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Original article

Extent of vascular plaque predicts future cardiovascular events in patients with systemic lupus erythematosus

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Abstract

Objective. Patients with SLE have increased prevalence of clinical cardiovascular disease (CVD) and subclinical atherosclerosis. Although 30–40% of patients with SLE have vascular plaque on ultrasound scanning, this study is the first to consider the relationship between total burden of plaque and subsequent CVD risk.

Methods. One hundred patients with SLE and without any previous clinical CVD underwent vascular ultrasound scans of both carotid and both common femoral bifurcations between 2011 and 2013. Clinical, serological, demographic and treatment data were collected at baseline. Patients were followed till 2020 to identify those who developed new onset coronary disease or stroke. Statistical analysis to identify factors associated with increased risk of developing CVD events was carried out.

Results. Thirty-six patients had plaque at baseline. During follow-up five patients (all had baseline plaque) developed coronary disease and two, without baseline plaque, developed lacunar strokes. Mean (S.D.) age of these patients was 46.5 (4.5) years. Patients with three or more baseline bifurcations with plaque were 10 times more likely to develop CVD than those with 0–2 bifurcations with plaques (OR 9.9, $P = 0.009$). TPA $> 16\text{mm}^2$ was associated with six-fold increased risk of CVD (OR $= 6.44$, $P = 0.028$). Patients with disease duration > 14 years were more likely than those with disease duration < 14 years to develop CVD (OR 8.3 $P = 0.043$)

Conclusions. The number of bifurcations with plaque and TPA in patients with SLE may be valuable in assessing risk of CVD and deciding on clinical measures to reduce this risk.

Key words: SLE, cardiovascular disease, plaque, atherosclerosis, ultrasound

Rheumatology key messages

- Seven of 100 SLE patients with baseline vascular scans experienced cardiovascular disease (CVD) events within 7.5 years.
- Baseline total plaque area $>16\text{mm}^2$ and/or ≥ 3 bifurcations with plaque predicted increased risk of CVD events.
- Quantifying plaque burden in patients with SLE may help rheumatologists manage cardiovascular risk.

Introduction

SLE is an autoimmune rheumatic disease with a prevalence of 97 per 100 000 in the United Kingdom [1]. Ninety percent of patients with SLE are women and the disease typically presents before the age of 50. Despite this, it is well-established that both clinically apparent cardiovascular disease (CVD) [2] and subclinical atherosclerosis detected by imaging [3–6] are significantly more common in patients with SLE compared with healthy controls.

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CLINICAL SCIENCE

Vascular ultrasound scanning has shown that prevalence of carotid plaque in patients with SLE is 30–40% [4–6]. Increased carotid intima media thickness (IMT) and presence of plaque at baseline were associated with increased risk of developing CVD over the next 10 years in multivariable analysis in 392 patients with SLE (mean follow up 8 years) [5]. In addition, atherosclerotic plaques occur in the absence of intima-media thickening [4, 7] and during follow-up CVD occurs more often in patients with coexistent carotid and femoral plaques [7].

The use of carotid ultrasound to optimize CVD prediction is recommended as part of CVD risk evaluation in autoimmune rheumatic diseases [8] and by several European and international groups for evaluation of risk in the general population [9, 10]. It is not clear, however, how best to use vascular ultrasound information to manage CVD risk in patients with SLE.

One possible advance would be to consider the overall burden of plaque, assessed by the number of carotid and common femoral bifurcations with plaque and/or total plaque area (TPA), in addition to presence of plaque in the assessment of CVD risk. This requires scanning techniques that include the femoral as well as the carotid arteries [11] and measurement of TPA. Few previous studies have reported on TPA in patients with SLE [12, 13] and none has looked at association of TPA with future CVD events in these patients.

In a previous paper published recently in *Rheumatology* [6], we described the results of scanning both carotid and both common femoral artery bifurcations of 100 patients with SLE without any previous CVD between 2011–2013 to determine IMT, TPA and echogenicity of plaques.

Here we report an analysis of clinical CVD events in those 100 patients up to 2020, showing that overall burden of plaque at baseline was strongly associated with these events. Conversely, apart from low complement factor C3, we found no clear association of conventional risk factors or biochemical or immunological serum markers with these events.

