; PCRE, Pooled Cohort Risk Equation; PROCAM, Prospective Cardiovascular Munster Study Risk Calculator; QRISK3, QRESEARCH Risk Estimator V.3; SCORE, Systematic Coronary Risk Evaluation; SLICC/ACR DI, Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index.

recent prospective study including 1887 patients with SLE (232 developed cardiovascular events), mFRS was superior to FRS and performed similarly to QRISK3 in the prediction of cardiovascular event development at/within 10 years.[15]

Regarding disease-specific determinants for the progression of atherosclerotic plaques in patients with SLE, our analysis disclosed that cumulative glucocorticoid dose and aPL positivity were independent predictors. The presence of aPL showed the strongest association with the development of new plaques compared with any other individual risk predictor, and aPL positivity is known to significantly increase the risk of cardiovascular events in SLE.[13 33 35] Moreover, aPL presence has been associated with accelerated atherosclerosis in SLE and even in asymptomatic aPL carriers,[40–42] highlighting the need for aPL assessment in SLE and even greater diligence for optimal CVR evaluation and management in aPL-positive patients with SLE. Glucocorticoid use, a modifiable risk factor that represents a major preventive target,[13] has been also reported to be an independent predictor of atherosclerosis progression and cardiovascular events in SLE, though the best measure of glucocorticoid exposure (current use, median daily or cumulative dose) as a predictor of cardiovascular damage has yet to be fully determined.[13 43] In addition to the cumulative glucocorticoid dose between their first (ever) administration and the end of follow-up, the cumulative dose over the 3-year follow-up period was also added in the analysis (online supplemental table 2, univariate analysis) so as to further examine the impact of the between the two ultrasound examinations dose of glucocorticoids on plaque progression. Remarkably, none of the aforementioned SLE features are included in any of the examined SLE-adapted CVR prediction models nor have been investigated as risk modifiers to tailor risk factor management to individual clinical phenotypes. Their recognition as CVR modifiers will help to incorporate their regular assessment and management in daily practice, for example, by introducing a prophylactic treatment with low-dose aspirin in patients with high-risk aPL profile[13 44] and minimising glucocorticoid exposure, in order to reduce cardiovascular harm.[13]

Lupus nephritis or renal failure has not been associated with plaque progression in the univariate analysis (online supplemental table 2), although previous studies have shown its association with both subclinical atherosclerosis and cardiovascular events in SLE.[45 46] The persistent use (at least 75% and 100% of follow-up time) of antiplatelets, statins, antihypertensives and hydroxychloroquine (HCQ) during the 3-year follow-up period was included in the univariate analysis, but no statistical significance was demonstrated for any of these treatments (online supplemental table 2). HCQ has been shown to prevent thrombotic cardiovascular events in several retrospective and prospective studies in SLE, and especially its long duration.[13 47 48] In our study, HCQ use was not found to have a protective role against subclinical atherosclerosis

at baseline, indicating the increased propensity for early development of new plaques in SLE. While QRISK3 missed a lower but not negligible proportion of high-risk patients according to plaque presence at baseline in a previous study from our group,[16] a good performance to predict plaque progression and a significant association with plaque progression in multivariate analysis was detected in the current study, supporting its role as a promising tool for CVR assessment in SLE. A positive correlation between QRISK3 and carotid IMT, carotid distention and diameter analysis, arterial stiffness,[37] pulse wave velocity[38] and carotid plaques[39] has been previously described. Regrettably, validation studies for cardiovascular events in multiethnic datasets are scarce for QRISK3, supporting the need for studies in individuals from various geographical settings as well as external validation in large, multicentre SLE populations.[13] In a

progression. This can be attributed to the fact that the vast majority of patients (approximately 80%) were on HCQ treatment both at baseline and during the follow-up time (table 1). In addition, a recent meta-analysis has shown that HCQ is not associated with subclinical atherosclerosis markers such as the presence of plaques or increased IMT.[49] This supports the distinction between subclinical atherosclerosis and vascular events since other factors such as inflammatory and prothrombotic states may also contribute to cardiovascular events in SLE.[49]

