Risk Factors for Development of Coronary Artery Disease in Women with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective***. To ascertain coronary artery disease (CAD) outcomes and predictive factors in a prospective study of patients with systemic lupus erythematosus (SLE) and matched healthy controls.

Methods. SLE patients and non-SLE age-matched controls without a history of CAD were recruited into a prospective study between 1997 and 1999. CAD events were assessed at clinic visit for SLE patients and through telephone interview and chart review for controls. All events were verified with patient medical records.

Results. Followup information was available on 237 controls and 241 SLE patients. The mean followup time was 7.2 years. Univariate analyses identified age and postmenopausal status as predictors of CAD in both the groups. Sedentary lifestyle, hypertension, the presence of metabolic syndrome, and the number of Framingham risk factors were predictive in the control group only. The 10-year risk of CAD score was predictive in both groups but was not as marked in the SLE group as in the controls. None of the lipid subfractions were predictive for CAD in the SLE group, whereas in the controls, a high triglyceride level ≥ 2.8 was predictive. Time-to-event multivariate analysis for CAD in all subjects revealed SLE itself, older age, and triglycerides ≥ 2.8 to be highly predictive for CAD.

Conclusion. In a prospective study of patients with SLE and matched controls followed over a median of 8 years, patients with SLE developed significantly more CAD events than controls. Accounting for demographic variability, CAD risk factors, and lipid factors, SLE is an independent risk factor for the development of CAD. (First Release Oct 15 2009; J Rheumatol 2009;36:2454–61; doi:10.3899/jrheum.090011)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is an inflammatory disease that typically affects young women. Coronary artery disease (CAD), including myocardial infarction (MI) and angina pectoris, is uncommon in young women but is a major cause of late morbidity and mortality among patients with SLE[1]. Mortality in SLE follows a bimodal pattern where early deaths are most often due to active SLE and infection, while late deaths after more than 2 years of disease course are often caused by CAD[2,3]. In a Toronto SLE cohort of 1087 patients followed from 1970 until 2004, the prevalence of CAD was 9.4%[4]. A similarly high prevalence for the development of CAD has been shown among the Hopkins Lupus Cohort[3] and the Pittsburgh SLE cohort[5]. It is now well established that SLE patients have an increased risk of atherosclerosis[2,3,5,6]. Overall, women with SLE are 5 to 8 times more likely and up to 50 times more likely in the 35–44 year age group than the general population to develop an atherosclerotic vascular event (which includes stroke and transient ischemic attack, TIA) than age- and sex-matched controls[7].

The Toronto Risk Factor Study (TRFS) was initiated in 1998 to compare the prevalence of cardiovascular risk factors in 250 women with SLE without clinical symptoms of CAD with 250 aged-matched controls without clinical symptoms of CAD[8]. Compared to matched controls, patients with SLE in this study were more likely to have hypertension, diabetes, and higher levels of very low-density lipoprotein (VLDL) cholesterol, total triglycerides (TG), and homocysteine. As well, SLE patients were more likely than controls to have premature menopause, sedentary lifestyle, and an at-risk body habitus. Nevertheless, there was no difference in the 10-year risk calculation for coronary heart disease using the Framingham risk factor assessment.

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The aim of our study was to ascertain the development of CAD in the lupus and control patients in the TRFS over 7 to 9 years of followup in order to determine which baseline risk factors predicted development of CAD.

MATERIALS AND METHODS

SLE patients. Patients with SLE have been followed prospectively at the University of Toronto Lupus Clinic since 1970 and constitute a cohort of more than 1300 patients. Clinical and laboratory information, including the details of therapy, are collected at 2–6 month intervals and stored on a computer database. Patients in this cohort are similar to SLE cohorts in other large centers[9].

A description of the 250 SLE patients who participated in the TRFS has been reported[8]. Briefly, 250 women with SLE who fulfilled ≥ 4 of the 1982 American College of Rheumatology classification criteria for SLE[10], or met 3 of the criteria and had a typical biopsy lesion of SLE[11], were approached to participate from May 1998 to June 2000. Patients with a history of MI, angina pectoris, stroke, TIA, or peripheral vascular disease were excluded.

Controls. A group of age-matched women attending a family practice unit for a routine annual physical examination were recruited as controls between May 1998 and June 2000. In addition to the above exclusions applied to SLE patients, the following exclusion criteria were applied to controls: a history of SLE or other chronic inflammatory arthritis, treatment with corticosteroids or antimalarial drugs within the past 6 months, known renal impairment (creatinine > 110 µmol/l) or significant proteinuria (> 1+ on dipstick analysis or > 500 mg/day).

Following development of CAD. Ethics approval to ascertain followup data for our study was obtained from the University Health Network Research Ethics Board in April 2007. SLE patients were followed at the University of Toronto Lupus Clinic at the Toronto Western Hospital at 2–6 month intervals, where clinical and laboratory information including the development of CAD (MI and/or angina pectoris) were collected. Information on the lupus patients was therefore available on the Lupus Clinic Oracle database. Control patients were followed at the Toronto Western Hospital Family Practice Unit. The development of CAD was confirmed through telephone interview and chart review. Authorization for release of medical information was obtained from any participant reporting an event. The clinic directors reviewed pertinent medical records. Supporting documentation included a hospital face sheet with diagnosis, discharge summary, admitting history, pertinent laboratory results, and other diagnostic tests such as electrocardiogram, echocardiogram, or coronary angiography.

