Risk Factors for Clinical Coronary Heart Disease in Systemic Lupus Erythematosus: The Lupus and Atherosclerosis Evaluation of Risk (LASER) Study

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ABSTRACT. **Objective.** Accelerated atherosclerosis and premature coronary heart disease (CHD) are recognized complications of systemic lupus erythematosus (SLE), but the exact etiology remains unclear and is likely to be multifactorial. We hypothesized that SLE patients with CHD have increased exposure to traditional risk factors as well as differing disease phenotype and therapy-related factors compared to SLE patients free of CHD. Our aim was to examine risk factors for development of clinical CHD in SLE in the clinical setting.

**Methods.** In a UK-wide multicenter retrospective case-control study we recruited 53 SLE patients with verified clinical CHD (myocardial infarction or angina pectoris) and 96 SLE patients without clinical CHD. Controls were recruited from the same center as the case and matched by disease duration. Charts were reviewed up to time of event for cases, or the same “dummy-date” in controls.

**Results.** SLE patients with clinical CHD were older at the time of event [mean (SD) 53 (10) vs 42 (10) yrs; p < 0.001], more likely to be male [11 (20%) vs 3 (7%); p < 0.001], and had more exposure to all classic CHD risk factors compared to SLE patients without clinical CHD. They were more likely to have been treated with corticosteroids (OR 2.46; 95% CI 1.03, 5.88) and azathioprine (OR 2.33; 95% CI 1.16, 4.67) and to have evidence of damage on the pre-event SLICC damage index (SDI) (OR 2.20; 95% CI 1.09, 4.44). There was no difference between groups with regard to clinical organ involvement or autoantibody profile.

**Conclusion.** Our study highlights the need for clinical vigilance to identify modifiable risk factors in the clinical setting and in particular with male patients. The pattern of organ involvement did not differ in SLE patients with CHD events. However, the higher pre-event SDI, azathioprine exposure, and pattern of damage items (disease-related rather than therapy-related) in cases suggests that a persistent active lupus phenotype contributes to CHD risk. In this regard, corticosteroids and azathioprine may not control disease well enough to prevent CHD. Clinical trials are needed to determine whether classic risk factor modification will have a role in primary prevention of CHD in SLE patients and whether new therapies that control disease activity can better reduce CHD risk. (First Release Dec 1 2009; J Rheumatol 2010;37:322–9; doi:10.3899/jrheum.090306)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
CORONARY HEART DISEASE
RISK FACTORS
DISEASE ACTIVITY
Accelerated atherosclerosis and premature coronary heart disease (CHD) are recognized complications of systemic lupus erythematosus (SLE)\textsuperscript{1}. The pathogenesis of CHD in SLE appears to be a complex interaction of inflammatory, metabolic, and therapy-related factors, and those patients at high risk are difficult to identify. There is an increased prevalence of classic risk factors such as hypertension and diabetes mellitus among patients with SLE\textsuperscript{2,3}. It is, however, argued that classic risk factors alone do not fully account for the burden of disease observed\textsuperscript{4}. Additional factors associated with SLE such as inflammatory factors, prothrombotic states, renal disease, and the potential effects of lupus therapies are also believed to be relevant.

There are a large number of studies examining subclinical atherosclerosis in SLE using measures not widely available in the routine clinical setting. Only a few studies have specifically examined the risk factors for clinical events, of which a number include vascular events other than CHD, including stroke, peripheral vascular disease, or venous thromboembolism. It cannot, however, be assumed that these events will share the same precise pathological processes or precipitants\textsuperscript{5-9}. As a result, findings of such studies have been variable and there is a lack of consistency across studies in factors identified.

We examined risk factors for the development of clinical CHD in the clinical setting in a multicenter UK network. The hypothesis tested was that patients with CHD have increased exposure to traditional risk factors, differing disease phenotype, and therapy-related factors compared to patients with SLE free of CHD.

