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# Risk Factors in the Progression of Subclinical Atherosclerosis in Women with Systemic Lupus Erythematosus

**Apinya Lertratanakul, MD**[1], **Peggy Wu, MD**[1], **Alan R. Dyer, PhD**[1], **George Kondos, MD**[2], **Daniel Edmundowicz, MD**[3], **James Carr, MD**[1], and **Rosalind Ramsey-Goldman, MD, DrPH**[1]

[1]Northwestern University Feinberg School of Medicine, Chicago, IL

[2]University of Illinois Chicago School of Medicine, Chicago, IL

[3]Temple University School of Medicine, Philadelphia, PA

## Abstract

**Objectives—**To investigate risk factors in the subclinical atherosclerosis progression as measured by coronary artery calcium (CAC) and aorta calcium (AC) in women with Systemic Lupus Erythematosus (SLE) (cases) and in comparison with a control population.

**Methods—**A cohort of 149 cases and 124 controls participated in the Study of Lupus Vascular and Bone Long-term Endpoints (SOLVABLE). Demographic information, cardiovascular and SLE risk factors, and laboratory assessments were collected at an initial visit. CAC and AC were measured by electron beam computed tomography (CT) or multi-detector CT at an initial and a follow-up visit. Logistic regression models were used to identify predictors of progression in CAC and AC; multivariate models were adjusted for age, hypertension, and total cholesterol/HDL ratio.

**Results—**Higher modified ACR/SLICC-DI (OR 2.15, 95%CI 1.33–3.57), use of a corticosteroid (OR 2.93, 95%CI 1.14–7.86), and use of aspirin (OR 4.23, 95%CI 1.53–11.74) were associated with CAC progression in multivariate models. Presence of SLE (OR 2.64, 95%CI 1.26–5.72), lower C3 (OR 0.54, 95%CI 0.33–0.87), lower C4 (OR 0.49, 95% CI 0.27–0.86), use of a corticosteroid (OR 2.73, 95%CI 1.03–7.64), higher corticosteroid dose (OR 1.77, 95%CI 1.12–3.00), higher lipoprotein(a) (OR 1.80, 95%CI 1.11–2.98), higher homocysteine (OR 2.06, 95%CI 1.06–4.29) were associated with AC progression in multivariate models.

**Conclusions—**Higher disease damage at the first study visit, as measured by the modified ACR/SLICC-DI, may predict increased risk in CAC progression, whereas higher disease activity at the first study visit, as measured by hypocomplementemia and use of corticosteroids, may predict increased risk in AC progression.

Patients with SLE have an increased risk of cardiovascular disease at a much earlier age than the general population[1]. SLE itself has been shown to be an independent risk factor in the progression of atherosclerosis[2]. The associated morbidity and mortality of cardiovascular disease has prompted the study of subclinical atherosclerosis in the SLE population, as measured with imaging studies such as carotid ultrasound and electron beam computed

Address for Correspondence: 240 E. Huron Street, Suite M-300, Chicago, IL 60611, Fax (312) 503-0994, Phone (312) 503-8003, apinya.lert@gmail.com.

tomography (CT) scans[3]. Higher aorta calcium scores (AC) and coronary artery calcification (CAC) have been shown to be more prevalent in SLE patients when compared with age- and sex-matched controls[4]. CAC has also been shown to occur at a younger age in the SLE population[4,5] when compared with controls.

Similarly, SLE patients appear to have an accelerated rate of atherosclerosis progression when compared with the general population, however the mechanisms or manner underlying this is not clear. Older age and longer disease duration were associated with carotid plaque progression in an early study[6], and in another, after controlling for age, traditional factors including higher LDL levels and current smoking status, as well as SLE-related factors, including higher serum C3 level and higher Systemic Lupus Activity Measure (SLAM) score, were associated with carotid plaque progression[7]. Carotid intima media thickness (IMT) progression has been associated also with higher serum creatinine, homocysteine level, and C3 level[7,8]. Kiani et al further investigated cumulative exposure to risk factors in progression of IMT, carotid plaque, and CAC[9]. In their multivariate analyses, progression in CAC was associated with age, current smoking, and lower high-sensitivity C-reactive protein (hsCRP), but not with SLE disease activity measures.

There are very few studies that have investigated risk factors in the progression of CAC and none that have explored risk factors for AC progression in those with SLE. We investigated baseline traditional and SLE-related risk factors in the progression of CAC and AC in women with SLE and in comparison with a control population. We hypothesized that not only would the rate of progression in CAC and AC be greater in those with SLE when compared with controls, but also that the risk factors for progression would differ between the groups. This is the first study to explore progression in AC in women with SLE.

## Methods

### Study Population and Data Collection

Details of our SLE study population and data collection have been described previously[10]. Briefly, women aged ≥18 years from the Chicago Lupus Database (CLD) who met at least 4 of the 1982 or updated 1997 American College of Rheumatology (ACR) classification criteria for SLE were invited to participate. The first 185 responders were enrolled in the Study of Lupus Vascular and Bone Long-term Endpoints (SOLVABLE) study. When compared with the 723 women in the CLD, those enrolled in SOLVABLE were older with longer disease duration, less likely to have positive anti-dsDNA, and more likely to be taking hydroxychloroquine and immunosuppressants (cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, or tacrolimus) but less likely to be taking corticosteroids. Race/ethnicity, smoking history, complement C3 and C4 levels were not significantly different between CLD and SOLVABLE.

Controls from the general population included 186 women without SLE These subjects were recruited using mailings to potential neighborhood controls for each case subject from an electronic public records. Further assessment and interview in those interested allowed selection of controls age (±5 years), ethnicity, and residence zip code matched to the cases.

