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Original Contribution

Incidence of and Risk Factors for Adverse Cardiovascular Events Among Patients With Systemic Lupus Erythematosus

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Patients with systemic lupus erythematosus (SLE) are at excess risk of cardiovascular events (CVEs). There is uncertainty regarding the relative importance of SLE disease activity, medications, or traditional risk factors in this increased risk. To gain insight into this, the authors analyzed data from a cohort of 1,874 patients with SLE who were seen quarterly at a single clinical center (April 1987–June 2010) using pooled logistic regression analysis. In 9,485 person-years of follow-up, the authors observed 134 CVEs (rate = 14.1/1,000 person-years). This was 2.66 times what would be expected in the general population based on Framingham risk scores (95% confidence interval: 2.16, 3.16). After adjustment for age, CVE rates were not associated with duration of SLE. However, they were associated with average past levels of SLE disease activity and recent levels of circulating anti-double-stranded DNA. Past use of corticosteroids (in the absence of current use) was not associated with CVE rates. However, persons currently using 20 mg/day or more of corticosteroids had a substantial increase in risk even after adjustment for disease activity. Thus, consistent with findings in several recent publications among cohorts with other diseases, current use of corticosteroids was associated with an increased risk of CVEs. These results suggest a short-term impact of corticosteroids on CVE risk.

angina pectoris; coronary artery bypass surgery; intermittent claudication; lupus erythematosus, systemic; myocardial infarction, prednisone; risk factors; stroke

Abbreviations: CVE, cardiovascular event; dsDNA, double-stranded DNA; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index instrument score.

Patients with systemic lupus erythematosus (SLE) have higher risk for cardiovascular events (CVEs) than the general population (1–4). This difference persists after controlling for traditional risk factors for CVEs (5). Reports have suggested that this higher risk is multifactorial, with contributions from traditional risk factors for CVEs, SLE disease activity, SLE-related immunologic factors, and SLE-related medications.

Despite much research in this area, most epidemiologic studies have been based on relatively few incident CVEs and do not take into consideration the fact that risk factors change over time. This makes it difficult to estimate parameters with precision, tease out associations of correlated risk factors, and assess the acute impact of medications and disease activity. As a result, there are a number of unanswered questions regarding risk factors and their relative importance. For example, although people exposed to higher doses of corticosteroids appear to be at higher risk, is this due to the fact that persons prescribed high-dose corticosteroids have higher levels of SLE disease activity or is it due to exposure to the corticosteroids themselves? If it is due to exposure to the corticosteroids themselves, is it related to long-term cumulative exposure or to the current dose? Although several studies have shown that persons with longer SLE duration are at higher risk, is this due to their ages, their cumulative exposures to corticosteroids, or SLE disease-related factors?

The Hopkins Lupus Cohort has data on the clinical experience of over 1,800 patients with SLE and more than

9,000 person-years of follow-up. The size of this cohort provides an opportunity to estimate the rate of CVEs in patients with SLE with good precision and to have moderate power to tease out correlated risk factors. Also, the fact that patients in this cohort were examined every 3 months by one physician allows us to assess the short-term impacts of disease activity and medication use.

MATERIALS AND METHODS

Hopkins Lupus Cohort

Since 1987, patients diagnosed with SLE have been invited to participate in the Hopkins Lupus Cohort. The study was approved by the Johns Hopkins University School of Medicine Institutional Review Board. Persons who provide informed consent are entered into the cohort. At enrollment, a comprehensive medical history, including date of lupus diagnosis and information on prior CVEs, is obtained from medical records and from the patient. At each quarterly clinic visit, a battery of physical and laboratory tests are performed, including measurements of complement, anti-double stranded DNA (dsDNA), and lupus disease activity. In addition, cohort members have had 1 or more measurements of other immunologic markers related to SLE, including anti-Smith, anti-ribonucleoprotein, anti-Ro, and anti-La and multiple measures of antiphospholipid antibodies (lupus anticoagulant by dilute Russell's viper venom time with confirmatory studies and anticardiolipin). This analysis is based on the cohort experience through June 2010.

Definition of CVEs

CVEs were defined as the occurrence of myocardial infarction, thrombotic stroke, clinically definite angina, percutaneous coronary intervention, a coronary bypass procedure, or claudication using clinical diagnoses consistent with those used in the Multi-Ethnic Study of Atherosclerosis (6). Specifically, myocardial infarction diagnosis was based on patient symptoms, electrocardiographic findings, cardiac echocardiogram, and/or cardiac biomarker levels. Thrombotic stroke was defined as rapid onset of neurologic deficit not secondary to brain trauma (closed head injury), tumor, infection (e.g., encephalitis or meningitis), or other nonvascular cause. In addition, there had to be a clinically relevant lesion shown on brain imaging, a duration greater than 24 hours, or death within 24 hours. A diagnosis of clinically definite angina required symptoms and objective evidence of reversible myocardial ischemia or obstructive coronary artery disease. Claudication was diagnosed based on symptoms in the lower body being relieved by rest and supported by evidence from ultrasonography, an arteriogram, or exercise tests.

