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Atherosclerotic Plaque Progression and Incident Cardiovascular Events in a 10-Year Prospective Study of Patients With Systemic Lupus Erythematosus: The Impact of Persistent Cardiovascular Risk Factor Target Attainment and Sustained DORIS Remission

Nikolaos Papazoglou, Petros P. Sfikakis, and Maria G. Tektonidou

Objective. Cardiovascular disease (CVD) is a leading cause of death in individuals with systemic lupus erythematosus (SLE). We assessed atherosclerotic plaque progression and incident cardiovascular events in patients with SLE over a 10-year follow-up.

Methods. We prospectively analyzed 738 carotid ultrasound measurements (413 in patients with SLE and 325 in age/sex-matched healthy controls [HCs]) to assess new plaque development from baseline to 3-, 7-, and 10-year follow-up. Multivariate mixed-effects Poisson regression models examined potential predictors of plaque progression, including patient characteristics, Systemic Coronary Risk Evaluation, traditional cardiovascular risk factor (CVRF) target attainment, Definition of Remission in SLE (DORIS), medications, and persistent triple anti-phospholipid antibody (aPL) positivity during follow-up. Ten-year incident cardiovascular events were recorded, and univariate Cox regression analysis assessed potential associations.

Results. Patients with SLE had a 2.3-fold higher risk of carotid plaque progression than HCs (incidence rate ratio [IRR] 2.26, $P = 0.002$). Plaque progression risk in patients with SLE was reduced by 32% (IRR 0.68, $P = 0.004$) per each sustainedly attained CVRF target during follow-up, including blood pressure, lipids, smoking, body weight, and physical activity. DORIS achievement ≥75% of follow-up was associated with a 43% decrease in atherosclerosis progression risk (IRR 0.57, $P = 0.033$). Ten-year risk of incident cardiovascular events was higher in individuals with SLE than HCs (eight versus one event, permutation-based log-rank $P = 0.036$) and was associated with persistent triple aPL positivity.

Conclusion. Patients with SLE experience a 2.3-fold higher 10-year atherosclerosis progression risk than HCs, mitigated by sustained CVRF control and prolonged clinical remission. Persistent triple aPL positivity is associated with increased incidence of CVD events.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder with an increased risk of premature atherosclerosis and cardiovascular disease (CVD) events.[1–4] Despite advances in management, patients with SLE still bear a substantial death risk, primarily due to CVD complications, although the majority of patients are young adult women.[5] Large cohort studies and systematic literature reviews have revealed a two to five times greater risk of CVD events in patients with SLE than in the general population, which is disproportionately magnified among younger individuals.[6–10]

Subclinical atherosclerosis, recognized as an independent predictor of CVD events, is more prevalent and progresses more rapidly in patients with SLE than in the general population or other high CVD risk disorders.[1,11] Few prospective studies examining the progression of atherosclerotic plaques in a three- to five-year follow-up period showed a two- to three-fold heightened risk for

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new plaque development in patients with SLE versus age- and sex-matched healthy controls (HCs).[11,12] However, there is no evidence about plaque progression and incident CVD events in patients with SLE compared to HCs during a 10-year follow-up.

Both traditional cardiovascular risk factors (CVRFs) and SLE-related parameters, including disease activity, disease duration, lupus nephritis, glucocorticoids, and anti-phospholipid antibodies (aPLs), have been identified as major predictors of clinical and subclinical CVD in patients with SLE.[1,13] The 2022 EULAR recommendations for cardiovascular risk management in individuals with rheumatic and musculoskeletal disorders including SLE and antiphospholipid syndrome (APS), highlighted meticulous assessment and control of modifiable CVRFs, along with minimal disease activity.[14] Traditional CVRF target attainment, as defined by the 2016 European Society of Cardiology (ESC) guidelines based on 10-year CVD risk classification,[15] can reduce CVD events in the general population. The impact of sustained traditional CVRF control and clinical remission in reducing the risk of accelerated atherosclerosis in individuals with SLE has not been previously evaluated in a 10-year timeframe.

Herein, we aimed to assess the progression of subclinical atherosclerosis and the development of cardiovascular events in patients with SLE versus age- and sex-matched HCs over a 10-year follow-up period. We investigated determinants of atherosclerotic plaque progression, including disease-related and traditional CVRFs, CVRF target attainment, and different durations of Lupus Low Disease Activity State (LLDAS)[16] and sustained Definition of Remission in SLE (DORIS).[17]

PATIENTS AND METHODS

Study design and population. This is a 10-year vascular ultrasound follow-up study of patients fulfilling the 2012 classification criteria for SLE[18] and HCs initially examined at our cardiovascular research laboratory in 2012 to 2013. At baseline assessment, 115 patients with SLE and 115 age- and sex-matched HCs without prior atherosclerotic CVD (ASCVD), active malignancy, pregnancy, or diabetes mellitus (DM) underwent a carotid ultrasound assessment. ASCVD included acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization procedures, stroke, transient ischemic attack, aortic aneurysm, and peripheral artery disease.

After the baseline evaluation, all participants were invited for a 3-, 7-, and 10-year ultrasound evaluation of new carotid plaque development. Incident CVD events were also assessed during follow-up. Follow-up duration was defined as the time between the baseline assessment and the first CVD event, death, or loss to follow-up, whichever occurred first. For those who missed a 10-year carotid ultrasound but had completed a 10-year follow-up visit, incident CVD events were recorded from their medical files. All participants gave written informed consent according to the Declaration of Helsinki principles, and our study received approval from our hospital's institutional review board (Laiko General Hospital Scientific Council number 16506).

Recorded parameters. *CVRFs.* We recorded the traditional CVRFs at baseline and at 3-, 7-, and 10-year follow-up visits: systolic and diastolic blood pressure, smoking (current status and pack-years), lipid profile (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides), estimated glomerular filtration rate (eGFR), physical activity in weekly exercise minutes, family history of coronary artery disease, body mass index (BMI; weight/height^2), waist circumference, and CVD-related medications (antihypertensives, lipid-lowering agents, antiplatelets, and antidiabetic drugs for patients diagnosed with DM during follow-up). We assessed individuals' CVD risk using the ESC-endorsed Systemic Coronary Risk Evaluation (SCORE) prediction tool,[19] which estimates the 10-year risk of fatal CVD in individuals 40 to 69 years old with no previous ASCVD or type II DM.

