

# FEATURED NEW INVESTIGATORS

## Differences in subclinical cardiovascular disease between African American and Caucasian women with systemic lupus erythematosus

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**Racial differences exist in disease rates and mortality in both cardiovascular disease (CVD) and systemic lupus erythematosus (SLE). The objective of this cross-sectional study was to compare the frequency and risk factors for subclinical CVD in African American (AA) and Caucasian women with SLE and no prior CVD events. Traditional CVD risk factors and SLE-related factors were assessed in 309 SLE women. Subclinical CVD was assessed by carotid ultrasound to measure intimamedial thickness (IMT) and plaque, and electron beam computed tomography (EBCT) was used to measure coronary artery calcium (CAC). AA women had less education and higher levels of body mass index, blood pressure, lipoprotein(a), C-reactive protein (CRP), fibrinogen, and erythrocyte sedimentation rate (ESR). However, AA women had lower albumin, more and longer duration of corticosteroid use, higher SLE disease activity and damage, and more dsDNA antibodies compared with Caucasian women after adjustment for age and study site. More AA women had carotid plaque (adjusted odds ratio (OR), 1.94; 95% confidence interval (CI), 1.03–3.65) and higher carotid IMT (0.620 vs 0.605 mm,  $P = 0.07$ ) but similar CAC compared with Caucasians. A multivariate analysis revealed that the following risk factor variables were significantly different between the racial groups and associated with plaque: blood pressure,**

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**current corticosteroid use, SLE disease activity, and SLE damage. All factors contributed to the result, but no individual risk factor fully accounted for the association between race and plaque. In conclusion, the presence of carotid plaque was higher in AA compared with Caucasian women with SLE, in contrast to studies of non-SLE subjects, in which AA have similar or less plaque than Caucasians. A combination of SLE-related and traditional CVD risk factors explained the racial difference in plaque burden. (Translational Research 2009;153:51–59)**

**Abbreviations:** AA = African American; ACL = anticardiolipin; ACR = American College of Rheumatology; BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; CVA = cerebrovascular accident; CVD = cardiovascular disease; DBP = diastolic blood pressure; dsDNA = double-stranded DNA; EBCT = electron beam computed tomography; HDLc = high-density lipoprotein cholesterol; IMT = intimamedial thickness; LDLc = low-density lipoprotein cholesterol; MI = myocardial infarction; OR = odds ratio; SBP = systolic blood pressure; SES = socioeconomic status; SLE = systemic lupus erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI = Systemic Lupus International Collaborating Clinics Damage Index; TIA = transient ischemic attack

## AT A GLANCE COMMENTARY

### Background

Cardiovascular disease (CVD) is the leading cause of death for women in the general population; it primarily affects postmenopausal women. Yet, even premenopausal systemic lupus erythematosus (SLE) women are at risk of accelerated CVD. Racial differences exist in disease rates and mortality in both CVD and SLE.

### Translational Significance

This study is significant, because it was the first to specifically evaluate racial differences for subclinical CVD in SLE women and identify risk factors, which included traditional and ones related to chronic inflammation and SLE disease.

Cardiovascular disease (CVD) is the leading cause of death for women in the general population in the United States<sup>1</sup>; it primarily affects postmenopausal women. Recognition of the elevated risk of accelerated CVD is increasing in systemic lupus erythematosus (SLE) women, which includes those who are premenopausal.<sup>2,3</sup>

Traditional CVD risk factors are important in SLE patients,<sup>2,4-6</sup> but several studies have suggested that lupus disease itself may be an important risk factor for CVD in these patients.<sup>7-9</sup> These observations support the hypothesis that traditional CVD risk factors do not fully account for the elevated and premature risk observed in SLE patients and that other factors related to SLE (ie, inflammatory and immune mediators, as well as thrombotic factors such as antiphospholipid antibodies) may also be important in the development of

these complications. Atherosclerosis is now accepted to be an inflammatory disease, and the role that inflammation plays in atherosclerosis has raised a putative mechanism that may underlie the increased risk of CVD reported in SLE patients.

