

# Coronary, Carotid, and Lower-extremity Atherosclerosis and Their Interrelationship in Danish Patients with Systemic Lupus Erythematosus

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**ABSTRACT.** *Objective.* Atherosclerosis is highly prevalent among patients with systemic lupus erythematosus (SLE), but has been demonstrated predominantly in non-European SLE cohorts and few investigations have included more than 1 imaging modality. We aimed to investigate the prevalence of atherosclerosis in 3 frequently affected vascular territories, the coronary, carotid, and lower-extremity arteries, in a Danish, predominantly population-based SLE cohort.

*Methods.* Patients with SLE without prior cardiovascular disease (CVD; n = 103) were screened for coronary artery calcification, carotid intima-media thickening and plaque, and abnormal ankle-brachial index by means of cardiac computed tomography, ultrasound of the carotid arteries, and ankle systolic blood pressure.

*Results.* In patients with SLE, the prevalence of atherosclerosis in any vascular territory was 41%. The distribution of the atherosclerotic manifestations showed an overlap with 45% of the patients having involvement in more than 1 vascular territory. However, more than one-third of the patients with SLE with coronary, carotid, or lower-extremity atherosclerosis exclusively demonstrated this particular manifestation. Based on a multiple logistic regression model, age ( $p < 0.001$ ), current smoking ( $p = 0.009$ ), and the Systemic Lupus International Collaborating Clinics (SLICC;  $p = 0.008$ ) were significant independent risk factors for atherosclerosis at any vascular territory.

*Conclusion.* Atherosclerosis is highly prevalent among Danish patients with SLE without prior CVD. Screening for atherosclerosis in 1 vascular territory is insufficient in diagnosing atherosclerosis in patients with SLE. In Danish patients with SLE, the presence of atherosclerosis was not only assigned to traditional CV risk factors, but also associated with SLICC. (First Release December 1 2015; J Rheumatol 2016;43:315–22; doi:10.3899/jrheum.150488)

## Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS  
CORONARY ARTERY CALCIUM  
CAROTID PLAQUE

ATHEROSCLEROSIS  
CAROTID INTIMA-MEDIA THICKNESS  
ANKLE BRACHIAL INDEX

A bimodal mortality pattern in systemic lupus erythematosus (SLE) has been described with a first peak within the first year after diagnosis, mostly attributable to active disease and infection, and a second peak occurring later, mainly attributable to cardiovascular disease (CVD)<sup>1</sup>. The survival in SLE has improved significantly over the last 50 years; however, CVD has remained a major cause of morbidity and mortality in patients with SLE<sup>2,3,4,5</sup>.

Compared with the general population, patients with SLE

have an up to 9-fold greater risk of CVD, with the risk being particularly marked in women younger than 55 years of age<sup>6,7,8</sup>.

Accelerated atherosclerosis is thought to be involved in the excess CVD burden in SLE.

Coronary artery calcification (CAC) and carotid plaque are closely associated with atherosclerosis and serve as surrogate markers of coronary and carotid atherosclerosis. CAC and carotid plaque have been found to be predictive for future CV events in the general population<sup>9,10,11</sup>. Abnormal ankle-brachial index (ABI) is associated with atherosclerosis in the lower-extremity arteries and correlates with increased mortality in the general population<sup>12</sup>.

In patients with SLE without prior CVD, CAC has been found to be more frequent compared with healthy controls (30.7% vs 8.7%) and was identified at a younger age in the patients with SLE<sup>13</sup>. In another study of CAC in young, asymptomatic patients with SLE (20–48 yrs), 28% had signs of coronary atherosclerosis<sup>14</sup>.

Roman, *et al* found increased rates of carotid plaque (37.1% vs 15.2%) in patients with SLE compared with

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controls<sup>15</sup>. Similarly, a prevalence of carotid plaque of 40% was found in a study by Manzi, *et al*<sup>16</sup>.