Individuals aged <40 years were classified as "low risk" unless a modifier was present. We evaluated the CVRF target attainment based on individual CVD risk classified by the SCORE (low–moderate, high, and very high) and additional CVD risk modifiers (Supplementary Table 1) following the 2016 ESC guidelines[15]: systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg; LDL <115 mg/dL in patients who were at low–moderate risk without CVD events (primary prevention), LDL <100 mg/dL or a reduction of at least 50% if the baseline LDL is between 100 and 200 mg/dL in patients who were at high risk without CVD events (primary prevention), and LDL <70 mg/dL or a reduction of at least 50% if the baseline LDL is between 70 and 135 mg/dL in patients classified as having very high CVD risk based on SCORE and CVD risk modifiers (primary prevention) or after the development of CVD events during the follow-up (secondary prevention); no target HDL, but >40 mg/dL in men and >45 mg/dL in women indicate lower risk; no target triglycerides, but <150 mg/dL indicates lower risk; no current smoking; BMI 20–25 kg/m^2 and waist circumference ≤94 cm in men and ≤80 cm in women; and ≥150 minutes per week of moderate aerobic physical activity (30 minutes for 5 days per week) or 75 minutes per week of vigorous aerobic physical activity (15 minutes for 5 days per week) or a combination thereof. In incident CVD event analysis, apart from SCORE, we also included the SCORE2 risk prediction model[20] endorsed by the 2021 ESC guidelines,[21] which incorporates LDL, HDL, and triglycerides in addition to SCORE parameters. SCORE2 estimates both nonfatal myocardial infarction or stroke risk and the cardiovascular death risk, providing a more comprehensive evaluation.

SLE-related features. Laboratory tests were performed semiannually, including complete blood count, erythrocyte sedimentation rate, serum creatinine, urinalysis, anti–double-stranded DNA antibodies, and C3 and C4 levels. The aPLs, including IgG and IgM anti-cardiolipin antibodies (aCLs) and anti-beta-2

glycoprotein I antibodies, and lupus anticoagulant (LA) were considered positive according to the Sydney APS classification criteria.[22] Persistent triple aPL positivity was defined as positivity of all three aPLs at all four timepoints throughout follow-up (baseline and 3-, 7-, and 10-year follow-up).

The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K),[23] Physician Global Assessment (PGA; scale 0–3), Systemic Lupus International Collaborating Clinics (SLICC) American College of Rheumatology Damage Index,[24] LLDAS, and DORIS remission measures were assessed semiannually. LLDAS was defined as SLEDAI-2K ≤4 without significant organ involvement, absence of new disease activity, PGA ≤1, prednisone dosage ≤7.5 mg/day, and standard maintenance doses of immunosuppressives and/or biologics.[16] For clinical remission, we used the DORIS definition: clinical SLEDAI-2K score of 0, PGA <0.5, prednisolone dosage ≤5 mg/day, and stable antimalarials, immunosuppressives, and/or biologics.[17] At each semiannual assessment during 10-year follow-up, LLDAS and DORIS were considered attained if their criteria were fulfilled over the preceding six-month period. For the initial years of our study, we retrospectively applied the LLDAS and DORIS criteria from medical files until 2016, when these definitions were introduced.[16,25] LLDAS achievement throughout 100% (LLDAS100), 75% (LLDAS75), and 50% (LLDAS50) of the follow-up period, and DORIS remission achievement throughout 100% (DORIS100), 75% (DORIS75), and 50% (DORIS50) of the follow-up period were also assessed. Disease-related medications were recorded at the baseline, and follow-up ultrasound assessments: cumulative dose of glucocorticoids (sum of dose before the baseline examination and during the 10-year follow-up), consistent reception of hydroxychloroquine (over the entire follow-up period), immunosuppressives (cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, leflunomide), and biologics (rituximab, belimumab).

Vascular ultrasound. All ultrasonographic assessments were conducted in our cardiovascular research laboratory by the same blinded, experienced operator. Healthy participants were recruited through flyers in the local community. Atherosclerotic plaques were assessed using a 14.0-MHz multifrequency linear array probe on a high-resolution ultrasound machine (Vivid 7 Pro; GE HealthCare). Measurements were performed bilaterally in the near and far walls of the common carotid artery, carotid bulb, and internal carotid artery. According to Mannheim consensus,[26] plaques were defined as focal structures encroaching ≥0.5 mm into the lumen or ≥50% compared with the surrounding intima-media thickness of the adjacent vascular wall or demonstrating an intima-media thickness ≥1.5 mm.

Statistical analysis. Qualitative variables were presented as frequencies and percentages and quantitative variables as median (interquartile range). The Shapiro–Wilk test was applied to assess the normality of data distributions. To evaluate differences between groups, we employed the Mann–Whitney U test for quantitative variables and the Pearson's chi-square or Fisher's exact tests for qualitative variables. To assess carotid plaque progression during 10-year follow-up in patients with SLE versus HC individuals, and within the group with SLE, we applied multivariate mixed-effects Poisson regression models with a random intercept to account for the within-person repeated measurements. Models were adjusted for the timepoints of carotid ultrasound measurements (as a qualitative covariate with three levels: 3, 7, and 10 years) and CVRFs. To account for the time needed for carotid plaque development between different vascular ultrasound measurements, the natural logarithm (ln) of the difference between two consecutive measurement times was used as an offset. Regarding missing ultrasound data, we examined the differences in baseline characteristics among individuals followed over the study period and those lost to follow-up. We also examined the differential impact of CVRF target attainment on carotid plaque progression between patients with SLE and HCs using multivariable Poisson mixed-effects regression models, which additionally included the interaction of patients with SLE and HCs with the sum of CVRF targets. Due to 21.8%, 31.3%, 18.5%, 18.5%, and 18.5% missing data over different follow-up timepoints (3, 7, or 10 years) for blood pressure, LDL cholesterol, smoking status, body weight, and physical activity, respectively, in the HC group, we employed multiple imputation by chained equations[27] and conducted the analysis following Rubin's rules.[28]