Interestingly, patients with no plaques at baseline developed almost twice more frequently new plaques during the 3-year follow-up. This may be explained by the fact that physicians tend to prescribe statins or antiplatelets in patients with arterial plaques even without the indication based on their lipid levels. Patients with versus those without plaques at baseline received more frequent statins at the time of first and last ultrasound examination and during the 75% and 100% of follow-up period (all p<0.05). No significant difference was detected in aspirin use at baseline, end of follow-up and 75% of follow-up period between the two groups. Our study has some limitations. The sample of our study is rather small; however, this is one of the largest samples included in vascular ultrasound follow-up studies in SLE.[50–53] All our patients were white Europeans, limiting the generalisability of our results to other populations. It should be also acknowledged that the CVR calculators used in our study were originally developed to predict the risk of future cardiovascular events; however, subclinical atherosclerosis is recognised as a major predictor for future cardiovascular events both in the general population[6] and in patients with SLE,[54] as well as an established modifier for CVR management.[6] Additionally, three of the examined CVR scores (QRISK3, PCRE and PROCAM) have yet to be validated in the Greek population, though they have all been introduced for risk estimation in European populations.

To conclude, the results of our study suggest that the generic CVR calculators compared with the SLE-adapted risk scores are less efficient to predict the progression of subclinical atherosclerosis in SLE, which may lead to suboptimal management of CVR in affected patients. Application of SLE-adapted risk scores, as well as strict monitoring of disease-specific features such as glucocorticoid exposure and aPL positivity presence, may improve CVR assessment and management in patients with SLE.

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Generic and disease-adapted cardiovascular risk scores as predictors of atherosclerosis progression in Systemic Lupus Erythematosus

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Supplemental Data

Supplementary Table 1. Overview of generic and SLE-adapted cardiovascular risk prediction tools

Risk equation	Population	Outcome	Time period	Variables
SCORE	General population from 11 European countries	Cardiovascular mortality (myocardial infarction, stroke)	10-year risk prediction	Gender; age; smoking (current); systolic BP; TC; LDL-cholesterol.
mSCORE	General population from 11 European countries	Cardiovascular mortality (myocardial infarction, stroke)	10-year risk prediction	SCORE estimate multiplied by a 1.5 factor for RA and other immune inflammatory diseases
FRS	General population, Framingham, Massachusetts, USA; recalibrated for European countries.	Fatal and non-fatal cardiovascular events (myocardial infarction, stroke)	10-year risk prediction	Gender; age; total cholesterol; HDL-cholesterol; systolic BP; smoking (current); DM; antihypertensive treatment.
mFRS	Toronto Lupus Clinic cohort	Fatal and non-fatal coronary artery disease events	10-year risk prediction	FRS estimate multiplied by a 2.0 factor
QRISK3	General population from the QRESEARCH database, UK	Fatal and non-fatal cardiovascular events (myocardial infarction, stroke)	10-year risk prediction	Gender; age; ethnicity; deprivation; systolic BP; body mass index; total cholesterol:HDL cholesterol ratio; smoking (cigarettes/day); family history of premature coronary heart disease; DM; treated hypertension; RA; atrial fibrillation; CKD; systolic BP variability; migraine; corticosteroids; SLE; treatment with atypical antipsychotics; severe mental illness; HIV/AIDs; erectile dysfunction.
PCRE	General population, USA	First fatal or non-fatal atherosclerotic cardiovascular event (myocardial infarction, stroke)	10-year risk prediction	Gender; age; TC; HDL-cholesterol; systolic BP; DM; smoking (current); antihypertensive treatment.
Globorisk	General population, USA, Honolulu, Puerto Rico; recalibrated for >100 countries.	Fatal cardiovascular disease (myocardial infarction, stroke)	10-year risk prediction	Gender; age; smoking (current); TC; DM; systolic BP.

| PROCAM	General population, Germany	Fatal and non-fatal cardiovascular events (myocardial infarction, stroke)	10-year risk prediction	Gender; age; LDL cholesterol; HDL cholesterol; systolic BP; smoking (current); triglycerides; DM; family history of premature myocardial infarction.

SCORE, Systematic Coronary Risk Evaluation; BP, blood pressure; TC, total cholesterol; LDL, low-density lipoprotein; mSCORE, modified SCORE; RA, rheumatoid arthritis; FRS, Framingham risk score; HDL, high-density lipoprotein; DM, diabetes mellitus; mFRS, modified Framingham risk score; SLE, systemic lupus erythematosus; QRISK3, QRESEARCH risk calculator version 3; CKD, chronic kidney disease; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; PCRE, Pooled Cohort Studies risk equation; PROCAM, Prospective Cardiovascular Müncher Study risk calculator.