In the general population, racial differences exist in both CVD events and subclinical CVD, which can be measured noninvasively by imaging various vascular beds, which include the carotid and coronary arteries. These subclinical markers are predictive of events and are reflective of systemic atherosclerotic burden.<sup>10-13</sup>

Racial differences also exist in SLE disease rates and severity. Compared with Caucasians, African Americans (AAs) have a higher incidence rate<sup>14-16</sup> and a prevalence<sup>16,17</sup> of SLE, as well as a decreased rate of survival.<sup>18-20</sup> Although socioeconomic status (SES) is an important determinant in predicting survival, several studies have demonstrated that race alone is an independent risk factor for mortality in SLE patients.<sup>18,19</sup> The Systemic Lupus International Collaborating Clinics Group, which is a multicenter international cohort, confirmed the increased risk of mortality in black/AA race.<sup>21</sup>

Based on these findings, we hypothesized that the racial differences in SLE disease are related to higher rates of underlying subclinical CVD in AA SLE patients compared with Caucasians. Little is known about racial differences with respect to subclinical CVD in SLE women. The objective of this study was to compare traditional and SLE related risk factors for CVD and to compare various measures of subclinical CVD, which include carotid intimamedial thickness (IMT), carotid plaque, and coronary calcification in AA and Caucasian women with SLE and no history of clinical CVD events.

## METHODS

**Study population.** A total of 309 SLE women, all of whom met at least 4 classification criteria for SLE,

aged 18 years or older, and without a history of clinical CVD events (which included myocardial infarction [MI], angina, percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery, cerebrovascular accident [CVA], or transient ischemic attack [TIA]), were enrolled from the Chicago Lupus Database and the Pittsburgh Lupus Registry for the purposes of this study. The Chicago Lupus Database is a cohort of 508 participants, and the Pittsburgh Lupus Registry includes 983 participants who meet the 1982 or updated 1997 American College of Rheumatology (ACR) classification for SLE.<sup>22,23</sup> In Chicago, all eligible women, aged 18 years or older, were invited to participate, with the first 180 women to respond being enrolled in the Study of Long-term Vascular and Bone Outcomes in Lupus Erythematosus (SOLVABLE). In Pittsburgh, all eligible women from the original cardiovascular study ( $n = 286$ ), aged older than 18 years and without a history of clinical CVD events were invited to participate in Heart Effects on Atherosclerosis and Risk of Thrombosis in Systemic Lupus Erythematosus (HEARTS). Identical protocols were used for both SOLVABLE and HEARTS.

For this analysis, only AA and Caucasian women who had not experienced a confirmed myocardial infarction or stroke, and who were not found by a physician to have angina or transient ischemic attack event at baseline, were included; 150 women were from SOLVABLE, and 159 women were from the HEARTS study.

**Data collection.** Participant visits included interview, examination, blood and urine collection, carotid artery B-mode ultrasound, and electron beam computed tomography (EBCT) of the coronary arteries. This research was carried out according to the principles of the Declaration of Helsinki, and the institutional review boards of Northwestern University, University of Illinois at Chicago, and University of Pittsburgh approved the protocols. All study participants provided informed consent prior to enrollment.

Data were collected using identical protocols at both sites for the SOLVABLE and HEARTS studies. A self-administered questionnaire was administered followed by interview and physical examination by a trained physician during the study visit. All specialized laboratory tests (eg, lipid, inflammatory markers, and antiphospholipid antibodies) for both sites were performed at the same laboratory. All sonographers were trained at the University of Pittsburgh Ultrasound Research Laboratory. All imaging tests for subclinical CVD were read at 1 site. Carotid ultrasounds were read at the University of Pittsburgh Ultrasound Research Laboratory, and EBCTs were read at the University of Pittsburgh Cardiovascular Institute.

