Arthritis Care & Research
Vol. 62, No. 6, June 2010, pp 881–887
DOI 10.1002/acr.20122

ORIGINAL ARTICLE

Atherosclerotic Vascular Events in a Multinational Inception Cohort of Systemic Lupus Erythematosus

M. B. UROWITZ,[1] D. GLADMAN,[1] D. IBAÑEZ,[1] S. C. BAE,[2] J. SANCHEZ-GUERRERO,[3] C. GORDON,[4] A. CLARKE,[5] S. BERNATSKY,[5] P. R. FORTIN,[6] J. G. HANLY,[7] D. J. WALLACE,[8] D. ISENBERG,[9] A. RAHMAN,[9] G. S. ALARCÓN,[10] J. T. MERRILL,[11] E. GINZLER,[12] M. KHAMASHTA,[13] O. NIVED,[14] G. STURFELT,[14] I. N. BRUCE,[15] K. STEINSSON,[16] S. MANZI,[17] R. RAMSEY-GOLDMAN,[18] M. A. DOOLEY,[19] A. ZOMA,[20] K. KALUNIAN,[21] M. RAMOS,[22] R. F. VAN VOLLENHOVEN,[23] C. ARANOW,[24] T. STOLL,[25] M. PETRI,[26] AND P. MADDISON,[27] FOR THE SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS

Objective. **To describe vascular events during an 8-year followup in a multicenter systemic lupus erythematosus (SLE) inception cohort and their attribution to atherosclerosis.**

Methods. **Clinical data, including comorbidities, were recorded yearly. Vascular events were recorded and attributed to atherosclerosis or not. All of the events met standard clinical criteria. Factors associated with atherosclerotic vascular events were analyzed using descriptive statistics, *t*-tests, and chi-square tests. Stepwise multivariate logistic regression was used to assess the association of factors with vascular events attributed to atherosclerosis.**

Results. **Since 2000, 1,249 patients have been entered into the cohort. There have been 97 vascular events in 72 patients, including: myocardial infarction (n = 13), angina (n = 15), congestive heart failure (n = 24), peripheral vascular disease (n = 8), transient ischemic attack (n = 13), stroke (n = 23), and pacemaker insertion (n = 1). Fifty of the events were attributed to active lupus, 31 events in 22 patients were attributed to atherosclerosis, and 16 events were attributed to other causes. The mean ± SD time from diagnosis to the first atherosclerotic event was 2.0 ± 1.5 years. Compared with patients followed for 2 years without atherosclerotic events (n = 615), at enrollment, patients with atherosclerotic vascular events were more frequently white, men, older at diagnosis of SLE, obese, smokers, hypertensive, and had a family history of coronary artery disease. On multivariate analysis, only male sex and older age at diagnosis were associated factors.**

Conclusion. **In an inception cohort with SLE followed for up to 8 years, there were 97 vascular events, but only 31 were attributable to atherosclerosis. Patients with atherosclerotic events were more likely to be men and to be older at diagnosis of SLE.**

INTRODUCTION

Since the first description of the bimodal mortality pattern of systemic lupus erythematosus (SLE) showing that coronary artery disease (CAD) is a significant cause of morbidity and mortality in this condition, multiple studies have addressed the nature of these clinical outcomes and the associated risk factors (1). However, the exact inci-

Dr. Urowitz's work was supported by the Canadian Institutes of Health Research (grant MOP-49529), the Lupus Foundation of Ontario, the Ontario Lupus Association, Lupus UK, the Lupus Foundation of America, the Lupus Alliance of Western New York, the Conn Smythe Foundation, The Lupus Flare Foundation, and the Tolfo family of Toronto, Ontario, Canada. Dr. Gladman's work was supported by the Canadian Institutes of Health Research. Dr. Bae's work was supported by the Brain Korea 21 Program. Dr. Gordon's work was supported by Lupus UK, the Arthritis Research Campaign, and the Wellcome Trust Clinical Research Facility, Birmingham, UK. Dr. Clarke's work was supported by the Singer Family Fund for Lupus Research, and is a Fonds de la Recherche en Sante du Quebec National Scholar. Dr. Bernatsky's work was supported by the Fonds de la Recherche en Sante du Quebec Jeune Chercheure and the McGill University Health Centre Research Institute, and is recipient of a Canadian Institutes of Health Research Junior Investigator Award and a Canadian Arthritis Network Scholar Award. Dr. Fortin is a Distinguished Senior Investigator of The Arthritis Society, with additional support from the Arthritis Centre of Excellence, University of Toronto. Dr. Hanly's work was supported by a grant from the Canadian Institutes of Health Research. Dr. Alarcón's work was supported by the University of Alabama at Birmingham (NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases grant P60-AR-48095). Drs. Nived and Sturfelt's work was supported by the Swedish Medical Research Council (grant 13489). Dr. Ramsey-Goldman's work was supported by the NIH (grants UL-1RR-025741, K24-AR-02318, and P60-AR-48098). Dr. Petri's work was supported by the Hopkins Lupus Cohort (grant AR-43727) and the Johns Hopkins University General Clinical Research Center (grant M01-RR-00052).

