Medicine®

OBSERVATIONAL STUDY

OPEN

Risk of Peripheral Arterial Occlusive Disease in Patients With Systemic Lupus Erythematosus

A Nationwide Population-Based Cohort Study

Ya-Wen Chuang, MD, Mei-Ching Yu, PhD, Cheng-Li Lin, MSc, Tung-Min Yu, MD, Kuo-Hsiung Shu, MD, and Chia-Hung Kao, MD

Abstract: Systemic lupus erythematosus (SLE) is associated with atherosclerosis, but the relationship between SLE and peripheral arterial occlusive disease (PAOD) remains unclear. We sought to investigate this relationship by comparing cardiovascular complications in patients with and without SLE.

Data on patients from 2000 to 2011 were collected from the National Health Insurance Research Database of Taiwan. The SLE cohort was frequency-matched according to age, sex, and history of diabetes mellitus (DM) with patients without SLE (control cohort). We evaluated the risk of cardiovascular complications, including hypertension, DM, stroke, chronic obstructive pulmonary disease, heart failure, coronary artery disease, and hyperlipidemia.

The study included 10,144 patients with SLE and 10,144 control patients. The incidence of PAOD was 9.39-fold higher (95% confidence interval [CI] = 7.70–11.15) in the SLE cohort than in the non-SLE cohort. Moreover, SLE was an independent risk factor for PAOD. The adjusted risk of PAOD was highest in patients with SLE who were aged ≤34 years (hazard ratio = 47.6, 95% CI = 26.8–84.4). The risk of PAOD was highest during the first year of follow-up and decreased over time.

Patients with SLE exhibit a higher incidence and an independently higher risk of PAOD compared with the general population. The PAOD risk is markedly elevated in patients with SLE who are young and in whom the disease is at an early stage.

(*Medicine* 94(46):e2121)

Abbreviations: aHR = adjusted hazard ratio, BNHI = Bureau of National Health Insurance, CI = confidence interval, DM = diabetes mellitus, ICD-9-CM = International Classification of Disease Ninth Revision Clinical Modification, LHID2000 = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, PAOD = peripheral arterial occlusive disease, SD = standard deviation, SLE = systemic lupus erythematosus.

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE). Many studies have indicated that SLE patients have higher risks of endothelial dysfunction and atherosclerosis compared with the general population.[1–4] Numerous cohort studies have reported that the risk of myocardial infarction is increased 2 to 10-fold in patients with SLE.[5–8] Epidemiological studies have further reported that patients with SLE also exhibit an increased risk of congestive heart failure and stroke.[9] Both traditional and disease-related factors contribute to the development of CVD in SLE patients.[10–13] Koenig et al suggested that the risk of CVD in patients with SLE is similar to the cardiovascular risk in patients with type 1 diabetes mellitus (DM).[14] Moreover, SLE per se is an independent risk factor for the development of CVD.[15]

Peripheral arterial occlusive disease (PAOD) is a manifestation of atherosclerosis that is associated with a 2.5 to 6-fold increase in cardiovascular mortality.[16,17] The prevalence and incidence of PAOD have been shown to be higher in patients with SLE than in the general population.[18–20] The risk factors for PAOD in patients with SLE include age, DM, dyslipidemia, smoking, an extended duration of steroid use, a Systemic Lupus International Collaborating Clinics Damage Index, use of azathioprine or warfarin, and plasma levels of thrombotic variables.[18–22] However, the risk factors for and incidence and consequences of PAOD in patients with SLE remain poorly investigated. Thus, we aimed to determine the incidence of PAOD in patients with SLE and analyze the risk factors for PAOD in such patients.

Editor: Carlos Guillen Astete.
Received: August 27, 2015; revised: October 7, 2015; accepted: October 9, 2015.
From the Division of Nephrology, Taichung Veterans General Hospital, Taichung (Y-WC, T-MY, K-HS); Department of Pediatric Nephrology, Chang Gung Children's Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan (M-CY); Management Office for Health Data, China Medical University Hospital (C-LL); College of Medicine, China Medical University, Taichung (C-LL); Graduate Institute of Clinical Medicine Science, School of Medicine (T-MY); Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University (C-HK); and Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan (C-HK).
Correspondence: Chia-Hung Kao, Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 40447, Taiwan (e-mail: d10040@mail.cmuh.org.tw).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All authors have contributed significantly, and that all authors are in agreement with the content of the manuscript: conception/design: Y-WC, C-HK; provision of study materials: C-HK; collection and/or assembly of data: all authors; data analysis and interpretation: all authors; manuscript writing: all authors; final approval of manuscript: all authors.
This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002); China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092); NRPB Stroke Clinical Trial Consortium (MOST 103-2325-B-039-006); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; Katsuzo and Kiyo Aoshima Memorial Funds, Japan; and CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan. No additional external funding received for this study.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002121