**Traditional CVD risk factors.** Information on age; demographics; self-reported race/ethnicity, education level, smoking history, and family history of CVD (MI and CVA); history of hypertension, diabetes, and hypercholesterolemia; current estrogen use, current aspirin use; and menopause status was obtained from the questionnaire. Although education level is not a direct measure of SES and access to care, we used this variable as a surrogate for SES. Data on current income level were collected, but several subjects refused to answer this question in the questionnaire. A decision was made to exclude the income level variable given that the missing data points would render the results difficult to interpret accurately. Menopause status was confirmed by measurements of follicle-stimulating hormone if the subject's status was uncertain (eg, irregular menses or hysterectomy without oophorectomy). Blood pressure was measured twice, and the mean of the 2 measurements was used for analysis. Height, weight, and waist/hip measurements were obtained. The laboratory tests included fasting lipids (total cholesterol, high-density lipoprotein cholesterol [HDLc], and triglycerides), homocysteine, glucose, insulin, and lipoprotein(a), which were measured in the Lipid Laboratory at the University of Pittsburgh Graduate School of Public Health and Prevention. The Friedewald equation was used to estimate low-density lipoprotein cholesterol (LDLc), unless the triglyceride level was  $>400$ ; in which case, LDLc was measured directly. Plasma glucose levels were determined by enzymatic assay, and plasma insulin levels were measured by radioimmunoassay. C-reactive protein (CRP) was measured using immunonephelometric assay at the Laboratory for Clinical Biochemistry Research at the University of Vermont.

**SLE-related factors.** Validated measures of lupus disease activity using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) as well as measures of disease damage using the Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI) were completed by trained physicians. The disease duration was calculated using the date the subject fulfilled the 4th American College of Rheumatology (ACR) classification criteria for lupus. Participants provided information on corticosteroid treatment (current use and duration of treatment) as well as on the current use of hydroxychloroquine and immunosuppressants (cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, and tacrolimus). Renal disease was defined as being present if the subject had fulfilled ACR classification criteria for lupus renal involvement (greater than 0.5 g/day or 3+ proteinuria and/or the presence of cellular casts) or had a renal biopsy with evidence of World Health Organization Class IIb, III, IV, or V lupus nephritis. Antiphospholipid antibodies: anticardiolipin (ACL) antibodies

(immunoglobulin G [IgG] and immunoglobulin M [IgM]; Incstar, Stillwater, Minn) and lupus anticoagulant (partial thromboplastin time or Russell's viper venom time with mix) were measured at the Coagulation Laboratory at University of Pittsburgh Medical Center. ACL IgG was considered positive if the result was more than 10 units and ACL IgM was considered positive if more than 15 units, as per laboratory standards. C3, C4, and native double-stranded DNA (dsDNA) antibodies (Crithidia luciliae) were measured locally at each site. dsDNA was dichotomized and considered positive if the titer was 1:10 or greater. Inflammatory markers included fibrinogen (modified clot-rate assay) measured at the Laboratory for Clinical Biochemistry Research at the University of Vermont, albumin (dye binding assay) measured at the Lipid Laboratory in the University of Pittsburgh Graduate School of Public Health and Prevention, and ESR (standard Westergren's method) measured locally at each site.

**Subclinical cardiovascular disease outcome measures.** Subclinical CVD was measured in the carotid arteries using B-mode ultrasound by centrally trained sonographers. Carotid plaque was defined as a distinct area protruding into the vessel lumen that was at least 50% thicker than the surrounding areas and was measured at 8 sites (bilateral internal carotid, external carotid, common carotid, and carotid bulb). The outcome measure used for analysis was the presence or absence of plaque (plaque index  $\geq 1$  vs plaque index = 0). IMT was measured using specialized reading software across 1-cm segments of both the right and left sides of the near and far walls of the distal common carotid artery and the far wall of the carotid bulb and internal carotid artery. The mean of all average IMT readings across the 8 sites were used as the outcome measure for analysis. The reproducibility of carotid duplex scanning using this technique has been previously documented in both the Pittsburgh SLE cohort and a non-SLE population.<sup>5,24</sup> The carotid duplex scans obtained at both sites were read.

In the coronary arteries, EBCT scanning was performed to measure vascular calcium using the Imatron C150 Ultrafast CT Scanner (Imatron, Inc., South San Francisco, Calif). Calcium scores were calculated with a densitometric program available on the Imatron C-150 scanner using the Agatston method. The outcome measures used for analyses were the absence or presence of coronary calcium. EBCTs were also read centrally.