The increased prevalence of atherosclerosis in patients with SLE has been demonstrated predominantly in non-European SLE cohorts and few investigations include more than 1 imaging modality.

In our study, we aimed to investigate the prevalence of atherosclerosis by investigation of CAC, carotid intima-media thickening and plaque, and abnormal ABI in a Danish, predominantly population-based SLE cohort. Further, we examined the interrelationship between these observed atherosclerotic manifestations and identified risk factors contributing to these manifestations.

## MATERIALS AND METHODS

**Study population.** In this cross-sectional study, we investigated a predominantly population-based SLE cohort. Patients were adults (age > 18) recruited from a longterm, prospective SLE cohort that includes a population-based cohort from the County of Funen, Southern Denmark<sup>17</sup>, and a clinic-based cohort from the rest of Southern Denmark. All patients were diagnosed according to Fries and Holman<sup>18</sup> and classified according to the revised 1997 American College of Rheumatology (ACR) criteria<sup>19</sup>.

Patients with a history of CVD (including myocardial infarction, arterial revascularization, stroke, or symptomatic lower-extremity disease) were excluded from our study. Pregnant patients were also excluded.

All patients underwent a structured study program, including extended interview, clinical examination, blood sampling, cardiac computed tomography (CT), ultrasound (US) of the carotid arteries, and ankle systolic blood pressure measurements.

Our study was carried out according to Good Clinical Practice, followed the Helsinki II Declaration, and was approved by the Local Ethics Committee (project-ID: S-20110111). Written informed consent was obtained from each participant.

**Clinical assessments.** Anthropometric measurements (height, weight, and waist and hip circumference) of all subjects were obtained. Blood pressure was measured after a resting period of 20 min. Hypertension (HTN) was defined as either a resting systolic or diastolic blood pressure > 140/90 or treatment with antihypertensive medication. Diabetes mellitus was defined as glycosylated hemoglobin  $\geq$  48 mmol/mol or the use of antidiabetic agent. Hypercholesterolemia was defined as a total cholesterol  $\geq$  5.0 mmol/l, low-density lipoprotein  $\geq$  3.0 mmol/l, or receiving lipid-lowering medication. Nephropathy was defined as s-creatinine > 120  $\mu$ mol/l. Smoking status was recorded as either past or current smoker. Using the Systematic Coronary Risk Evaluation (SCORE) based on age, sex, smoking status, systolic blood pressure, and total cholesterol<sup>20</sup>, the total CV mortality risk within 10 years was estimated. Individuals were classified into 4 categories: low risk (< 1%), moderate risk ( $\geq$  1% to < 5%), high risk ( $\geq$  5% to < 10%), and very high risk ( $\geq$  10%). Information was also collected on family history of CVD defined as a first-degree relative having myocardial infarction or stroke before the age of 55 years in men and 65 years in women.

SLE-related risk factors including disease duration and cumulative clinical manifestations of SLE were obtained<sup>19</sup>. SLE disease activity and cumulative organ damage were measured using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)<sup>21</sup> and the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC)<sup>22</sup>. Information was provided on past and current use of corticosteroid, hydroxychloroquine, and immunosuppressants including cyclophosphamide, azathioprine, methotrexate, and mycophenolate mofetil. Also, past and current uses of antiaggregants and anticoagulants were recorded. Laboratory analyses consisted of tests for antinuclear antibodies (ANA), anti-dsDNA antibodies, and serum complement C3 and C4 levels. ANA were determined

by indirect immunofluorescence on Hep-2 cell monolayers. Anti-dsDNA was measured by ELISA.

The presence of antiphospholipid antibodies (aPL) was obtained. Demonstration of lupus anticoagulant,  $\beta$ 2-glycoprotein 1 antibodies, and/or cardiolipin antibodies in 2 consecutive measurements after SLE diagnosis was considered positive for aPL. Patients positive for aPL and with a history of venous thrombosis and/or pregnancy morbidity were considered as having aPL syndrome (APS).