dence and prevalence of atherosclerotic events is unknown. A few studies have attempted to identify risk factors for CAD in lupus (2–5). To date, these studies have found elevated total cholesterol and older age at diagnosis of SLE to be significantly associated with CAD. Other factors implicated in one or two studies have been hypertension (2,3), previous cardiac involvement with SLE, obesity (2), and longer duration of corticosteroid use (3). However, lupus populations vary with regard to organ involvement, and it has not been possible to adequately address these variables in the past, given the limited power of previous studies. Furthermore, incident SLE subjects were rarely studied.

To address this complex clinical problem with appropriate epidemiologic tools in a relatively uncommon disease such as SLE would be impossible without a concerted international effort. The Systemic Lupus International Collaborating Clinics (SLICC) is a group of rheumatologists and methodologists from 27 international centers who have a particular interest and expertise in SLE. The cooperating centers all follow large cohorts of SLE patients in standardized databases. The group has been working together since 1987 (6). SLICC has developed an international registry of newly diagnosed SLE patients in order to provide a large diverse population to carry out a prospective longitudinal study. One of the major objectives of the study is to determine the prevalence and type of atherosclerotic vascular disease in SLE and to identify associated risk factors. The SLICC group has shown that a significant number of CAD risk factors are present within the first year of disease (7).

The aims of this SLICC investigation were to describe the vascular events occurring during the first 8 years of followup and to attribute the vascular events to atherosclerosis.

[1]M. B. Urowitz, MD, D. Gladman, MD, D. Ibañez, MSc: Toronto Western Hospital, Toronto, Ontario, Canada; [2]S. C. Bae, MD: Hospital for Rheumatic Diseases and Hanyang University Medical Center, Seoul, Korea; [3]J. Sanchez-Guerrero, MD: Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico; [4]C. Gordon, MD: Medical School, University of Birmingham, Birmingham, UK; [5]A. Clarke, MD, S. Bernatsky, MD: Montreal General Hospital and McGill University Health Centre, Montreal, Quebec, Canada; [6]P. R. Fortin, MD: Toronto Western Hospital and University of Toronto, Toronto, Ontario, Canada; [7]J. G. Hanly, MD: Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia, Canada; [8]D. J. Wallace, MD: Cedars-Sinai/David Geffen School of Medicine, University of California, Los Angeles; [9]D. Isenberg, MD, A. Rahman, MD: University College, London, UK; [10]G. S. Alarcón, MD, MPH: University of Alabama, Birmingham; [11]J. T. Merrill, MD: Oklahoma Medical Research Foundation, Oklahoma City; [12]E. Ginzler, MD: State University of New York Downstate Medical Center, Brooklyn; [13]M. Khamashta, MD: St. Thomas' Hospital and King's College London School of Medicine, London, UK; [14]O. Nived, MD, G. Sturfelt, MD: University Hospital Lund, Lund, Sweden; [15]I. N. Bruce, MD: University of Manchester, Manchester, UK; [16]K. Steinsson, MD: Landspitali University Hospital, Reyjkavik, Iceland; [17]S. Manzi, MD: University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [18]R. Ramsey-Goldman, MD: Northwestern University and Feinberg School of Medicine, Chicago, Illinois; [19]M. A. Dooley, MD: University of North Carolina, Chapel Hill; [20]A. Zoma, MD: Hairmyres Hospital, East Kilbride, UK; [21]K. Kalunian, MD: University of California School of Medicine, San Diego; [22]M. Ramos, MD: Unidad de Enfermedades, Barcelona, Spain; [23]R. F. Van Vollenhoven, MD: The Karolinska Institute, Stockholm, Sweden; [24]C. Aranow, MD: Columbia University Medical Center, New York, New York; [25]T. Stoll, MD: Kantonsspital, Schaffhausen, Switzerland; [26]M. Petri, MD: Johns Hopkins University School of Medicine, Baltimore, Maryland; [27]P. Maddison, MD: North West Wales National Health Service Trust, Bangor, UK.