The Institutional Review Boards of Northwestern University and the University of Illinois at Chicago approved the protocols, and all of the study participants provided informed consent prior to enrollment. Data were collected at an initial visit and at a follow-up visit. At each visit, each participant provided blood and urine samples for laboratory tests and was given a self-administered questionnaire. Vascular imaging, as described below, was also performed at the visits.

## SLE-related factors

Measures of lupus disease activity (Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K])[11] and disease damage (American College of Rheumatology Systemic Lupus International Collaborating Clinics Damage Index [ACR/SLICC-DI]) were completed by trained physicians. These physicians were fellows-in-training who performed disease assessment an average 5 times weekly, with review by RR-G, for one year in the Northwestern Medical Faculty Foundation Lupus Clinic before performing the disease activity assessment for SOLVABLE. The indices were then checked for accuracy by RR-G with the original source document. Disease duration was calculated using the date the 4$^{th}$ ACR classification criteria for lupus[12,13] were fulfilled. Self-reported information on use of corticosteroids, hydroxychloroquine, and immunosuppressants (see Table 1 for details) were also collected at each visit. Medication use for SLE was verified with CLD, our longitudinal database, in 10% of the study sample and found to be 100% consistent with the medical record. The ACR/SLICC-DI score - excluding coronary artery bypass grafting, myocardial infarction (MI), stroke, and angina - was used for analysis.

## Traditional Cardiovascular Risk Factors

Age, self-reported race/ethnicity, smoking history, previous cardiovascular events, and current medication use were obtained from the questionnaire. Blood pressure and waist circumference were measured twice and the mean of the 2 measurements was used for analysis.

Laboratory tests included fasting lipids (total cholesterol, triglycerides, and high-density lipoprotein [HDL], low-density lipoprotein [LDL]), homocysteine, fasting glucose (by enzymatic assay), and lipoprotein(a), were measured in the Lipid Laboratory at the Pittsburgh Graduate School of Public Health and Prevention. LDL cholesterol was estimated using the Friedewald equation if the triglyceride level was <400 mg/dl; otherwise the LDL level was measured directly. C-reactive protein (CRP) was measured using an immunonephelometric assay at the Laboratory for Clinical Biochemistry Research at the University of Vermont. Fibrinogen by modified clot-rate assay was measured also at the University of Vermont.

Hypertension at baseline was defined a priori as present if systolic blood pressure was ≥140 or diastolic blood pressure ≥90 or if subject was on an anti-hypertensive medication.

## Imaging

Subclinical cardiovascular disease was measured by electron beam computed tomography (EBCT) or multidimensional computed tomography (MDCT) of the coronary arteries and

aorta according to a standardized protocol. Both CT methods have been shown to be comparable in the Multi-Ethnic Study of Atherosclerosis (MESA)[14]. CAC and AC scores from the EBCT or MDCT examinations were read at the University of Pittsburgh Cardiovascular Institute.

### Subclinical CVD outcome measures

CAC scores were dichotomized, with low CAC defined as CAC<10 Agatston units (AU) and high CAC defined as CAC≥10 AU[15].

CAC progression at follow-up was also dichotomized using MESA guidelines: If CAC=0 AU at baseline, progression was defined as CAC>0 AU at follow-up. If 0<CAC<100 AU at baseline, progression was defined as an annualized change of ≥10 AU at follow-up. If CAC≥100 AU at baseline, progression was defined as an annualized percent change ≥10% at follow-up[16].

Although AC progression was not defined in the MESA study, we used a strategy similar to the MESA definition of CAC progression. Because the mean AC measurement was roughly a factor of 10 higher than the CAC measurements, low risk AC was defined as <100 AU and high risk AC was defined as ≥100 AU, and progression was dichotomized as follows: If AC=0 AU at baseline, progression was defined as AC>0 AU at follow-up. If 0<AC<1000 AU at baseline, progression was defined as an annualized change of ≥100 AU at follow-up. If AC≥1000 AU at baseline, progression was defined as an annualized percent change ≥10% at follow-up.

### Statistical analysis

Patient demographic data, laboratory values, and subclinical CVD measures were described as means, standard deviations, and percentages. Progression in CAC and AC were analyzed as dichotomous variables (absence or presence of progression as defined above).

Based on a two-sided test at the 5% level, we had estimated the minimum detectable odds ratios with 80% power for progression rates ranging from 15% to 35% to be 2.9–2.0.

Univariate logistic regressions were used to estimate the relationships of progression of CAC and AC with the various cardiovascular risk factors in cases and controls separately. These models were further adjusted for age, total cholesterol/HDL ratio, and presence of hypertension. Smoking status and diabetes were not included in the adjustment covariates due to few subjects self-identified as smokers (9.4% of cases and 8.9% of controls) or as diabetic (8.7% of cases, 3.2% of controls) (defined as fasting glucose ≥126 or self-reported diabetes or on a diabetes medication). Statin use in controls also could not be modeled due to the limited number taking a statin (5.6%). Time to follow-up was calculated as the lapsed time between baseline and the follow-up visit. Follow-up time was not significantly correlated with progression measures and was thus not included in the models.

Logistic regression results were reported as odds ratios (OR) with 95% confidence intervals (95%CI). Odds ratios were calculated for continuous variables higher one standard deviation.

The data from cases and controls were then combined and the presence of SLE, i.e. cases vs. controls, was univariately regressed against the progression variables as an independent variable. This model was also adjusted for age, total cholesterol/HDL ratio, and presence of hypertension.

All data analyses were performed in the R environment, version 2.15.2 (2012).