Subcohort used in the present analysis

Patients who had a CVE before cohort entry were excluded from the present analysis. Any follow-up that came after a gap of 1 year or more in cohort visits was not included in the analysis. Follow-up for each patient was censored after the patient's first CVE.

Table 1. Observed and Expected Cardiovascular Events in the Hopkins Lupus Cohort, Baltimore, Maryland, 1987–2010

Subgroup	Observed No. of CVEs	Expected No. of CVEs[a]	Rate Ratio	95% Confidence Interval
Entire cohort	109	41	2.66	2.16, 3.16
Sex				
Female	93	35	2.67	2.12, 3.21
Male	16	6	2.62	1.34, 3.90
Age, years				
18–39	29	5	5.28	3.36, 7.21
40–49	31	12	2.69	1.75, 3.64
50–59	26	14	1.90	1.17, 2.64
60–69	16	8	2.11	1.08, 3.15
≥70	7	3	2.51	0.65, 4.36
Ethnicity				
White	57	21	2.72	2.01, 3.43
Black	52	19	2.73	1.99, 3.47
Other	0	1	0	
Calendar year				
1987–1992	11	2	5.35	2.19, 8.52
1993–1998	15	6	2.72	1.34, 4.09
1999–2004	40	16	2.57	1.77, 3.36
2005–2009	42	17	2.45	1.71, 3.19

Abbreviation: CVE, cardiovascular event.
[a] Based on the Framingham Risk Formula.

Resulting cohort and duration of follow-up

A total of 1,874 patients were eligible to be included in our analysis. Ninety-five percent of these patients fulfilled 4 or more of the American College of Rheumatology Classification Criteria for SLE classification. The large majority (1,738; 93%) were female, and most were either white (1,050; 56%) or black (696; 37%). The mean age at cohort entry was 37 years (standard deviation = 12). Many patients (735; 39%) joined the cohort within 1 year of SLE diagnosis, whereas 510 (27%) joined from 1 to 5 years after diagnosis and 629 (34%) joined 5 or more years after diagnosis.

The analysis was based on a total of 9,485 person-years of follow-up. The follow-up duration varied, with 363 patients (19%) followed for less than 1 year, 776 (41%) followed for 2–5 years, 451 (24%) followed for 5–10 years, and 284 (15%) followed for more than 10 years. The median time between cohort visits was 91 days, and 85% of the visits occurred within 115 days of the previous visit. As a result, 80% of the person-months used in our analysis were based on measurements made within the last 3 months or less.

Definitions of risk factors

SLE disease activity was quantified based on the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-Systemic Lupus Erythematosus Disease Activity Index instrument score (SLEDAI), a modification of the

Table 2. Rates of Cardiovascular Events by Demographic and Traditional Risk Factors, Baltimore, Maryland, 1987–2010

Subgroup	Observed No. of CVEs	Person-Years of Follow-up	Rate of Events per 1,000 Person-Years	Rate Ratio Adjusted for Age[a]		*P* Adjusted for Age[a]
				RR	95% CI	
Entire cohort	134	9,485	14.1			
Demographic variables						
Age						
18–39	37	4,627	8.0	1.00	Referent	
40–49	36	2,574	14.0	1.75	1.11, 2.77	0.017
50–59	30	1,572	19.1	2.39	1.48, 3.87	0.0004
60–69	21	556	37.8	4.74	2.77, 8.09	<0.0001
≥70	10	155	64.4	8.09	4.02, 16.29	<0.0001
Sex						
Female	114	8,800	13.0	1.00	Referent	
Male	20	685	29.2	2.15	1.33, 3.46	0.0017
Ethnicity						
White	69	4,993	13.8	1.00	Referent	
Black	1	4,004	16.0	1.25	0.89, 1.77	0.19
Other	64	488	2.0	0.20	0.03, 1.43	0.11
Calendar year						
1987–1992	24	859	28.0	1.00	Referent	
1993–1998	19	1,728	11.0	0.35	0.19, 0.65	0.0007
1999–2004	44	3,263	13.5	0.37	0.23, 0.62	0.0001
2005–2009	46	3,470	13.3	0.33	0.20, 0.54	<0.0001
Traditional CVE risk factors						
Most recent systolic BP, mm Hg						
<120	34	3,932	8.6	1.00	Referent	
120–129	33	2,160	15.3	1.61	0.99, 2.60	0.054
130–139	24	1,590	15.1	1.44	0.85, 2.43	0.18
140–159	26	1,436	18.1	1.53	0.91, 2.58	0.11
≥160	17	362	47.0	3.52	1.93, 6.43	<0.0001

Table continues

SLEDAI (7, 8). Anti-dsDNA was assessed using the Crithidia assay. Information regarding each patient's corticosteroid exposure before cohort entry was collected from patient histories and medical records at cohort entry.