Patients and methods

Patients

One hundred patients were recruited from the Lupus Clinic at University College London Hospital (UCLH). All met the American College of Rheumatology 1997 revised criteria for SLE [14] and had no previous history of CVD. Absence of CVD (defined as coronary artery disease, stroke, or myocardial infarction with confirmatory evidence from blood tests including raised troponin and/or creatine kinase and/or imaging including coronary angiography, computed tomography or magnetic resonance imaging of the brain) was confirmed by analysis of medical records. All patients gave informed consent. The study was approved by the combined UCL/UCLH Research Ethics Committee (Reference 06/Q0505/79). Recruitment started in October 2011 and was completed in April 2013. Follow-up continued till December 2020. Research conformed to the principles of the Declaration of Helsinki.

SLE disease activity was determined by the BILAG-2004 Index [15]. Persistently active disease was defined as a Numerical BILAG-2004 >5 on at least two clinic visits from the previous four visits [6]. Numerical BILAG-2004 score was calculated using the method previously published [16]. Blood results from the day of the scan or nearest clinic visit were obtained from tests carried out as part of routine clinical practice. Data on therapy, traditional CVD risk factors and previous serology were obtained from medical records. The following factors were included in the analysis.

Demographic—age at scan, sex.

Disease associated—Age at diagnosis, duration of disease at time of scan, previous renal lupus ever, persistent disease activity.

Traditional CVD risk factors—Ever-smoker, diabetes, diagnosis of hypertension, systolic BP at scan, total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL).

Serum values at time of scan—Urea, creatinine, albumin, anti-dsDNA, complement C3, ESR, CRP.

Medication at time of scan—Prednisolone, immunosuppressants, statins, angiotensin converting enzyme inhibitors, aspirin.

Serum positivity ever—anticardiolipin, lupus anticoagulant.

Ultrasound scanning

All scans were performed by the same experienced vascular scientist (MG) using the Philips iU22 ultrasound system (Philips Ultrasound, Bothell, USA) with a linear array L9-3 MHz transducer. The methods have been described in detail in our previous paper [6]. Briefly, both carotid and both femoral bifurcations were scanned. IMT was measured using the system's automated software and the mean of IMT from both carotids (IMTcc) was used in statistical analysis.

An arterial bifurcation was classified as being affected by plaque if there was a focal thickening of >1.2 mm [17, 18]. The ultrasound images of these plaques were stored as DICOM files and transferred to a PC for measurement of plaque area using a dedicated software program (Carotid Plaque Texture Analysis. (LifeQ Medical Ltd – www.lifeqmedical.com). Total plaque area (TPA) was defined as the sum of the cross-sectional areas of all plaques seen in longitudinal images in all four bifurcations. Supplementary Figs S1 and S2, available at *Rheumatology* online, illustrate different sized plaques.

Statistical methods Extent of vascular plaque predicts future cardiovascular events in patients with systemic lupus erythematosus

Initially we explored the data for the ability of baseline IMT, number of bifurcations with plaque and TPA to

predict future events using the Area Under the Receiver Operator Characteristic (ROC) curve (AUC). This was also done for those conventional risk factors and biochemical and immunological tests that could be considered as continuous variables. Factors that were categorical variables were analysed by constructing 2 by 2 tables, carrying out chi-squared analysis and expressing probability by Fisher's exact test.

For the continuous variables that had shown statistically significant association with future CVD events, we then used the cut-off points for maximum sensitivity combined with maximum specificity to construct 2 by 2 tables to identify subgroups at increased risk for future cardiovascular events. Odds ratios were used to demonstrate the magnitude of their predictive ability. Subsequently life table analysis was used to determine the cumulative event free survival for the high-risk subgroups detected. Finally, a bivariate analysis was performed using a combination of TPA and duration of the disease to determine whether this combination could identify a subgroup with an even higher risk.

We also compared the predictive ability of the variables described above with that of QRISK3 [19], a risk calculation algorithm that includes SLE, treatment with corticosteroids and chronic renal impairment as well as traditional risk factors in estimating 10-year risk of a CVD event. We used QRISK3 to calculate this 10-year risk for each of the 100 patients based on information available at baseline.

The IBM SPSS statistical package, version 19 was used. $p < 0.05$ (2-sided) was considered significant.