**MATERIALS AND METHODS**

**Patients.** Thirteen UK centers from the British Isles Lupus Assessment Group (BILAG) and the British Society of Rheumatology Lupus Special Interest Group participated between August 2003 and July 2006. Rheumatologists identified SLE patients in their clinics using existing clinic or research databases. All subjects fulfilled the modified 1997 American College of Rheumatology (ACR) criteria for SLE\textsuperscript{10}, which were verified by chart review at the time of data collection.

**Cases.** A case was defined as a patient with SLE who had a history of a first myocardial infarction (MI) or first diagnosis of angina pectoris after SLE diagnosis. MI was confirmed on the basis of 2 of the following 3: typical anterior/retrosternal chest pain; typical electrocardiographic changes or an elevation of cardiac enzymes (creatine kinase or troponin)\textsuperscript{11}. Angina pectoris was defined as exertional or stress-related central chest pain relieved by rest or glyceryl trinitrate. In addition, confirmation of diagnosis of angina by a consultant cardiologist or by objective test such as a stress test or angiography was required.

**Controls.** For each case identified, 2 control subjects were recruited from the same center. The controls had no history of CHD and were matched for date of SLE onset (within 2 yrs) to enable matching for disease duration. Disease onset in all subjects was defined as the date that 4 ACR criteria were fulfilled\textsuperscript{10}. Where more than 2 potential control subjects were identified for a case, random-number generation was employed to allow unbiased selection of 2 controls. We therefore matched cases and controls only on the basis of disease duration. This is because disease duration and duration of corticosteroid exposure are difficult to distinguish from each other as they are closely associated. By matching on disease duration we hoped to determine better the role of corticosteroid exposure to CHD risk.

Subjects were excluded if inadequate clinical information to confirm diagnosis of SLE and/or CHD was available from case note reviews or if they refused to provide informed consent. Sixty-one suitable cases were identified, of which 8 were excluded, and 121 controls were identified of which 25 were excluded (Figure 1). Two suitable controls were identified for 43/53 cases, and one control subject was identified for each of the 10 remaining cases because of (i) inability to match for disease duration, or (ii) because inadequate information was available from chart review, or (iii) the control subject declined to participate in the study. Therefore a total of 53 cases and 96 controls were recruited.

**Study design.** Data were collected by retrospective chart review using a pre-designed form to standardize the information collected. Clinical and serological data were collected for each case up to the time of the coronary event. For matched controls we collected the same data up to a preassigned “dummy” date that was taken as the date of the event in their respective case (Figure 2).

Information collected included clinical features, laboratory observations (inflammatory markers, biochemistry, hematology, and autoantibody profile), the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) score\textsuperscript{12}, and details of therapy exposure. The SDI was assessed in patients using information gathered from clinic note reviews up to the visit prior to diagnosis of the coronary event. Therefore the coronary event did not contribute to this score. Corticosteroid treatment was categorized as “previous use” or “never used,” and the average daily dose was calculated where available. Details of immunosuppressive treatment were also collected. The presence of cardiovascular risk factors prior to the event or dummy date was noted.

Hypertension was defined as a systolic blood pressure of > 140 mm Hg or diastolic > 90 mm Hg or receiving treatment with an antihypertensive drug. Hypercholesterolemia was defined as total cholesterol > 5.2 mmol/l, or receiving lipid-lowering therapy (when total cholesterol had not been recorded prior to an event, a value 3–6 months after the event was sought from the chart review and recorded where available). A positive family history of cardiovascular disease was defined as MI, angina, or sudden cardiac death in a first-degree relative: male < 55 years or female < 60 years of age. Diabetes mellitus was defined as fasting plasma glucose > 7.0 mmol/l or current diabetic therapy. Smoking was recorded if the patient was noted in their medical record to have smoked prior to the clinical event or dummy date.