## Results

Of the 185 women with SLE (cases) enrolled (23 did not have a follow-up visit; 5 refused participation, 9 did not respond, 4 relocated, and 5 were deceased). Four cases did not have a baseline CAC measurement and an additional 9 women did not have follow-up CAC measurements, leaving 149 cases available for analyses. Of the 186 controls enrolled (54 did not have a follow-up visit; 7 refused participation, 14 did not respond, 1 relocated, and 32 were not yet due for a follow-up at time of analysis). In addition, 8 controls did not have follow-up CAC measurements, leaving 124 available for analyses. Of these women, 113 cases and 122 controls had baseline and follow-up AC.

Baseline characteristics in cases were not significantly different between those included and not included in the progression analyses, except the included cases had a lower BMI than those not included (p=0.03). The controls not included had higher GFR than the included controls (p=0.039).

Time to follow-up re-examination was 3.67±0.93 years and 4.00±1.08 (p=0.008) years in the 149 cases and 124 controls, respectively.

### Demographics and Traditional Cardiovascular Risk Factors

The mean±SD age at first study visit was 43.1±9.9 and 46.3±10.3 years in the 149 cases and 124 controls, respectively (Table 1). About 63% of cases and 68% of controls were Caucasian. Mean total cholesterol/HDL ratios were 3.7±1.4 mg/dl and 3.5±1.0 mg/dl in cases and controls, respectively. Mean waist circumference was 88.1±17.1 cm in cases and 89.5±17.3 cm in controls. Almost 50% of cases and 25% of controls had hypertension.

Over 7% of cases were on statins compared with 5.6% of controls, 17.4% cases and 7.3% of controls were taking aspirin, and 8.7% cases and 7.3% of controls were taking estrogen (as hormone replacement therapy or oral contraceptives). Twelve cases (6.5%) had experienced cardiovascular events at the time of initial visit; one case with angina, MI, and angioplasty, another with angina and angioplasty, one with MI alone, six with stroke, three with transient ischemic attack. These events were verified by physician (RR-G) review of medical records.

### SLE Factors

In cases, the mean±SD scores for the SLEDAI-2K and the modified ACR/SLICC-DI were 3.8±3.4 and 1.5±1.7, respectively (Table 1). The average disease duration was 12.2±9.0 years. Forty-six percent had positive anti-double-stranded DNA antibodies (anti-dsDNA), defined as >10 by the Crithidia method, and the mean±SD anti-dsDNA titer was 76.8±166.1.

About 38% of cases were taking corticosteroids at the first study visit, with a mean corticosteroid dose of 4.4±7.8 mg. Approximately 73% of subjects were taking hydroxychloroquine, and 35.6% taking immunosuppressants (see Table 1 for details).

### Imaging Markers

Due to protocol difficulties, the first 40 study participants did not have AC scores. The protocol was revised and the subsequent participants had AC measurements scored.

Twenty-seven cases (18.1%) had CAC progression at follow-up, compared with 16 controls (12.9%). Thirty-two cases (28.3%) had progression in AC at follow-up compared with 22 controls (18.0%). The relative risk for progression in cases compared to controls was 1.77 (95%CI 1.03–3.05) for CAC and 1.57 (95%CI 0.97–2.53) for AC.

## Progression

Of the cases who had both AC and CAC measured at baseline and at follow-up (N=112), 13 (11.6%) had progression in both beds (Table 2). In controls, of those who had both AC and CAC measured at baseline and at follow-up (N=122), 13 (10.7%) had progression in both. Progression in AC was correlated with progression in CAC in cases ($r=0.19$, $p=0.045$) and controls ($r=0.45$, $p<0.001$).

## Progression Risk Factors

### Coronary Artery Calcium Progression

In univariate models, CAC progression in cases was associated with older age, higher total cholesterol/HDL ratio, lower GFR, higher homocysteine, higher fibrinogen level, higher modified ACR/SLICC-DI score, and use of aspirin (Table 3). In multivariate models, higher modified ACR/SLICC-DI and aspirin use remained associated with CAC progression in cases (OR 2.15, 95%CI 1.33–3.57 and OR 4.23, 95%CI 1.53–11.74, respectively), and corticosteroid use became associated (OR 2.93, 95%CI 1.14–7.86). In controls, CAC progression was univariately associated with older age, higher lipoprotein(a), and aspirin use. In multivariate models, no risk factors remained significant.

In the model of combined cases and controls, presence of SLE was not significant univariately nor in multivariate models.

### Aorta Calcium Score Progression

AC progression in cases was univariately associated with older age, presence of hypertension, lower GFR, higher lipoprotein(a), homocysteine, and corticosteroid dose (Table 4). In multivariate models, higher lipoprotein(a) (OR 1.80 95%CI 1.11–2.98), homocysteine level (OR 2.06, 95%IC 1.06–4.29), lower C3 (OR 0.54, 95%CI 0.33–0.87) and C4 levels (OR 0.49, 95%CI 0.27–0.86), and higher corticosteroid dose (OR 1.77, 95%CI 1.12–3.00) remained associated. Use of corticosteroid became associated with AC progression (OR 2.73, 95%CI 1.03–7.64).

AC progression in controls was univariately associated with older age. In multivariate models, no risk factors were significant.

In the model of combined cases and controls, presence of SLE was not significant in the univariate model but in multivariate models, presence of SLE became significantly associated with AC progression (OR 2.64, 95%CI 1.26–5.72).

## Discussion

We have investigated subclinical atherosclerosis in both the coronary artery and the aorta in women with SLE in an attempt to further elucidate and identify modifiable risk factors. This is the first study to explore aortic atherosclerosis progression in women with SLE.