METHODS

Data Source

Data for this study were collected from the National Health Insurance Research Database (NHIRD). The NHIRD was created by the National Health Research Institute (NHRI), and it contains the claims data from the Taiwan National Health Insurance (NHI) program. The Taiwan NHI was established in 1995 by combining 13 existing insurance programs into 1 nationwide, single-payer health insurance program. The Taiwan NHI is a compulsory insurance program for residents of Taiwan, and it covered nearly 99% of the 23 million residents in 1998. The NHIRD includes a registry for beneficiaries, historical disease records, and medical service information, and this database is renewed every year. All original personal identification information on insured people is removed, and the NHRI assigns a scrambled and anonymous identification number to each insured person for safeguarding patient privacy before releasing the database for research. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115). The IRB also specifically waived the consent requirement.

In the NHIRD, diseases are recorded based on the criteria of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). In this study, the history of SLE was collected from the catastrophic illness registry and the history of comorbidities was recorded from inpatient and outpatient files. All insurance claims should be scrutinized by medical reimbursement specialists and peer review according to the standard diagnosed criteria in the study. If these doctors or hospitals make wrong diagnoses or coding, they will be punished with a lot of penalties. Therefore, the diagnoses of PAOD and SLE in this study were highly reliable. In addition, some related studies with the same diagnosed method and criteria by ICD-9 coding were already accepted for publication.[23–26]

Study Population

The SLE cohort was established using patients >20 years old with a new onset of SLE (ICD-9-CM 710.0) between January 1, 2000 and December 31, 2011. The SLE diagnosis date was used as the index date of the SLE cohort. The comparison cohort included insured patients without SLE, was 4-fold larger than the SLE cohort, and was frequency-matched according to age (per 5 years), sex, and history of DM (ICD-9-CM 250). We randomly assigned a month and day but the same year as that of matched cases as the index date for the comparison cohort. We excluded people with a history of PAOD (ICD-9-CM 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 447.8, and 447.9). The follow-up period ended when the study patients withdrew from the insurance, at the time of PAOD event occurrence, or on December 31, 2011.

In addition to demographic factors, comorbidities were considered here as confounding factors. Comorbidities were defined as diseases that were diagnosed in the patients before the index date. The comorbidities included hypertension (ICD-9-CM 401-405), cancer (ICD-9-CM 140-208), stroke (ICD-9-CM 430-438), chronic obstructive pulmonary disease (COPD; ICD-9-CM 491, 492, and 496), heart failure (HF; ICD-9-CM 428), coronary artery disease (CAD; ICD-9-CM 410-414), hyperlipidemia (ICD-9-CM 272), smoking (ICD-9-CM 305.1), and asthma (ICD-9-CM 493). In addition, steroid use, warfarin use, and various biologic therapies (including azathioprine, cyclosporin, immunoglobulin, mycophenolate, and tacrolimus) were analyzed between the SLE patients and the controls.

Statistical Analysis

We calculated the mean and standard deviation (SD) in the case of patient age and determined the number and percentage for age group, sex, and comorbidities in order to describe the distribution of the study population. A t test was use to analyze the difference in age distribution between the study cohorts, and a χ^2 test was used in the case of age group, sex, comorbidities, and medications. The PAOD incidence density was calculated as the total number of PAOD events divided by the sum of the follow-up years (per 1000 person-year) for each group. We used the Kaplan–Meier method to obtain the PAOD cumulative-incidence curves for the SLE and control cohorts, and then applied the log-rank test to evaluate the difference between these 2 incidence curves. To assess the PAOD risk in SLE patients, we calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) by using single-variable and multivariable Cox proportional hazard models. We also used the Cox model to measure the risk of PAOD in patients with SLE after stratification according to distinct demographic factors, comorbidities, and medications.