Results

New cardiovascular events during follow-up period

Of the 100 patients recruited, 98 were women and 2 were men. All patients were followed up till the end of 2020, with the exception of three patients who died from non-cardiovascular causes (in 2015, 2016 and 2017) and nine lost to follow-up between 2016 and 2019. The mean (S.D.) duration of follow-up from the first scan was 7.5 (0.5) years. The baseline characteristics of these 100 patients were published in our previous paper and are also included in Supplementary Table S1, available at *Rheumatology* online. Although 14 of the 100 studied were taking aspirin at baseline, review of the medical records showed that none of them was taking this drug for primary prevention of CVD. In 12 cases, aspirin was prescribed due to previous positive tests for antiphospholipid antibodies (aPL) in the absence of thrombosis. We were unable to identify the reason for taking aspirin in the other two cases. Of 34 patients who had ever been positive for aPL, five were on anticoagulation due to previous thrombosis. One of these five suffered a CVD event during the course of this study.

Seven patients developed CVD for the first time during the follow-up period. Five had coronary events whereas two had lacunar strokes. Details are shown in Table 1. All the patients who developed events were women with mean (S.D.) age at event of 46.5 (4.5) years and mean (S.D.) duration of SLE of 25.2 (1.5) years.

Baseline factors associated with development of new cardiovascular events

The ability of baseline IMT, bifurcations with plaque, TPA, and those conventional risk factors, biochemical and immunological tests consisting of continuous variables to predict future cardiovascular events was tested using the Area Under Curve (AUC) method. The results are shown in Table 2.

Variables with AUC > 0.70, suggesting ability to predict events and those with AUC < 0.30, suggesting potential ability to predict no events, are highlighted in bold.

Effects of baseline categorical risk factors potentially related to CVD risk are shown in Table 3. These factors are listed in the methods section. Overall, none of the traditional risk factors or measures of disease activity in Tables 2 and 3 were associated with increased risk of developing cardiovascular events except low complement factor C3.

The combination of disease duration with TPA at baseline identifies a subgroup at high risk of new cardiovascular events

Tables 2 and 3 showed that only disease duration at time of scan, low C3, TPA and number of bifurcations with plaque were associated with new cardiovascular events. The AUC values for these variables were 0.757, 0.733, 0.759 and 0.724 respectively and there was no significant difference between them on statistical comparison of the ROC curves. To investigate this finding further, these four factors highlighted in bold in Table 2 were reclassified as categorical variables using their cut-off points associated with maximum sensitivity combined with maximum specificity and tested in 2x2 tables. The results are shown in Table 4.

Although the ROC analysis of disease duration suggested 20 years as the cut-off point for maximum sensitivity with maximum specificity, we also used 14 years which gives a higher sensitivity and is still statistically significant (Table 4). Thus, disease duration of >14 years identified a high-risk group of 45 patients that contained 6 of the 7 clinical events.

Survival curves showing results of life table analysis using the number of bifurcations with plaque (0–2 *vs* 3–4), TPA (<16 mm^2 *vs* >16 mm^2) and C3 (<0.88 g/l *vs* ≥ 0.88 g/l) are shown in Fig. 1A–C respectively. Patients with plaques at three or more bifurcations have a cumulative event-free survival of 0.65 which translates to a cumulative event rate of 35% (Log Rank $P = 0.001$) at 9 years or an average annual event rate of 3.9% (Fig. 1A). Patients with TPA > 16 mm^2 have a cumulative event-free survival of 0.78 which translates to a cumulative event rate of 22% (Log Rank $P = 0.015$) at 9 years or an average annual event rate of 2.4%

Table 1 Description of the seven patients who developed clinical cardiovascular disease during follow-up

Patient Study ID	Age at scan	Age at event	Event	Conventional Risk Factors	Bifurcations with Plaque	TPA mm^2	Disease Duration at scan (years)
1	41	42	Stroke	Hypertension Hypercholesterolaemia	0	0	22
2	60	61	CABG	Hypertension Hypercholesterolaemia	1	28	33
3	59	60	NSTEMI	Hypertension Hypercholesterolaemia	3	94	38
4	49	51	CAD	Hypertension Hypercholesterolaemia Past Smoker	3	149	15
5	63	66	CAD	Hypertension	3	120	38
6	37	43	Stroke		0	0	6
7	53	54	CABG	Hypertension	4	92	25

CABG: coronary artery bypass graft, NSTEMI: non-ST elevation myocardial infarction, CAD: coronary artery disease confirmed on imaging. In both cases of CAD, the patient underwent percutaneous coronary intervention with insertion of a stent to a stenosed vessel. Both strokes were lacunar strokes confirmed by magnetic resonance imaging.