Statistical methods

To facilitate the analysis, the data set was formatted to consist of 1 record per person-month of cohort follow-up. Each person-month record contained a variable indicating whether a CVE had occurred during that month. In addition, each record contained the clinical and medication history of the patient up until that time based on information supplied at the most recent quarterly visit.

In some instances, some variables were not assessed at a quarterly visit. The proportion not assessed was generally less than 1% but was as high as 4% for some variables and was 11% for total serum cholesterol. When a variable was missing, we used the most recent assessment of the variable at a prior clinic visit in our analysis for that point in time.

Some of the biomarkers (high density lipoprotein cholesterol, anti-Smith, anti-Ro, anti-La, and anti-ribonucleoprotein) were not part of the quarterly battery of tests and were only measured once or a few times. For these variables, we assigned the value of the measurement at that time to all of a patient's person-months.

To estimate the number of CVEs that would be expected in a general population cohort with similar values for age, sex, cholesterol, high density lipoprotein, systolic blood pressure, hypertension medication, and diabetes, we used a Framingham risk formula (9). Using this formula, we derived an estimate of the probability of an event in a

Table 2. Continued

Subgroup	Observed No. of CVEs	Person-Years of Follow-up	Rate of Events per 1,000 Person-Years	Rate Ratio Adjusted for Age[a]		*P* Adjusted for Age[a]
				RR	95% CI	
Mean past systolic BP[a], mm Hg						
<120	34	4,081	8.3	1.00	Referent	
120–129	42	2,903	14.5	1.51	0.96, 2.38	0.077
130–139	31	1,653	18.8	1.59	0.96, 2.63	0.073
140–159	24	777	30.9	2.26	1.29, 3.95	0.0042
≥160	3	68	44.2	3.17	0.95, 10.51	0.0596
Most recent total cholesterol measure						
<150	14	1,829	7.7	1.00	Referent	
150–199	62	4,381	14.2	1.63	0.91, 2.92	0.099
200–249	34	2,535	13.4	1.36	0.72, 2.54	0.34
≥250	23	708	32.5	3.50	1.79, 6.81	0.0002
Mean past total cholesterol measure						
<150	5	1,389	3.6	1.00	Referent	
150–199	63	4,678	13.5	3.11	1.25, 7.76	0.015
200–249	43	2,798	15.4	3.01	1.18, 7.65	0.021
≥250	22	589	37.4	8.22	3.10, 21.79	<0.0001
Body mass index[b]						
<20	5	787	6.4	1.00	Referent	
20–25	31	2,866	10.8	1.54	0.60, 3.97	0.37
25–30	38	2,525	15.1	1.89	0.74, 4.81	0.18
≥30	49	2,947	16.6	2.09	0.83, 5.25	0.12
Diabetes mellitus						
No	105	8,555	12.3	1.00	Referent	
Yes	29	927	31.3	2.00	1.32, 3.03	0.0011

Abbreviations: BP, blood pressure; CI, confidence interval; CVE, cardiovascular event; RR, rate ratio.
[a] Age refers to the age of the patient at each month of follow-up.
[b] Weight (kg)/height $(m)^2$.

single month, which allowed us to calculate the expected number of cases over the observed follow-up time. To quantify the degree to which the rates of CVEs in our cohort exceeded expectations, we estimated the rate ratio by dividing the observed number of events by the expected number of events. A confidence interval was calculated based on the assumption that the observed number of events followed a Poisson distribution.

To estimate the rate of CVEs in each subgroup, we calculated the number of events divided by the number of person-months at risk and converted the results to rates per person-year. To assess whether associations between risk factors and rates of events persisted after controlling for potential confounding variables, we applied pooled logistic regression (10). Pooled logistic regression has been shown to be approximately equivalent to Cox regression, and it has practical advantages (10). Because age was an important confounder of most of the variables, we provide an age-adjusted rate ratio for each variable. We fit supplementary multiple regression models for specific variables, controlling for additional confounders relevant to those specific variables. Finally, we fit a final multivariable model that included the variables that appeared to be most important based on the age-adjusted and supplementary regression models. The analysis was performed using SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Overall rate of CVEs

There were 134 incident CVEs (14.1 per 1,000 person-years of follow-up, 95% confidence interval: 11.9, 16.7). The events consisted of 65 strokes, 27 myocardial infarctions, 29 cases of angina or coronary procedures, and 13 cases of claudication.