**Statistical methods.** For univariate analyses, *t*-tests were used to compare means between the 2 racial groups for continuous variables that were normally distributed. The Wilcoxon rank sum test was used to compare the intergroup differences for nonparametric continuous variables, and unadjusted odds ratios (ORs) were calculated

for the 2 groups for dichotomous variables. For multivariate analyses, linear regression was used to compare adjusted differences in means, and quantile regression was used to compare adjusted differences in medians between the 2 racial groups with adjustment for age and study site. Logistic regression was used to calculate age and study site adjusted OR for the 2 groups. Adjustment was performed for age because age is strongly related to subclinical CVD as well as many other variables; an adjustment was also performed by study site to account for any unidentifiable confounding factors between the 2 sites. Carotid IMT was analyzed as a continuous variable, whereas carotid plaque and coronary calcification were dichotomized as absent versus present, given the skewing of the data caused by the large number of subjects with zero values for both of these measures.

## RESULTS

In all, 309 SLE women were included in the analysis from both sites; 63 women were AA, and 246 women were Caucasian. AA women were significantly younger compared with the Caucasian women ( $44.6 \pm 10.3$  years vs  $47.6 \pm 10.6$  years,  $P < 0.05$ ), but this difference in age was no longer significant after adjustment for study site.

**Traditional CVD risk factors (Table I).** The AA women had higher mean body mass index (BMI) ( $29.5$  vs  $27.1$  kg/m<sup>2</sup>) and diastolic blood pressure (DBP) ( $77.8$  vs  $74.7$  mm Hg) than Caucasian women, with the differences remaining significant after adjustment for age and study site. Systolic blood pressure (SBP) was higher in AAs after adjustment for age and study site. AAs were only slightly less educated with an adjusted mean difference of less than 1 year of education. Of the traditional CVD risk factors measured in the laboratory, only lipoprotein(a) differed between the 2 races, with AAs having higher levels compared with Caucasians.

**Lupus related factors (Table I).** AAs had higher disease activity, (mean SLEDAI scores  $4.4$  vs  $2.6$ ), higher damage (mean SLICC-DI  $2.5$  vs  $1.3$ ), more current corticosteroid use ( $61.9\%$  vs  $36.3\%$ ), longer mean duration of corticosteroid use ( $10.9$  vs  $9.2$  years), and higher frequency of dsDNA antibody positivity compared with Caucasians. No differences were observed in current hydroxychloroquine use, current immunosuppressant use (with all immunosuppressants combined as well as evaluated individually [data for individual immunosuppressants not shown]), or renal disease. AAs also had more inflammation with higher fibrinogen and ESR, and lower albumin, but they did not differ from Caucasians with regard to antiphospholipid antibodies.

**Subclinical cardiovascular outcomes (Table II).** Compared with Caucasians, more AAs had carotid plaque ( $43.5\%$  vs  $29.6\%$ ; adjusted OR,  $1.94$ ;  $95\%$

**Table I.** Unadjusted and adjusted\* differences in means and odds ratios for traditional CVD risk factors, SLE-related risk factors, thrombotic factors, and inflammatory markers between AA and Caucasian women with SLE