**CAC measurement.** CAC was assessed using a GE 64-slice CT scanner (Discovery VCT; GE Healthcare) with the following technical settings: gantry rotation time 500 ms,  $16 \times 2.5$  mm collimation, 120 kV tube voltage, 200 mA tube current, and a prospectively echocardiogram-triggered scan acquisition gating at 50% of the R-R interval. The scan data were acquired during an inspiratory breath hold. CAC was quantified using dedicated software, Smartscore (GE Healthcare), and was expressed as Agatston score calculated by summing scores from each focus in the coronary arteries and classified as none (Agatston 0 U), mild (Agatston 1–99 U), moderate (Agatston 100–399 U), and high CAC (Agatston  $\geq$  400 U)<sup>23</sup>. Coronary atherosclerosis in this investigation was defined as Agatston > 99 U.

All analyses of CT scans were performed by 1 experienced examiner.

**Carotid atherosclerosis.** B-mode US scans were performed to image the carotid arteries using a LOGIQ E9, GE Healthcare US machine with an 11-MHz linear transducer. Each image contained 2 cine loops and was stored digitally for later blinded analysis. Carotid intima-media thickness (IMT) was measured between the lumen-intima and media-adventitia interfaces in the far wall of 2 segments of the carotid artery (common carotid artery and carotid bifurcation) on both sides. The analysis of IMT was performed semiautomatically as a mean of minimum 200 measurements per location site. IMT was measured using 2 separate images at end-diastole in each segment (1 cm proximally to the bifurcation and in the bulb). Each image was also investigated for plaques using the definition from the Atherosclerosis Risk in Communities study<sup>24</sup>. Epidemiological data on B-mode US scan of the carotid arteries have shown that IMT > 1.00 mm is associated with a significantly increased CV risk<sup>25,26,27</sup>. Therefore, carotid atherosclerosis was defined as mean IMT > 1.00 mm and/or the presence of a carotid plaque at any carotid location. All the US scans were performed by 1 experienced examiner.

**Lower-extremity atherosclerosis.** Systolic blood pressure was measured in both arms. Subsequently, the systolic blood pressure was measured twice in the dorsalis pedis and posterior tibial arteries bilaterally using a hand-held Doppler probe. The highest value of the arm pressures and the highest value of the ankle pressures were used to calculate the ABI. Patients were classified as having peripheral arterial disease (PAD) if ABI  $\leq$  0.90<sup>28</sup> and poorly compressible arteries (PCA) if ABI  $\geq$  1.4<sup>29</sup>. Lower-extremity atherosclerosis was defined as PAD or PCA. All the measurements were performed by 1 experienced examiner.

Atherosclerosis was defined as the presence of coronary atherosclerosis, carotid atherosclerosis, or lower-extremity atherosclerosis.

**Statistical analysis.** Continuous variables are presented as mean ( $\pm$  SD) or median (range), and categorical variables are given as frequencies and percentages. The Student t test (Gaussian distributed data) and the Wilcoxon rank-sum test (non-Gaussian distributed data) were used to test for differences between independent continuous variables, and the chi-square test was used to test for differences between categorical variables.

To define potential explanatory variables of atherosclerosis, univariate logistic regression was applied on demographic and clinical variables. To prevent Type 2 errors, a p value < 0.2 was required to be included in a multivariate logistic regression model, in which stepwise subset selection was applied for adjustment. A p value < 0.05 was considered to be statistically significant. The analysis was performed using STATA 13.1.

## RESULTS

**Study population.** A total of 126 patients with SLE were

invited to our study, 92 patients from the population-based cohort and 34 patients from the clinic-based cohort. The 2 cohorts were alike based on demographic and SLE-related characteristics (data not shown). Of the 126 patients with SLE initially included, 21 had a history of CVD at the time of enrollment. Because of inadequate data, 2 patients were excluded, resulting in a study population of 103 patients.