Table 3. Rates of Cardiovascular Events by Systemic Lupus Erythematosus-Related Risk Factors, Baltimore, Maryland, 1987–2010

Subgroup	Observed No. of CVEs	Person-Years of Follow-up	Rate of Events per 1,000 Person-Years	Rate Ratio Adjusted for Age[a]	95% CI	*P* Adjusted for Age[a]
Duration of SLE, years						
<3	25	1,852	13.5	1.00	Referent	
3–6	18	1,928	9.3	0.63	0.34, 1.15	0.13
6–10	29	2,168	13.4	0.84	0.49, 1.44	0.53
10–15	24	1,731	13.9	0.81	0.46, 1.42	0.46
≥15	38	1,807	21.0	1.02	0.61, 1.71	0.94
Age at diagnosis, years						
<40	77	7,147	10.8	1.00	Referent	
40–49	22	1,480	14.9	0.77	0.45, 1.31	0.33
50–59	24	606	39.6	1.49	0.82, 2.70	0.19
≥60	11	212	51.8	1.22	0.51, 2.90	0.66
Recent SELENA-SLEDAI index						
0	36	3,792	9.5	1.00	Referent	
1 or 2	30	2,421	12.4	1.44	0.89, 2.35	0.14
3 or 4	31	1,787	17.3	2.09	1.29, 3.39	0.0027
≥5	37	1,485	24.9	3.36	2.11, 5.34	<0.0001
Mean SELENA-SLEDAI index						
0–1	23	2,125	10.8	1.00	Referent	
1–2.5	35	2,875	12.2	1.23	0.73, 2.09	0.44
2.5–5	49	3,091	15.9	1.79	1.09, 2.94	0.023
≥5	27	1,393	19.4	2.78	1.57, 4.91	0.0004
History of musculoskeletal activity						
No	63	4,902	12.9	1.00	Referent	
Yes	71	4,584	15.5	1.04	0.74, 1.46	0.83
Recent musculoskeletal activity						
No	115	8,761	13.1	1.00	Referent	
Yes	19	723	26.2	1.78	1.09, 2.89	0.021
History of skin activity						
No	51	3,468	14.7	1.00	Referent	
Yes	83	6,017	13.8	0.88	0.62, 1.25	0.48
Recent skin activity						
No	106	7,893	13.4	1.00	Referent	
Yes	28	1,593	17.6	1.32	0.87, 2.01	0.19
History of immunologic activity						
No	40	2,744	14.6	1.00	Referent	
Yes	94	6,741	13.9	1.13	0.78, 1.64	0.54
Recent immunologic activity						
No	69	5,814	11.9	1.00	Referent	
Yes	65	3,671	17.7	1.85	1.31, 2.61	0.0005

Table continues

Table 3. Continued

Subgroup	Observed No. of CVEs	Person-Years of Follow-up	Rate of Events per 1,000 Person-Years	Rate Ratio Adjusted for Age[a]	95% CI	*P* Adjusted for Age[a]
Renal involvement						
None	66	5,112	12.9	1.00	Referent	
Protein in urine	27	2,118	12.7	1.14	0.73, 1.79	0.56
Nephrotic syndrome	6	891	6.7	0.69	0.30, 1.60	0.39
Renal insufficiency	35	1,364	25.7	2.03	1.34, 3.05	0.0007
Recent renal activity						
No	115	8,662	13.3	1.00	Referent	
Yes	19	823	23.1	2.14	1.31, 3.89	0.0023
Most recent serum creatinine, mg/dL						
<1.0	69	6,934	10.0	1.00	Referent	
1.0–1.19	35	1,458	24.0	2.16	1.44, 3.25	0.0002
≥1.20	30	1,090	27.5	2.36	1.53, 3.64	<0.0001
History of hemolytic anemia						
No	113	8,571	13.2	1.00	Referent	
Yes	21	899	23.4	2.04	1.28, 3.25	0.0028
Recent hematocrit						
Normal	88	6,233	12.5	1.00	Referent	
Low[b]	56	3,250	17.2	1.56	1.10, 2.20	0.012
History of low C3						
No	47	3,830	12.3	1.00	Referent	
Yes	87	5,652	15.4	1.63	1.13, 2.34	0.0082
Recent low C3						
No	91	7,294	12.5	1.00	Referent	
Yes	42	2,188	19.1	1.95	1.04, 2.84	0.0004
History of low C4						
No	59	4,583	12.9	1.00	Referent	
Yes	75	4,899	15.3	1.55	1.10, 2.20	0.013
Recent low C4						
No	104	7,735	13.4	1.00	Referent	
Yes	13	810	16.0	1.62	0.90, 2.90	0.11
History of anti-dsDNA						
No	48	3,594	13.4	1.00	Referent	
Yes	96	5,886	14.6	1.33	0.90, 1.96	0.15
Recent anti-dsDNA						
No	83	6,992	11.9	1.00	Referent	
Yes	50	2,488	20.1	2.14	1.50, 3.06	<0.0001
Lupus anticoagulant						
Never positive	72	6,608	10.9	1.00	Referent	<0.0001
Positive at any time	62	2,741	22.6	2.11	1.50, 2.97	
Never assessed	0	137				

Abbreviations: C3, complement component 3; C4, complement component 4; CI, confidence interval; CVE, cardiovascular event; dsDNA, double stranded DNA; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index instrument score.