Table 2 Ability of baseline continuous variables to predict future cardiovascular events assessed using receiver operator curve analysis

Variable	Auc (95% CI)	*P*	Cut-off for max sensitivity and max specificity
Intima-media thickness in common carotid artery (cm)	0.409 (0.214, 0.603)	0.422	
Bifurcations with plaque	**0.724 (0.512, 0.937)**	**0.049**	**1.0**
Total plaque area (mm^2)	**0.759 (0.536, 0.981)**	**0.023**	**16 mm^2**
Age at scan (years)	0.665 (0.486, 0.844)	0.146	
Age at diagnosis (years)	0.430 (0.292, 0.568)	0.539	
Disease duration at scan (years)	**0.757 (0.548, 0.965)**	**0.024**	**20 years**
Systolic blood pressure at scan (mmHg)	0.619 (0.408, 0.830)	0.295	
Prednisolone dose at scan (mg per day)	0.625 (0.448, 0.802)	0.271	
Total cholesterol (mmol/l)	0.429 (0.408, 0.830)	0.530	
High density lipoprotein cholesterol (HDL) (mmol/l)	0.391 (0.246, 0.536)	0.337	
Total cholesterol/HDL ratio	0.588 (0.439, 0.736).	0.441	
Low density lipoprotein cholesterol (mmol/l)	0.469 (0.302, 0.635)	0.782	
Creatinine (micromol/l)	0.493 (0.263, 0.723)	0.952	
Urea (mmol/l)	0.546 (0.322, 0.770)	0.685	
Albumin (g/l)	0.494 (0.262, 0.726)	0.957	
Anti-dsDNA (IU/l)	0.482 (0.285, 0.678)	0.871	
C3 (g/l)	**0.733 (0.567, 0.899)**	**0.041**	**0.88**
Erythrocyte sedimentation rate (mm/h)	0.624 (0.411, 0.838)	0.274	
C-reactive protein (mg/dl)	0.496 (0.294, 0.698)	0.973	

Bold text = variables that had significant association with future CVS events.

(Fig. 1B). Patients with C3 $<$ 0.88 g/l have a cumulative event-free survival of 0.77 (Log Rank $P = 0.024$) at 9 years with a similar annual event rate (Fig. 1C). However, C3 levels vary with time and a value of 0.88 g/l is only just below the lower limit of normal in our clinical laboratory. For three of the 7 patients who had events we found that C3 was $\geq$ 0.88 g/l in 50% or more of visits between 2011–13. Therefore, we investigated combined predictive value of disease duration and TPA rather than low C3 and TPA.

Disease duration of $>$14 years identified a high-risk group of 45 patients that contains 6 of the clinical events. TPA $>$ 16 mm^2 was also present in 20 of these patients. This subgroup of 20 patients contained five clinical events resulting in a 9-year event free survival of 0.67 (Log Rank $P = 0.037$) (Fig. 2).

Comparison with CVD risk calculated using QRISK3

This comparison was carried out to assess whether scanning identified patients who would not have been identifiable using QRISK3. According to this calculation four patients were in the high-risk category with 10-year risk $>$ 20%, 24 were in the medium-risk category (10-

Table 3 Predictive value of baseline categorical variables for new cardiovascular events during the follow-up period expressed as Odds Ratios

Variable	Categories	N	Events	*P* Fisher's exact test	OR (95% CI)
Hypertension	Absent	51	1 (2.0%)		
	Present	49	6 (12.2%)	0.057	6.97 (0.808, 60.2)
Diabetes	Absent	98	7 (7.1%)		
	Present	2	0	1.000	0.93 (0.89, 0.98)
Ever smoker	No	49	5 (10.2%)		
	Yes	29	2 (6.9%)	1.000	0.65 (0.11, 3.59)
Persistently active disease	No	50	2 (4.0%)		
	Yes	48	5 (10.4%)	0.264	2.79 (0.52, 15.1)
Sex	Female	95	7 (7.4%)		
	Male	5	0	1.000	0.93 (0.87, 0.98)
Renal lupus ever	No	61	3 (4.9%)		
	Yes	39	4 (10.3%)	0.427	2.21 (0.47, 10.5)
Anti-cardiolipin positive ever	No	81	4 (4.9%)		
	Yes	13	2 (15.4%)	0.192	3.50 (0.57, 21.4)
Lupus anti-coagulant positive ever	No	78	4 (5.1%)		
	Yes	12	1 (8.3%)	0.520	1.68 (0.17, 16.5)
Taking immunosuppressants at time of scan	No	55	2 (3.6%)		
	Yes	45	5 (11.1%)	0.238	3.31 (0.61, 18.0)
Taking statins at time of scan	No	87	5 (5.7%)		
	Yes	13	2 (15.4%)	0.225	2.98 (0.51, 17.3)
Taking aspirin at time of scan	No	86	4 (4.7%)		
	Yes	14	3 (21.4%)	0.055	5.59 (1.1, 28.3)
Taking ACE inhibitor at time of scan	No	65	4 (6.2%)		
	Yes	35	3 (8.6%)	0.693	1.43 (0.30, 6.78)