The study population included 89% women and 98% were white. Mean age was  $49.2 \pm 14.1$  years and mean disease duration was  $11.1 \pm 8.5$  years. Cumulative SLE clinical manifestations included skin rash (malar/discoid; 57%), photosensitivity (63%), ulcers (26%), arthritis (88%), serositis (46%), renal disorder (24%), neurologic disorder (13%), hematologic disorder (55%), anti-dsDNA positivity (90%), and ANA positivity (100%).

The characteristics of the study population are detailed in Table 1.

**Prevalence and distribution of atherosclerosis.** Overall, 44 patients (42.7%) had signs of CAC (Agatston  $> 0$  U) with scores ranging from 1 U to 9725 U. Mild CAC was found in 19 patients (18.4%), moderate CAC in 10 patients (9.7%), and high CAC in 15 patients (14.6%). CAC  $> 99$  U was found in 25 patients (24.7%). The mean carotid IMT was  $0.71 \pm 0.27$  mm. Carotid atherosclerosis was found in 27 patients (26.2%), with the presence of plaques at any location in 16 patients (15.5%). Lower-extremity atherosclerosis was found in 12 patients (11.6%) distributed with PAD in 5 patients and PCA in 7 patients.

Atherosclerosis, as defined above, was found in 42 patients (41%).

According to the total CV mortality risk measured by SCORE, there were more patients with a low risk among patients without atherosclerosis; however, 36% of the patients with atherosclerosis achieved a low risk. There were more patients with a high or a very high risk among patients with atherosclerosis than among those without.

Figure 1 shows the prevalence of atherosclerosis stratified by age category ( $< 35$ , 35–44, 45–54, 55–64, and  $> 64$  yrs). In the age groups  $< 35$  years and 35–44 years, 13.3% and 20.0% of the patients with SLE had atherosclerosis, respectively. Throughout the age groups, the prevalence of atherosclerosis increased, with a very large increase between the age groups 45–54 years and 55–64 years.

The distribution of the atherosclerotic involvement in the 3 vascular beds is shown in Figure 2.

If examination for atherosclerosis only included cardiac CT, 11 of 27 patients with carotid atherosclerosis and 8 of 12 patients with lower-extremity atherosclerosis would not have been identified. If only carotid US had been performed, atherosclerotic manifestations in 9 of 25 patients with coronary atherosclerosis and 7 of 12 patients with lower-extremity atherosclerosis had remained unidentified. Correspondingly, investigation exclusively with systolic ankle blood pressure measurements would leave more than 80% of the patients

with coronary atherosclerosis and carotid atherosclerosis without a proper diagnosis of atherosclerosis.

**Comparison of patients with and without atherosclerosis in univariate analysis.** In univariate analysis, the presence of atherosclerosis was significantly associated with age ( $p < 0.001$ ), male sex ( $p = 0.006$ ), waist circumference ( $p = 0.020$ ), hypercholesterolemia ( $p = 0.001$ ), current smoking ( $p = 0.029$ ), and SLICC ( $p = 0.005$ ).

HTN had a borderline association to atherosclerosis ( $p = 0.067$ ); nevertheless, patients with atherosclerosis demonstrated a significantly higher systolic blood pressure ( $p = 0.015$ ).

The presence of aPL was more common in patients without atherosclerosis, but not significantly. When the components of aPL status were examined individually, lupus anticoagulant was significantly less common in patients with atherosclerosis ( $p = 0.008$ ).

There were no differences in the presence of APS between patients with and without atherosclerosis.

All variables that in the univariate analysis demonstrated a  $p$  value  $< 0.2$  were included in the multivariate analysis. This included age, sex, current smoking, waist circumference, diabetes, cumulative renal disorder, aPL, cumulative use of hydroxychloroquine, SLICC, hypercholesterolemia, triglycerides, complement C3, and HTN.

In the multiple logistic regression model, age ( $p < 0.001$ ), SLICC ( $p = 0.008$ ), and current smoking ( $p = 0.009$ ) remained statistically significant independent risk factors for atherosclerosis. The presence of aPL was in the multiple logistic regression model negatively associated to atherosclerosis ( $p = 0.011$ ; Table 2).