SAS 9.4 software (SAS Institute, Cary, NC, USA) was used for data management and statistical analysis. The PAOD cumulative-incidence curve was drawn using R software (R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ (2-sided testing) was considered statistically significant.

TABLE 1. Comparison of Demographics and Comorbidities Between Patients With Systemic Lupus Erythematosus and Controls

	Control Subjects (N = 10,144) N (%)	SLE (N = 10,144) N (%)	*P* Value
Sex			0.89
Female	8763 (86.4)	8770 (86.5)	
Male	1381 (13.6)	1374 (13.5)	
Age, year			0.48
≤34	4175 (41.2)	4151 (40.9)	
35–49	3514 (34.6)	3465 (34.2)	
>50	2455 (24.2)	2528 (24.9)	
Mean (SD)	40.5 (15.0)	40.9 (15.2)	0.13*
Comorbidity			
DM	412 (4.06)	407 (4.01)	0.86
Hypertension	2021 (19.9)	2102 (20.7)	0.16
Hyperlipidemia	1105 (10.9)	1156 (11.4)	0.26
COPD	769 (7.58)	782 (7.71)	0.73
HF	327 (3.22)	321 (3.16)	0.81
CAD	867 (8.55)	872 (8.60)	0.90
Stroke	337 (3.32)	311 (3.07)	0.30
Asthma	587 (5.79)	609 (6.00)	0.51
Smoking	97 (0.96)	86 (0.85)	0.41
Medication			
Steroid use	9110 (89.8)	9153 (90.2)	0.31
Warfarin	139 (1.37)	118 (1.16)	0.19

χ^2 test. CAD = coronary artery disease COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus HF = heart failure.
* t test.

RESULTS

This study enrolled 10,144 patients with SLE and 10,144 patients without SLE (comparison cohort) (Table 1). Males accounted for only 13.5% of the study population, and the mean age of the 2 cohorts was 41 years. The SLE cohort and non-SLE cohort were well matched for sex, age group, comorbidities, and medications. The mean follow-up duration was 5.22 ± 3.64 years for the SLE cohort and 6.05 ± 3.19 years for the control cohort.

Table 2 shows the risk of PAOD associated with SLE, demographic factors, and selected comorbidities and medications. According to the single-variable Cox proportional hazard model, SLE, sex, CAD, and warfarin were significantly associated with an increased risk of PAOD. After adjustment for age and the comorbidities of DM, hypertension, hyperlipidemia, COPD, HF, CAD, stroke, asthma, smoking, and medication of steroid use, and warfarin, the PAOD risk inpatients with SLE was 9.39-fold higher than that for patients without SLE (HR = 9.39, 95% CI = 7.70–11.5). The PAOD cumulative-incidence curve plotted for the SLE cohort was also significantly higher than the curve plotted for the comparison cohort (Fig. 1; $P < 0.001$, log-rank test).

Table 3 shows the risk of PAOD in patients with SLE according to distinct demographic factors, comorbidities, steroid use, and warfarin, further indicating that the PAOD risk in SLE patients was significantly higher than that of control patients. The PAOD risk in female patients with SLE was 9.90-fold higher than that in female patients in the comparison cohort (HR = 9.90, 95% CI = 7.98–12.3), but this risk in male patients with SLE was only 5.96-fold higher than that in control male patients (HR = 5.96, 95% CI = 3.50–10.2). Moreover, the PAOD risk was 2.92-fold higher in elderly patients (aged >50 years) with SLE than in patients without SLE. By contrast, in the population group aged ≤34 years, the risk of PAOD in patients with SLE was 47.6-fold higher than that in patients without SLE (HR = 47.6, 95% CI = 26.8–84.4). Furthermore, in the study population lacking any of the examined comorbidities, SLE clearly increased the risk of PAOD (HR = 19.7, 95% CI = 14.3–27.3). Among the nonmedication subjects, SLE patient still had great risk of PAOD than control patients.