Persistently active disease was defined as a BILAG-2004 score >5 on at least two clinic visits from the previous four visits [6]. Score calculated according to the formula A = 12, B = 8, C = 1, D = E = 0.

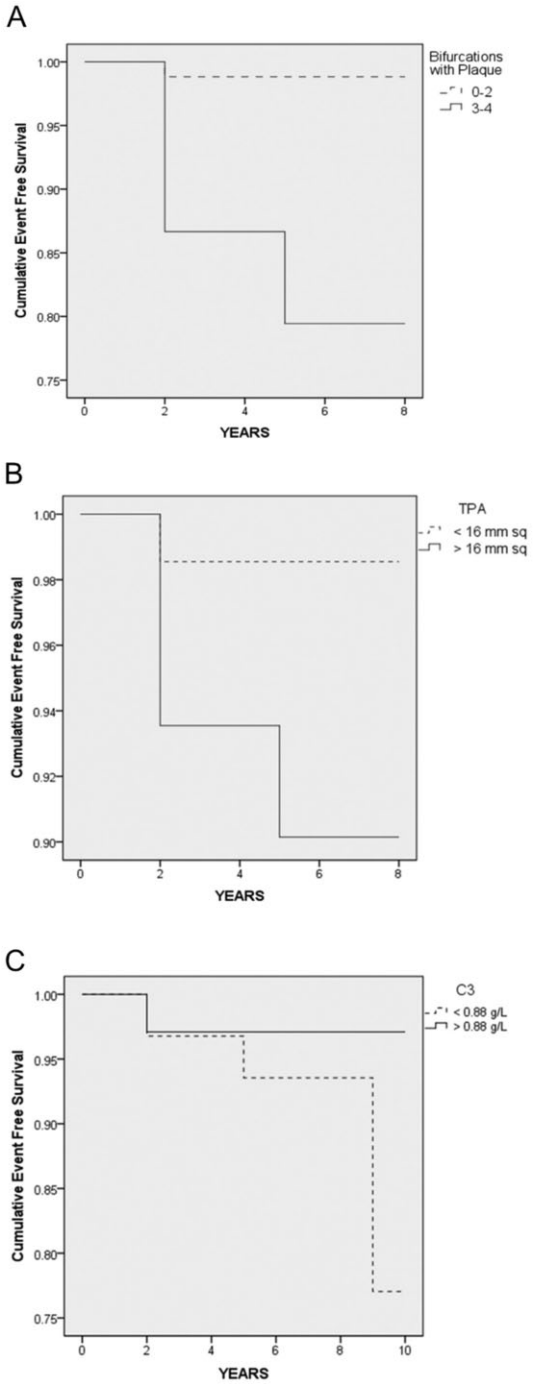
Table 4 Predictive values of number of bifurcations with plaque, TPA, disease duration at scan and C3 for future CVD events expressed as OR

Variable	Cut-off point	N	Events	*P* Fisher's exact test	OR (95% CI)
Bifurcations With Plaque 0-1 vs 2-4	0-1	73	3		
	2-4	27	4	0.083	4.06 (0.84, 19.4)
Bifurcations With Plaque 0-2 vs 3-4	0-2	85	3 (3.5%)		
	3-4	15	4 (26.7%)	0.009	9.94 (1.96, 50.4)
Total plaque area (TPA)	<16 mm^2	69	2 (2.9%)		
	>16 mm^2	31	5 (16.1%)	0.028	6.44 (1.17, 35.3)
Disease duration at scan <20 vs > 20 years	<20 years	69	2 (2.9%)		
	>20 years	31	5 (16.1%)	0.028	6.44 (1.17, 35.31)
Disease duration at scan <14 vs > 14 years	<14 years	55	1 (1.8%)		
	>14 years	45	6 (13.3%)	0.043	8.31 (1.00, 71.8)
C3	< 0.88 g/l	31	5 (16.1%)		6.44 (1.17,35.31)
	> 0.88 g/l	69	2 (2.9%)	0.032	

year risk 7.5% to 20%) and 72 were in the low-risk category (10-year risk < 7.5%). Four patients who actually developed an event were in the intermediate category and three in the low-risk category. None was in the QRISK3 high-risk category.