[a] Age refers to the age of the patient at each month of follow-up.

[b] "Low" means less than 36% for females and less than 41% for males.

Comparison with the general population

Of the 1,874 patients, 1,183 (62%) had available high density lipoprotein measurements (which were not part of the quarterly battery of tests), and 4 of these had missing information about other Framingham risk factors (Table 1). Among the remaining 1,179 patients, we observed 109 incident CVEs. Considering the age, sex, cholesterol level, high density lipoprotein level, blood pressure, diabetes, and smoking characteristics of this cohort, based on the Framingham formula we would have expected only 41 cases, resulting in an estimated rate ratio of 2.66. The excess over the expected number of events was substantially higher among the younger cohort members and during the early years of the cohort (1987–1992).

Examining CVE subtypes, we found that the largest excess was for strokes (10 expected, 62 observed; rate ratio = 6.2, 95% confidence interval: 4.7, 7.8). For cardiac events, the excess was smaller (29 expected, 51 observed; rate ratio = 1.8, 95% confidence interval: 1.3, 2.3).

Association between CVEs and demographic factors

CVE incidence rates increased substantially with age. Men had a significantly higher rate than did women. The rate was also substantially higher during the early years of the cohort (Table 2).

Association between CVEs and traditional CVE risk factors

CVE rates were positively associated with blood pressure and total serum cholesterol levels (Table 2). This was true whether the risk factors were defined based on the most recent value or the mean of values calculated in past cohort visits. When the recently measured blood systolic blood pressure and the mean past systolic blood pressure were both included in the same regression model, we found that the impact of mean past systolic blood pressure on CVE risk was statistically significant after controlling for the current level (per 10-mm Hg increase, rate ratio = 1.26, $P = 0.0054$), whereas the impact of the most recently measured systolic blood pressure on CVE risk was no longer significant after controlling for mean past systolic blood pressure (per 10-mm Hg increase, rate ratio = 1.05, $P = 0.42$). Using a similar approach, we also found that the mean past level of cholesterol was more strongly associated with CVE rates than was the most recently measured cholesterol level. Also, when both systolic and diastolic blood pressures were included in the same model, systolic blood pressure was the stronger predictor.

Association between CVEs and SLE-related risk factors

After adjustment for age, there was no association between CVE incidence and either duration of SLE or age at SLE diagnosis (Table 3). CVE incidence was significantly higher in person-months with high SLE disease activity, as measured by the most recent SELENA-SLEDAI index and by mean SELENA-SLEDAI index during prior cohort participation. However, mean SELENA-SLEDAI index during cohort participation was not significantly associated with CVE rates after controlling for the most recently measured SELENA-SLEDAI index in a multiple variable model.

The incidence of CVEs was not significantly higher among patients with a history of skin involvement, musculoskeletal involvement, or immunologic activity (i.e., anti-dsDNA or low complement), although patients had higher rates of CVEs during person-months in which there was recent musculoskeletal activity or immunologic activity (such as anti-dsDNA or low complement). Low complement was correlated with the presence of anti-dsDNA and with SELENA-SLEDAI index (of which it is a part), and after controlling for anti-dsDNA and SLEDAI index in a multivariable model, low complement was no longer a statistically significant predictor of CVEs. Persons with renal activity (as measured by the SLEDAI renal component) had higher rates of CVEs. High levels of serum creatinine, which indicate renal insufficiency, were also associated with CVEs.

Cohort members who had the lupus anticoagulant as measured by the Russell Viper Venom Time had higher rates of CVE. CVE rates were not significantly higher among those ever positive for anti-Smith, anti-Ro, anti-La, or anti-ribonucleoprotein relative to those without these antibodies (data not shown).

Association between CVEs and corticosteroid use

Patients currently taking corticosteroids at a dose of 10 mg/day or more had significantly higher rates of CVEs. Those with a cumulative dose equivalent of more than 10 mg/day for 10 years also had higher rates of CVEs. However, no excess rate was observed among individuals with a cumulative dose equivalent to 10 mg/day for 3–10 years (Table 4).