In the group with SLE, models included patients' age, the sum of sustainedly attained CVRF targets during follow-up for blood pressure, LDL, smoking, body weight, and physical activity, as per the 2016 ESC guidelines,[15] DORIS75 (≥75% of follow-up), and medications (antihypertensives, lipid-lowering agents, and antiplatelets) at baseline. For patients for whom CVRF-related medication reception differed significantly between baseline and 10-year assessments, we controlled for their reception at 100% and ≥75% of follow-up. For LDL target, considering the 2019 American College of Cardiology/American Heart Association guidelines,[29] which included inflammatory disorders among ASCVD risk enhancers, and the 2021 ESC guidelines,[21] which stated that inflammatory conditions should be treated as in high-risk groups in the general population, we conducted a sensitivity analysis using the following LDL level goals: LDL <100 mg/dL for patients with SLE without CVD events (high risk/primary prevention) and <70 mg/dL for those developing CVD events during the 10-year follow-up (very high risk/secondary prevention).

We further assessed the 10-year incidence of CVD events using a permutation-based log-rank test to compare patients with SLE versus HCs, and we performed a univariate Cox regression analysis of CVD events to identify potential associations in the cohort with SLE. Covariates included in all analyses were selected either based on significant associations in the univariate analyses or were predetermined as clinically significant based on the

relevant literature.[1,11–13,30–34] Statistical analyses were performed using STATA (version 12.0; College Station) and R (version 4.3.1; R Core Team, 2023).

Data availability. Individual participant data from this study can be obtained from the corresponding author after deidentification upon reasonable request. Requests should be directed to mtektonidou@gmail.com or mtektonidou@med.uoa.gr.

RESULTS

After a baseline vascular ultrasound assessment of 230 individuals (115 patients with SLE and 115 age- and sex-matched HCs), data from 205 of 230 participants (89.1%; 111 patients with SLE and 94 HCs) were included in our analysis involving 738 carotid ultrasound measurements (413 from patients with SLE and 325 from HCs) at four timepoints (baseline and 3-, 7-, and 10-year follow-up; Supplementary Figure 1, flowchart). Baseline characteristics of patients with SLE and HCs are presented in Table 1. All individuals were White Europeans, representing local demographic characteristics. At baseline, patients with SLE had a higher prevalence of pack-years smoking; antihypertensive, antiplatelet, and anticoagulant treatment reception; and carotid plaque presence compared to HCs. Eight individuals (three patients with SLE and five HCs) were diagnosed and started receiving antidiabetic drugs during follow-up, maintaining good control (median hemoglobin A1c 6.6). CVRF-related medication reception at baseline and 10-year follow-up is shown in Supplementary Table 2. Each attained CVRF target per assessment and the sum of attained targets per assessment and throughout follow-up in the cohort with SLE are presented in Supplementary Table 3.

Disease-related parameters are shown in Table 2. In total, 85 of 111 patients (76.6%) maintained LLDAS ≥75% of their follow-up duration, whereas 53 of 111 patients (47.7%) achieved DORIS remission status ≥75% of follow-up. LLDAS and DORIS criteria at each semiannual assessment, along with annual SLICC scores, are displayed in Supplementary Tables 4 and 5, respectively. A total of 31 patients (27.9%) had a history of lupus nephritis at baseline, and 6 experienced a renal flare during the 10-year follow-up. No new patients with lupus nephritis were observed. At baseline, 34.2% of patients were aPL positive and 18.0% had coexistent APS. During follow-up, 25.2% had persistent aPL positivity and 4.5% had persistent triple aPL positivity. A total of 25 individuals (10.9%) were lost to follow-up (4 patients with SLE and 21 HCs). Their baseline CVRF characteristics did not differ

Table 1. Baseline demographic characteristics, cardiovascular risk parameters, and medications in the entire cohort*

Characteristic	Overall (n = 205)	SLE (n = 111)	Healthy controls (n = 94)	*P* value
White participants, n (%)	205 (100)	111 (100)	94 (100)	NA
Age, y	43.0 (35.1–53.0)	43.0 (36.0–52.0)	43.0 (34.5–52.8)	0.683
Female, n (%)	187 (91.2)	101 (91.0)	86 (91.5)	0.900
Systolic blood pressure, mm Hg	118.0 (110.0–128.0)	116.0 (109.0–124.0)	120.0 (111.0–133.8)	0.075
Diastolic blood pressure, mm Hg	72.5 (66.0–79.0)	71.0 (66.0–75.2)	76.0 (66.2–84.0)	**0.014**
Smoking, pack-years	1.4 (0.0–16.0)	6.0 (0.0–20.0)	0.0 (0.0–12.9)	**<0.001**
Smoking current, n (%)	76 (37.1)	45 (40.5)	31 (33.0)	0.264
Family history of CAD, n (%)	27 (13.2)	16 (14.4)	11 (11.7)	0.567
Total cholesterol, mg/dL	198.0 (175.0–226.0)	188.5 (170.8–223.8)	200.0 (181.0–228.0)	0.070
LDL, mg/dL	115.0 (96.0–137.0)	107.5 (92.0–132.5)	121.0 (101.0–139.0)	**0.027**
HDL, mg/dL	59.5 (49.0–70.0)	59.0 (49.0–71.2)	60.0 (48.0–67.0)	0.662
Triglycerides, mg/dL	86.0 (64.0–126.0)	93.0 (63.0–125.2)	79.0 (65.0–129.0)	0.645
BMI, kg/m^2	24.4 (21.5–28.1)	24.6 (21.3–28.4)	24.2 (21.8–28.0)	0.801
eGFR, mL/min/1.73 m^2	111 (102–117)	111 (102–116)	110 (101–117)	0.894
Exercise, min/wk	90.0 (0.0–210.0)	60.0 (0.0–210.0)	90.0 (0.0–210.0)	0.527
Antihypertensives, n (%)	56 (27.3)	40 (36.0)	16 (17.0)	**0.002**
Lipid-lowering agents, n (%)	17 (8.3)	10 (9.0)	7 (7.4)	0.686
Antiplatelets, n (%)	34 (16.6)	34 (30.6)	0 (0.0)	**<0.001**
Anticoagulants, n (%)	28 (13.7)	26 (23.4)	2 (2.1)	**<0.001**
Antidiabetic drugs, n (%)[a]	8 (3.9)	3 (2.7)	5 (5.3)	0.474
HbA1c, %[a]	6.6 (6.4–6.8)	6.6 (6.5–6.6)	6.7 (6.2–6.9)	0.764
SCORE	0.1 (0.0–0.6)	0.1 (0.0–0.7)	0.1 (0.0–0.5)	0.582
SCORE2	1.2 (0.0–3.1)	1.2 (0.0–3.1)	1.2 (0.0–3.2)	0.926