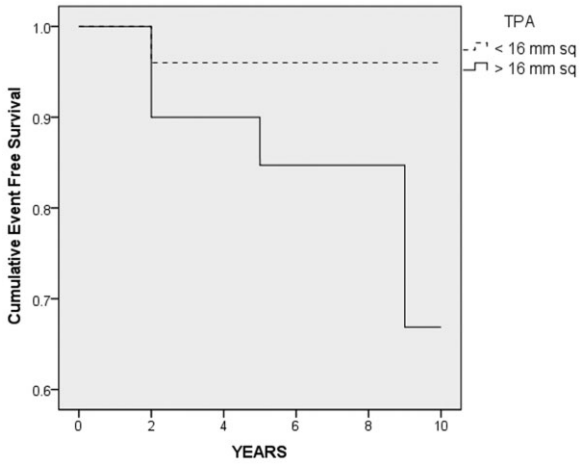
By ROC analysis the AUC for QRISK3 was 0.647 (95% CI 0.415, 0.879), which was considerably lower than the AUC for TPA - 0.759 (95% CI 0.536, 0.981). The *p*-value for the comparison of these AUC values was 0.0243.

FIG. 1 Effects of number of bifurcations with plaque, TPA and low C3 on CVD risk



A) Survival curve showing occurrence of CVD events during follow-up in patients with plaques at >3 bifurcations at baseline compared to those with plaques at 0-2 bifurcations.**B)** Survival curve showing occurrence of CVD events during follow-up in patients with TPA >16mm^2 at baseline compared to those with TPA<16mm^2.**C)** Survival curve showing occurrence of CVD events during follow-up in patients with C3<0.88g/l at baseline compared to those with C3>0.88g/l.

FIG. 2 Combined effect of TPA and disease duration on CVD risk



Survival curve showing occurrence of CVD events during follow-up in patients with disease duration >14 years and TPA >16mm^2 at baseline compared to those with disease duration > 14 years and TPA<16mm^2.

Discussion

Although it is recognized that patients with SLE have increased risk of CVD events, it has been very difficult to translate this knowledge into preventive strategies to reduce this risk [20]. Clinical trials of statins demonstrated no significant reduction of subclinical atherosclerosis in 200 patients assessed by coronary computed tomography [21] or in 221 patients with paediatric-onset SLE assessed by carotid ultrasound scanning [22]. It is possible that these trials were not long enough or did not reduce LDL sufficiently to have a detectable effect on atherosclerosis outcomes. The Lupus Atherosclerosis Prevention Study (LAPS) of Petri *et al.* had a two year follow-up period [21] whereas the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study included only patients with childhood-onset SLE and had a three year follow-up period [22].

Tselios *et al.* carried out a systematic review of studies identifying traditional, disease-associated and imaging factors associated with development of clinical CVD and subclinical atherosclerosis in patients with SLE [23]. After assessing 101 papers and identifying multiple associations, they provided a guide to CVD risk monitoring in patients with SLE that stressed regular assessment of traditional risk factors and disease activity and awareness of antiphospholipid-antibody positivity. Multiple imaging techniques were included in the review and only carotid ultrasound was found to be associated with increased risk of CVD. It was suggested that carotid scanning might be useful in patients with >1 traditional risk factor plus renal impairment [23].