Clinical assessments. Information on traditional and nontraditional cardiovascular risk factors as well as lupus-specific factors that may influence the development of CAD was collected. Clinical assessments on each SLE and control participant in the study were performed at study initiation using described methods[8]. Each SLE patient and control underwent a complete history and physical examination according to a standard protocol. This assessment included basic demographic data, organ-specific disease-related symptoms (for the SLE group), and physical findings. Overall disease activity at presentation to the clinic and at the time of the study was derived by calculation of the SLE Disease Activity Index (SLEDAI-2K)[12]. In addition, the adjusted mean SLEDAI score (AMS), which reflects the extent of disease activity over time, was calculated for each patient[13].

Therapy at the time of the baseline assessment was also noted, including the current dose and mean dose of prednisone since the prior visit, as well as the use of antimalarial and immunosuppressive medications. Data were also collected on the following risk factors for all patients: blood pressure at study onset, presence of diabetes and specific therapy, smoking history along with current smoking status and number of pack-years, body mass index (BMI) in kg/m^2, waist-hip ratio, recent change in body weight, and presence of metabolic syndrome using the International Diabetes Federation definition[14]. Information on a history of thyroid disease or current thyroid replacement therapy, menstrual status, use of oral contraceptives or hormone replacement therapy was collected. In addition, a trained interviewer administered 2 questionnaires. One questionnaire ascertained a family history of premature coronary heart disease (defined as a definite MI or sudden death in a first-degree relative: male, age < 55, or female, age < 65 yrs) and its associated risk factors, as well as any family history of SLE. The second questionnaire assessed the level of physical activity using the Physical Activity Index[15].

Laboratory methods. Routine clinical samples. Laboratory assessment included hemoglobin levels, leukocyte and platelet counts, serum creatinine levels, urine microscopy, fasting plasma glucose levels, antibodies to double-stranded DNA, complement (C3 and C4) levels, antibodies to cardiolipin (IgG > 23 IU), C-reactive protein (CRP), and the partial thromboplastin time (> 32 s).

Lipids. Levels of the following measures were assessed using described methods[8]: total cholesterol, TG, VLDL, intermediate-density lipoprotein, low-density lipoprotein (LDL), high-density lipoprotein (HDL), lipoprotein(a) [Lp(a)], LDL size, and Apo E phenotype.

Homocysteine. Plasma homocysteine levels were measured, using described methods[8]. In addition, since homocysteine levels are inversely correlated with folate levels, plasma folate and red blood cell (RBC) folate concentrations were also measured.

Outcomes. Outcomes included (1) CAD events, defined as the occurrence of MI and/or angina pectoris due to atherosclerosis and (2) all-cause mortality. MI was defined on the basis of definite electrocardiographic (ECG) abnormalities or symptoms of chest pain with probable ECG abnormalities and abnormal cardiac enzymes, or typical symptoms and abnormal cardiac enzymes, or naked-eye fresh MI or coronary occlusion at post mortem[16]. Angina was defined as severe pain or discomfort over the upper or lower sternum or anterior left chest and left arm. Events were recorded at clinic visit for SLE patients and through telephone interview and chart review for controls. All events were verified with patient medical records.

Statistical analysis. Demographic features of SLE patients were compared to controls using t tests and chi-squared tests. As few patients experienced a CAD outcome, nonparametric tests were performed to compare the characteristics of SLE patients who developed CAD to those who did not — namely Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous ones. Categorical classification of Framingham risk factors was determined using currently accepted definitions, as outlined[8]. For continuous variables, means, standard deviations and median values are provided. P values indicate comparisons between median levels between groups. In most cases, continuous variables were dichotomized to reflect normal/abnormal levels and compared. The same analysis was performed to establish differences within controls who developed CAD versus those who did not.

A time-to-event regression model was performed to establish the role of baseline lipid subfractions, other metabolic risk factors, lifestyle variables, and demographic characteristics in relation to the development of CAD. SLE patients and controls were included in a single model. SLE patients who did not have a CAD were censored as of the time of their last clinic visit or time of death. Controls were censored as of the time of last contact or time of death. Variables retained for the model were those that were statistically significant either in SLE patients or in controls in the univariate analyses. This stepwise approach was used to limit the number of variables in the model.