* Baseline demographic characteristics, cardiovascular risk parameters, and medications refer to baseline unless stated otherwise. Values represent median (interquartile range) unless alternately specified. SCORE: prediction of 10-year fatal cardiovascular disease corresponding to the 2016 ESC guidelines in low-risk countries. SCORE2: prediction of both the 10-year nonfatal myocardial infarction or stroke risk and 10-year cardiovascular death risk corresponding to the 2021 ESC guidelines in moderate-risk countries. *P* values represent differences between patients with SLE and controls at baseline assessment unless stated otherwise. *P*-values in bold indicate statistically significant differences ($P < 0.05$). BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; SCORE, Systemic Coronary Risk Evaluation; SLE, systemic lupus erythematosus.

[a] The antidiabetic drugs and HbA1c values at 10-year follow-up among participants diagnosed with diabetes mellitus between baseline and 10-year follow-up were evaluated: three patients with SLE and five healthy controls.

Table 2. Disease-related characteristics in patients with SLE*

Characteristic	SLE (n = 111), n (%)
Disease duration, median (IQR), y	7.0 (1.5–14.0)
Cumulative prednisone dose, median (IQR), g[a]	12.6 (2.8–27.5)
Prednisone daily dose during follow-up, median (IQR), mg	0.3 (0.0–4.4)
Consistent hydroxychloroquine reception[b]	60 (54.1)
Immunosuppressive reception at baseline	44 (39.6)
SLEDAI-2K at baseline, median (IQR)	0.0 (0.0–4.0)
SLICC at baseline, median (IQR)	0.0 (0.0–1.0)
LLDAS50	97 (87.4)
LLDAS75	85 (76.6)
LLDAS100	43 (38.7)
DORIS50	76 (68.5)
DORIS75	53 (47.7)
DORIS100	25 (22.5)
Antiphospholipid syndrome at baseline	20 (18.0)
aPL positivity at baseline	38 (34.2)
Persistent aPL positivity	28 (25.2)
Persistently high aPL titers	13 (11.7)
Persistent triple aPL positivity	5 (4.5)
Persistent LA positivity	6 (5.4)
Persistent aCL (IgM or IgG) positivity	21 (18.9)
Persistent anti-β2 GPI (IgM or IgG) positivity	20 (18.0)
History of major SLE manifestations at baseline	
Lupus nephritis	31 (27.9)
Central nervous system involvement	12 (10.8)
Pericarditis	20 (18.0)
Pleuritis	12 (10.8)
Alopecia	13 (11.7)
Severe cytopenia	8 (7.2)
Pneumonitis	1 (0.9)

* Clinical characteristics and medications refer to baseline unless stated otherwise. anti-β2 GPI: anti-beta-2 glycoprotein I antibody; aCL, anti-cardiolipin antibody; aPL, anti-phospholipid antibody; DORIS, Definition of Remission in SLE; DORIS50, DORIS remission achievement ≥50% of the follow-up period; DORIS75, DORIS remission achievement ≥75% of the follow-up period; DORIS100, DORIS remission achievement throughout 100% of the follow-up period; IQR, interquartile range; LA, lupus anticoagulant; LLDAS, Lupus Low Disease Activity State; LLDAS50, LLDAS achievement ≥50% of the follow-up period; LLDAS75, LLDAS achievement ≥75% of the follow-up period; LLDAS100, LLDAS achievement throughout 100% of the follow-up period; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC, Systemic Lupus International Collaborating Clinics.
[a] Cumulative prednisone exposure was evaluated before the baseline examination and during the 10-year follow-up.
[b] Consistent hydroxychloroquine reception refers to 100% reception throughout the follow-up period.

from those of study participants, except for higher systolic blood pressure and BMI in the excluded individuals (Supplementary Table 6).

Carotid plaque progression in patients with SLE versus controls. Carotid plaque presence was significantly higher in patients with SLE versus HC individuals at all carotid ultrasound timepoints (Table 3). Univariate analysis of plaque progression in patients with SLE versus HCs is presented in Supplementary Table 7. In Table 4, multivariate analysis model 4A revealed a 2.3-fold higher risk of plaque progression in patients with SLE versus controls (incidence rate ratio [IRR] 2.26, 95% confidence interval [CI] 1.34–3.81, $P = 0.002$) after controlling for baseline SCORE; eGFR; antihypertensive, lipid-lowering, and antiplatelet agents; and the number of carotid plaques at baseline. Based on this model, the expected 10-year evolution of the number of carotid plaques in patients with SLE versus HCs is shown in Figure 1A. In model 4B, which includes CVRFs not incorporated in SCORE, the incidence rate for carotid plaque progression remained significantly higher in patients with SLE versus HCs (IRR 2.20, 95% CI 1.33–3.64, $P = 0.002$), adjusting for age, smoking, eGFR, medications, and the number of carotid plaques at baseline. Because antihypertensive and lipid-lowering agent reception was higher at 10-year follow-up compared to baseline assessment ($P < 0.001$ for both; Supplementary Table 2), we also adjusted for their reception at 100% and ≥75% of follow-up; carotid plaque progression remained significantly higher in patients with SLE versus HCs (Table 4, models C, D, E, and F).