It is important to identify serological or imaging biomarkers that predict which patients within a cohort with

SLE will develop CVD. Preventive measures might then be focussed on that subgroup. In a series of papers, McMahon and colleagues in California have studied pro-inflammatory high density lipoprotein (piHDL), leptin, and plasma soluble TNF-like weak inducer of apoptosis (sTWEAK) and combined them with diabetes to create a score called PREDICTS [20, 24–26]. They recently reported on CVD events in 401 patients with SLE and 197 control subjects followed for a mean of 120.4 months. In the SLE group there were 20 deaths, 18 new cardiac events, 40 new cerebrovascular events (including both strokes and transient ischaemic attacks) and 11 new peripheral arterial events [20]. High PREDICTS score at baseline was strongly associated with developing any of these outcomes (AUC 0.71, HR 3.7, $p < 0.0001$) or with cardiac events (HR 7.3, $P = 0.02$) or with cerebrovascular events (HR 4.0, $P = 0.001$) [20]. The cohort studied by this group underwent carotid ultrasound scanning and both IMT and plaque at baseline were associated with increased risk of CVD events [20]. The actual prevalence of plaque is lower in this group than in most other groups—16.3% *vs* 30–40% [26]. There are no reports that PREDICTS has been used outside the group that invented it, perhaps because the cell-free assay for piHDL is not widely available.

Few other groups have reported on longitudinal follow-up of CVD events in patients with SLE who underwent baseline vascular ultrasound scanning. Kao *et al.* followed 382 women with SLE for a mean of 8 years [5]. There were 35 incident hard CVD events (defined by the authors as confirmed new coronary or cerebrovascular events) in 17 patients and these patients were more likely to be older, have longer use of corticosteroids, increased total cholesterol and blood pressure. Both baseline plaque (HR 4.67, $P = 0.01$) and carotid IMT (HR 1.35 per 0.05 mm increment, $p < 0.01$) were associated with increased risk of hard CVD events [5].

Haque *et al.* described a follow-up study of 200 female British patients with SLE who had undergone baseline carotid ultrasound scans [27]. Only 124 patients, however, had follow-up data. Of these, they reported CVD events in 12 patients (including 7 coronary and 5 strokes) but this was on the basis of patient interview with no confirmation from medical records or imaging. Bearing in mind the caveat of missing data and unconfirmed CVD diagnoses, this group found no association between baseline IMT or plaque and CVD events but did find associations with use of cyclophosphamide ever, triglyceride level and damage score at baseline [27].

Ajeganova *et al.* reported on patients from the Swedish SLE Vascular Impact Cohort [28]. They compared data from 99 patients with SLE and 109 controls with similar age, sex and traditional risk factors. Five patients in the SLE group and only one control suffered new CVD events over a median follow-up of 10.1 years. The events in the SLE group were unusual in that all were cerebrovascular, three occurred in patients with antiphospholipid syndrome (APS) who were triple-positive for anti-cardiolipin, anti-beta-2-glycoprotein I and lupus anticoagulant and a fourth occurred in a patient who was double-positive for these antiphospholipid antibodies. Outcomes in this group may thus represent APS rather than lupus. Statistical analysis was in terms of risk of death or CVD events i.e. a composite adverse outcome, even though none of the seven deaths in the SLE group were cardiovascular. The authors concluded that increased IMT at baseline combined with history of APS and damage score was predictive of their composite adverse outcome (not CVD *per se*).

Frerix *et al.* compared 90 patients with systemic sclerosis (SSc) and 100 with SLE [7]. This paper was notable because, unlike most published work in the field of SLE, both the carotid and femoral bifurcations were scanned. Follow-up for CVD events was only available for 51 patients with SLE and there were 11 events in 8 patients (5 coronary, 3 cerebrovascular, 3 peripheral arterial). Analysis of the SSc and SLE groups together showed that the presence of both carotid and femoral plaque at baseline was a strong risk factor for subsequent CVD events (HR 6.55, $P = 0.003$), but presence of either carotid or femoral plaque alone was not (HR 1.32, $P = 0.731$). These authors therefore stressed the importance of scanning all four bifurcations, as we have done.

None of these groups measured TPA. In a paper from Toronto, Eder *et al.* scanned carotid arteries of 103 patients with SLE, of whom 27 had confirmed previous coronary artery disease (CAD) [12]. Both cIMT and TPA were significantly higher in patients with previous CAD but the relationship was much stronger for TPA.