At the initial visit, more cases had higher CAC than did controls, despite their younger age. In addition, the proportion of cases with progression at follow-up compared with controls was significantly higher, with about a 77% greater likelihood of CAC progression. There is a trend towards higher likelihood of progression in AC at follow-up in cases, suggesting that there are factors related to SLE that infer a greater risk of progression in aortic calcification.

Subjects who did have CV events at baseline (N=12 cases) were not excluded from analysis; this study investigated baseline risk factors for CAC and AC progression over a particular time, and the prior occurrence of a clinical CV event may already be represented in the CV risk factors assessed at baseline. Of note, of the 12 subjects, 5 had CAC at baseline and 6 had AC at baseline. At follow-up, all 12 had no CAC nor AC present. This may be explained by interventions such as medication and other risk factor modifications which we sought to capture at our baseline measurements.

After enrollment, 5 subjects died before the follow-up visit. The mean ± SD modified SLEDAI was not significantly different from the original N=185 enrolled cases (mean ± SD 5.6 ± 6.1 and 3.5 ± 3.4, p=0.48) but the modified SLICC was higher than in the original enrolled cases cases (mean ± SD 3.5 ± 3.4 and 1.6 ± 1.8, p=0.02). The subjects who died were older but not significantly so (p=0.10), but did have longer duration of disease (p=0.06), which could have contributed to their deaths.

While many studies have described increased and earlier subclinical atherosclerosis in the SLE population, the factors specific to SLE that suggest this higher risk are not clear. Interestingly, we found that the presence of SLE was not significant in unadjusted models, but once traditional cardiovascular risk factors were accounted for, the presence of SLE became significant in AC progression. While this should be considered in the context of a smaller sample size, cases were younger but much more likely to be hypertensive when compared with the controls, and controlling for these factors may have allowed an association to emerge. Presence of SLE was not associated with CAC progression whereas disease damage, as measured by the modified ACR/SLICC-DI, was associated with CAC progression. This suggests that there may be additional factors in SLE other than disease damage that affect risk for CAC progression.

Other than age and hypertension, which are accounted for in our models, homocysteine was also noted to be significantly higher in cases than in the controls. Homocysteine has been found to be a predictor of presence of CAC[5,17], progression in plaque[6] and IMT[8]. Higher homocysteine was associated with progression in CAC and AC. The association with CAC progression was abrogated by age, presence of hypertension, and cholesterol/HDL ratio, but not so in AC progression. Rasouli et al studied plasma homocysteine levels in 133 asymptomatic non-SLE patients and found that those with homocysteine ≥12 μmol/L demonstrated more progression in CAC compared with those with homocysteine levels <12 μmol/L[18]. Our average homocysteine level in cases was <12 μmol/L and may not have been high enough for an association with CAC progression to be apparent. However, while homocysteine levels were not significantly different between cases and controls at the first two levels of the progression definition (comprising baseline CAC ≤100), the homocysteine level was significantly higher in cases than controls in those with baseline CAC >100.

The presence of SLE was associated with AC progression in our multivariate models, while the modified ACR/SLICC-DI was not significant, suggesting other factors at play. We did find that higher homocysteine levels were associated with increased risk for AC progression. Li et al found that homocysteine produced a significant increase in the proliferation of rat aortic calcifying and non-calcifying vascular smooth muscle cells and increased the activity of alkaline phosphatase activity and calcium content in the calcifying vascular smooth muscle cells[19]. An in vitro study by Campenhout et al suggested that homocysteine significantly increased calcium deposition in the infrarenal abdominal aorta[20]. It is possible that homocysteine plays a more important role in aorta calcification than coronary calcification.

Lipoprotein(a) was associated with AC progression in cases, even after controlling for age, cholesterol/HDL ratio, and presence of hypertension. While lipoprotein(a) levels have been found to be higher in those with SLE when compared with controls and thought to be a factor in the increased cardiovascular risk seen in SLE[21], the means levels in our cases were not significantly higher than the controls. However, the mean lipoprotein(a) level for the cases who had AC progression was 60.04 mg/dl compared with 34.95 mg/dl in the cases who did not have AC progression (p=0.01). Lipoprotein(a) levels are associated with cardiovascular events as suggested in the Copenhagen Heart Study, which found that a 10 mg/dL increase in lipoprotein(a) levels was associated with a multifactorially adjusted hazard ratio of 1.09 (1.06 to 1.12) for MI and 1.06 (1.04 to 1.08) for ischemic heart disease[22]. While we did not investigate events due to the small number of events in our population, the significant association with AC progression with a higher level of lipoprotein(a) is intriguing. The lack of association between lipoprotein(a) and CAC in our data is consistent with the Guerra et al study, which reported no relationship between lipoprotein(a) and the presence of CAC in a population-based sample of 1288 men and women[23], suggesting that lipoprotein(a) might not have a role in the development or progression of CAC.

Controlling for age, presence of hypertension, and cholesterol/HDL ratio abrogated all associations between traditional risk factors and CAC progression in cases. Previous studies have suggested that traditional/Framingham risk factors alone are not sufficient to explain

the increased risk of atherosclerosis in patients with SLE[2,24], and this is supported by our finding that after controlling for cardiovascular risk factors included in the FRS calculation, SLE-related factors remained associated with CAC and AC progression.

Increased damage (excluding cardiovascular damage), as measured by the modified ACR/SLICC-DI, inferred a greater risk for CAC progression in cases after controlling for traditional cardiovascular risk factors. In our population, the most commonly scored portions of the modified ACR/SLICC-DI were alopecia (24%), avascular necrosis (21%), and cataracts (21%), which is suggestive of long-term effects of corticosteroid use which could in turn represent higher overall disease severity. Use of a corticosteroid at initial visit was indeed associated with CAC progression in our adjusted models, although current and cumulative doses were not.