## DISCUSSION

Several previous studies of atherosclerosis in patients with SLE have been performed, but only a few are population-based and of European origin, and more than 1 imaging modality is rarely used.

This cross-sectional study demonstrated signs of atherosclerosis in 1 or more territories among more than 40% of Danish patients with SLE. However, the overlap between the atherosclerotic manifestations detectable in the vascular territories was not sufficient to examine just 1 single vascular territory in diagnosing atherosclerosis.

In an American multiethnic cohort, consisting of predominantly women and with a mean age of 44 years, the prevalence of CAC was 43% and a CAC  $> 100$  U was found in 9%<sup>30</sup>. These results correspond to our results to a certain extent. However, we found a much higher prevalence of CAC  $> 100$  U, indicating more patients with a greater extent of coronary atherosclerosis. In the same study, carotid plaque was found in 18% of the patients with SLE, which corresponds to our results<sup>30</sup>.

In a study of a mixed African American and white SLE cohort, CAC was found in 42% and carotid plaque in 30%

Table 1. Comparison of patients with SLE with and without atherosclerosis. Values are mean ± SD, median (range), or n (%) unless otherwise specified.

Characteristics	Total, n = 103	Atherosclerosis, n = 42	Non-atherosclerosis, n = 61	p
Age, yrs	49.2 ± 14.1	57.3 ± 13.3	43.7 ± 11.9	< 0.0001
Females	92 (89)	32 (76)	60 (98)	< 0.0001
White	101 (98)	42 (100)	59 (97)	0.51
BMI, kg/m <sup>2</sup>	25.2 ± 5.5	25.5 ± 5.9	25.0 ± 5.1	0.69
Waist circumference, cm	85.7 ± 14.3	89.7 ± 16.1	82.8 ± 12.4	0.02
Systolic blood pressure, mmHg	120.9 ± 17.9	126.3 ± 19.4	117.3 ± 15.9	0.01
Diastolic blood pressure, mmHg	74.7 ± 8.3	75.8 ± 8.0	73.9 ± 8.5	0.24
Hypertension	60 (58)	29 (69)	31 (51)	0.07
Total cholesterol, mmol/l	4.8 ± 1.0	4.9 ± 1.1	4.8 ± 0.9	0.30
LDL cholesterol, mmol/l	2.8 ± 0.8	2.9 ± 0.8	2.7 ± 0.7	0.32
HDL cholesterol, mmol/l	1.5 ± 0.4	1.4 ± 0.4	1.5 ± 0.4	0.70
Triglycerides, mmol/l	1.3 ± 0.6	1.4 ± 0.5	1.2 ± 0.7	0.12
Lipid-lowering agents	13 (13)	10 (24)	3 (5)	0.01
Hypercholesterolemia	53 (51)	30 (71)	23 (38)	0.001
HbA1c	37.2 ± 7.8	38.7 ± 8.5	36.1 ± 7.2	0.03
Diabetes	9 (9)	6 (14)	3 (5)	0.15
Nephropathy	3 (3)	2 (5)	1 (2)	0.57
Former smoker	41 (40)	14 (33)	27 (44)	0.30
Current smoker	23 (22)	14 (33)	9 (15)	0.03
Family history of CVD	26 (25)	11 (26)	15 (25)	1.00
SCORE				
< 1%	65 (63)	15 (36)	50 (82)	< 0.0001
> 1% to < 5%	20 (19)	12 (29)	8 (15)	0.08
≥ 5% to ≤ 10%	8 (8)	6 (14)	2 (3)	0.06
≥ 10%	10 (10)	9 (21)	1 (2)	0.001
SLE duration, yrs	11.1 ± 8.5	12.0 ± 9.6	10.5 ± 7.6	0.61
SLICC	1 (0–9)	2 (0–9)	1 (0–8)	0.002
SLEDAI	4 (0–14)	4 (0–14)	3 (0–8)	0.44
Anti-dsDNA	39 (38)	17 (40)	22 (36)	0.53
hsCRP, mg/l	4.3 ± 6.9	4.1 ± 6.7	4.4 ± 7.1	0.51
ESR	15.3 ± 12.6	15.9 ± 11.9	14.8 ± 13.1	0.45
Complement C3	0.9 ± 0.3	1.0 ± 0.3	0.9 ± 0.3	0.18
Complement C4	0.2 ± 0.7	0.2 ± 0.1	0.2 ± 0.1	0.65
aPL	51 (49)	17 (40)	34 (56)	0.16
Lupus anticoagulant	22 (21)	3 (7)	19 (31)	0.006
aCL	34 (33)	11 (26)	23 (38)	0.29
Anti-β2-glycoprotein	37 (36)	11 (26)	26 (43)	0.14
APS	21 (20)	9 (21)	12 (20)	1.00
Treatment				
Prednisone use ever	90 (87)	35 (83)	55 (90)	0.37
Prednisone use currently	45 (44)	21 (50)	24 (39)	0.32
Hydroxychloroquine use ever	92 (89)	35 (83)	57 (93)	0.12
Hydroxychloroquine use currently	64 (62)	24 (57)	40 (66)	0.41
Immunosuppressive use ever	72 (70)	29 (69)	43 (71)	1.00
Immunosuppressive use currently	38 (37)	15 (36)	23 (38)	1.00
Antiaggregant use ever	34 (33)	15 (36)	19 (31)	0.67
Antiaggregant use currently	27 (26)	13 (31)	14 (23)	0.37
Anticoagulant use ever	21 (20)	8 (19)	13 (21)	0.81
Anticoagulant use currently	15 (15)	6 (15)	9 (15)	1.00