Multivariable analysis showed that sustained CVRF target attainment was significantly associated with reduced carotid plaque progression risk among patients with SLE. A protective but not statistically significant effect was observed in the HC group (Supplementary Table 8, models A, B, and C). The interaction of patients with SLE and HCs with the sum of CVRF targets did not reach statistical significance (for interaction, $P > 0.692$ in all models), suggesting a beneficial effect of CVRF target attainment in both groups.

Carotid plaque progression among patients with SLE. A significant increase in plaque prevalence was observed from baseline to 3-, 7-, and 10-year follow-up among patients with SLE (21.6%, 31.2%, 42.9%, and 54.7%, respectively, $P < 0.001$; Table 3). Univariate analysis of CVRFs and disease-related variables for carotid plaque progression in the cohort with SLE is presented in Supplementary Table 9. In multivariate analysis, plaque progression risk was reduced by 32% for each CVRF sustainedly on target (IRR 0.68, 95% CI 0.53–0.89, $P = 0.004$) after controlling for age and reception of antihypertensives, lipid-lowering agents, and antiplatelets at baseline (Table 5, model A). Figure 1B shows the expected 10-year evolution of the number of carotid plaques in patients with SLE with varying numbers of CVRF targets sustainedly attained during the 10-year follow-up. A prolonged remission status, ≥75% of follow-up (DORIS75), was associated with a 43% decrease in atherosclerosis progression risk (IRR 0.57, 95% CI 0.34–0.95, $P = 0.033$; Table 5, model A). Figure 1C shows the expected 10-year evolution of the number of carotid plaques in patients with DORIS remission ≥75% of follow-up versus those without. Sensitivity analysis of carotid

Table 3. Carotid plaque presence and number of plaques in patients with SLE and HCs*

Characteristic	Baseline			3-Year follow-up			7-Year follow-up			10-Year follow-up		
	Patients with SLE (n = 111)	HCs (n = 94)	*P* value[a]	Patients with SLE (n = 109)	HCs (n = 91)	*P* value[a]	Patients with SLE (n = 98)	HCs (n = 69)	*P* value[a]	Patients with SLE (n = 95)	HCs (n = 71)	*P* value[a]
Carotid plaque presence, n (%)	24 (21.6)	7 (7.4)	**0.005**	34 (31.2)	10 (11.0)	**0.001**	42 (42.9)	9 (13.0)	**<0.001**	52 (54.7)	21 (29.6)	**0.001**
Number of carotid plaques, median (IQR)	0 (0–0)	0 (0–0)	**0.004**	0 (0–1)	0 (0–0)	**<0.001**	0 (0–2)	0 (0–0)	**<0.001**	1 (0–2)	0 (0–1)	**<0.001**

* Carotid plaque presence and the number of plaques in patients with SLE and HCs at baseline and follow-up assessments. The total numbers of individuals for each timepoint correspond to participants with carotid ultrasound measurements at baseline and 3-, 7-, and 10-year assessments (Supplementary Figure 1, flowchart). HC, healthy control; IQR, interquartile range; SLE, systemic lupus erythematosus.
[a] *P* values represent the difference in carotid plaque presence and in the number of plaques in patients with SLE versus HCs at different assessments (baseline and 3, 7, and 10 years). *P* values in bold indicate statistically significant differences ($P < 0.05$).

plaque progression in patients with SLE using revised LDL cutoffs showed similar results (Supplementary Table 10).

Because lipid-lowering agent reception in patients with SLE was significantly higher at 10-year follow-up compared to baseline ($P < 0.001$; Supplementary Table 2), further adjustment for their reception at 100% and ≥75% of follow-up was made; sustained CVRF control and DORIS remission ≥75% of follow-up remained significantly correlated with lower plaque progression risk (Table 5, models B and C). Although achieving LLDAS throughout the entire follow-up (LLDAS100) was associated with reduced plaque progression in univariate analysis, this association was not significant in multivariate analysis (Supplementary Table 11).

Cardiovascular events in patients with SLE versus controls. During the 10-year follow-up, eight CVD events occurred in patients with SLE (two sudden cardiac deaths due to cardiac arrest, two acute coronary syndromes, two transient ischemic attacks, and two peripheral artery disease events) versus one CVD event (transient ischemic attack) among HCs. The incidence of CVD events was significantly higher in patients with SLE than HC individuals (permutation-based log-rank $P = 0.036$).

Cardiovascular events among patients with SLE. In exploratory univariate Cox regression analysis of incident CVD events, persistent aCL, LA, and triple aPL positivity over the 10-year follow-up, and antiplatelet reception at baseline, were associated with CVD events in patients with SLE (Supplementary Table 12), but these results should be interpreted with caution due to wide CIs. Baseline SCORE2 had a marginal statistical significance (hazard ratio [HR] 1.17, 95% CI 1.00–1.36, $P = 0.048$), whereas SCORE showed a trend toward significance for CVD events (HR 1.26, 95% CI 0.99–1.60, $P = 0.050$). However, in seven of eight patients who developed CVD events, the estimated 10-year risk of developing CVD according to both SCORE and SCORE2 predictions at baseline was low to moderate. The incorporation of carotid ultrasound at baseline assessment enhanced the ability to predict the 10-year risk for CVD events from 12.5% (using only SCORE/SCORE2) to 37.5%, representing a three-fold increase in the detection rate (Supplementary Table 13). Given that disease activity is a major predictor of CVD events in patients with SLE,[14] we examined the impact of DORIS75 in multivariate models (Supplementary Table 14). No association was found, but the low statistical power to perform a multivariate analysis given the low CVD event rates should be considered.

DISCUSSION

This study examines, for the first time to our knowledge, the progression of carotid atherosclerotic plaques in patients with SLE versus age- and sex-matched HCs over four serial timepoints in a 10-year follow-up period and the impact of sustained CVRF control and clinical remission. We found a 2.3-fold increased risk of new atherosclerotic plaques in patients with SLE versus HC individuals, mitigated by sustained CVRF target attainment and prolonged disease remission. We also observed a significantly higher incidence of CVD events in patients with SLE versus HCs, associated with persistent aCL, LA, and triple aPL positivity.