Cumulative corticosteroid doses equivalent to >10mg/day over 10 years and current corticosteroid use of >10mg/day have been found to be associated with higher risk of cardiovascular events[24]. Despite our average current corticosteroid dose of 4.4mg/day, a higher corticosteroid dose was significantly associated with AC progression. The mean baseline corticosteroid dose was higher in AC progressors compared with non-progressors (7.91 vs. 3.94 mg/day, p=0.06), but not different in CAC progressors compared with non-progressors. Although the distribution of baseline C3 and C4 levels in those with AC progression were not significantly different in those without AC progression, hypocomplementemia and use of a corticosteroid were also significantly associated with progression in AC in multivariate models. This suggests that more active disease could contribute to the risk for AC progression in SLE.

The relationship between C3 and subclinical CVD progression has not yet been elucidated. While some have reported increased risk for IMT or carotid plaque progression with higher C3 levels[7,8] and noted a relationship between higher C3 and increased vascular stiffness[25], Kiani et al reported a trend towards a relationship between lower C3 levels and CAC progression and similarly a possible association between higher C3 and IMT progression[9]. Perhaps progression in each vascular bed occurs in the context of a different milieu – higher C3 and increased vascular stiffness in association with progression in the carotid bed and lower C3 and active SLE disease in coronary and aortic vascular beds.

In some studies, damage has not been found to be associated with progression using IMT or plaque as measures of subclinical atherosclerosis[6,7,26]. Kiani et al investigated progression in CAC measuring disease activity by the SLEDAI. Similar to their study, we did not find an association between baseline disease activity by a modified SLEDAI-2K or anti-dsDNA in the progression of CAC. This may suggest that the long-standing inflammatory milieu involved in SLE may be more important in the progression of CAC.

We did not find statin use to be associated with progression in either CAC or AC in cases. Similarly, Petri et al studied the effects of atorvastatin on CAC progression in women with SLE without clinical cardiovascular disease and did not find a significant relationship[27]. Use of aspirin was associated with a greater risk for CAC progression. It may be that those

taking aspirin at the initial study were already identified as those who may benefit from aspirin use, but it must be noted that few cases were taking aspirin.

More cases were found to have progression in both vascular beds than controls, which is consistent with Yiu et al's findings[4]. In that study, calcification was only present in controls of age >45 years old, mostly in the coronary arteries, whereas in the SLE patients aged >49 years, all had CAC and 60% had calcification in at least 2 vascular beds. Reflecting similar findings, our cases with progression in both beds had a mean age of 46.5 years vs. 56.9 years in the controls. Yiu's observations could suggest that development of CAC occurs earlier than AC, which may be supported by our findings that CAC progression was associated with disease damage whereas AC progression was associated with active disease at baseline.

We did find that progression in CAC and AC were correlated, as they have been in the general population[28–30], but as they are still independently associated with different risk factors, utilizing both imaging modalities in the identification of SLE patients at risk for cardiovascular morbidity may be useful. Furthermore, both CAC and AC have been found independently in those with low or intermediate FRS scores[28,30], which does suggest that these traditional cardiovascular risk factors are necessary but not sufficient in the assessment of cardiovascular risk.

We recognize several limitations of this study. Firstly, these are small cohorts, with approximately 20% cases and over 30% controls that could not be included in analyses, with a smaller number with AC measured in cases. Thusly, the noted relationship between AC progression and lipoprotein(a) and corticosteroid dose must be interpreted in the context of lower power.

The MESA definition was designed for CAC progression and our definition using the MESA model may not be appropriate for AC progression. Unfortunately, there is no guideline in the literature for clinically relevant thresholds in AC. In addition, definitions that are used in the current literature were established for use in the general population and may not be applicable to those with SLE.

We also investigated only baseline measurements of risk factors. Karp et al found that the risk of heart disease may be affected more by recent rather than baseline risk factor values[31], and we may not be seeing the full effect of these risk factors on the progression of CAC and AC.

In the pursuit of identifying not only those SLE patients specifically at risk for early and aggressive cardiovascular events, but also modifiable risk factors to prevent the aggressive atherosclerosis seen in SLE, many investigations into subclinical atherosclerosis have been done. We have shown that that higher baseline modified ACR/SLICC-DI is a significant predictor of an increased risk in progression of CAC, even after controlling for traditional cardiovascular risk factors, whereas baseline active disease may be more important in the progression of AC. Conventional risk factor modification is not likely sufficient in the SLE population, and more aggressive prevention of disease flares and disease damage may also be important in the prevention of cardiovascular disease in SLE. Progression in each

vascular bed may be associated with different risk factors, suggesting the utility of both in determining those at risk for cardiovascular disease.

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### Significance and Innovations

- Progression in coronary artery calcium and progression in aorta calcium have different risk factors in women with systemic lupus erythematosus after controlling for traditional cardiovascular risk factors.
- Increased initial disease damage, as measured by the modified ACR/SLICC-DI, may be a risk factor for progression in coronary artery calcium whereas increased initial disease activity, as measured by low complement and use of corticosteroids, may be a risk factor for progression in aorta calcium in women with systemic lupus erythematosus.