Traditional CVD risk factors	AA (n = 63)	Caucasian (n = 246)	Unadjusted			Adjusted*		
			Meandifference	OR	P value	Mean Difference	OR	P value
Patient characteristics								
Age, years	44.6 ± 10.3	47.6 ± 10.6	-3.0	—	0.048	-0.9	—	0.522
Education, years	14.8 ± 2.4	15.1 ± 2.7	-0.3	—	0.431	-0.8	—	0.023
Current smoking, %	15.9	8.1	—	2.1	0.069	—	2.2	0.069
Family history of CVD, %	42.9	50.2	—	0.7	0.299	—	0.8	0.530
Menopausal, %	44.4	49.6	—	0.8	0.466	—	1.9	0.140
Current estrogen, %	7.9	10.6	—	0.7	0.536	—	0.9	0.827
Current ASA, %	9.5	14.6	—	0.6	0.295	—	0.6	0.225
Hypertension <sup>†</sup>	60.3	35.4	—	<b>2.8</b>	<0.001	—	3.7	<0.001
Diabetes <sup>†</sup>	11.1	5.7	—	2.1	0.134	—	2.2	0.118
Hypercholesterolemia <sup>†</sup>	25.4	25.8	—	1.1	0.851	—	1.1	0.838
Physical factors								
BMI, kg/m <sup>2</sup>	29.5 ± 6.8	27.1 ± 6.8	<b>2.4</b>	—	0.014	2.9	—	0.004
Waist-hip ratio	0.85 ± 0.1	0.84 ± 0.1	0.01	—	0.749	0.01	—	0.618
SBP, mm Hg	122.9 ± 18.5	119.0 ± 17.4	3.8	—	0.126	5.8	—	0.016
DBP, mm Hg	77.8 ± 11.4	74.7 ± 9.4	<b>3.1</b>	—	0.028	4.3	—	0.003
Laboratory values								
Lipoprotein(a), mg/dL	60.9 ± 39.6	40.0 ± 39.6	<b>21.3</b>	—	<0.001	20.5	—	0.001
Total cholesterol, mg/dL	189.9 ± 37.6	190.9 ± 40.9	-0.99	—	0.865	0.37	—	0.949
HDLc, mg/dL	55.6 ± 15.1	55.8 ± 16.0	-0.16	—	0.943	-0.69	—	0.765
LDLc, mg/dL	111.8 ± 33.1	109.4 ± 33.6	2.4	—	0.624	3.5	—	0.471
Median triglycerides <sup>§</sup> , mg/dL	108 (69, 149)	109 (82, 154)	-1.0	—	0.209	0.2	—	0.983
Glucose, mg/dL	89.0 ± 13.6	92.3 ± 20.1	-3.3	—	0.228	-2.8	—	0.318
Insulin, mU/L	16.8 ± 13.6	15.1 ± 12.5	1.7	—	0.366	2.2	—	0.254
Median CRP <sup>††</sup> , mg/L	2.7 (1.1, 6.5)	1.9 (0.7, 4.7)	0.8	—	0.110	1.2	—	0.017
Homocysteine, μmol/L	11.3 ± 3.3	10.5 ± 4.0	0.7	—	0.200	0.5	—	0.359
SLE-related factors								
SLEDAI	4.4 ± 4.5	2.6 ± 2.7	<b>1.8</b>	—	<0.001	1.2	—	0.006
SLICC-DI	2.5 ± 2.3	1.3 ± 1.5	<b>1.2</b>	—	<0.001	1.4	—	<0.001
Disease duration, i	14.4 ± 8.8	14.4 ± 8.0	0.03	—	0.978	1.6	—	0.152
Duration of CS use years	10.9 ± 8.6	9.2 ± 7.9	1.6	—	0.249	2.9	—	0.034
Current CS, %	61.9	36.3	—	<b>2.9</b>	<0.001	—	3.1	<0.001
Current HCQ, %	65.1	58.1	—	1.3	0.317	—	0.9	0.833
Current immunosuppressant use <sup>‡</sup> , %	30.2	22.0	—	0.3	0.271	—	0.4	0.379
Renal disease, %	31.7	24.8	—	1.4	0.265	—	1.3	0.396
C3, mg/dL	98.8 ± 28.1	100.5 ± 25.8	-1.7	—	0.652	-0.4	—	0.912
C4, mg/dL	21.7 ± 8.8	19.6 ± 7.4	2.1	—	0.061	2.5	—	0.026
dsDNA ( <i>Crithidia</i> ), %	50.8	24.4	—	<b>3.2</b>	<0.001	—	2.2	0.014
Thrombotic factors								
LAC, %	16.7	15.9	—	1.1	0.899	—	1.5	0.403
ACL IgG, %	18.0	17.8	—	1.0	0.971	—	1.4	0.439
ACL IgM, %	12.0	18.2	—	0.6	0.303	—	0.6	0.301
Antiphospholipid antibodies <sup>  </sup> , %	36.5	32.9	—	1.2	0.616	—	0.2	0.508
Inflammatory markers								
Median fibrinogen, mg/dL	362 (294, 390)	320 (246, 383)	<b>42</b>	—	0.004	52.1	—	0.002
ESR, mm/h	25.0 ± 19.8	14.1 ± 14.1	<b>10.9</b>	—	<0.001	10.1	—	<0.001
Albumin, g/dL	4.0 ± 0.6	4.4 ± 0.5	-0.4	—	<0.001	-0.3	—	<0.001

NOTES: Results reported as mean ± SD for continuous variables, median (interquartile range) for continuous variables with non-normal distribution, and % for categorical variables. Differences in means and medians (if data not normally distributed) were calculated for continuous variables and odds ratios (OR) were calculated for categorical variables.