SLE: systemic lupus erythematosus; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CVD: cardiovascular disease; SCORE: Systematic Coronary Risk Evaluation; SLICC: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; hsCRP: high-sensitivity C-reactive protein; ESR: erythrocyte sedimentation rate; aPL: antiphospholipid antibodies; aCL: anticardiolipin antibodies; APS: aPL syndrome; HbA1c: glycosylated hemoglobin.

of the patients<sup>31</sup>. The prevalence of CAC was in accordance with our findings, while the prevalence of carotid plaque was higher than ours. This may be because of the use of a different plaque definition, which includes a distinct area protruding

into the vessel lumen that is at least 50% thicker than the surrounding areas. However, ethnic differences could also be of importance because significantly more African American patients were diagnosed with plaque.



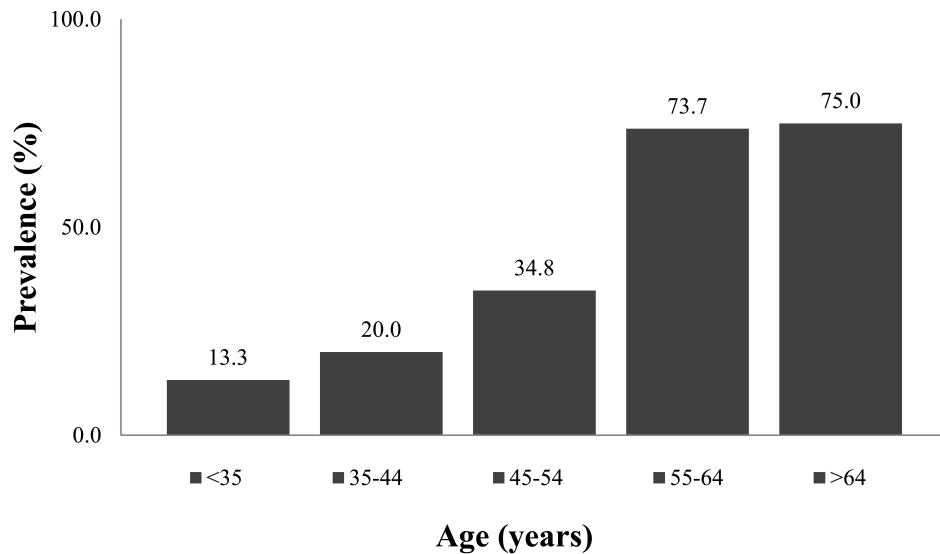


Figure 1. Prevalence of atherosclerosis stratified by age category.