To tease out the relative importance of current use and past use, we examined the association between current use and CVE rates among those with low levels of past exposure. We found that, even among those with low levels of past exposure to corticosteroids, those with a current dose of 10 mg/day or higher had a significantly higher risk of a CVE, especially among those with 20 mg/day or more (rate ratio = 5.2; Table 4). However, when we looked at the association between past exposure to corticosteroids and CVE rates among those with not currently using corticosteroids, we saw a less pronounced association that was not statistically significant (for persons with more than 10 mg/day for 10 years, rate ratio = 1.7; $P = 0.14$). Finally, when the current dose of corticosteroid and cumulative dose of corticosteroid were put in the same multiple regression model, current use was the stronger predictor, and cumulative dose was no longer significantly associated with CVE risk.

Association between CVEs and other medications

We observed a reduced rate of CVEs among patients who had been taking hydroxychloroquine for the last 6 months (Table 5). There was also a significantly lower rate of CVE among those with more than 1 year of past use of hydroxychloroquine. When both current and past use of

Table 4. Rates of Cardiovascular Events by Recent and Past Corticosteroid Use, Baltimore, Maryland, 1987–2010

Subgroup of Corticosteroid Use	Observed No. of CVEs	Person-Years of Follow-up	Rate of Events per 1,000 Person-Years	Rate Ratio Adjusted for Age[a]	95% CI	*P* Adjusted for Age[a]
None ever taken	22	1,650	13.3	1.00	Referent	
Currently taking	88	4,845	18.2	1.58	0.99, 2.52	0.057
Past (not current) use	23	2,902	7.9	0.64	0.36, 1.16	0.14
Current dose, mg/day						
None	46	4,640	9.9	1.00	Referent	
1–9	32	2,600	12.3	1.3	0.8, 2.0	0.31
10–19	31	1,538	20.2	2.4	1.5, 3.8	0.0002
≥20	25	707	35.4	5.1	3.1, 8.4	<0.0001
Cumulative past dose, mg[b]						
None	22	1,650	13.3	1.00	Referent	
<3,650[c]	14	1,414	9.9	0.8	0.4, 1.6	0.56
3,650–10,950[d]	26	1,887	13.8	1.2	0.7, 2.2	0.49
10,950–36,499[e]	41	3,195	12.8	1.1	0.6, 1.8	0.83
≥36,500[f]	30	1,185	25.3	2.2	1.2, 3.7	0.0066
Mean dose during cohort among those with high cumulative dose (≥36,500), mg/day						
<10	11	455	24.2	1.0	Referent	
≥10	19	731	26.0	1.2	0.5, 2.5	0.72
Current dose among those with low cumulative past dose (<10,950 mg), mg/day						
None	35	3,458	10.1	1.00	Referent	
1–9	11	878	12.5	1.3	0.7, 2.6	0.43
10–19	9	420	21.5	2.8	1.3, 5.8	0.0063
≥20	7	196	35.6	5.4	2.4, 12.3	<0.0001
Cumulative past dose among those with low (or no) current dose, mg[b]						
None	22	1,650	13.3	1.00	Referent	
<3,650[c]	12	1,242	9.7	0.8	0.4, 1.6	0.48
3,650–10,950[d]	12	1,443	8.3	0.7	0.4, 1.4	0.35
10,950–36,499[e]	19	2,198	8.6	0.7	0.4, 1.2	0.21
≥36,500[f]	12	588	20.4	1.7	0.8, 3.5	0.14

Abbreviations: CI, confidence interval; CVE, cardiovascular event.
[a] Age refers to the age of the patient at each month of follow-up.
[b] This includes information on corticosteroid exposure before cohort participation.
[c] A cumulative dose of 3,650 mg equals 10 mg/day for 1 year or an equivalent cumulative exposure.
[d] One to 3 years with 10 mg/day or an equivalent cumulative exposure.
[e] Three to 10 years with 10 mg/day or an equivalent cumulative exposure.
[f] Ten or more years with 10 mg/day or an equivalent cumulative exposure.

hydroxychloroquine were included in the same model, past use of hydroxychloroquine was no longer significantly associated with CVEs.

CVE rates were somewhat elevated while patients were taking immunosuppressant drugs (rate ratio = 1.43; $P = 0.044$). However, this association largely disappeared in a multiple regression model that was adjusted for SLE disease activity (rate ratio = 1.24; $P = 0.23$).

Multivariable models

The variables that appeared to be most important were included in a multivariable model to determine which variables were independently associated with CVEs (Table 6). Even after controlling for all the other variables in the model, there was a strong association between CVE and age, sex, year before 1993, mean systolic blood pressure, serum cholesterol

Table 5. Rates of Cardiovascular Events by Recent and Past Medication Use, Baltimore, Maryland, 1987–2010