ABBREVIATIONS: ASA, aspirin; CS, corticosteroid; HCQ, hydroxychloroquine; LAC, lupus anticoagulant; ESR, erythrocyte sedimentation rate.

\*Adjusted for age and study site.

<sup>†</sup>Self-reported history of hypertension, diabetes, and hypercholesterolemia.

<sup>‡</sup>Immunosuppressants included cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, and FK506.

<sup>§</sup>Results for triglycerides, CRP and fibrinogen reported as Median (interquartile range).

<sup>||</sup>Antiphospholipid antibodies considered positive if any 1 of the 3 antiphospholipid antibodies were positive (Lupus anticoagulant, ACL IgG, or ACL IgM). ACL IgG is positive if more than 10 units, and ACL IgM is positive if more than 15 units, as per University of Pittsburgh Coagulation Laboratory standards.

**Table II.** Comparison of carotid plaque, CAC, and IMT between AA and Caucasian women with SLE

Subclinical markers of CVD	AA	Caucasian	Unadjusted			Adjusted*		
			Mean difference	OR	P value	Mean difference	OR	P value
Plaque >0, %	43.5	29.6	—	1.83	0.038	—	1.94	0.041
CAC >0, %	45.0	42.1	—	1.12	0.689	—	1.55	0.189
IMT, mm	0.620 ± 0.125    0.605 ± 0.110		0.015	—	0.354	0.024	—	0.070

NOTES: Differences in mean calculated for continuous variables and ORs calculated for categorical variables.

ABBREVIATIONS: CAC, coronary artery calcium.

\*Adjusted for age and study site.

confidence interval [CI], 1.03–3.65), and AAs had higher carotid IMT, with a mean difference of 0.024 mm adjusted by age and study site, which was borderline significant ( $P = 0.07$ ). The racial difference in carotid plaque persisted despite adjustment for years of education (adjusted OR, 2.02; 95% CI, 1.06–3.87). No significant differences were observed in the presence of coronary calcium (45.0% vs 42.1%; adjusted OR, 1.55; 95% CI, 0.81–2.98) between the AA and Caucasian SLE women.

**Multivariate analysis (Table III).** We performed multivariate analyses to examine the association of carotid plaque and race, with adjustment for multiple risk factors. The models were adjusted *a priori* for age and study site. The risk factor covariates were selected for inclusion in this model if they differed significantly between the 2 races and were also associated with plaque with  $P < 0.20$  when added individually into a model that included race, age, and study site. If variables were redundant, only 1 was chosen to avoid collinearity (eg, DBP was included, but SBP was excluded; current corticosteroid use was included, but duration of use was excluded). Adjustment for DBP, corticosteroid use, SLEDAI, and SLICC-DI only modestly altered the OR when each covariate was added individually (see Table III). When all covariates were included in the model simultaneously, the OR for plaque in AA women compared with Caucasian women was 1.29 (95% CI, 0.64–2.58). Interestingly, the only traditional cardiovascular risk factor covariates that met criteria for inclusion into the model was blood pressure—SBP and DBP, with all others being lupus-related factors.

## DISCUSSION

This study is the first to investigate racial differences in subclinical CVD at various vascular beds in SLE women. We found that AA women with SLE are 2 times more likely to have carotid plaque than Caucasians. In our study, the traditional risk factors that were more prevalent in AA women with lupus included higher levels of blood pressure, BMI, and lipoprotein(a). Education level was slightly lower in AAs. For lupus-related factors, AAs had more disease activity, greater disease damage, more corticosteroid use, longer duration of corticosteroid use, increased presence of dsDNA anti-

bodies, and higher levels of inflammatory markers than Caucasian women with SLE. A combination of lupus-related factors and traditional CVD risk factors generally explained the racial differences in plaque burden.

It is well known that AAs have an increased rate of adverse cardiovascular events and related mortality compared with Caucasians in the general population.<sup>1</sup> Despite this increased risk of clinical events, AAs do not necessarily have more subclinical disease compared with Caucasians. Many studies suggest that patterns of atherosclerotic CVD may be different between AAs and Caucasians.