RESULTS

Study population. We collected baseline demographic, laboratory, and biochemical data for 250 patients and 250 controls matched for age at study onset. Followup information regarding the development of CAD was available for 241 of the SLE patients and 237 controls. Nine SLE patients were excluded (6 patients were lost to followup and 3 were sub-

sequently found to have had an event prior to study onset). Despite repeated efforts, 13 controls were lost to followup. Study followup time (based on the time from the initiation of the original study to the earliest of death, CAD, last clinic visit for SLE patients, or last contact date for controls) was 7.2 years (± 2.3). The median followup time was 8.1 years (Table 1). In the SLE patients the mean duration of SLE at study onset was 13.7 years (± 9.7), and the mean SLEDAI-2K score was 4.4 (± 4.5). Their Systemic Lupus International Collaborating Clinics Damage Index was 1.33 ± 1.62. Among the SLE patients, 55.0% were taking steroids, 53.9% were taking antimalarials, and 31.1% were taking immunosuppressives at the study start. In total, 10 (4.2%) of the SLE patients have died since the original study, compared to only 1 (0.4%) in the control group (p = 0.007). Causes of death in the lupus patients were malignancy in 3, respiratory failure in 1, systemic inflammatory response syndrome in 1, cerebral aneurysm in 1, sudden death with thrombocytopenia in 1, and unknown in 3. The control patient died of malignancy.

A greater proportion of SLE patients had a below-college level of education (p < 0.0001), underwent menopause at a younger age (p < 0.0001), had higher levels of creatinine (p = 0.0002), maintained a more sedentary lifestyle (p = 0.02), and had an increased waist-hip ratio (p < 0.0001) relative to controls (Table 1). However, there was no difference between the 2 groups in the BMI or prevalence of metabolic syndrome. In addition there was no difference in the 10-year risk calculation for coronary heart disease based on classic Framingham risk factors (data not shown).

Outcomes. The main outcome evaluated in this followup study was the development of CAD. In the SLE group, 17 (7.1%) patients and among the controls 5 (2.1%) patients (p = 0.01) developed CAD.

Demographic and lipid subfractions among SLE patients and controls categorized by the development of CAD. Univariate analyses were performed to compare demographic, clinical, and biochemical variables of SLE patients and controls who developed CAD relative to those who did not develop CAD. SLE patients with CAD were more likely to be older (p = 0.002) and postmenopausal (p = 0.03) compared to SLE patients without CAD (Table 2). There was no difference in level of education, racial distribution, age at menopause, use of oral contraceptives, serum creatinine levels, physical activity index, waist-hip ratio, and BMI between SLE patients who developed CAD relative to SLE patients without CAD. Controls with CAD were more likely to be older (p = 0.006), postmenopausal (p = 0.02), and were more likely to have a lower level of education (p = 0.03) and a sedentary lifestyle (p = 0.05) compared to controls without CAD (Table 2). Median age at study onset was 56.0 years among SLE patients who developed CAD compared to 69.0 years among controls who developed CAD (p = 0.055). There was no difference in racial distribution, age at menopause, use of oral contraceptives, serum creatinine levels, waist-hip ratio, and BMI between control patients who developed CAD relative to control patients without CAD.

A comparison between groups revealed that CRP levels were higher among SLE patients with CAD compared to SLE patients without CAD (p = 0.02), but this was not the case among non-SLE controls (Table 3). Controls with CAD were more likely to have elevated TG relative to controls without CAD (p = 0.005). Differences between groups in total cholesterol, LDL, VLDL, total TG, HDL, Lp(a), homocysteine, and RBC folate did not reach significance.

Framingham risk factors and metabolic syndrome among SLE patients and controls by development of CAD. We com-

Table 1. Demographic information of participants at baseline.

Characteristic	SLE, n = 241	Controls, n = 237	p
Age, yrs*	44.2 ± 12.2	44.5 ± 14.4	0.77
White/Black/Chinese/other, %	77/10/6/7	89/3/5/3	0.003
Education, < college, no. (%)	95 (40.1)	36 (15.2)	< 0.0001
Menopause			
Postmenopausal, no. (%)	95 (39.4)	65 (27.4)	0.006
Age at menopause, yrs	(n = 89) 45.5 ± 5.8	(n = 46) 49.3 ± 4.0	< 0.0001
Oral contraceptive, no. (%)	12 (5.0)	32 (13.6)	0.001
Serum creatinine*, µmol/l	78.9 ± 32.0	70.5 ± 10.4	0.0002
≥ 110 µmol/l, no. (%)	21 (8.9)	0 (0)	< 0.0001
Sedentary lifestyle†*	37.1 ± 10.3*	41.1 ± 11.2*	< 0.0001
< 28, no. (%)	38 (15.8)	21 (8.9)	0.02
Waist-hip ratio*	0.80 ± 0.06*	0.78 ± 0.05*	< 0.0001
> 0.80, no. (%)	112 (46.5)	70 (29.5)	0.0001
Body mass index, kg/m^2*	25.1 ± 6.4*	25.6 ± 5.9*	0.43
> 27 kg/m^2, no. (%)	66 (27.4)	71 (30.0)	0.53
Metabolic syndrome, no. (%)	25 (10.4)	20 (8.4)	0.47
Length of followup, yrs*	7.0 ± 2.4*	7.5 ± 2.2	0.05

* Mean ± standard deviation; † lifestyle scale[15].