Supplementary Table 2. Univariate regression analysis of atherosclerotic plaque progression in 124 patients with systemic lupus erythematosus

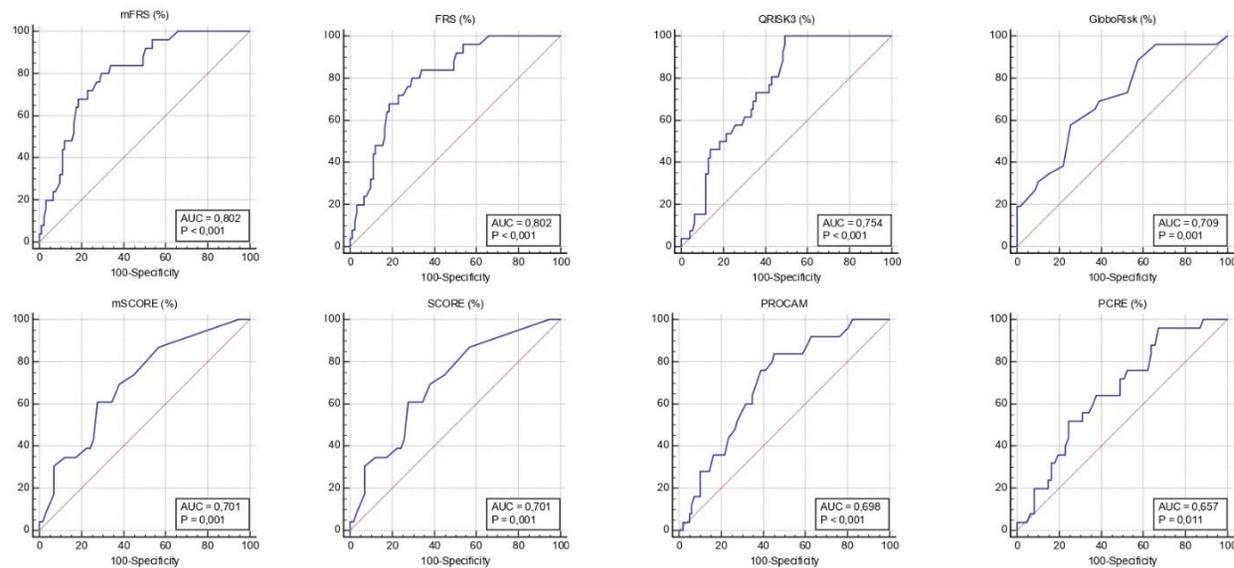| Variables	Univariate Analysis	
	OR (95% CI)	P value
Age (per 1 year increase)	1.09 (1.04 -1.14)	<0.001
Sex (female)	0.49 (0.14-1.77)	0.276
Disease duration (per 1 year increase)	1.05 (0.99-1.11)	0.095
SLEDAI-2K (per 1 unit increase)	1.01 (0.87-1.16)	0.937
SLICC/ACR-DI (per 1 unit increase)	1.38 (0.94-2.02)	0.098
Antiphospholipid antibody positivity	3.55 (1.41-8.97)	0.007
Lupus Nephritis	0.86 (0.29-2.56)	0.789
Chronic Kidney disease	1.70 (0.41-7.07)	0.469
BMI, kg/m² (per 1 unit increase)	1.07 (0.99-1.15)	0.061
Smoking	1.32 (0.55-3.19)	0.537
Smoking, pack-years (per 1 pack-year increase)	1.03 (0.99-1.05)	0.062
Hyperlipidemia	1.24 (0.52-2.97)	0.624
Total cholesterol (per 1 unit increase)	1.01 (0.99-1.01)	0.526
LDL (per 1 unit increase)	1.01 (0.99-1.02)	0.679
HDL (per 1 unit increase)	1.01 (0.99-1.04)	0.305
Triglycerides (per 1 unit increase)	1.00 (0.99-1.01)	0.620
Hypertension	1.44 (0.60-3.50)	0.415
Glucocorticoids	2.04 (0.78-5.29)	0.144
Glucocorticoids cumulative dose total*, gr (per 1 gr increase)	1.02 (1.00-1.05)	0.049
Glucocorticoids cumulative dose during follow-up, gr (per 1 gr increase)	1.03 (0.96 -1.11)	0.404
Immunosuppressives	1.11 (0.46-2.67)	0.816
Hydroxychloroquine at baseline	0.55 (0.22-1.33)	0.183
Hydroxychloroquine at end of follow-up	0.61 (0.22-1.67)	0.337
Hydroxychloroquine follow-up 75	0.65 (0.24-1.78)	0.404
Hydroxychloroquine follow-up 100	0.93 (0.35-2.47)	0.884
Antiplatelets at baseline	0.88 (0.35-2.22)	0.780
Antiplatelets at end of follow-up	1.44 (0.60-3.50)	0.415
Antiplatelets follow-up 75	1.23 (0.50-3.01)	0.649
Antiplatelets follow-up 100	1.20 (0.48-3.00)	0.696
Statins at baseline	1.15 (0.29-4.51)	0.844
Statins at end of follow-up	2.20 (0.85-5.70)	0.104
Statins follow-up 75	2.20 (0.85-5.70)	0.104
Statins follow-up 100	2.20 (0.85-5.70)	0.104
Antihypertensives at baseline	1.04 (0.42-2.59)	0.928
Antihypertensives drugs at end of follow-up	1.38 (0.57-3.34)	0.474
Antihypertensives drugs follow-up 75	1.42 (0.58-3.48)	0.448
Hypertension drugs follow-up 100	1.26 (0.50-3.15)	0.622
Plaques at baseline	1.94 (0.76-4.98)	0.167

SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR DI: Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index; BMI: body mass index; LDL: low density cholesterol; HDL: high density cholesterol; follow-up 75: duration of continuous treatment ≥75% of follow-up period; follow-up 100: continuous treatment during the entire follow-up period.

 *Glucocorticoids cumulative dose total: dose between glucocorticoids first (ever) administration and   the end of follow-up.
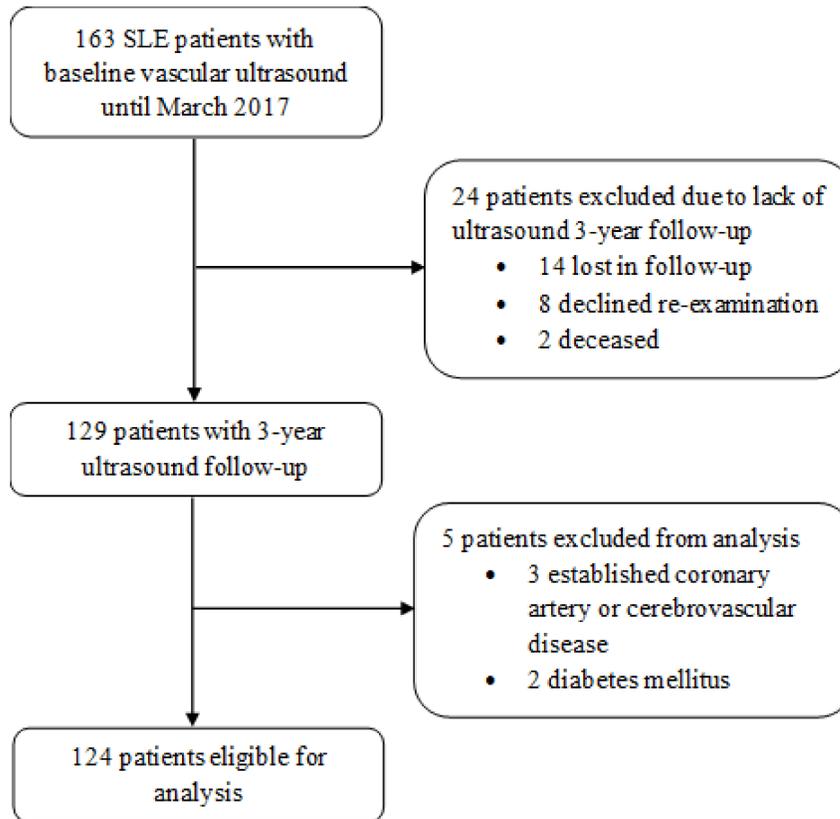
Supplementary Figure 1

Flow chart of patients with systemic lupus erythematosus (SLE) eligible for analysis after applying exclusion criteria.

Supplemental material

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Supplementary Figure 2

Receiver-operating characteristics curve analysis of each cardiovascular risk score for the prediction of the progression of subclinical atherosclerosis in 124 patients with systemic lupus erythematosus.

SCORE: Systematic Coronary Risk Evaluation; mSCORE: modified SCORE; FRS: Framingham Risk Score; mFRS: modified FRS; QRISK3: QRESEARCH risk estimator, version 3; PCRE: Pooled Cohort Risk Equations; PROCAM: Prospective Cardiovascular Munster Study risk calculator.