Clinical features of SLE such as malar rash, serositis, etc., were based on the physician’s contemporaneous notes and clinic letters. In general each clinical feature or laboratory observation was noted as “ever present” and classified into organ systems as per the “classIC” BILAG index\textsuperscript{13}. Renal disease was defined as any patient with persistent proteinuria (> 500 mg/day), otherwise unexplained microscopic hematuria, chronic renal insufficiency, nephrotic syndrome, or any grade of verified lupus nephritis. For all cases followup data were also recorded, including recurrent coronary events, interventions undertaken, and vital status at the time of the study. Information was verified from additional primary or secondary care physicians as appropriate.

**Statistical analysis and ethics.** Data were analyzed using Stata 9.2 statisti-
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Comparisons were made between cases and controls by means of a 2-sample t-test for continuous variables and by chi-square analysis for categorical variables. Two-sided p values < 0.05 were considered to be significant. Logistic regression was used for multivariable analyses, with adjustment for disease duration to account for matching. There were some subjects in whom information was missing with regard to cardiovascular risk factors (details of hypertension missing for 1 case and 2 controls; hypercholesterolemia for 8 cases and 16 controls; family history of CHD for 14 cases and 22 controls; smoking status for 3 controls). For those variables where information was missing the analysis was undertaken using only those records that were complete, and raw data figures as well as the percentage are given where appropriate. The study was approved by the North-West Multicentre Research Ethics Committee (Reference number 03/8/012). Informed consent was obtained locally for all subjects. Data collection was permitted by the ethics committee for deceased patients from review of case records.

RESULTS

Cardiovascular events. Cases and controls were well matched for disease duration [mean (SD) 11 (8) vs 10 (8) yrs, respectively]. Of the 53 SLE patients with CHD, 23 (43%) cases had an MI and 30 (56%) had angina. Seven (32%) cases with MI fulfilled 2 of 3 criteria and 15 (68%) fulfilled all 3 criteria for MI. One additional patient presented with central crushing chest pain followed by sudden death attributed to MI. All cases with angina pectoris had a diagnosis verified by a consultant cardiologist, except one patient who presented to a general internist with documented chest pain characteristic of angina associated with a rise in creatine kinase and a minor rise in troponin, consistent with acute coronary syndrome but not MI. In view of the convincing clinical history of angina, supporting biochemical tests, and review by general internist, this case was included. Angina was confirmed using an objective confirmatory test in 24/30 patients. The mean (SD) age at the time of the first coronary event was 53 (10) years. The age at time of the event ranged from 33 to 73 years, and notably 12 (23%) events occurred under age 45 years (Figure 3). Of 52 patients that survived the initial event, 12 (23%) subsequently died over a mean (SD) of 8 (5) years. Eighteen (35%) cases underwent coronary interventions; 12 had balloon angioplasty or coronary stent insertion and 6 underwent coronary revascularization. Seven patients (39% of those with any intervention) underwent multiple interventions, although none had a second bypass graft. Of the 18

Figure 1. Selection of cases and controls. CHD: coronary heart disease; SLE: systemic lupus erythematosus.

Figure 2. Overview of study design and data acquisition window for exposures in cases and controls.

Figure 3. Distribution of age at onset of first coronary heart disease event in patients with systemic lupus erythematosus.
patients that underwent an intervention, a successful outcome was achieved in 5 (28%) patients, i.e., they remained symptom and medication-free at the time of study assessment. Of the remainder, 8 (44%) patients continued on medication or remained symptomatic, 3 patients died, and the outcome is unknown in 2 patients.

**Demographics.** Cases were older than controls at the time of the event [mean (SD) 53 (10) vs 42 (10) yrs; p < 0.001] and were more likely to be male [11 (20%) vs 3 (7%); p < 0.001]. All further analyses were adjusted for age and gender. The other subject characteristics are described in Table 1. Prior to the CHD event, cases also had higher body weight compared to controls, and in the 25 cases and 38 controls in whom body mass index (BMI) could be calculated, the mean (SD) BMI was higher in cases [mean 28 (6) vs 25 (5); p < 0.01].