Table 2. Analysis of demographic and clinical characteristics among SLE and control patients by development of coronary artery disease (CAD).

Characteristic	SLE			Controls		
	No CAD, n = 224	CAD, n = 17	p†	No CAD, n = 232	CAD, n = 5	p†
Age, yrs	43.5 ± 11.9*	53.6 ± 12.4		44.1 ± 14.1	65.6 ± 13.6	
Median	43.0	56.0	0.002	42.0	69.0	0.006
Caucasian/Black/Chinese/other, %	75/11/7/7	94/0/0/6	0.32**	88/3/5/3	100/0/0/0	1.00**
Education, < college, no. (%)	87 (39.6)	8 (47.1)	0.54	33 (14.2)	3 (60.0)	0.03
Postmenopausal, no. (%)	84 (37.5)	11 (64.7)	0.03	61 (26.3)	4 (80.0)	0.02
Age at menopause*, yrs	(n = 78) 45.6 ± 5.9	(n = 11) 45.0 ± 5.8	0.59	(n = 43) 49.4 ± 4.1	(n = 3) 47.7 ± 1.5	
Median	47.0	46.0		50.0	48.0	0.19
Oral contraceptive, no. (%)	11 (5.0)	1 (5.9)	0.87	32 (13.9)	0 (0)	1.00
Serum creatinine*, µmol/l	78.9 ± 32.9	78.1 ± 19.1		70.3 ± 10.2	76.4 ± 18.2	
Median	70.0	70.0	0.47	70.0	76.0	0.49
≥ 110 µmol/l, no. (%)	20 (9.1)	1 (5.9)	1.00	0 (0)	0 (0)	NA
Sedentary lifestyle*	37.0 ± 10.5	38.7 ± 8.4		41.3 ± 11.2	30.9 ± 9.9	
Median	34.9	36.5	0.31	40.9	29.6	0.05
< 28, no. (%)	36 (16.1)	2 (11.8)	1.00	19 (8.2)	2 (40.0)	0.06
Waist-hip ratio*	0.80 ± 0.06	0.82 ± 0.05		0.77 ± 0.05	0.82 ± 0.08	
Median	0.79	0.81	0.12	0.77	0.85	0.16
> 0.80, no. (%)	102 (45.5)	10 (58.8)	0.29	67 (29.8)	3 (60.0)	0.15
BMI, kg/m^2*	25.0 ± 6.4	26.3 ± 6.1		25.5 ± 5.8	29.7 ± 6.7	
Median	23.7	23.8	0.30	24.3	30.7	0.14
> 27 kg/m^2	59 (26.3)	7 (41.2)	0.26	68 (29.3)	3 (60.0)	0.16
Length of followup*, yrs	7.3 + 2.2	3.2 ± 2.4		7.5 + 2.1	3.1 ± 1.8	
Median	8.1	3.5	< 0.0001	8.2	2.8	0.002
Disease duration, yrs*	13.6 ± 9.7	15.0 ± 10.6				
Median	11.8	16.0	0.65			
SLEDAI-2K	4.27 ± 4.40	5.94 ± 5.71				
Median	4.00	6.00	0.19			
SLICC Damage Index	1.32 ± 1.61	1.50 ± 1.67				
Median	1.00	1.00	0.62			
Steroids, no. (%)	117 (52.7)	14 (82.4)	0.02			
Antimalarials, no (%)	119 (53.4)	11 (64.7)	0.37			
Immunosuppressives, no. (%)	70 (31.4)	4 (23.5)	0.50			

† Wilcoxon rank-sum test to compare medians or Fisher's exact test to compare percentages as appropriate. * Mean ± standard deviation; ** comparing Caucasian to all others. BMI: body mass index; SLEDAI: SLE Disease Activity Index; SLICC: SLE International Collaborating Clinics. NA: not available.

pared the prevalence of Framingham risk factors among patients with SLE and controls who developed CAD compared to participants who did not develop CAD (Table 4). The presence of hypertension (p = 0.02), the presence of metabolic syndrome (p = 0.005), a greater number of Framingham risk factors (p = 0.05), and a greater 10-year Framingham risk of a CAD-related event (p = 0.003) were more common among controls with CAD compared to controls without CAD. Among SLE patients with CAD compared to SLE patients without CAD, only the 10-year Framingham risk of a CAD-related event was greater, although the magnitude of the risk was very small. While other risk factors were also more prevalent among patients who developed CAD relative to patients who did not develop CAD, these differences did not reach significance.

Multivariate analysis. A multivariate time-to-event analysis performed to identify risk factors for the development of CAD revealed that age [hazard ratio (HR) 1.08, p < 0.0001], total TG levels (HR 7.96, p < 0.0002), and SLE itself (HR 4.23, p = 0.007) were significant predictors for the development of CAD (Table 5). Postmenopausal status, education, hypertension, number of risk factors, Framingham 10-year risk, sedentary lifestyle, metabolic syndrome, CRP, and homocysteine were not independent predictors of CAD. However, when metabolic syndrome is substituted for TG it is a significant predictor (HR 2.7, p = 0.03).