## Table 1

Baseline Risk Factors[δ] in Women with SLE (Cases) and Controls from the Study of Lupus Vascular and Bone Longterm Endpoints (2002-present), Chicago, IL

| | Cases (N=149) | Controls (N=124) | P-value* |
|---|---|---|---|
| ***Traditional CV Risk Factors*** | | | |
| Age (years, mean ±SD) | 43.1 ± 9.9 | 46.3 ± 10.3 | 0.01 |
| Hypertension (N (%)) | 74 (49.7) | 31 (25.0) | <0.001 |
| Waist Circumference (cm) | 88.1 ± 17.1 | 89.5 ± 17.3 | 0.52 |
| Total Cholesterol/HDL Ratio | 3.7 ± 1.4 | 3.5 ± 1.0 | 0.13 |
| GFR (ml/min) | 84.0 ± 22.2 | 80.8 ± 18.4 | 0.20 |
| Diabetes (N (%))[$] | 13 (8.7) | 4 (3.2) | 0.08 |
| Smoker (N (%)) | 14 (9.4) | 11 (8.9) | 1.00 |
| Lipoprotein(a) (mg/dl) | 47.3 ± 45.5 | 37.8 ± 37.4 | 0.06 |
| Fibrinogen (mg/dl) | 326.9 ± 103.3 | 322.0 ± 87.7 | 0.67 |
| CRP (mg/dl) | 4 ± 8.3 | 3.1 ± 4.9 | 0.25 |
| Homocysteine (mg/dl) | 10.9 ± 3.7 | 8.7 ± 3.2 | <0.001 |
| Framingham Risk (%)[&] | 4.1 ± 4.0 | 4.6 ± 4.7 | 0.41 |
| Race (%) | | | |
| Caucasian | 63.1 | 67.7 | 0.45 |
| African-American | 26.2 | 23.4 | 0.67 |
| Asian | 6.0 | 2.4 | 0.24 |
| Hispanic | 4.7 | 6.5 | 0.60 |
| ***SLE-Related Factors*** | | | |
| SLEDAI-2K | 3.8 ± 3.4 | - | - |
| ACR/SLICC-DI[**] | 1.5 ± 1.7 | - | - |
| Anti-dsDNA (by Crithidia) | 76.8 ± 166.1 | - | - |
| Positive Anti-dsDNA(N (%)) | 69 (46.3) | - | - |
| Current corticosteroid dose (mg) | 4.4 ± 7.8 | - | - |
| Cumulative corticosteroid dose (mg) | 102.7 ± 112.0 | | |
| Complement component 3 (C3) (mg/dl) | 99.7 ± 28.4 | - | - |
| Complement component 4 (C4) (mg/dl) | 19.6 ± 8.9 | - | - |
| Disease Duration (y) | 12.2 ± 9.0 | - | - |
| ***Current Medication Use*** | | | |
| Hydroxychloroquine (N (%)) | 109 (73.2) | - | - |
| Corticosteroids (N (%)) | 57 (38.3) | - | - |
| Immunosuppressants (N(%))[μ] | 53 (35.6) | - | - |
| Estrogen (N (%)) | 13 (8.7) | 9 (7.3) | 0.82 |
| Aspirin (N (%)) | 26 (17.4) | 9 (7.3) | 0.02 |
| Statin (N (%)) | 11 (7.4) | 7 (5.6) | 0.63 |

[δ](mean±SD)

[*] two-sided t-test used for continuous variables, and Fisher's exact test for proportions

[$] fasting glucose ≥ 126 or on diabetes medication or self-reported diabetes

[&] 10-year general cardiovascular disease risk

[**] Excluding coronary artery bypass grafting, myocardial infarction, stroke, and angina

[μ] mycophenolate mofetil, azathioprine, methotrexate

SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000

Mod ACR/SLICC-DI: American College of Rheumatology/Systemic Lupus International Collaborative Clinics Damage Index, excluding coronary artery bypass grafting, myocardial infarction, stroke, and angina.

**Table 2**

Progression Categories for Coronary Artery Calcium (CAC) and Aorta Calcium (AC) in Women with SLE (cases) and Controls from the Study of Lupus Vascular and Bone Long-term Endpoints (2002-present), Chicago, IL

| | | Low without Progression (N(%)) | Low with Progression (N(%)) | High to Low (N(%)) | High without Progression (N(%)) | High with Progression (N(%)) | Relative Risk (95% CI) |
|---|---|---|---|---|---|---|---|
| **CAC** | Cases (N=149) | 106 (71.1) | 14 (9.4) | 2 (1.3) | 14 (9.4) | 13 (8.7) | 1.77 (1.03–3.05) |
| | Controls (N=124) | 101 (81.5) | 10 (8.1) | 3 (2.4) | 4 (3.2) | 6 (4.8) | |
| **AC** | Cases (N=113) | 71 (62.8) | 15 (13.3) | 4 (3.5) | 6 (5.3) | 17 (15.0) | 1.57 (0.97–2.53) |
| | Controls (N=122) | 88 (72.1) | 10 (8.2) | 2 (1.6) | 10 (8.2) | 12 (9.8) | |

Low CAC defined as < 10 Agatston units, low AC defined as < 100 Agatston units. High CAC defined as ≥ 10 Agatston units, high AC defined as ≥ 100 Agatston units.

Progression definition:

If CAC = 0 Agatston units at baseline, progression was defined as CAC > 0 Agatston units at follow-up. If 0 < CAC < 100 Agatston units at baseline, progression was defined as an annualized change of ≥ 10 Agatston units at follow-up. If CAC ≥ 100 Agatston units at baseline, progression was defined as an annualized percent change ≥ 10% at follow-up. If AC = 0 Agatston units at baseline, progression was defined as AC > 0 Agatston units at follow-up. If 0 < AC < 1000 Agatston units at baseline, progression was defined as an annualized change of ≥ 100 Agatston units at follow-up. If AC ≥ 100 Agatston units at baseline, progression was defined as an annualized percent change ≥ 10% at follow-up.