Dr. Fortin has received consultant fees, speaking fees, and/or honoraria (less than $10,000) from AstraZeneca.

Address correspondence to M. B. Urowitz, MD, Centre for Prognosis Studies, 1-319 Main Pavilion, Toronto Western Hospital, 399 Bathurst Street, Ontario M5T 2S8, Canada. E-mail: m.urowitz@utoronto.ca.

Submitted for publication July 13, 2009; accepted in revised form January 28, 2010.

PATIENTS AND METHODS

The SLICC registry for atherosclerosis (SLICC-RAS). Twenty-six SLICC centers from 11 countries in North America, Europe, and Asia participated in this study. An inception cohort of 1,249 SLE patients has been assembled according to a standardized protocol between 2000 and 2008 to study risk factors for atherosclerosis. Data collected include clinical and laboratory features of lupus, CAD risk factors, and atherosclerotic outcomes based on a glossary of established definitions.

Patients. Patients were enrolled in the registry within 15 months of their date of diagnosis based on ≥4 American College of Rheumatology (ACR) classification criteria (8). Demographic, clinical, and laboratory features of lupus, CAD risk factors, and atherosclerotic outcome and attribution data collected were submitted to the coordinating center at the University of Toronto at enrollment and once annually. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index 2000 update (SLEDAI-2K) (9) and the adjusted mean SLEDAI-2K (10). Damage was measured by the SLICC/ACR Damage Index (11,12).

Definitions of atherosclerotic outcomes and attribution. Myocardial infarction was defined on the basis of definite electrocardiographic (EKG) abnormalities or symptoms of chest pain with probable EKG abnormalities and abnormal cardiac enzymes, typical symptoms and abnormal cardiac enzymes, or fresh myocardial infarction or coronary occlusion at postmortem examination (13). Its attribution to atherosclerosis was inactive SLE at the time of the event (based on the treating physician opinion and not associated with increase or new therapy), any of typical atherosclerotic changes on angiogram, and evidence of atherosclerosis elsewhere (cerebrovascular, peripheral vascular). Examinations to confirm these criteria were at the discretion of the treating physician.

Angina was defined as severe pain or discomfort over the upper or lower sternum or anterior left chest and left arm on exertion, relieved at rest. Its attribution to athero-

sclerosis was inactive SLE at the time of the event (based on the treating physician opinion and not associated with increase or new therapy), any of typical atherosclerotic changes on angiogram, and evidence of atherosclerosis elsewhere (cerebrovascular, peripheral vascular).

Congestive heart failure was diagnosed clinically or on chest radiograph. Its attribution to atherosclerosis was inactive SLE at the time of the event (based on the treating physician opinion and not associated with increase or new therapy), any of typical atherosclerotic changes on angiogram, and evidence of atherosclerosis elsewhere (cerebrovascular, peripheral vascular).

Insertion of a pacemaker was attributed to atherosclerosis by inactive SLE at the time of the event (based on the treating physician opinion and not associated with increase or new therapy), any of typical atherosclerotic changes on angiogram, and evidence of atherosclerosis elsewhere (cerebrovascular, peripheral vascular).

Intermittent claudication consisted of classic symptoms, including cramping pain and weakness in the legs, especially the calves, on walking that disappears after rest. Its attribution to atherosclerosis was inactive SLE at the time of the event (based on the treating physician opinion and not associated with increase or new therapy), typical atherosclerotic changes on angiogram, and evidence of atherosclerosis elsewhere (cardiac, cerebrovascular).

Transient ischemic attack was defined as a transient and completely reversible neurologic deficit with complete recovery within 24 hours. Its attribution to atherosclerosis was inactive SLE at the time of the event (based on the treating physician opinion and not associated with increase or new therapy), typical atherosclerotic changes on angiogram, and evidence of atherosclerosis elsewhere (cardiovascular, peripheral vascular).