DISCUSSION

It is well established that women with SLE have a much higher than expected rate of atherosclerotic cardiovascular disease, with an estimated relative risk of 5- to 8-fold[5,7]. After an average followup of 7.2 years, SLE patients in the TRFS had, as expected, a greater rate of CAD, 7.1% (vs 2.1% in the control group), confirming a dramatically increased prevalence of CAD in women with SLE in our case-control study of women followed in the same healthcare facility.

This elevated rate of atherosclerosis may be attributable to cardiovascular risk factors that affect the general population, SLE itself, or its treatment, but the relative role of con-

Table 3. Analysis of lipid subfractions and CRP levels among SLE and control patients by development of coronary artery disease (CAD). Values are mean ± standard deviation; unless otherwise indicated.

Characteristic	SLE			Controls		
	No CAD, n = 224	CAD, n = 17	p†	No CAD, n = 232	CAD, n = 5	p†
Total cholesterol	4.65 ± 1.07	5.15 ± 1.65		4.80 ± 0.95	5.44 ± 1.24	
Median	4.48	5.07	0.19	4.75	4.99	0.29
≥ 5.2, no. (%)	59 (27.4)	6 (40.0)	0.37	71 (30.7)	2 (40.0)	0.65
LDL cholesterol	2.75 ± 0.93	3.16 ± 1.49		2.94 ± 0.85	3.00 ± 0.68	
Median	2.65	3.08	0.20	2.88	3.09	0.80
> 3.4, no. (%)	42 (19.5)	5 (33.3)	0.20	69 (29.9)	1 (20.0)	1.00
VLDL cholesterol	0.44 ± 0.35	0.50 ± 0.29		0.37 ± 0.23	0.94 ± 0.87	
Median	0.37	0.42	0.24	0.31	0.44	0.16
Total triglycerides	1.36 ± 0.86	1.74 ± 1.08		1.16 ± 0.57	2.70 ± 2.26	
Median	1.16	1.36	0.10	1.05	1.38	0.12
≥ 2.8, no. (%)	9 (4.2)	2 (13.3)	0.16	4 (1.7)	2 (40.0)	0.005
HDL triglycerides	0.28 ± 0.11	0.27 ± 0.10		0.27 ± 0.09	0.38 ± 0.21	
Median	0.27	0.31	0.98	0.26	0.23	0.35
Lp(a)	16.0 ± 17.1	17.8 ± 18.7		14.9 ± 16.7	9.9 ± 14.1	
Median	9.6	14.8	0.94	8.0	2.8	0.38
> 30, no. (%)	37 (20.0)	2 (20.0)	1.00	29 (15.0)	0 (0)	1.00
Homocysteine	9.6 ± 4.2	10.3 ± 5.6		6.4 ± 3.1	8.9 ± 3.3	
Median	9.2	10.0	0.81	6.2	8.6	0.08
> 15, no. (%)	233 (10.7)	2 (13.3)	0.67	2 (0.9)	0 (0)	1.00
RBC folate	1091 ± 539	1215 ± 541		1015 ± 418	1253 ± 600	
Median	925	1173	0.29	936	1353	0.38
CRP	0.32 ± 0.86	0.47 ± 0.71		0.33 ± 0.84	0.59 ± 0.63	
Median	0.10	0.23	0.02	0.13	0.32	0.19
Quartile**, no. (%)						
Q1	86 (40.8)	4 (23.5)		76 (33.0)	1 (20.0)	
Q2	52 (24.6)	3 (17.7)	0.05†	50 (21.7)	1 (20.0)	0.36††
Q3	32 (15.2)	4 (23.5)		56 (24.4)	1 (20.0)	
Q4	41 (19.4)	6 (35.3)		48 (20.9)	2 (40.0)	

† Wilcoxon rank-sum test to compare medians or Fisher's exact test to compare percentages as appropriate. ** Q1 < 0.08; Q2 0.08 to < 0.16, Q3 0.16 to 0.35, Q4 > 0.35. †† Mantel-Haenszel chi-square test.

Table 4. Framingham risk factors among SLE and control patients by development of coronary artery disease (CAD).

Characteristic	SLE			Controls		
	No CAD, n = 224	CAD, n = 17	p*	No CAD, n = 232	CAD, n = 5	p*
Hypertension, no. (%)	69 (30.8)	8 (47.1)	0.17	29 (12.6)	3 (60.0)	0.02
Hypercholesterolemia, no. (%)	71 (31.7)	9 (52.9)	0.07	85 (36.6)	2 (40.0)	1.00
Low HDL, < 0.9, no. (%)	19 (8.8)	1 (6.7)	1.00	24 (10.4)	1 (20.0)	0.43
Current smoker, no. (%)	38 (17.0)	2 (11.8)	0.75	41 (17.7)	2 (40.0)	0.22
Diabetes, no. (%)	10 (4.5)	1 (5.9)	0.56	2 (0.9)	(0)	1.00
Metabolic syndrome, no. (%)	21 (9.4)	4 (23.5)	0.08	17 (7.3)	3 (60.0)	0.005
Family history of CHD†, no. (%)	83 (37.1)	9 (52.9)	0.19	94 (40.5)	3 (60.0)	0.40
No. of risk factors	1.29 ± 1.00	1.76 ± 1.35		1.19 ± 0.97	2.20 ± 1.30	
Median	1.00	1.00	0.19	1.00	3.00	0.05
10-year risk	2.93 ± 3.99	5.76 ± 4.24		3.17 + 4.60	11.6 ± 7.89	
Median	0.0	6.0	0.004	0.0	8.0	0.003