**Classical CHD risk factors.** All classic CHD risk factors examined occurred more frequently in cases compared to controls, and in the age and gender adjusted analysis, hypertension (adjusted OR 2.56, 95% CI 1.05, 6.25) and a family history of premature CHD (adjusted OR 3.62, 95% CI 1.15, 11.34) were associated with CHD events (Table 2). Only 2 subjects in the entire cohort had diabetes mellitus.

**SLE organ involvement.** In the whole population studied, the mean (SD) time from onset of autoimmune features (first SLE organ involvement) to fulfilling 4 ACR criteria was 4.8 (7.8) mean (SD) time from onset of autoimmune features (first SLE organ involvement). In the whole population studied, the subjects in the entire cohort had diabetes mellitus.

**Table 1.** Comparison of demographic and key lupus characteristics in cases and controls. All data are mean (SD) unless otherwise indicated.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases, n = 53</th>
<th>Controls, n = 96</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration, yrs</td>
<td>11 (8)</td>
<td>10 (7)</td>
<td>—</td>
</tr>
<tr>
<td>Age at event time, yrs</td>
<td>53 (10)</td>
<td>42 (10)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>11 (20)</td>
<td>3 (7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>46 (88)</td>
<td>71 (77)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg, *n = 94</td>
<td>74 (17)</td>
<td>66 (12)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

* Total number of subjects for whom information was available for this variable if values were not available for entire group. NS: nonsignificant p value > 0.05.

**Table 2.** Exposure of cardiovascular risk factors in SLE patients with coronary heart disease.

<table>
<thead>
<tr>
<th>Risk Factor, n*</th>
<th>Unadjusted OR (95% CI)</th>
<th>Age and Gender-Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, n = 146</td>
<td>3.52 (1.65, 7.54)</td>
<td>2.56 (1.05, 6.25)</td>
</tr>
<tr>
<td>Hyperlipidemia, n = 129</td>
<td>3.91 (1.57, 9.71)</td>
<td>3.06 (0.99, 9.52)</td>
</tr>
<tr>
<td>Smoker — ever, n = 146</td>
<td>1.89 (1.06, 2.72)</td>
<td>1.54 (0.52, 2.56)</td>
</tr>
<tr>
<td>Family history, n = 113</td>
<td>3.04 (1.23, 7.53)</td>
<td>2.56 (1.15, 11.34)</td>
</tr>
<tr>
<td>Body mass index, n = 63</td>
<td>1.14 (1.03, 1.27)</td>
<td>1.05 (0.91, 1.21)</td>
</tr>
</tbody>
</table>

*n: total number of subjects for whom information was available regarding this variable if values were not available for the entire group.

**Table 3.** Clinical, serological, and therapeutic exposures in SLE patients with coronary heart disease. Values in bold type are statistically significant.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Unadjusted OR (95% CI)</th>
<th>Age and Gender-Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>0.79 (0.37, 1.67)</td>
<td>1.26 (0.50, 3.20)</td>
</tr>
<tr>
<td>Vasculitis*</td>
<td>1.29 (0.48, 3.48)</td>
<td>1.63 (0.49, 5.42)</td>
</tr>
<tr>
<td>Neuropsychiatric disease</td>
<td>0.86 (0.43, 1.71)</td>
<td>0.95 (0.41, 2.21)</td>
</tr>
<tr>
<td>SLICC Damage Index Score†</td>
<td><strong>2.20 (1.09, 4.44)</strong></td>
<td>1.73 (0.73, 4.11)</td>
</tr>
<tr>
<td>Antiphospholipid antibody or lupus anticoagulant</td>
<td>0.95 (0.44, 2.03)</td>
<td>2.57 (0.93, 7.09)</td>
</tr>
<tr>
<td>Anti-Sm antibody</td>
<td>0.38 (0.10, 1.39)</td>
<td>0.32 (0.07, 1.56)</td>
</tr>
<tr>
<td>Anti-Ro antibody</td>
<td>0.59 (0.28, 1.24)</td>
<td>0.58 (0.23, 1.47)</td>
</tr>
<tr>
<td>Anti-La antibody</td>
<td>0.38 (0.13, 1.07)</td>
<td>0.39 (0.11, 1.39)</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td><strong>2.46 (1.03, 5.88)</strong></td>
<td>2.63 (0.97, 7.16)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td><strong>2.33 (1.16, 4.67)</strong></td>
<td><strong>3.18 (1.33, 7.59)</strong></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>0.92 (0.30, 2.87)</td>
<td>1.25 (0.32, 4.91)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1.35 (0.51, 3.62)</td>
<td>1.40 (0.44, 4.50)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0.75 (0.19, 3.05)</td>
<td>1.22 (0.22, 6.69)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>1.13 (0.54, 2.39)</td>
<td>1.11 (0.46, 2.66)</td>
</tr>
</tbody>
</table>