In the general population, AAs have consistently been reported to have higher IMT in the carotid arteries than Caucasians, particularly in the common carotid artery.<sup>25–27</sup> In our study, we detected a similar trend toward AA SLE women having higher IMT compared with Caucasians, with an adjusted mean difference of 0.024 mm ( $P = 0.07$ ).

In contrast, studies of racial differences in coronary artery calcification have been conflicting. Many studies have reported that AAs in the general population have a lower burden of coronary artery calcification.<sup>28–33</sup> One large physician referral-based population study reported a higher prevalence rate of coronary artery calcium in AA women as compared with Caucasian women<sup>34</sup>; yet several other studies could not demonstrate any differences in coronary calcification between AA and Caucasian women.<sup>28,35,36</sup> It has been suggested that the prevalence of coronary calcium increases with age, with Caucasians having a higher rate of progression with increasing age, which results in larger racial differences in older populations.<sup>37,38</sup> Most of these latter studies had younger cohorts, which may explain the lack of racial differences observed in coronary calcification. In our study of relatively young women, we also found no significant differences in coronary artery calcification in AAs compared with Caucasians.

Carotid plaque has also generally been reported to be more frequent in Caucasians compared with AAs in the general population. One early study demonstrated that Caucasians have a higher prevalence of occlusive atherosclerotic disease in the extracranial arteries,

**Table III.** Multivariate adjusted OR for carotid plaque in AA compared with Caucasian women with SLE

Adjusting variables	OR for Plaque in AA vs Caucasians	95% CI
Age and study site	1.94	1.03, 3.64
DBP alone	1.68	0.87, 3.21
Corticosteroid use alone	1.73	0.90, 3.31
SLEDAI alone	1.79	0.94, 3.41
SLICC-DI alone	1.57	0.81, 3.10
DBP, corticosteroid use, SLEDAI, SLICC-DI	1.29	0.64, 2.58

NOTES: Risk-factor variables were selected for inclusion into the model if they differed significantly between the 2 races and were also associated with plaque with a *P* value less than 0.20 when added individually into a model that included race, age, and study site. ORs for plaque are shown with each explanatory risk factor variable added individually and then when added simultaneously into a model that includes age and study site.

whereas AAs have more disease in the intracranial vessels.<sup>39</sup> In the general population and the diabetic population, AA women were found to have less carotid plaque burden than Caucasian women.<sup>26,27</sup> In contrast, we found that carotid plaque was observed more frequently in AA women compared with Caucasian women with SLE.

The reason for these differences in the prevalence of subclinical CVD between those in the general population and the lupus women in our study is not known. It is possible that the relative role of important risk factors may be contributing to differences observed in our population compared with the reports from the general population. Differences may exist in traditional CVD risk factors between our SLE population and the general population, or it may be that the addition of lupus related factors may be affecting the risk of developing subclinical disease at different rates. Alternatively, synergistic effects of the lupus-related factors in combination with the traditional risk factors may be driving the differential risk between the racial groups in both populations. The combination of SLE-related risk factors and hypertension in the AA SLE women, as observed in this study, may be contributing to the greater risk of subclinical CVD among AA SLE women, as well as the increased risk of mortality in these women. To explore these potential explanations, we are collecting data on healthy controls to characterize and compare the risk factors and prevalence of subclinical CVD in the SLE women and age–race matched healthy controls from the general population.

Although not specifically designed to study racial differences in subclinical CVD, 2 earlier studies have reported an absence of racial differences in the preva-

lence of carotid plaque.<sup>9,40</sup> The findings described in these studies are in contrast to the results of our study and may be explained by several differences in methodology. In our study, only asymptomatic patients without a history of clinical CVD were included, whereas 25 of 204 subjects had a history of clinical CVD (MI, angina, CVA, or TIA) in the study by Roman et al.<sup>9</sup> In the study by Maksimowicz-McKinnon et al,<sup>40</sup> 5% had a CVA and 4% had an MI. Insufficient information is provided to estimate the prevalence of angina or TIA among the latter cohort. Furthermore, in the latter study, only 14% of their subjects had plaque, which is in contrast to 45% in our subjects and 37% in Roman et al's<sup>9</sup> subjects. Plaque was defined similarly in both Roman et al's<sup>9</sup> and our studies, but the latter study does not describe the criteria that were used to determine the presence of plaque. Roman et al<sup>9</sup> compared “whites” versus “non-whites,” and inclusion of other non-AA subjects in the “non-white” category may have precluded detecting differences in subclinical carotid disease. Last, the 2 previous studies included male lupus subjects, who were excluded from our study.