* Wilcoxon rank-sum test to compare medians or Fisher's exact test to compare percentages as appropriate. † Definite myocardial infarction or sudden death in a first-degree relative: male age < 55 or female age < 65 years. CHD: coronary heart disease.

ventional cardiovascular risk factors remains controversial. The underlying basis of this increased risk has been examined retrospectively or prospectively in a number of large SLE cohorts by comparing characteristics of SLE patients with cardiovascular disease to those of patients lacking it[3-6,17-19]. Multivariate analyses of these cohorts showed to

Table 5. Predictors of CAD based on multivariate time-to-event analysis.

	Parameter Estimate ± SE	Hazard Ratio (95% CI)	p
Group, SLE vs controls	1.44 ± 0.53	4.23 (1.49, 11.97)	0.007
Age	0.078 ± 0.018	1.08 (1.04, 1.12)	< 0.0001
Total triglycerides, ≥ 2.8 vs < 2.8	2.07 ± 0.56	7.96 (2.65, 23.97)	0.0002

different degrees that traditional and other cardiovascular risk factors such as older age, smoking, hypertension, hypercholesterolemia, hypertriglyceridemia, lower HDL cholesterol levels, obesity, and higher levels of homocysteine were more common in SLE patients with CAD. Heterogeneous results have also been reported with respect to SLE-specific risk factors in these cohorts, with some of these studies demonstrating in univariate or multivariate analyses that SLE patients with CAD have a longer disease duration, greater corticosteroid exposure, higher levels of CRP, more antiphospholipid or oxidized LDL antibodies, and a higher SLE damage index, and are more likely to have had neuropsychiatric or renal disease, or vasculitis.

None of the above studies included a control group and none examined actual clinical events. The TRFS was conducted to prospectively ascertain the predictive value of various risk factors for CAD determined at the beginning of the study in 250 SLE patients and compare results with a control group of 250 patients from a family practice clinic. We reported previously[8] that initial comparison of cardiovascular risk factor profiles in SLE and control patients revealed that patients with SLE had a greater frequency of hypertension and diabetes, and had a slightly greater number of classic Framingham risk factors (1.01 vs 0.7) at the beginning of the study. Despite this, the overall Framingham 10-year risk was not significantly different, suggesting other risk factors may be more relevant. In fact, SLE patients were more likely to have had higher TG and VLDL cholesterol, a more sedentary lifestyle, abnormal waist-hip ratios, elevated creatinine, and greater homocysteine levels.

In our current study, CAD occurred in 7.1% of the patients with SLE. This rate of CAD was comparable to the 6.2% to 11.7% rate observed in other large SLE cohorts[3-6,18,19]. Interestingly, most of the traditional and nontraditional CAD risk factors did not explain the increased CAD in these SLE patients. In a univariate analysis, SLE patients with CAD were more likely to be older, postmenopausal, have a higher CRP (0.47 vs 0.32 mg/dl), and to have a slightly greater, but clinically insignificant 10-year Framingham risk (5.76% vs 2.93%). In contrast, control patients with CAD were more likely to have hypertension or be postmenopausal, and to have a clinically significant higher 10-year Framingham risk (11.6% vs 3.17%). Age, total triglyceride levels, and SLE itself were the strongest predictors of CAD in a multivariate analysis. Thus our results show in a prospective controlled study that SLE-related factors are important risk factors for accelerated CAD in women with SLE.

Our study did not detect the effects of traditional CAD risk factors, such as hypertension, smoking, and hypercholesterolemia, which were previously associated with CAD in lupus cohorts from London[17], Baltimore[3], Toronto[4], and Pittsburgh[5], and in the LUMINA study[19]. First, this difference from those studies may reflect a lack of statistical power due to the relatively small number of patients with CAD in our current study. This disparity with other studies could also be due to differences in the prevalence of risk factors in the different patient populations. For example, hypertension was present in 63% of the Pittsburgh non-CAD SLE patients, but in only 30% of the patients in our study. Only 11.8% of the patients in our study were current smokers, whereas the smoking (past or present) was reported in 53%, 41%, and 56% of the Pittsburgh, Toronto, and Baltimore cohorts, respectively. Treatment for some of the risk factors, such as hypertension, has improved over the years, perhaps lessening their impact on CAD. Excluding patients with preexisting CAD may have eliminated patients where traditional CAD risk factors had a greater influence, as observed in a study by Esdaile, *et al*[7]. Nevertheless, our present data do not discount the overall role of traditional risk factors for CAD in SLE patients and the need to treat these risk factors. Rather, in this group of SLE patients, SLE-related factors and to a lesser extent elevated TG or the presence of the metabolic syndrome play a more prominent role in predisposition to CAD.