Only sporadic longitudinal studies have examined atherosclerotic plaque progression in patients with SLE versus HCs.[11,12,31] In a previous three-year follow-up study from our group, the risk of plaque progression in patients with SLE (including both men and women) was significantly higher in patients with SLE (OR 2.81) than age- and sex-matched HCs but not in patients with rheumatoid arthritis versus HCs.[11] A five-year follow-up study showed a two-fold increased risk for plaque progression in women with SLE versus controls, associated with larger waist circumference and no reception of hydroxychloroquine.[12] In another study of White British women with SLE with a median five-year follow-up, new plaques were developed in 26% of patients.[30]

Guidelines for CVD prevention in the general population defined specific treatment goals for each of CVRFs and

Table 4. Multivariate mixed-effects Poisson regression models of carotid plaque progression in patients with SLE versus healthy controls*

Characteristic	IRR (95% CI)	*P* value
Model A (including SCORE)		
Patients with SLE vs healthy controls	2.26 (1.34–3.81)	**0.002**
Antihypertensives	1.02 (0.61–1.71)	0.938
Lipid-lowering agents	1.64 (0.77–3.48)	0.198
Antiplatelets	0.99 (0.55–1.78)	0.971
SCORE	1.16 (0.96–1.42)	0.132
eGFR	0.80 (0.63–1.01)	0.059
Number of carotid plaques	0.88 (0.60–1.29)	0.520
Model B		
Patients with SLE vs healthy controls	2.20 (1.33–3.64)	**0.002**
Age, y	1.06 (1.03–1.08)	**<0.001**
Smoking	2.12 (1.36–3.30)	**<0.001**
Antihypertensives	1.05 (0.64–1.73)	0.851
Lipid-lowering agents	1.21 (0.60–2.41)	0.594
Antiplatelets	1.16 (0.67–2.02)	0.601
eGFR	0.84 (0.67–1.05)	0.128
Number of carotid plaques	0.71 (0.50–1.02)	0.064
Model C (including SCORE)		
Patients with SLE vs healthy controls	2.25 (1.32–3.82)	**0.003**
Antihypertensive reception ≥75% of the follow-up period	1.18 (0.73–1.91)	0.744
Lipid-lowering agent reception ≥75% of the follow-up period	1.10 (0.63–1.91)	0.744
Antiplatelets	1.00 (0.56–1.82)	0.982
SCORE	1.21 (1.02–1.45)	**0.034**
eGFR	0.82 (0.65–1.04)	0.106
Number of carotid plaques	0.87 (0.59–1.26)	0.455
Model D		
Patients with SLE vs healthy controls	2.22 (1.33–3.71)	**0.002**
Age, y	1.06 (1.04–1.09)	**<0.001**
Smoking	2.08 (1.33–3.23)	**0.001**
Antihypertensive reception ≥75% of the follow-up period	0.93 (0.59–1.47)	0.754
Lipid-lowering agent reception ≥75% of the follow-up period	0.95 (0.56–1.61)	0.855
Antiplatelets	1.15 (0.66–2.02)	0.620
eGFR	0.85 (0.68–1.06)	0.160
Number of carotid plaques	0.74 (0.52–1.04)	0.081
Model E (including SCORE)		
Patients with SLE vs healthy controls	2.32 (1.37–3.93)	**0.002**
Antihypertensive reception 100% of the follow-up period	0.97 (0.55–1.72)	0.916
Lipid-lowering agent reception 100% of the follow-up period	1.26 (0.77–3.48)	0.606
Antiplatelets	0.98 (0.54–1.78)	0.957
SCORE	1.22 (1.02–1.47)	**0.032**
eGFR	0.81 (0.63–1.01)	0.088
Number of carotid plaques	0.89 (0.61–1.30)	0.541
Model F		
Patients with SLE vs healthy controls	2.19 (1.32–3.63)	**0.002**
Age, y	1.06 (1.04–1.09)	**<0.001**
Smoking	2.06 (1.33–3.20)	**<0.001**
Antihypertensive reception 100% of the follow-up period	1.02 (0.59–1.76)	0.944
Lipid-lowering agent reception 100% of the follow-up period	0.79 (0.35–1.81)	0.578
Antiplatelets	1.18 (0.55–1.78)	0.553
eGFR	0.87 (0.69–1.09)	0.232
Number of carotid plaques	0.73 (0.60–1.29)	0.079

* Variables refer to baseline assessment unless specified otherwise. All models are also adjusted for the timepoints of carotid ultrasound measurements (as a qualitative covariate). SCORE prediction of 10-year fatal cardiovascular disease corresponding to the 2016 European Society of Cardiology guidelines in low-risk countries. *P*-values in bold indicate statistically significant variables ($P < 0.05$). CI, confidence interval; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio; SCORE, Systemic Coronary Risk Evaluation; SLE, systemic lupus erythematosus.

highlighted the importance of their attainment.[15] Importantly, a suboptimal CVRF control was recently shown in a multicenter cross-sectional study of 3,401 patients with SLE from 24 countries and across 4 continents.[35] Although previous publications identified hypertension,[36] dyslipidemia,[36] increased waist circumference,[12] and SCORE[11] as predictors of intima-media