* Vasculitis defined as digital lesion, splinter hemorrhage, or peripheral gangrene. SLICC: Systemic Lupus International Collaborating Clinics. At least one item scoring.
that were treated with steroids, doses were available for 89 subjects. The mean (SD) steroid dose for cases (n = 40) was 8.1 (10) mg and for controls (n = 49) 9.1 (12) mg. The increased azathioprine exposure was, however, significant in both the unadjusted and adjusted analyses (adjusted OR 3.18; 95% CI 1.33, 7.59). In contrast, there were no differences in exposure to other immunosuppressive agents between the groups. Only 3 patients had been prescribed mycophenolate mofetil. With regard to other therapies, aspirin exposure was similar between the groups [20 (25%) vs 13 (21%); p = 0.37], and a higher proportion of cases had been prescribed a lipid-lowering drug prior to the event date [7 (14%) vs 2 (2%); p = 0.005], consistent with the increased frequency of hypercholesterolemia.

**DISCUSSION**

In this UK-wide case-control study we found that SLE patients with clinical CHD were older, more likely to be male, and had more exposure to classic CHD risk factors. They were also more likely to have been treated with corticosteroids and azathioprine and have evidence of damage on the pre-event SLICC damage index. The older age at event is consistent with other studies that have shown an older age at time of diagnosis is associated with CHD. The mean age at the time of first coronary event in this study was 53 years, which accords with the range of 47–51 years reported in previous studies. Male patients were overrepresented in the cases, as noted by Petri, et al. Overall, 20% of cases were male compared to 7% of controls. The control group is consistent with the expected background gender distribution of SLE in the UK and confirms the risk of CHD in men with SLE to be particularly increased.

Classic risk factors for CHD, i.e., hypercholesterolemia, hypertension, smoking, and family history of CHD, were associated with clinical CHD; after adjustment for age and gender, hypertension and family history of CHD remained significantly associated with CHD events. These results are in keeping with 3 previous North American studies that used clinical CHD as an outcome, and contrasts with studies that included other cardiovascular outcomes in addition to CHD, where the contribution of classic risk factors is less clear (Table 4). This is because additional factors may contribute to the risk of other outcomes, e.g., atrial fibrillation and valvular heart disease are likely to also be important in stroke risk; similarly, the hierarchy of risk factors for peripheral vascular disease also differs from CHD. Our study confirms the findings of previous prospective cohort studies that classic risk factors play a key role in the development of CHD.

Table 4. Summary of studies examining risk factors for clinical cardiovascular events in patients with SLE. Values are mean (range or ± SD).