Table 4 presents the risk of PAOD in SLE patients according to follow-up time. The results suggest that PAOD events occurred at an increased frequency in the early stages of the follow-up period. The rate of PAOD incidence in patients with SLE was 21.9-fold higher than that in control patients when the follow-up time was <1 year (HR = 32.0, 95% CI = 18.7–54.5), but this rate dropped to 10.8-, 4.99-, and 3.59-fold higher relative to control patients when the follow-up period was 1 to 3 years (HR = 10.8, 95% CI = 7.25–16.1), 4 to 5 years (HR = 4.99, 95% CI = 3.37–7.39), and >5 years (HR = 3.59, 95% CI = 2.49–5.18), respectively.

Compared with patients without SLE, SLE patients without various biologic therapies used demonstrated a significantly higher risk of PAOD (adjusted HR = 10.6, 95% CI = 8.63–13.1), followed by SLE patients with various biologic therapies (adjusted HR = 8.10, 95% CI = 6.54–10.0) (Table 5). SLE patients who received various biologic therapies treatment exhibited significantly lower risk of PAOD (adjusted HR = 0.74, 95% CI = 0.64–0.86) than SLE patients without various biologic therapies used.

DISCUSSION

Based on our research, this is the first population-based cohort study to determine the incidence of and risk factors for

TABLE 2. Cox Model Results Presented With Hazard Ratios and 95% Confidence Intervals of Peripheral Arterial Occlusive Disease Associated With Systemic Lupus Erythematosus and Covariates

	Crude		Adjusted	
Variable	**HR (95% CI)**		**HR (95% CI)**	
SLE (ref = ''No'')	9.00	(7.38, 11.0)***	9.39	(7.70, 11.5)***
Age, years	1.00	(0.99, 1.00)	0.99	(0.98, 1.00)
Sex (ref = ''men'')	1.33	(1.08, 1.63)**	1.32	(1.07, 1.63)*
Baseline comorbidities (ref = ''no'')				
DM	1.05	(0.75, 1.47)	1.15	(0.80, 1.65)
Hypertension	0.95	(0.81, 1.12)	0.96	(0.79, 1.17)
Hyperlipidemia	1.02	(0.83, 1.25)	0.99	(0.79, 1.24)
COPD	1.25	(1.00, 1.57)	1.39	(1.09, 1.77)**
HF	1.22	(0.85, 1.74)	1.11	(0.75, 1.64)
CAD	1.35	(1.10, 1.65)**	1.60	(1.25, 2.04)***
Stroke	1.07	(0.72, 1.58)	1.14	(0.76, 1.72)
Asthma	1.05	(0.80, 1.38)	0.96	(0.72, 1.27)
Smoking	1.28	(0.64, 2.56)	1.52	(0.76, 3.07)
Medication				
Steroid use	0.53	(0.44, 0.62)***	0.43	(0.36, 0.51)***
Warfarin	2.03	(1.32, 3.13)**	2.02	(1.29, 3.17)**

Adjusted HR: multivariable analysis including age and the comorbidities of DM, hypertension, hyperlipidemia, COPD, HF, CAD, stroke, asthma, smoking, and medication of steroid use, and warfarin.

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HF = heart failure.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

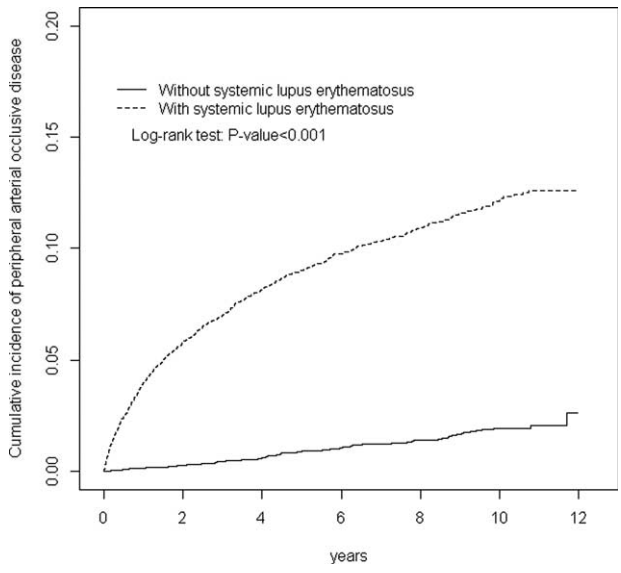

FIGURE 1. Cumulative incidence of peripheral arterial occlusive disease in patients with (dashed line) and without (solid line) systemic lupus erythematosus.