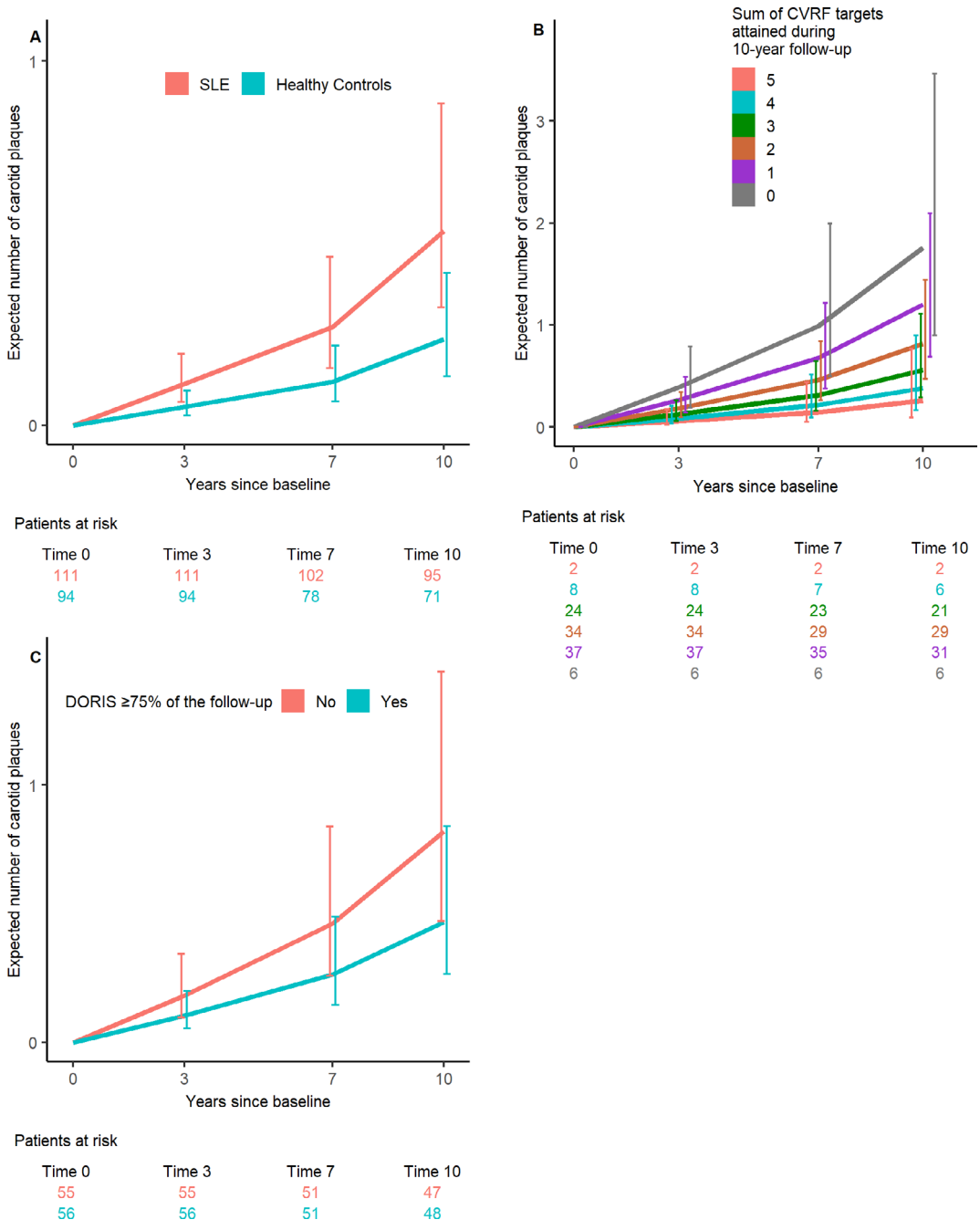

Figure 1. Expected 10-year evolution of the number of carotid plaques (A) for typical patients with SLE and healthy controls (HCs), (B) for typical individuals with SLE with varying numbers of cardiovascular risk factor (CVRF) targets sustainedly attained, and (C) for typical individuals with SLE with versus without DORIS remission for ≥75% of follow-up. (A) Typical individuals are patients with SLE or HCs with baseline characteristic values (included in multivariate model 4A of plaque progression in patients with SLE vs HCs) set at the median for quantitative and at the mode for qualitative variables: no use of antihypertensives, lipid-lowering agents or antiplatelets, Systemic Coronary Risk Evaluation 0.1, estimated glomerular filtration rate 111 mL/minutes/1.73 m^2, and no carotid plaques. (B) Typical individuals with SLE are patients with baseline characteristic values (included in multivariate model 5A of plaque progression in patients with SLE) set at the median for quantitative and at the mode for qualitative variables: 43 years old; no reception of antihypertensives, lipid-lowering agents, or antiplatelets; and no DORIS remission ≥75% of follow-up. (C) Typical individuals with SLE are patients with baseline characteristic values (included in multivariate model 5A) set at the median for quantitative and at the mode for qualitative variables: 43 years old; no reception of antihypertensives, lipid-lowering agents, or antiplatelets; and two CVRF targets sustainedly attained during the follow-up. DORIS, Definition of Remission in SLE; SLE, systemic lupus erythematosus.

Table 5. Multivariate mixed-effects Poisson regression analysis of carotid plaque progression in patients with SLE*

Characteristic	IRR (95% CI)	*P* value
Model A		
Age, y	1.03 (1.01–1.06)	**0.010**
Antihypertensives	0.64 (0.37–1.09)	0.100
Lipid-lowering agents	1.11 (0.50–2.46)	0.800
Antiplatelets	0.89 (0.51–1.55)	0.671
Sum of CVRF targets consistently attained throughout the follow-up period	0.68 (0.53–0.89)	**0.004**
DORIS75	0.57 (0.34–0.95)	**0.033**
Model B		
Age, y	1.04 (1.02–1.06)	**0.001**
Antihypertensives	0.70 (0.41–1.19)	0.187
Lipid-lowering agent reception ≥75% of the follow-up period	0.66 (0.36–1.20)	0.174
Antiplatelets	0.82 (0.47–1.44)	0.482
Sum of CVRF targets consistently attained throughout the follow-up period	0.67 (0.51–0.87)	**0.003**
DORIS75	0.56 (0.33–0.94)	**0.028**
Model C		
Age, y	1.04 (1.01–1.07)	**0.002**
Antihypertensives	0.68 (0.40–1.16)	0.158
Lipid-lowering agent reception 100% of the follow-up period	0.60 (0.23–1.59)	0.306
Antiplatelets	0.87 (0.50–1.51)	0.616
Sum of CVRF targets consistently attained throughout the follow-up period	0.67 (0.52–0.88)	**0.003**
DORIS75	0.57 (0.34–0.96)	**0.035**