Subgroup of Medication Use	Observed No. of CVEs	Person-Years of Follow-up	Rate of Events per 1,000 Person-Years	Rate Ratio Adjusted for Age[a]	95% CI	*P* Adjusted for Age[a]
Hydroxychloroquine use[b]						
Never	46	2,570	17.9	1.00	Referent	
Past (not current)	20	984	20.3	1.13	0.67, 1.91	0.65
Currently used but for <6 consecutive months	14	827	16.9	1.02	0.56, 1.86	0.95
Current use for ≥6 consecutive months	54	5,104	10.6	0.54	0.36, 0.79	0.0019
No. of prior months on hydroxychloroquine						
<12	26	1,594	16.3	0.58	0.40, 0.86	0.99
≥12	62	5,322	11.7	1.00	0.62, 1.62	0.0057
NSAID use[b]						
Never	52	4,106	12.7	1.00	Referent	
Past (not current)	46	2,761	16.7	1.17	0.69, 1.56	0.45
Current	36	2,616	13.8	0.94	0.70, 1.60	0.78
No. of prior months on NSAIDs						
<12	21	2,129	9.8	1.21	0.83, 1.75	0.34
≥12	61	3,298	18.9	0.78	0.47, 1.30	0.32
Immunosuppresant use[b]						
Never	56	4,646	12.1	1.00	Referent	
Past (not current)	5	304	16.4	1.25	0.50, 3.13	0.63
Current	73	4,535	16.1	1.43	1.01, 2.03	0.044
No. of prior months on immunosuppressants						
<12	17	862	19.7	1.92	1.11, 3.31	0.019
≥12	61	3,976	15.3	1.32	0.92, 1.90	0.13
Aspirin use[b]						
Never	80	6,743	11.9	1.00	Referent	
Past (not current)	22	1,160	19.0	1.5	1.0, 2.5	0.068
Current	32	1,583	20.2	1.4	0.9, 2.1	0.11
No. of prior months on Aspirin						
<12	30	1,218	24.6	2.1	1.4, 3.3	0.0004
≥12	24	1,525	15.7	1.0	0.7, 1.6	0.89

Abbreviations: CI, confidence interval; CVE, cardiovascular event; NSAID, nonsteroidal anti-inflammatory drug.
[a] Age refers to the age of the patient at each month of follow-up.
[b] These do not include use of medications prior to cohort participation.

during prior cohort visits, lupus anticoagulant, current corticosteroid dose, and presence of anti-dsDNA.

There was some evidence of an independent association between CVEs and recent SELENA-SLEDAI, even after controlling for one of the components of SLEDAI, anti-dsDNA (per unit difference, rate ratio = 1.05; $P = 0.069$), When a multivariable model was fit without including anti-dsDNA, the association between recent SLEDAI and CVE rates was statistically significant (per unit difference, rate ratio = 1.07; $P = 0.0047$).

After adjustment for the other variables, hydroxychloroquine was no longer statistically significantly associated with a decreased rate of CVEs. However, assessing the effect of hydroxychloroquine while controlling for cholesterol and diabetes would not be appropriate because hydroxychloroquine affects cholesterol and blood glucose. When the multivariable model was fit without including cholesterol and diabetes, we still did not obtain strong evidence of lower rates of CVE among those on hydroxychloroquine for the last 6 months ($P = 0.13$).

Table 6. Joint Relation Between Predictors and Cardiovascular Event Rates Based on a Multivariable Model, Baltimore, Maryland, 1987–2010

Predictor	Rate Ratio Based on Full Model	95% CI	*P* Value
Age per 10 years	1.63	1.421, 1.88	<0.0001
Male sex	1.56	1.01, 2.67	0.046
Year before 1993	1.64	0.99, 2.63	0.053
Mean systolic blood pressure per 10-mm Hg increase[a]	1.17	1.02, 1.35	0.022
Mean serum cholesterol per 10-mg/dL increase[a]	1.04	1.01, 1.08	0.018
Diabetes mellitus	1.52	0.99, 2.33	0.057
SELENA-SLEDAI per unit increase	1.05	1.00, 1.11	0.062
Anti-dsDNA present in most recent visit	1.56	1.05, 2.31	0.026
Serum creatinine, mg/dL			
<1.0	1.00	Referent	
1.0–1.19	1.64	1.07, 2.50	0.023
≥1.2	1.15	0.72, 1.85	0.56
Low hematocrit	1.18	0.82, 1.69	0.38
History of hemolytic anemia	1.28	0.79, 2.09	0.32
History of lupus anticoagulant	1.74	1.22, 2.47	0.0021
Current corticosteroid dose, mg/day			
0	1.00	Referent	
1–9	1.01	0.63, 1.60	0.98
10–19	1.47	0.90, 2.38	0.12
≥20	2.54	1.44, 4.48	0.0013
Hydroxychloroquine in past 6 consecutive, months	0.77	0.54, 1.12	0.17

Abbreviations: CI, confidence interval; dsDNA, double stranded DNA; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index instrument score.

[a] Mean during prior cohort participation.