Stroke was defined as irreversible or partially reversible motor and/or sensory deficits of sudden or recent onset on the basis of vascular occlusion or insufficiency, including complete or incomplete stroke or stroke in evolution. Its attribution to atherosclerosis was inactive SLE at the time of the event (based on the treating physician opinion and not associated with increase or new therapy), any of typical atherosclerotic changes on angiogram, and evidence of atherosclerosis elsewhere (cerebrovascular, peripheral vascular).

Statistical analysis. Data presented for descriptive purposes are the mean ± SD for continuous variables as well as percentages for categorical variables. Patients with atherosclerotic vascular events were compared with patients with no atherosclerotic vascular events using *t*-tests and chi-square tests. Stepwise logistic regression analysis was used to determine the contribution of multiple putative risk factors and their association with the presence of vascular events attributed to atherosclerosis. Adequacy of model fit was established with the Hosmer and Lemeshow goodness-of-fit test. Factors included in the model were those that were significantly different in the univariate analysis. Finally, comparisons between patients with vascular events attributed to atherosclerosis and patients with events attributed to SLE were made using nonparametric tests due to the small sample size, including Fisher's exact test and Wilcoxon's rank sum test. A multivariate analysis was not conducted with the group of patients because of sample size limitations.

Table 1. Characteristics of the SLICC-RAS cohort at enrollment*

	Value
Women	1,117 (89.4)
Race/ethnicity, %	
White	49
African American	15
Hispanic	16
Asian	16
Other	4
Age at diagnosis, mean ± SD years	34.3 ± 13.3
Disease duration, mean ± SD months	5.5 ± 4.1
SLEDAI-2K score, mean ± SD	5.49 ± 5.59
Corticosteroids	849 (69.7)
Immunosuppressive agents	485 (39.8)
Antimalarials	771 (63.3)

* Values are the number (percentage) unless otherwise indicated. SLICC-RAS = Systemic Lupus International Collaborating Clinics registry for atherosclerosis; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000 update.

RESULTS

Characteristics of the SLICC-RAS cohort at enrollment. Of the 1,249 patients enrolled, 1,117 (89%) were women, 49% were white, 15% were African American, 16% were Hispanic, 16% were Asian, and 4% were other. The mean age at presentation was 34 years, and the mean disease duration at entry to the cohort was 5.5 months. The mean SLEDAI-2K score was 5.5 and the majority of patients were already receiving corticosteroid and antimalarial therapy (Table 1).

Vascular events. Ninety-seven vascular events occurred in 72 patients. The majority of the events (n = 61) were cardiovascular in nature, including myocardial infarction (n = 13), angina (n = 15), congestive heart failure (n = 24), pacemaker insertion (n = 1), and peripheral vascular disease (n = 8). Thirty-six events were cerebrovascular, including transient ischemic attacks (n = 13) and stroke (n = 23).

Attribution of vascular events. Of the 97 vascular events, only 31 (in 22 patients) were attributed to atherosclerosis and occurred at a mean ± SD of 2.0 ± 1.5 years after entry into the cohort. Of the 14 events due to myocardial infarction, intermittent claudication, or transient ischemic attack, 10 were confirmed by imaging studies. Fifty of the 97 vascular events were attributed to active lupus, and 16 were attributed to other causes (Table 2).

Baseline comparison of patients with and without atherosclerotic vascular events followed for at least 2 years. Baseline variables for the 22 patients with atherosclerotic vascular events were compared with 615 SLE patients who

Table 2. Attribution of vascular events*

	Attributed to atherosclerosis	Attributed to active SLE	Attributed to other causes†
Total no. of events	31	50	16
Stroke	0	20	3
Congestive heart failure	5	12	7
Transient ischemic attack	2	10	1
Peripheral vascular disease	4	3	1
Angina	12	2	1
Myocardial infarction	8	2	3
Pacemaker insertion	0	1	0

* SLE = systemic lupus erythematosus.
† List of causes: coagulopathy (n = 3), pregnancy complications (n = 2), fluid overload (n = 2), postoperative complications (n = 1), vertebral artery dissection (n = 1), pulmonary disease (n = 1), gastrointestinal bleed (n = 1), renal failure on dialysis (n = 1), coronary artery spasm (n = 1), hypertension (n = 1), and unknown (n = 2).