In contrast, our results are consistent with a retrospective case-control study of patients from the Stockholm SLE cohort[6], which did not associate traditional CAD risk factors with CAD in SLE patients. Instead, this report identified nontraditional risk factors (decreased HDL, and increased TG, Lp(a), and homocysteine) and SLE-related factors (greater cumulative dose of prednisone, higher CRP, lupus anticoagulant levels, and anti-oxidized LDL antibodies) as being responsible for CAD in the setting of SLE. Esdaile, *et al* found in a retrospective study that Framingham risk equations could not explain the elevated risk of CAD in SLE[7]. Further supporting our current results, some of the other cohorts also implicated SLE-related factors, such as greater corticosteroid exposure[3,5,17,20], SLE damage index[19], SLE duration[3,5,19], lupus anticoagulant[17,19], CRP levels[19], and the occurrence of neuropsychiatric or renal disease, or vasculitis[20] in SLE-associated CAD.

The presence of elevated TG levels (< 2.8 mmol/l) was an independent risk factor for CAD in the multivariate analysis in our study, although TG levels > 2.8 mmol/l occurred in only 13% of patients with CAD. Consistent with these data, other groups have reported that SLE patients with CAD[6,7] or carotid artery atherosclerosis[21,22] had greater TG levels than SLE patients without atherosclerosis.

The increased TG levels in our study may originate from SLE-associated inflammation, which can alter TG metabolism directly by lowering lipoprotein lipase activity[23-25] and indirectly through insulin resistance (see above). Indeed, the characteristic dyslipoproteinemia of SLE consists of elevated TG and VLDL levels, and decreased HDL levels[24-27]. Corticosteroids can also augment TG levels, but the magnitude of their effect appears to be much less than SLE itself[24]. TG levels correlate well with lupus activity and tumor necrosis factor-α levels, indicating they may be primarily a marker for active SLE[23,24]. On the other hand, TG are an independent risk factor for CAD[28,29], especially in women, due to the formation of atherogenic, remnant TG-rich lipoproteins[29], and the strong association of elevated TG with insulin resistance and the metabolic syndrome[28]. In this regard, Sato, *et al*[30] found that remnant-like particle-cholesterol (likely derived from TG-rich VLDL) was increased in postmenopausal patients with SLE. This is also reflected in the predictive ability of the metabolic syndrome, which is defined by the presence of central obesity, elevated TG, reduced HDL, hyptertension, or diabetes.

There are several limitations to our study. Because we aimed to predict the cardiovascular risk using baseline values at the beginning of the study, there is no followup information on risk factors that can accumulate or change over time[31]. As a result of the relatively small number of SLE patients with CAD, our study may have lacked sufficient statistical power to detect the influence of some risk factors. This problem, which is common to many SLE studies, is being addressed by the multicenter international SLE inception cohort[31]. Only clinically apparent CAD was monitored during the 7-year average period of followup. MI is more likely to present with atypical symptoms in women[32], making diagnosis more difficult. Moreover, computed tomography studies suggest a high rate of asymptomatic CAD in SLE patients[33-35]. Therefore, our study likely underestimated the true extent of CAD in lupus patients. Another possible limitation may be the difference in the rigor of the followup process in patients and controls. While the family medicine patients were not followed regularly according to a standard protocol, the outcomes are hard outcomes, and recorded in hospital records and in family medicine clinics. In patients reviewed by telephone interview the outcomes were confirmed by obtaining physician records. Last, data were not available for some potential CAD risk factors such as levels of insulin, small dense LDL particles, or oxidized LDL or HDL, which might be relevant to CAD in patients with SLE.

In summary, the results of a prospective, controlled study of clinical CAD events in patients with SLE showed that the development of CAD and mortality were significantly greater in SLE patients than control subjects, and that the dominant risk factors in multivariate analyses were lupus itself, age, and high TG levels, but not the traditional Framingham risk factors. Taken together with other studies on clinical and subclinical CAD, which also highlighted lupus-specific factors to varying extents, this finding emphasizes the need to identify measurable lupus-related factors that accelerate atherosclerosis in SLE and to determine prospectively the value of screening for subclinical atherosclerotic disease.