Relative Risks were calculated as the ratio of the proportion of all cases who progressed and the proportion of all controls who progressed.

**Table 3**

Associations of Coronary Artery Calcium Progression with Baseline Cardiovascular Risk Factors in Women with SLE (cases) and Controls from the Study of Lupus Vascular and Bone Long-term Endpoints (add years of study), Chicago, IL

| | Unadjusted | | | | Adjusted[δ] | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases | | Controls | | Cases | | Controls | |
| | OR[&] | 95% CI | OR[&] | 95% CI | OR[&] | 95% CI | OR[&] | 95% CI |
| ***Traditional Risk Factors*** | | | | | | | | |
| Age | **1.90** | **1.20–3.09**[$] | **4.73** | **2.37–10.99**[$] | - | - | - | - |
| Hypertension | 1.61 | 0.69–3.83 | 2.72 | 0.89–8.09 | - | - | - | - |
| Total cholesterol/High-density Lipoprotein Ratio | **1.30** | **0.90–1.87**[$] | 1.38 | 0.82–2.30 | - | - | - | - |
| Current Smoker | 0.32 | 0.02–1.73 | 1.57 | 0.22–6.92 | 0.27 | 0.01–1.51 | 1.29 | 0.17–6.97 |
| Fasting Glucose | 1.30 | 0.86–2.08 | 1.59 | 1.01–2.84 | 1.11 | 0.74–1.75 | 1.18 | 0.67–1.94 |
| Waist Circumference | 1.00 | 0.66–1.47 | 1.16 | 0.70–1.91 | 0.72 | 0.42–1.18 | 0.75 | 0.37–1.43 |
| Glomerular Filtration Rate | **0.49** | **0.27–0.83**[$] | 0.58 | 0.27–1.12 | 0.65 | 0.34–1.21 | 2.11 | 0.80–5.70 |
| Lipoprotein(a) | 1.25 | 0.86–1.79 | **1.85** | **1.20–3.02**[$] | 1.14 | 0.76–1.68 | 1.58 | 0.92–2.93 |
| Fibrinogen | **1.56** | **1.03–2.39**[$] | 1.28 | 0.75–2.20 | 1.46 | 0.91–2.36 | 0.76 | 0.39–1.42 |
| Homocysteine | **1.95** | **1.09–3.59**[$] | 1.16 | 0.66–1.86 | 1.66 | 0.86–3.15 | 1.05 | 0.47–2.09 |
| C-Reactive Protein | 0.89 | 0.37–1.46 | 0.94 | 0.47–1.47 | 0.78 | 0.26–1.53 | 0.71 | 0.29–1.24 |
| ***SLE-Related Factors*** | | | | | | | | |
| Presence of SLE[%] | 1.49 | 0.77–2.97 | - | - | 2.08 | 0.98–4.57 | - | - |
| ACR/SLICC-DI[**] | **2.24** | **1.45–3.56**[$] | - | - | **2.15** | **1.33–3.57**[$] | - | - |
| SLEDAI-2K | 0.91 | 0.55–1.42 | - | - | 1.00 | 0.60–1.57 | - | - |
| Disease Duration | 1.37 | 0.91–2.02 | - | - | 1.21 | 0.78–1.85 | - | - |
| Complement component 3 (C3) (mg/dl) | 0.92 | 0.60–1.40 | - | - | 0.70 | 0.44–1.11 | - | - |
| Complement component 4 (C4) (mg/dl) | 0.87 | 0.54–1.33 | - | - | 0.64 | 0.37–1.07 | - | - |
| Corticosteroid Dose | 0.97 | 0.58–1.47 | - | - | 1.03 | 0.61–1.64 | - | - |
| Cumulative Corticosteroid dose | 1.41 | 0.94–2.11 | - | - | 1.45 | 0.95–2.24 | - | - |
| Anti-dsDNA Level | 1.20 | 0.80–1.73 | - | - | 1.26 | 0.83–1.88 | - | - |
| ***Current Medication Use*** | | | | | | | | |

| | Unadjusted | | | | Adjusted[δ] | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases | | Controls | | Cases | | Controls | |
| | OR[&] | 95% CI | OR[&] | 95% CI | OR[&] | 95% CI | OR[&] | 95% CI |
| Hydroxychloroquine | 0.68 | 0.28–1.73 | - | - | 0.74 | 0.30–1.97 | - | - |
| Estrogen | 2.18 | 0.55–7.35 | 3.92 | 0.76–16.89 | 1.39 | 0.33–4.02 | 2.01 | 0.28–12.78 |
| Statin[*] | 2.86 | 0.70–19.29 | - | - | 2.65 | 0.59–11.06 | - | - |
| Aspirin | **3.90** | **1.50–9.99[$]** | **6.87** | **1.53–29.62[$]** | **4.23** | **1.53–11.74[$]** | 2.64 | 0.48–14.43 |
| Corticosteroid | 1.98 | 0.85–4.64 | - | - | **2.93** | **1.14–7.86[$]** | - | - |

[δ] Adjusted for age, total cholesterol/high-density lipoprotein ratio, and presence of hypertension

SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, excluding complement score

ACR/SLICC-DI: American College of Rheumatology/Systemic Lupus International Collaborative Clinics Damage Index

[*] Too few controls reported statin use to be incorporated into a regression model

[&] Odds ratio, calculated for a 1 standard deviation higher risk factor level for continuous variables