<table>
<thead>
<tr>
<th>Author</th>
<th>Mean Age at Time of Event, yrs</th>
<th>CHD Only</th>
<th>Cardiovascular Outcomes</th>
<th>Classic Risk Factors</th>
<th>Lupus/Other Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gladman⁶, n = 45</td>
<td>48 (25–73)</td>
<td>Yes</td>
<td>—</td>
<td>Hypertension, congestive heart failure, hypercholesterolemia, hypertriglyceridaemia, hyperglycemia, diabetes mellitus</td>
<td>Pericarditis, myocarditis</td>
</tr>
<tr>
<td>Manzi¹, n = 33⁷</td>
<td>48 (22–72)</td>
<td>Yes</td>
<td>—</td>
<td>Hypercholesterolemia, postmenopausal status</td>
<td>Older age at diagnosis*, duration of steroid use</td>
</tr>
<tr>
<td>Svenungsson⁸, n = 26</td>
<td>No CHD, stroke, or PVD</td>
<td></td>
<td>High VLDL, LDL, lipoprotein a, low HDL</td>
<td>ESR, CRP, orosomucoid, α-1-antitrypsin, LAC, homocysteine, osteoporosis, cumulative steroid dose</td>
<td></td>
</tr>
<tr>
<td>Petri⁷, n = 19</td>
<td>Yes</td>
<td>—</td>
<td>Hypercholesterolemia, hypertension</td>
<td>Older age at diagnosis, longer disease duration, duration of steroid use</td>
<td></td>
</tr>
<tr>
<td>Bessant¹⁶, n = 29</td>
<td>No</td>
<td>“Survivors” only, stroke, PVD</td>
<td>Hypertension, high total cholesterol, high triglycerides</td>
<td>LAC, less hydroxychloroquine use</td>
<td></td>
</tr>
<tr>
<td>Freire³, n = 10</td>
<td>43</td>
<td>No CHD, stroke</td>
<td>Older age</td>
<td>Longer disease duration, SLE clinical features not assessed</td>
<td></td>
</tr>
<tr>
<td>Ho¹⁷, n = 42</td>
<td>No CHD, stroke, PVD, venous thrombosis</td>
<td></td>
<td>Smoking</td>
<td>Macucutaneous manifestations, serosal manifestations, SLAM, steroid therapy</td>
<td></td>
</tr>
<tr>
<td>Urowitz⁹, n = 118</td>
<td>No CHD, stroke, PVD</td>
<td></td>
<td>Hypertension, smoking, hypercholesterolemia, no. of traditional risk factors</td>
<td>Raynaud’s, renal disease, neuropsychiatric disease, vasculitis, elevated prothrombin time, steroid therapy/immunosuppressives, less antimalarials</td>
<td></td>
</tr>
</tbody>
</table>

* Significant variables after controlling for age. ¹ SLE cases vs non-SLE controls. CHD: coronary heart disease; PVD: peripheral vascular disease; LAC: lupus anticoagulant; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VLDL: very low density lipoprotein; HDL: high density lipoprotein; SDI: SLICC Damage Index Score; SLAM: Systemic Lupus Activity Measure.
opment of CHD in lupus patients\(^7,22\). A recent study has sug-
ggested that, although our recognition and treatment of class-
cic risk factors such as hypertension and hypercholes-
terolemia has improved over time, a number of SLE patients
eligible for treatment remain untreated\(^23\). One contributing
factor for this observation may be the lack of any trials to
delineate whether aggressive risk factor modification will
reduce clinical events in SLE and the logistical difficulties
of conducting such studies in the setting of SLE\(^24\). Our
study, however, highlights the need for such intervention tri-
als against clinical outcomes to answer this key question in
SLE.

In agreement with others, we found that SLE-related fac-
tors are also important in CHD development\(^8,9,17\). The
SLICC/ACR damage index (SDI) prior to the event showed
a significant association with clinical CHD in the unadjus-
ted analysis. It has been noted that patients who develop SLE
at an older age accrue damage at a higher rate than SLE
patients with a younger age of onset\(^25\) and hence the less
significant result after age and gender adjustment. The main
damage items that scored among cases were skin scarring,
aloepecia, premature gonadal failure, and claudication.
Interestingly, few SDI items in these patients included fac-
tors directly attributable to the consequences of cortico-
steroid use, e.g., cataracts or osteoporosis, suggesting that
SLE-associated disease activity and damage resulting from
this may be important in the predisposition to CHD. Of note,
uncontrolled exacerbation of classic risk factors in SLE, which
may provide a further mechanism by which persistent dis-
ease and therapy together mediate cardiovascular risk in
SLE\(^29\).