REFERENCES

1. Nikpour M, Urowitz MB, Gladman DD. Premature atherosclerosis in systemic lupus erythematosus. Rheum Dis Clin North Am 2005;31:329-54, vii-viii.
2. Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976;60:221-5.
3. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med 1992;93:513-9.
4. Urowitz MB, Ibanez D, Gladman DD. Atherosclerotic vascular events in a single large lupus cohort: prevalence and risk factors. J Rheumatol 2007;34:70-5.
5. 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.
6. Svenungsson E, Jensen-Urstad K, Heimburger M, Silveira A, Hamsten A, de Faire U, et al. Risk factors for cardiovascular disease in systemic lupus erythematosus. Circulation 2001;104:1887-93.
7. Esdaile JM, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, du Berger R, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001;44:2331-7.
8. Bruce IN, Urowitz MB, Gladman DD, Ibanez D, Steiner G. Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. Arthritis Rheum 2003;48:3159-67.
9. Gladman DD, Urowitz MB. Systemic lupus erythematosus — clinical features. In: Hochberg MC, Silman A, Smolen J, Weinblatt M, Weisman M, editors. Rheumatology. Edinburgh: Mosby; 2008:1277-97.
10. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
11. Lee P, Urowitz MB, Bookman AA, Koehler BE, Smythe HA, Gordon DA, et al. Systemic lupus erythematosus. A review of 110 cases with reference to nephritis, the nervous system, infections, aseptic necrosis and prognosis. Q J Med 1977;46:1-32.
12. Gladman DD, Ibanez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. J Rheumatol 2002;29:288-91.
13. 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.
14. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome — a new worldwide definition. Lancet 2005;366:1059-62.
15. Kannel WB, Sorlie P. Some health benefits of physical activity. The Framingham Study. Arch Intern Med 1979;139:857-61.
16. Tunstall-Pedoe H, Kuulasmaa K, Amouyel 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.
17. Bessant R, Duncan R, Ambler G, Swanton J, Isenberg DA, Gordon C, et al. Prevalence of conventional and lupus-specific risk factors for cardiovascular disease in patients with systemic lupus erythematosus: A case-control study. Arthritis Rheum 2006;55:892-9.
18. Bessant R, Hingorani A, Patel L, MacGregor A, Isenberg DA, Rahman A. Risk of coronary heart disease and stroke in a large British cohort of patients with systemic lupus erythematosus. Rheumatology 2004;43:924-9.
19. Toloza SM, Uribe AG, McGwin G Jr, Alarcon GS, Fessler BJ, Bastian HM, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXIII. Baseline predictors of vascular events. Arthritis Rheum 2004;50:3947-57.
20. 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.
21. Selzer F, Sutton-Tyrrell K, Fitzgerald SG, Pratt JE, Tracy RP, Kuller LH, et al. Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. Arthritis Rheum 2004;50:151-9.
22. Telles RW, Lanna CC, Ferreira GA, Souza AJ, Navarro TP, Ribeiro AL. Carotid atherosclerotic alterations in systemic lupus erythematosus patients treated at a Brazilian university setting. Lupus 2008;17:105-13.
23. Svenungsson E, Gunnarsson I, Fei GZ, Lundberg IE, Klareskog L, Frostegard J. Elevated triglycerides and low levels of high-density lipoprotein as markers of disease activity in association with up-regulation of the tumor necrosis factor alpha/tumor necrosis factor receptor system in systemic lupus erythematosus. Arthritis Rheum 2003;48:2533-40.
24. Sarkissian T, Beyenne J, Feldman B, Adeli K, Silverman E. The complex nature of the interaction between disease activity and therapy on the lipid profile in patients with pediatric systemic lupus erythematosus. Arthritis Rheum 2006;54:1283-90.
25. de Carvalho JF, Bonfa E, Borba EF. Systemic lupus erythematosus and "lupus dyslipoproteinemia". Autoimmun Rev 2008;7:246-50.
26. Borba EF, Bonfa E. Dyslipoproteinemias in systemic lupus erythematosus: influence of disease, activity, and anticardiolipin antibodies. Lupus 1997;6:533-9.
27. Ilowite NT, Samuel P, Ginzler E, Jacobson MS. Dyslipoproteinemia in pediatric systemic lupus erythematosus. Arthritis Rheum 1988;31:859-63.
28. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. CMAJ 2007;176:1113-20.
29. Jacobson TA, Miller M, Schaefer EJ. Hypertriglyceridemia and cardiovascular risk reduction. Clin Ther 2007;29:763-77.
30. Sato H, Miida T, Wada Y, Maruyama M, Murakami S, Hasegawa H, et al. Atherosclerosis is accelerated in patients with long-term well-controlled systemic lupus erythematosus (SLE). Clin Chim Acta 2007;385:35-42.
31. 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.
32. Kosuge M, Kimura K, Ishikawa T, Ebina T, Hibi K, Tsukahara K, et al. Differences between men and women in terms of clinical features of ST-segment elevation acute myocardial infarction. Circ J 2006;70:222-6.
33. Asanuma Y, Oeser A, Shintani AK, Turner E, Olsen N, Fazio S, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003;349:2407-15.
34. Von Feldt JM, Scalzi LV, Cucchiara AJ, Morthala S, Kealey C, Flagg SD, et al. Homocysteine levels and disease duration independently correlate with coronary artery calcification in patients with systemic lupus erythematosus. Arthritis Rheum 2006;54:2220-7.
35. Kiani AN, Magder L, Petri M. Coronary calcium in systemic lupus erythematosus is associated with traditional cardiovascular risk factors, but not with disease activity. J Rheumatol 2008;35:1300-6. Epub 2008 May 15