DISCUSSION

Consistent with previous reports, we found that, after controlling for traditional risk factors, individuals with SLE are at increased risk for CVEs (1–5). Our estimate of the overall rate ratio of 2.66 is lower than some earlier estimates (3–5) but consistent with more recent estimates (1, 2, 11). Also consistent with all previous reports, the excess risk was most pronounced among individuals under 40 years of age (3, 4, 11).

If the higher rates of CVEs among SLE patients are due, in part, to the cumulative effect of immunologic processes associated with SLE disease activity, one would expect that those who have had SLE longer would be at higher risk of a CVE. However, after adjusting for age, we did not observe a positive association between duration of SLE and rates of CVEs. This is consistent with most of the previous studies of this relation (3, 5, 12–15) with one exception (2). Several studies reported a positive association between subclinical markers of CVE and SLE duration (16, 17), but the investigators did not adjust for age.

We observed a dose-dependent increase in CVE rates in patients currently taking corticosteroids. Those on 20 mg/day or more had a 5-fold increased rate after adjustment for age, and current use had a stronger association with CVE than did cumulative past use. Three previous studies of other large non-SLE cohorts similarly found that current (but not past) use of corticosteroids was associated with higher CVE rates (18–20). All 3 studies found that the increased risk was highest among those with higher current doses. Our findings, along with these previous consistent findings, suggest that there is an acute impact of corticosteroids on CVE risk.

One alternative explanation for the observed association between current use of corticosteroids and CVE risk, raised by Huiart et al. (19), is that current use of corticosteroids is merely a marker for a flare of disease activity that is the real cause of the increased CVE risk. However, in our multivariable analysis, the association between corticosteroids and CVEs persisted after we controlled for the disease activity level measured at the time of the corticosteroid prescription decision (Table 6).

Another possibility is that association between current use of corticosteroids and CVE risk is due to their impact on traditional risk factors, such as blood pressure or serum lipids. In our analysis, the effect of corticosteroid use on CVE risk persisted after we controlled for blood pressure and serum cholesterol, which suggests that the association is independent of the effect of corticosteroids on these risk factors. However, the blood pressure and serum cholesterol measurements used in our analyses were those taken at the most recent visit, which might have been several months earlier, so we cannot totally rule out the possibility that corticosteroids resulted in an increase in those risk factors in the intervening time that affected the risk of a CVE.

Although the univariate results suggested that those on hydroxychloroquine had a reduced rate of CVE, we did not obtain strong evidence of a protective effect ($P = 0.13$) in a multivariable model in which we controlled for other variables. In contrast, several other studies observed a protective effect of hydroxychloroquine on thrombosis, thrombovascular events (21, 22), vascular events (23), and survival (24, 25) among SLE patients. Hydroxychloroquine has been shown to reduce serum cholesterol (26, 27), reduce glucose (26), and be negatively associated with the presence of carotid plaque (17) and vascular damage (28).

For each measure of disease activity in Table 3 (SLEDAI, musculoskeletal, skin, low complement, anti-dsDNA), the impact of recent activity appeared greater than the impact of

a history of that type of disease activity. These findings and the fact that we did not observe an association between disease duration and CVE suggest that the impact of disease activity is more acute. Alternatively, these results are consistent with the possibility that levels of current disease activity are indicators of other clinical problems or higher doses of medications, which lead to the CVE. There was only a moderate association between SELENA-SLEDAI and CVE rates after adjusting for medication use.

To our knowledge, the present study is the largest cohort study of CVE rates in terms of number of SLE patients, duration of follow-up, and frequency of follow-up visits. However, there are some limitations to using this observational clinical cohort to address our study questions. First, this is a single-center cohort, so the CVE experience reflects the type of patient that comes to our center and the treatment strategies used there over the last 23 years. Second, clinical variables were only assessed quarterly, so the blood pressure, SLE disease activity, and other variables attributed to a person-month in the analysis might not represent the actual values of those variables in that month. This would have less affect on variables such as treatments (which tend to be stable between visits) and means across prior visits. Third, although sometimes patients attended more frequently than quarterly, sometimes patients missed visits, and in each month of follow-up, the most recent measurement of a variable in our analysis was more than 3 months earlier for 20% of the visits. Fourth, as noted above, some auto-antibodies (anti-Ro, anti-La, anti-ribonucleoprotein, and anti-Smith) were only measured once during cohort participation, so our information about them is limited. Many of these limitations tend to result in misclassification of predictors during person-months, which could attenuate estimates of associations.

In summary, the rate of CVEs in our SLE cohort was observed to be 2.66 times higher than would be expected in the general population with similar levels of traditional risk factors. After adjustment for age, the excess risk was not associated with SLE duration but was associated with current disease activity and anti-dsDNA. Most interestingly, consistent with several other recent studies, the excess risk was more strongly associated with the current dose of corticosteroid than with cumulative past dose of corticosteroids, which suggests a short-term impact of corticosteroid use on CVE risk.

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