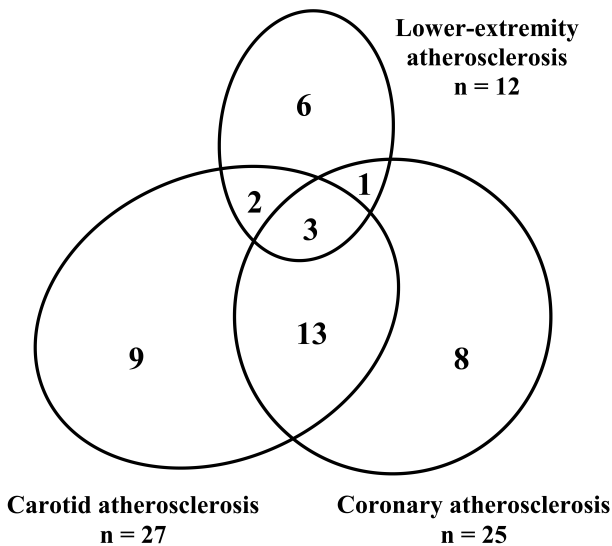


Figure 2. The distribution of the atherosclerotic involvement in the three vascular beds.

Although atherosclerosis has been found to have an early onset in patients with SLE compared with the general population, age remains a risk factor for atherosclerosis in patients with SLE<sup>32</sup>. In our study, we also observed an early onset of atherosclerosis and a substantial increment in the prevalence of atherosclerosis when the patients with SLE reached an age of 55 years. This pattern is in accordance with the trend in the general Danish population, where atherosclerosis has been found to have an onset around middle age<sup>33</sup>. The combination of SLE and age-related risk may

Table 2. Independent explanatory factors for the presence of atherosclerosis in a multivariate analysis.

Risk Factor	OR	95% CI	p
Age, yrs	1.09	1.04–1.14	< 0.001
SLICC	1.71	1.15–2.54	0.008
Current smoking	5.89	1.55–22.42	0.009
Antiphospholipid antibodies	0.19	0.05–0.68	0.011
Cumulative renal disorder	2.83	0.79–10.05	0.107
Male	8.38	0.62–112.72	0.109
Waist circumference, cm	1.03	0.99–1.07	0.158

SLICC: Systemic Lupus International Collaborating Clinics.

explain the very high prevalence of atherosclerosis among middle-aged patients with SLE.

Autopsy studies in the general population have demonstrated a close relationship between the presences of atherosclerosis in the 3 vascular territories where atherosclerosis often is encountered: the coronary, carotid, and lower-extremity arteries<sup>34,35</sup>. In accordance with this, we found an overlap between coronary atherosclerosis, carotid atherosclerosis, and lower-extremity atherosclerosis (Figure 2). However, the relationship between atherosclerosis in the vascular territories did not allow us to examine just 1 single vascular territory, because 33% of the patients with carotid atherosclerosis and 32% with coronary atherosclerosis exclusively had this single atherosclerotic manifestation.

The study population was comparable to other cohorts concerning SLE manifestations, even if renal disorder was relatively infrequent (24%). In the total population of 126 patients with SLE, the prevalence of renal disorder was 29%, which fairly corresponds with previous enumerations in the

cohort<sup>36</sup>. However, a small number of patients with SLE from the population-based cohort may not have participated in the study.