did not have atherosclerotic vascular events and were followed for at least 2 years. A 2-year followup for the controls was chosen since the atherosclerotic vascular events occurred at an average of 2 years after entry into the cohort. Men make up 11% of the inception cohort but make up 41% of the patients with atherosclerotic events. Other features of patients with atherosclerotic events were white ethnicity, older age at diagnosis of SLE, hypertensive, obese, smokers, and a positive family history for CAD (Table 3). There was no difference at baseline in the frequency of hypercholesterolemia, diabetes mellitus, and use of corticosteroids, antimalarials, or immunosuppressive drugs between patients with and without atherosclerotic vascular events. SLEDAI-2K score at presentation as well as adjusted mean SLEDAI-2K score at year 2 were similar in both groups. A stepwise multivariate analysis including the items that were significant on the univariate analyses revealed only older age at diagnosis (odds ratio [OR] 1.08, 95% confidence interval [95% CI] 1.05–1.11) and male sex (OR 3.67, 95% CI 1.41–9.52) as being independently associated with atherosclerotic vascular events. Hosmer and Lemeshow goodness-of-fit test $P = 0.59$, indicating that the model fit is adequate.

Patients with vascular events due to lupus compared with those with atherosclerotic vascular events. We then compared patients with atherosclerotic events with those with vascular events due to lupus (Table 4). Male sex, older age at diagnosis, white race, and use of antimalarials at baseline were associated with atherosclerotic vascular events.

DISCUSSION

This study reports on atherosclerotic events in an international inception cohort of patients with SLE. Of the 97 vascular events documented among the 1,249 patients, only 31 events were attributable to atherosclerosis. These events occurred within 2 years of entry into the cohort, or approximately 2.5 years from diagnosis. In long-term followup studies, the prevalence of atherosclerotic vascular events varies from 8–13% (14,15) and usually occurs at a mean of 8–9 years from diagnosis (1,15).

This study describes atherosclerotic vascular events in 22 (1.8%) of 1,249 patients. As previously noted, SLE patients with atherosclerotic vascular events tend to be

Table 3. A comparison between patients with atherosclerotic vascular events (AVEs) due to atherosclerosis and all other patients*

At enrollment	Patients with AVEs	All other patients†	*P*
No. of patients	22	615	
White	17 (77.3)	328 (53.3)	0.03
Men	9 (40.9)	72 (11.7)	< 0.0001
Age at diagnosis, mean ± SD years	54.6 ± 13.1	34.6 ± 13.7	< 0.0001
Hypertension	14 (73.6)	197 (32.3)	0.002
Obese‡	12 (57.1)	163 (28.1)	0.004
Smoker (current or ex)	14 (63.6)	225 (36.6)	0.01
Family history of CAD (adjusted for age)§	9 (42.9)	117 (20.0)	0.02
Hypercholesterolemia	12 (54.6)	228 (37.4)	0.10
Diabetes mellitus	2 (10.5)	14 (2.4)	0.08
Corticosteroids	17 (77.3)	417 (68.5)	0.38
Antimalarials	16 (72.7)	386 (63.5)	0.38
Immunosuppressive drug use	6 (27.3)	227 (37.3)	0.34
SLEDAI-2K score at presentation, mean ± SD	3.32 ± 3.09	5.53 ± 5.63	0.11
Adjusted mean SLEDAI-2K score at year 2, mean ± SD	3.02 ± 3.11	4.15 ± 3.78	0.12

* Values are the number (percentage) unless otherwise indicated. CAD = coronary artery disease; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000 update.
† Followed for at least 2 years.
‡ Body mass index >27 kg/m^2 for women and >25 kg/m^2 for men.
§ First-degree relative age <65 years for women and age <55 years for men.