[**] Excluding coronary artery bypass grafting, myocardial infarction, stroke, and angina

[$] Statistically significant, $p < 0.05$

[%] modeled with combined cases and controls data

**Table 4**

Associations of Aorta Calcium Progression with Baseline Cardiovascular Risk Factors in Women with SLE (cases) and Controls from the Study of Lupus Vascular and Bone Long-term Endpoints (2002-present), Chicago, IL

| | Unadjusted | | | | Adjusted[δ] | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases | | Controls | | Cases | | Controls | |
| | OR[&] | 95% CI | OR[&] | 95% CI | OR[&] | 95% CI | OR[&] | 95% CI |
| ***Traditional Risk Factors*** | | | | | | | | |
| Age | **2.66** | **1.57–4.86**[$] | **2.80** | **1.66–5.07**[$] | - | - | - | - |
| Hypertension | **2.62** | **1.12–6.43**[$] | 2.45 | 0.91–6.47 | - | - | - | - |
| Total Cholesterol/High-Density Lipoprotein Ratio | 1.36 | 0.96–2.03 | 1.41 | 0.90–2.23 | - | - | - | - |
| Waist Circumference | 1.06 | 0.71–1.55 | 1.03 | 0.65–1.60 | 0.65 | 0.37–1.08 | 0.67 | 0.37–1.16 |
| Current Smoking Status | 2.31 | 0.62–8.30 | 1.82 | 0.37–6.95 | 2.13 | 0.51–8.91 | 1.40 | 0.27–6.03 |
| Fasting Glucose | 1.26 | 0.75–2.29 | 1.39 | 0.91–2.27 | 0.98 | 0.57–1.67 | 1.06 | 0.65–1.67 |
| Glomerular Filtration Rate | **0.46** | **0.24–0.81**[$] | 0.60 | 0.41–1.06 | 0.68 | 0.35–1.27 | 1.33 | 0.60–2.82 |
| Lipoprotein(a) | **1.84** | **1.21–2.88**[$] | 1.15 | 0.74–1.72 | **1.80** | **1.11–2.98**[$] | 0.86 | 0.50–1.37 |
| Fibrinogen | 1.20 | 0.81–1.79 | 1.18 | 0.74–1.90 | 0.93 | 0.57–1.47 | 0.84 | 0.48–1.43 |
| Homocysteine | **2.60** | **1.40–5.27**[$] | 0.85 | 0.45–1.38 | **2.06** | **1.06–4.29**[$] | 0.57 | 0.26–1.14 |
| C-Reactive Protein | 0.91 | 0.46–1.43 | 0.90 | 0.49–1.37 | 0.79 | 0.31–1.48 | 0.71 | 0.34–1.17 |
| ***SLE-Related Factors*** | | | | | | | | |
| Presence of SLE[%] | 1.80 | 0.97–3.36 | - | - | **2.64** | **1.26–5.72**[$] | - | - |
| ACR/SLICC-DI[**] | 1.29 | 0.84–1.96 | - | - | 1.00 | 0.60–1.63 | - | - |
| SLEDAI-2K | 1.27 | 0.84–1.92 | - | - | 1.29 | 0.82–2.08 | - | - |
| Disease Duration | 1.28 | 0.86–1.89 | - | - | 1.11 | 0.71–1.71 | - | - |
| Complement component 3 (C3) (mg/dl) | 0.84 | 0.56–1.26 | - | - | **0.54** | **0.33–0.87**[$] | - | - |
| Complement component 4 (C4) (mg/dl) | 0.84 | 0.53–1.27 | - | - | **0.49** | **0.27–0.86**[$] | - | - |
| Corticosteroid dose | **1.52** | **1.04–2.27**[$] | - | - | **1.77** | **1.12–3.00**[$] | - | - |
| Cumulative Corticosteroid Dose | 1.09 | 0.72–1.62 | - | - | 1.02 | 0.65–1.56 | - | - |
| Anti-dsDNA Level | 1.29 | 0.90–1.88 | - | - | 1.38 | 0.92–2.10 | - | - |
| ***Current Medication Use*** | | | | | | | | |

| | Unadjusted | | | | Adjusted[δ] | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases | | Controls | | Cases | | Controls | |
| | OR[&] | 95% CI | OR[&] | 95% CI | OR[&] | 95% CI | OR[&] | 95% CI |
| Hydroxychloroquine | 0.80 | 0.31–2.17 | - | - | 0.84 | 0.30–2.46 | - | - |
| Estrogen | 1.01 | 0.14–4.99 | 1.33 | 0.19–6.00 | 0.60 | 0.08–3.21 | 0.64 | 0.07–3.65 |
| Statin[*] | 1.01 | 0.14–4.99 | - | - | 0.89 | 0.10–5.74 | - | - |
| Aspirin | 1.10 | 0.36–3.08 | 2.47 | 0.49–10.28 | 1.11 | 0.33–3.49 | 0.97 | 0.17–4.64 |
| Corticosteroid | 1.89 | 0.82–4.38 | - | - | **2.73** | **1.03–7.64**[$] | - | - |

[δ]Adjusted for age, total cholesterol/high-density lipoprotein ratio, and presence of hypertension

SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, excluding complement score

ACR/SLICC-DI: American College of Rheumatology/Systemic Lupus International Collaborative Clinics Damage Index

[*]Too few controls reported statin use to be incorporated into a regression model

[&]Odds ratio, calculated for a 1 standard deviation higher risk factor level for continuous variables

[**]Excluding coronary artery bypass grafting, myocardial infarction, stroke, and angina

[$]Statistically significant, $p < 0.05$

[%]modeled with combined cases and controls data