Traditional CV risk factors fail to fully account for the accelerated atherosclerotic process<sup>37</sup>. However, it has been shown that the high risk of CVD in patients with SLE appears to be mediated by the increase in traditional risk factors and that this increase in risk factors diverges from controls<sup>38</sup>. It has been speculated that patients with SLE may be more sensitive to the effects of traditional risk factors for atherosclerosis than the general population, resulting in an excess risk of atherosclerosis<sup>39</sup>.

In our present study, we found that patients with atherosclerosis had a higher prevalence of hypercholesterolemia compared with those without. Nevertheless, hypercholesterolemia showed not to be significantly associated to atherosclerosis in the multiple regression model.

Although HTN is not an independent risk factor for atherosclerosis in our study, we found that patients with atherosclerosis had a significantly higher mean systolic blood pressure than patients without. A recent review on treatment of HTN in patients with SLE concluded that current HTN therapeutic guidelines may not adequately apply to patients with SLE, and large-scale clinical trials are needed to confirm their value in reducing CVD risk in SLE<sup>40</sup>.

It has been indicated that chronic inflammation and autoimmunity are involved in the pathogenesis of atherosclerosis<sup>41</sup>, corresponding to the demonstration of increased SLEDAI associated with an increased risk of CVD of 5%<sup>42</sup>. The increase in time-adjusted mean SLEDAI, which is cumulative disease activity, has also been found to correlate with increased risk of CVD<sup>43</sup>. In our study, we did not find any association between inflammatory markers, high-sensitivity C-reactive protein, erythrocyte sedimentation rate, and SLEDAI and the presence of atherosclerosis. However, in our study design, we provide only a cross-sectional measure of inflammation.

Although aPL have been described to be implicated in atherogenesis, our study, as well as other investigations, found no positive association between aPL and atherosclerosis<sup>15</sup>. In our study, we found a significantly negative association between aPL and atherosclerosis. Interestingly, this association was absent in the patients whose clinical manifestation to aPL was venous thrombosis and/or pregnancy morbidity.

Cumulated organ damage measured as SLICC was significantly associated with atherosclerosis, in our multivariate model. This trend has been demonstrated by others as well<sup>16</sup>. SLICC has been found to be associated with disease activity and medical treatment including corticosteroids<sup>44</sup> and therefore in our study, the cumulative disease activity is probably best measured by SLICC.

An association between SLICC and atherosclerosis may indicate that disease activity is involved in the accelerated atherogenesis of patients with SLE.

High and very high SCORE were significantly more frequent in patients with atherosclerosis, but SCORE fails to identify 36% of patients with SLE with atherosclerosis. Similar results were found in asymptomatic middle-aged Danes in which 37% of those with CAC had low SCORE<sup>45</sup>. The SCORE is based on age, sex, smoking status, blood pressure, and cholesterol level. All these factors were risk factors for atherosclerosis in our study. Nevertheless, the SD for age among the patients with atherosclerosis is wide and therefore some young patients with SLE tend to have low SCORE. Additionally, a recent study on the general population in Asia showed that the SCORE fails to identify atherosclerosis in women<sup>46</sup>.

One of the limitations of our study is the cross-sectional design, which means that selection and temporal biases may have occurred. Especially in terms of variables related to disease activity and inflammation, the cross-sectional design limits the investigation of the effect of cumulative disease activity and inflammation on atherosclerosis. Likewise, the use of dichotomized medications may be insensitive during calculation, but variables of cumulated doses were unfortunately not available.

An additional limitation is the inclusion of a relatively small study population. Also, a small number of patients with SLE from the population-based cohort may not have participated in our study, perhaps leading to selection biases.

Atherosclerosis is highly prevalent but differently distributed in 3 vascular beds among Danish patients with SLE without prior CVD. Our results indicate that screening for atherosclerosis in 1 vascular territory is insufficient and that patients with SLE with an increased risk of CVD would not be identified using SCORE. Traditional CV risk factors are important, but not alone responsible for the accelerated development of atherosclerosis in SLE. Patients with a high SLICC are at greater risk of having atherosclerosis.

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