Table 4. A comparison between patients with vascular events due to atherosclerosis and patients with vascular events due to SLE*

	Patients with vascular events due to atherosclerosis	Patients with vascular events due to SLE	*P*
No. of patients†	22	42	
White	17 (77.3)	21 (50.0)	0.03
Men	9 (40.9)	8 (19.1)	0.06
Age at diagnosis, mean ± SD years	54.6 ± 13.1	41.2 ± 13.8	0.0004
Hypertension	14 (63.6)	28 (66.7)	0.81
Obese‡	12 (57.1)	15 (36.6)	0.12
Diabetes mellitus	2 (10.5)	1 (2.4)	0.23
Smoker (current or ex)	14 (63.6)	16 (38.1)	0.052
Family history of CAD (adjusted for age)§	9 (42.9)	13 (31.7)	0.39
Hypercholesterolemia	12 (54.6)	19 (45.2)	0.48
Antiphospholipid antibodies at enrollment, no./total (%)	8/20 (40.0)	15/35 (42.9)	0.84
aCL	3/17 (17.7)	5/32 (15.6)	1.00
LAC	6/20 (30.0)	14/35 (40.0)	0.46
Corticosteroids	17 (77.3)	30 (71.4)	0.62
Antimalarials	16 (72.7)	15 (36.6)	0.006
Immunosuppressive drug use	6 (27.3)	21 (50.0)	0.08
SLEDAI-2K score, mean ± SD	3.32 ± 3.09	5.93 ± 7.47	0.43
Adjusted mean SLEDAI-2K score at year 2, mean ± SD	3.02 ± 3.11	4.91 ± 4.82	0.15

* Values are the number (percentage) unless otherwise indicated. SLE = systemic lupus erythematosus; CAD = coronary artery disease; aCL = anticardiolipin antibody; LAC = lupus anticoagulant; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000 update.
† There were 31 atherosclerotic vascular events in 22 patients and 50 vascular events due to SLE in 42 patients.
‡ Body mass index >27 kg/m^2 for women and >25 kg/m^2 for men.
§ First-degree relative age <65 years for women and age <55 years for men.

older at SLE diagnosis than those without these events (2,3). In this study, patients with atherosclerotic vascular events were 20 years older than those without events, accounting in part for the earlier onset of atherosclerotic vascular events (within 2.5 years of SLE diagnosis) in this inception cohort. In univariate analyses, patients with vascular events due to atherosclerosis were more likely to have the classic risk factors for atherosclerotic disease than patients without atherosclerotic vascular events who had been followed for at least 2 years. They were more likely to be men, older, hypertensive, obese, smokers, and have a family history of CAD. Disease activity at presentation and over the first 2 years was similar in patients who had atherosclerotic vascular events and patients who did not. There was also no difference in the baseline use of medications between the two groups. However, in multivariate analysis, only male sex and older age remained independently associated with atherosclerotic vascular events.

In the Baltimore study of 229 patients, 29 events were reported. In a multivariate analysis, patients with events had higher cholesterol, a history of hypertension, a longer mean SLE duration, and greater duration and use of corticosteroids (Table 5). However, although the cohort was followed for 4 years, it was a prevalent cohort with a mean SLE disease duration of 12 years in those with atherosclerotic vascular events compared with 8 years in those without (2). In the Pittsburgh cohort, also a prevalent cohort of 498 women, there were 33 events. The risk factors identified in a multivariate analysis included older age at diagnosis, longer SLE duration, longer duration of corticosteroid use, hypercholesterolemia, and postmenopausal status. In this cohort, the SLE disease duration in those with atherosclerotic vascular events was 13.0 years compared with 10.0 in those without (3). In the LUMINA (LUpus in MInorities, NAture versus nurture) cohort, which includes patients within 5 years of diagnosis, in 546 patients there were 34 vascular events, including angina, myocardial infarction, vascular interventions, strokes, and peripheral vascular events. Risk factors identified in multivariate analysis included older age, current smoking status, longer followup time, elevated C-reactive protein level, and the presence of antiphospholipid antibodies (16). In the Toronto cohort, of 1,087 patients who did not have atherosclerotic vascular events prior to entry to the cohort, 144 atherosclerotic vascular events were documented. In a multivariate analysis of risk factors for atherosclerotic vascular events, neuropsychiatric disease, vasculitis, and number of Framingham CAD risk factors were associated with coronary artery events (15). In the inception patients in the Toronto Cohort that included 561 patients seen within 1 year of diagnosis and followed through 9 years of followup, 9.6% had atherosclerotic vascular events. A multivariate analysis of risk factors for atherosclerotic vascular events revealed neuropsychiatric disease and smoking to be associated with atherosclerotic vascular events (15).