* Variables refer to baseline assessment unless specified otherwise. CVRF targets attained throughout the follow-up period represented targets consistently attained by the last follow-up assessment (at 3, 7, or 10 years) according to the 2016 European Society of Cardiology guidelines concerning blood pressure, low-density lipoprotein, smoking, body weight (body mass index and waist circumference), and physical activity. All models are also adjusted for the timepoints of carotid ultrasound measurements (as a qualitative covariate). *P*-values in bold indicate statistically significant variables ($P < 0.05$). CI, confidence interval; CVRF, cardiovascular risk factor; DORIS75, Definition of Remission in SLE remission achievement ≥75% of the follow-up period; IRR, incidence rate ratio; SLE, systemic lupus erythematosus.

thickness or plaque acceleration in patients with SLE, no previous study examined the enduring impact of sustained CVRF target attainment on preventing plaque progression in a long-term follow-up. Although LDL and BMI attainment rates were almost double at each timepoint separately, sustained CVRF target attainment over the entire follow-up was only 22.5%, 23.4%, and 18.0% for LDL, body weight, and physical activity, respectively. The lower sustained target rates emphasize the need for consistent efforts to manage CVRFs in patients with SLE by encouraging lifestyle changes including healthy diet, regular exercise, and early initiation of lipid-lowering medications after appropriate CVD risk stratification.[14]

Regarding disease-related predictors of plaque progression in patients with SLE, previous studies were mainly focused on the baseline disease activity status overlooking the dynamic nature of disease activity over time.[12,30] Our study uniquely tracks multiple durations of LLDAS and DORIS throughout the entire follow-up period. The 2022 EULAR recommendations for CVD risk management in rheumatic diseases state that low disease activity should be maintained in patients with SLE to also reduce cardiovascular risk.[14] Interestingly, our results showed that none of the examined LLDAS durations (LLDAS50, LLDAS75, or LLDAS100) prevented plaque progression in multivariate analysis. In contrast, maintaining DORIS ≥75% of follow-up correlated with a 43% reduction in plaque progression risk. These findings support the importance of prioritizing a sustained remission rather than a low disease activity state for the prevention of atherosclerosis development and progression in patients with SLE.

We also examined incident CVD events during the 10-year follow-up in association with disease-related risk factors, the ESC-endorsed risk prediction tools SCORE/SCORE2, and CVRF targets. CVD events in patients with SLE are linked to both traditional CVRFs and disease-related features.[32,33] We found that persistent aCL, LA, and triple aPL positivity were associated with incident CVD events in patients with SLE in univariate analysis. Positive aPLs have been described as independent predictors of subsequent CVD events in patients with SLE,[14,37] but the impact of persistent triple aPL positivity in multiple measures over a 10-year follow-up is described for the first time. Two events in the group with SLE occurred in patients with positive aPLs who were subsequently diagnosed with APS. The distinction between atherothrombotic events attributable to APS and those due to atherosclerosis remains unclear. Evidence has also shown that aPL-mediated oxidative stress, endothelial dysfunction, and the oxidized LDL/β_2 glycoprotein I complex–induced differentiation of macrophages to foam cells promote atherogenesis.[38] Although the results of our analysis reached statistical significance, they should be validated by multivariate analyses in larger prospective studies with higher incidence rates.

Although long-term hydroxychloroquine exposure has been associated with reduced CVD risk in patients with SLE,[34] consistent hydroxychloroquine reception was not found to protect against plaque progression or CVD events in our cohort, possibly due to its reception by most patients throughout follow-up. Glucocorticoid reception, although a well-established predictor of CVD events,[39] was not correlated with atherosclerosis progression or CVD event occurrence in our study, probably due to low doses received (median daily prednisone dose 0.3 mg). Lack of associations between the above medications and incident CVD events may also be explained by their small numbers.

Regarding the generic CVD risk prediction tools, although there was a marginally significant association between SCORE2 and CVD events and a trend toward significance between SCORE and CVD events in univariate analysis, both tools had limitations in their predictive ability. Median baseline SCORE2 (1.2%) failed to predict seven of eight CVD events, and SCORE (0.1%) did not predict any of the two CVD deaths in the cohort with SLE. This observation aligns with recent studies, including those conducted by our

group, suggesting that generic CVD prediction tools, such as Framingham and SCORE, may underestimate CVD risk in patients with SLE.[40–42] However, data from various cohorts have shown that SCORE may perform better than Framingham in predicting plaque progression, the extent and severity of coronary artery disease, and CVD deaths.[41,43,44] In the present study, the incorporation of baseline carotid ultrasound resulted in a three-fold increase in detection rate compared to generic SCORE/SCORE2 tools, suggesting its additive role in CVD risk assessment.

The strengths of the study include the following assessments for the first time: (a) 10-year atherosclerotic plaque progression in patients with SLE versus age- and sex-matched HC individuals, (b) predictive role of the sustained target attainment for each CVRF as defined by the ESC and two generic prediction scores, and (c) impact of LLDAS and DORIS at multiple time periods (50%, 75%, and 100% of the entire follow-up time) given that disease activity fluctuates over time and the assessment at only one timepoint would lead to underestimations. All ultrasound examinations, from baseline to the last assessment, were performed by the same blinded assessor who has performed >2,000 ultrasounds in our cardiovascular research laboratory since 2010.[11,31] There was a relatively small loss to follow-up (10.9%) considering the duration of follow-up (10 years) that was more pronounced in the HC group, reflecting the challenges of long-term evaluations in healthy populations. We also assessed for the first time the impact of persistent triple aPL positivity on incident CVD events. A limitation of the study is the lack of statistical power to perform a multivariate analysis of incident CVD events for all potential predictors due to low event rates; however, these rates are similar to those reported in recent prospective studies.[45,46] Additionally, our cohort consisted solely of White Europeans, limiting the generalizability of our findings to more ethnically diverse populations. Given that aPLs have been associated with CVD events in the general population,[47,48] lack of testing for aPL positivity in HCs might be an additional limitation.

Our findings showed that sustained CVRF control and prolonged clinical remission can substantially reduce atherosclerosis progression risk in patients with SLE, highlighting the need for consistent efforts to achieve both targets in this young adult population at high risk. Additionally, persistent triple aPL positivity was associated with incident CVD events, supporting the importance of their early identification and appropriate management.[14] Further research should validate these findings in larger and more diverse cohorts with SLE.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Tektonidou confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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