Our study is unique in combining detailed follow-up data on 100 patients, scanning of both carotid and femoral bifurcations and measurement of TPA. Like Frerix *et al.* [7], we confirm the importance of scanning all four bifurcations, since there is a significant gain through being able to identify patients with plaque in more than two sites. We found no associations between traditional risk factors and subsequent CVD events whereas some other groups did find associations with age, lipid levels and hypertension [5, 20, 27, 28]. We also found no association with medications, though other authors have reported that corticosteroids may promote development of CVD in patients with SLE whereas antimalarials may be protective as described in the systematic review by Tselios *et al.* [23]. Those authors also suggested an association of higher disease activity with CVD and we did not find this association. Low C3 levels can be a marker of disease activity but it seems unlikely that the association we found between C3 < 0.88 g/l and CVD events reflects disease activity because this level lies almost within the normal range for our clinical laboratory. It is possible that complement might exert a direct effect on atherogenesis, separate from any link to lupus activity. Relationships between complement and atherosclerosis, however, are complex and may be either protective or pro-atherogenic (reviewed in [29]). Considering C3 specifically, C3-deficient mice fed a pro-atherogenic diet developed increased atherogenesis [30, 31] but in

human studies elevated C3 was associated with increased risk of coronary disease [32]. We therefore place no emphasis on the apparent relationship with C3.

Limitations of our study include the relatively small numbers of patients and CVD events, and that we did not collect baseline data on body mass index and cumulative corticosteroid dose. There were only two diabetics in the study so effects of this traditional risk factor could have been missed. Furthermore, this is a study in a single clinic population and may not be generalizable. It will be important to repeat similar work in other populations.

The very strong predictive value of TPA and number of bifurcations with plaque, however, leads us to suggest that vascular ultrasound scanning may have a place in assessing CVD risk in patients with SLE. Tselios *et al.* suggested that these scans could be done in patients with previous nephritis and/or $>$ 1 traditional risk factor [23]. Given our findings, we suggest that disease duration should be a third criterion for scanning such that patients with disease duration $>$ 14 years should be offered a scan of both carotid and both femoral bifurcations with measurement of TPA. Such patients with plaque at $>$2 bifurcations and/or TPA $>$ 16 mm^2 are at high risk and could be referred for cardiac assessment which may include ECG stress tests and/or imaging to uncover subclinical coronary disease. Based on the findings they could also be considered for prophylactic therapy to reduce BP and LDL to targets that have been shown to be effective in reducing future cardiovascular events in asymptomatic high risk non-SLE individuals [9].

Furthermore, an intriguing idea is that changes in TPA could be monitored to assess success of measures to control cardiovascular risk factors. In Argentina, Perez *et al.* have recently reported on a population of 1317 patients with high cardiovascular risk who entered a programme designed to optimize control of hypertension, diabetes and dyslipidaemia. Carotid TPA fell in 35% but rose in 51% [33].

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Author contributions: SCC and AR designed the original scanning study. SCC recruited the subjects. JB carried out follow-up analysis of patients followed till 2020. JB, SCC, AR, FF and DAI collected and analysed clinical, demographic and disease activity data. SCC and MG carried out the scanning. MG and AN analysed the scan results and carried out statistical analysis. FF carried out statistical analysis. AR wrote the final manuscript. All authors contributed to manuscript preparation and approved the final manuscript.

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Data availability statement

Data are available on request to the authors.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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If a patient develops herpes zoster, filgotinib treatment should be temporarily interrupted until the episode resolves. Screening for viral hepatitis and monitoring for reactivation should be performed. Malignancy: Immunomodulatory medicinal products may increase the risk of malignancies. Malignancies were observed in clinical studies (see SmPC). Fertility: In animal studies, decreased fertility, impaired spermatogenesis, and histopathological effects on male reproductive organs were observed (see SmPC). The potential effect of filgotinib on sperm production and male fertility in humans is currently unknown. Haematological abnormalities: Do not start therapy, or temporarily stop, if Absolute Neutrophil Count (ANC) <1 × 10^9 cells/L, ALC <0.5 × 10^9 cells/L or haemoglobin <8 g/dL. Temporarily stop therapy if these values are observed during routine patient management. Vaccinations: Use of live vaccines during, or immediately prior to, filgotinib treatment is not recommended. 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Lactose content: Contains lactose; patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take filgotinib. **Pregnancy/Lactation:** Filgotinib is contraindicated in pregnancy. Filgotinib should not be used during breast-feeding. Women of childbearing potential must use effective contraception during and for at least 1 week after cessation of treatment. **Driving/Using machinery:** No or negligible influence, however dizziness has been reported. **Side effects:** See SmPC for full information. Common (≥1/100 to <1/10): nausea, upper respiratory tract infection, urinary tract infection and dizziness. Uncommon (≥1/1000 to <1/100): herpes zoster, pneumonia, neutropenia, hypercholesterolaemia and blood creatine phosphokinase increase. 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