In the 2 inception cohorts with disease duration at entry of less than 1 year (the Toronto inception cohort and the current SLICC-RAS cohort study), the classic Framingham risk factors were not clearly independently associated with atherosclerotic vascular events because there was a shorter exposure to these risk factors perhaps mitigating their impact. It is possible that over time these risk factors will exert their influence. Furthermore, the LUMINA, To-

Table 5. Summary of risk factors for atherosclerotic vascular events in 5 cohorts*

	Baltimore (n = 229) (2)	Pittsburgh (n = 498) (3)	LUMINA (n = 546) (16)	Toronto inception (n = 561) (15)	SLICC (n = 637)†
Type of cohort	Prevalent	Prevalent	Inception, 5 years	Inception, 1 year	Inception, 1 year
Older age at diagnosis	√	√	√		√
Longer duration of SLE	√	√	√		
Male sex					√
Longer duration of prednisone use	√	√			
Hypercholesterolemia	√	√			
Hypertension	√				
Postmenopausal status		√			
Smoking			√	√	
Neuropsychiatric lupus				√	
C-reactive protein			√		
Antiphospholipid antibodies			√		

* Thirty-seven patients in SLICC have also been used in the Toronto inception study but had 3 more years of followup in the SLICC registry. LUMINA = LUpus in MInorities, NAture versus nurture; SLICC = Systemic Lupus International Collaborating Clinics; SLE = systemic lupus erythematosus.
† Includes only patients followed for at least 2 years.

ronto, and SLICC studies included cerebrovascular and peripheral vascular atherosclerotic vascular events, while the Baltimore and Pittsburgh studies included only CAD events. Although there were no cerebrovascular accidents reported in the current study, there were 2 instances of transient ischemic attack and 4 with peripheral vascular disease. This difference in outcomes might have an effect on the nature of the associated factors.

We have previously demonstrated in this cohort that risk factors for atherosclerotic disease accumulate early in the course of the disease (17). However, as suggested earlier, these risk factors have not yet exerted their full impact. In early disease it is likely that male sex and older age states associated with increased risk factors for atherosclerotic vascular events are dominant. This should not deter from the necessity for aggressive intervention in the treatment of classic CAD risk factors.

Atherosclerotic vascular events documented in this cohort included cardiac, cerebrovascular, and peripheral vascular events. Cardiac and cerebral events are common disease features of SLE. These clinical presentations often pose a diagnostic challenge because they are often confounded by comorbid conditions. In addition, atherosclerotic events may mimic SLE presentations; for example, chest pain and stroke syndromes can be on the basis of active SLE or atherosclerosis. Furthermore, this is made more difficult by the fact that the patients who presented with atherosclerotic vascular events early in the course of their SLE disease had similar risk factors to patients who presented with a lupus vascular event, except with regard to older age at diagnosis, white race, and use of antimalarials. Unlike other studies where antimalarials have been suggested to be protective for atherosclerotic or thrombotic disease, in the current study, patients with atherosclerotic events more often took antimalarials than those who did not have atherosclerotic events (18–20). The reason for this is unclear. Although it is possible that patients with atherosclerotic events had had more severe disease prior to enrolling in the SLICC-RAS, at 2 years, patients without atherosclerotic events actually had higher disease activity measured by the adjusted mean SLEDAI-2K. Therefore, the reason for the lower use of antimalarials in these patients is unknown. Clinicians must adopt attribution rules, as used in this study, to differentiate those events due to the disease itself from those due to atherosclerosis. In addition to the clinical attribution rules, most patients in this study had confirmatory laboratory and imaging studies.

A limitation of this study is the relatively short duration of followup of an inception cohort, and therefore the number of events is small. Nevertheless, 31 events in 22 patients were detected within 2.5 years of diagnosis, highlighting the fact that in some individuals (older men) these events may occur very early in the disease. Another possible limitation is the interval between assessments being 1 year, which may not reveal the full impact of disease activity on the development of atherosclerotic events. The strengths of this study are the size of the inception cohort, its multiethnic composition, the uniform collection of data on a common data retrieval protocol, and the use of standardized clinical attribution rules for atherosclerotic vascular events. Nevertheless, in patients with known atherosclerotic disease, active lupus may make the attribution of an event more difficult, and in cases of active lupus, subclinical atherosclerosis may be missed. However, in the majority of cases the attribution rules helped clarify the situation. Patients in this cohort will continue to be followed for 5 years.