Several studies have examined the risk factors for subclinical CVD in SLE patients, but none have studied racial differences in risk factors systematically in SLE patients. Traditional CVD risk factors that include male sex, hyperlipidemia, hypertension, postmenopausal status, obesity, smoking, and diabetes mellitus were found to be predictive of clinical and subclinical CVD in SLE patients.<sup>2-6,40</sup> Carotid plaque has been associated with both traditional CVD risk factors, which include older age,<sup>4,5,41</sup> higher SBP,<sup>5,41</sup> higher LDLc,<sup>5</sup> and lower HDL3 cholesterol,<sup>41</sup> as well as SLE-related factors, which include older age at diagnosis,<sup>9</sup> longer duration of SLE,<sup>9</sup> higher damage index score,<sup>9</sup> less aggressive immunosuppressive therapy,<sup>9</sup> longer duration of prednisone use,<sup>5</sup> and cumulative prednisone dose.<sup>4</sup>

We recognize that our study has several limitations that should be taken into consideration when evaluating the results. The study population consisted of relatively fewer AA women than Caucasian women. Therefore, we did not have adequate power to determine fully the associations between risk factors and the various measures of subclinical disease within the AA group.

Furthermore, we excluded women with clinical CVD. In the Pittsburgh original cardiovascular study, 17.6% of Caucasians and 32.3% of AAs had a history of cardiovascular events; in SOLVABLE, 7% of Caucasians and 8% of AAs had a history of baseline cardiovascular events. Exclusion of women with clinical events may have introduced bias, as a higher proportion of AA subjects were excluded for having clinical events compared with Caucasians. Despite excluding a higher proportion of AA subjects, we were still able to demonstrate

a difference in the presence of carotid plaque between the 2 races.

Although bias may have been introduced by the exclusion criteria, the focus of our study was asymptomatic women, which we determined *a priori* was important for the purposes of a prospective study to determine the true incidence of clinical CVD, as well as for the purposes of a cross-sectional analysis in which clinical disease may influence health behaviors and thus risk factor exposure. Particularly, because atherosclerosis is a chronic inflammatory disease that may lead to activation of inflammatory and endothelial cells in the diseased areas, an increase in measured markers of inflammation may be reflective of the total burden of atherosclerosis in all arterial beds rather than as a risk factor that contributes to CVD. We attempted to overcome this limitation by excluding women with the greatest burden of atherosclerosis (ie, those patients with known clinical CVD). Nevertheless, the cross-sectional nature of this study precludes us from making any conclusions on CVD prediction based on the various risk factors. We plan on following this cohort longitudinally, which will allow us to overcome this limitation in the future.

Another limitation in this study is that antiphospholipid antibodies were measured at 1 occasion at the study visit because of the cross-sectional study design and may have led to misclassification. Although 2 serial positive measurements are necessary for the diagnosis of antiphospholipid syndrome, the purpose of this cross-sectional study was not to study the correlation between race and antiphospholipid syndrome, but to measure antiphospholipid positivity at the baseline visit. We hope to address this issue in the future, as our study is ongoing, with subjects returning for regular follow-up visits. We are confident that in the longitudinal analyses we can address the issue of association between race and antiphospholipid positivity (with at least 2 positive measurements) and/or syndrome (by including clinical criteria).

However, given these limitations, the results support our findings that in SLE women without clinical CVD, AAs were more likely to have carotid plaque than Caucasians. The CVD risk factors associated with racial differences in plaque for our study were a combination of both lupus-related and traditional factors, which would provide a potential explanation for the differential findings in our study of SLE women compared with the general population. A longitudinal investigation of both racial groups in women with and without SLE will provide valuable information regarding the relative role of lupus-related factors in the progression of subclinical CVD and incidence of clinical CVD events.

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