A surprising finding is the lack of association between
CHD events and aPL or LAC. Other studies using clinical
outcomes have been inconsistent in this regard (Table 4). A
lack of statistical power in most studies to date is the most
likely explanation for this inconsistency. Others have found
an association between LAC and cardiovascular disease out-
comes in studies that include stroke, MI, and peripheral vas-
cular disease\(^8,16\). There is also evidence that aPL may be
pro- or anti-atherogenic\(^27,30\) and therefore measurement of
specific aPL subtypes may have more predictive value than
routine clinical tests.

Of the cases surviving their initial event 18 (35\%) subse-
dually underwent a coronary intervention including bal-
loon angioplasty, coronary artery stent insertion, or revascu-
larization. A favorable outcome was observed in one-third of
these patients over a mean (SD) of 8 (5) years’ followup.
Although a few small case series have described an accept-
able immediate outcome in patients with SLE undergoing
coronary intervention, the long or medium term outcome in
these patients remains unknown\(^31-33\).

It is important to consider the limitations of a study such as
this. The association between SDI and azathioprine expo-
sure is interesting; however, in view of the retrospective
data collection, we lacked accurate disease activity meas-
ures over time on which to base any firm conclusions from
these observations. The relatively small sample size is also
a key limitation. Some difficulty was encountered collecting
data because of missing information in medical records. For
example, information was missing in up to 20\% of subjects
with regard to patient-assigned ethnicity, hyperlipidemia,
and family history. However, we deliberately designed the
study to match by center as we anticipated that the quality of
data collection and missing information might be an issue,
and our analysis suggested that data quality did indeed bal-
ance out between cases and controls according to the
recruiting center. Complete data regarding most other vari-
ables were available in 98\% or more of the subjects. To limit
information bias, data were verified from other sources
including cardiology and general practice records. In keep-
ing with many studies, an accurate measure of corticosteroid
exposure was difficult to ascertain owing to the retrospec-
tive nature of data collection. As a result, previous cortico-
steroid exposure of any length or dose appeared to be the
most robust and verifiable measure and was therefore used
in the analysis. As with any case-control study, bias intro-
duced regarding case ascertainment and left censorship may
be an issue. However, all participating centers had clinical
or research databases allowing sampling from all eligible
patients, including those that had died. Cases did have a
shorter time from first criteria being met to diagnosis. This
might have resulted in an underestimation of the exposure to
immunosuppressant therapy in some subjects as data regard-
ing treatment were collected from the time of diagnosis, i.e., the time 4 ACR criteria were fulfilled. A longer delay to fulfilling criteria in the controls, however, would bias our results towards the null hypothesis. This observation of shorter time between onset of symptoms and diagnosis in cases with CHD is also consistent with the hypothesis that these patients had more aggressive active disease.

To our knowledge, this is the largest study to date examining risk factors for verified CHD as a discrete clinical outcome in SLE. Our results confirm that classic risk factors and certain SLE-related characteristics are associated with an increased risk of CHD. Our study highlights the importance of male gender and classic risk factors and the need for clinical vigilance to identify modifiable risk factors in the clinical setting. The higher pre-event SDI, azathioprine exposure prior to events, shorter time to diagnosis from symptom onset, and the pattern of damage items in cases suggest that a persistent active lupus phenotype contributes to CHD risk. In this regard, corticosteroids and azathioprine may not control disease well enough to prevent CHD. Evidence from clinical trials is now needed to resolve the question of whether classic risk factor modification will have a role in preventing clinical CHD events in SLE patients and to determine whether new therapies that better control disease activity can reduce the CHD risk.

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