ACKNOWLEDGMENTS

We are grateful for the generous donation of our patients' time and the dedication of all of the fellows, research coordinators, and research assistants in the SLICC network to the completion of this work.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Urowitz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Urowitz, Gladman, Gordon, Clarke, Fortin, Hanly, Isenberg, Merrill, Khamashta, Nived, Sturfelt, Bruce, Steinsson, Manzi, Aranow, Stoll, Maddison.

Acquisition of data. Urowitz, Gladman, Bae, Sanchez-Guerrero, Gordon, Clarke, Bernatsky, Fortin, Hanly, Wallace, Isenberg, Rahman, Alarcón, Merrill, Ginzler, Khamashta, Nived, Sturfelt, Bruce, Steinsson, Manzi, Ramsey-Goldman, Dooley, Zoma, Kalunian, Ramos, Van Vollenhoven, Aranow, Stoll, Petri, Maddison.

Analysis and interpretation of data. Urowitz, Gladman, Ibañez, Gordon, Clarke, Bernatsky, Fortin, Hanly, Wallace.

REFERENCES

1. Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality in systemic lupus erythematosus. Am J Med 1976;60:221–5.
2. Petri M, Perez-Gutthan S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med 1992;93:513–9.
3. Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham study. Am J Epidemiol 1997;145:408–15.
4. Gladman DD, Urowitz MB. Morbidity in systemic lupus erythematosus. J Rheumatol 1987;14 Suppl 13:223–6.
5. Manzi S, Selzer F, Sutton-Tyrrel K, Fitzgerald S, Rairie JE, Tracy RP, et al. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. Arthritis Rheum 1999;42:51–60.
6. Isenberg DA, Gladman DD. The Systemic Lupus International Collaborating Clinics group: origins and outcomes. Lupus 2001;10:375–7.
7. Urowitz MB, Gladman D, Ibanez D, Fortin P, Sanchez-Guerrero J, Bae S, et al. Clinical manifestations and coronary artery disease risk factors at diagnosis of systemic lupus erythematosus: data from an international inception cohort. Lupus 2007;16:731–5.
8. Hochberg MC, for the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
9. Gladman DD, Ibanez D, Urowitz MB. SLE Disease Activity Index 2000. J Rheumatol 2002;29:288–91.
10. Ibanez D, Urowitz MB, Gladman DD. Summarizing disease features over time. I. Adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. J Rheumatol 2003;30:1977–82.
11. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Sanchez-Guerrero, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.
12. Gladman DD, Urowitz MB, Goldsmith CH, Fortin P, Ginzler E, Gordon C, et al. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:809–13.
13. Tustall-Pedoe H, Kuulasmaa K, Abouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA project: registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation 1994;90:583–612.
14. Nikpour M, Urowitz MB, Gladman DD. Premature atherosclerosis in systemic lupus erythematosus. Rheum Dis Clin North Am 2005;31:329–54.
15. Urowitz MB, Ibanez D, Gladman DD. Atherosclerotic vascular events (AVE) in a single large lupus cohort: prevalence and risk factors. J Rheumatol 2007;34:70–5.
16. Toloza SM, Uribe AG, McGwin G Jr, Alarcon GS, Fessler BJ, Bastian HM, et al, for the LUMINA Study Group. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXIII. Baseline predictors of vascular events. Arthritis Rheum 2004;50:3947–57.
17. Urowitz MB, Gladman D, Ibanez D, Fortin P, Sanchez-Guerrero J, Bae S, et al. Accumulation of coronary artery disease risk factors over three years: data from an international inception cohort. Arthritis Rheum 2008;59:176–80.
18. Urowitz MB, Gladman DD, Tom BD, Ibanez D, Farewell VT. Changing patterns in mortality and disease outcome for patients with systemic lupus erythematosus. J Rheumatol 2008; 35:2152–8.
19. Alarcon GS, McGwin G, Bertoli AM, Fessler BJ, Calvo-Alen J, Bastian HM, et al. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort. Ann Rheum Dis 2007;66:1168–72.
20. Ruiz-Irastorza G, Egurbide MV, Pijoan JI, Garmendia M, Villar I, Martinez-Berriotxoa A, et al. Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. Lupus 2006;15:577–83.