PAOD among patients with SLE by performing appropriate comparisons with non-SLE controls. Our results revealed that the risk of PAOD in the SLE cohort was 9.38-fold higher than that in the control cohort, and that SLE was an independent risk factor for PAOD. The PAOD risk was elevated in young patients with SLE, particularly in patients aged <34 years. Moreover, the risk of PAOD in patients with SLE was highest in the first year after SLE diagnosis and then it declined.

A 2004 American study conducted by Fischer et al determined that in patients with SLE, the overall relative risk of developing myocardial infarction was 2.67-fold higher than that in patients without SLE.[6] A California study reported that patients with SLE were 1 to 3-fold more likely to be admitted to the hospital with congestive heart failure than were patients without SLE.[9] Manzi et al demonstrated that the risk of CVD in SLE patients was >50-fold higher than that in non-SLE controls.[27] Patients with SLE were also reported to be associated with a 1.65 to 5-fold higher risk of PAOD compared with control groups.[18,19] In a large, multicenter cohort study, 5.3% of 637 patients with SLE developed PAOD over a mean follow-up period of 4.4 years.[20] However, our study revealed for the first time that the incidence of PAOD is higher in patients with SLE than in the general population. Previous studies have reported that renal disease, cytokines, inflammatory mediators, antiphospholipid antibodies, and SLE treatment contribute to the development of CVD in SLE.[10–13,28] Furthermore, the prevalence of atherosclerosis was reported to be elevated among patients with SLE.[2] Shang et al demonstrated that SLE was an independent risk factor for atherosclerosis and arterial stiffness.[3] Moreover, another study showed that SLE per se was a significant predictor for the development of CVD.[15] This finding agrees with our result showing that SLE per se is an independent risk factor for PAOD.

Our results revealed that the PAOD risk was high in young patients with SLE (particularly patients aged <34 years old) and was lower than that in elderly patients. A Swedish population-based study conducted by Bengtsson et al demonstrated that the

TABLE 3. Incidence and Adjusted Hazard Ratios of Peripheral Arterial Occlusive Disease Stratified According to Sex and Age and Compared Between the SLE Cohort and the Non-SLE Cohort

	Control Subjects			SLE			Compared to SLE	
Variables	**Event**	**PY**	**Rate**	**Event**	**PY**	**Rate**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
All	110	61,344	1.79	869	52,978	16.4	9.00 (7.38, 11.0)***	9.38 (7.69, 11.4)***
Sex								
Female	93	53,412	1.74	787	46,412	17.0	9.60 (7.74, 11.9)***	9.90 (7.98, 12.3)***
Male	17	7932	2.14	82	6566	12.5	5.69 (3.37, 9.59)***	5.96 (3.50, 10.2)***
Age								
≤ 34	12	26,756	0.45	462	23,342	19.8	43.4 (24.5, 76.9)***	47.6 (26.8, 84.4)***
35–49	37	21,301	1.74	258	18,643	13.8	7.87 (5.58, 11.1)***	8.11 (5.74, 11.5)***
>50	61	13,287	4.59	149	10,992	13.6	2.90 (2.15, 3.90)***	2.92 (2.17, 3.94)***
Comorbidity†								
No	39	42,864	0.91	623	36,146	17.2	18.6 (13.4, 25.7)***	19.7 (14.3, 27.3)***
Yes	71	18,479	3.84	246	16,832	14.6	3.76 (2.89, 4.90)***	3.78 (2.90, 4.93)***
Medication								
Steroid use								
No	7	6418	1.09	145	3581	40.5	30.9 (14.4, 65.9)***	31.0 (14.5, 66.5)***
Yes	103	54,925	1.88	724	49,397	14.7	7.77 (6.32, 9.55)***	7.81 (6.35, 9.60)***
Warfarin								
No	103	60,727	1.70	855	52,503	16.3	9.44 (7.70, 11.6)***	9.82 (8.01, 12.1)***
Yes	7	617	11.3	14	475	29.5	2.68 (1.08, 6.65)*	2.83 (1.05, 7.59)*

Rate: incidence rate, per 1000 person-years. Adjusted HR: multivariable analysis including age and the comorbidities of DM, hypertension, hyperlipidemia, COPD, HF, CAD, stroke, asthma, smoking, and medication of steroid use, and warfarin.

† The comorbidity group included patients with any one of these comorbidities: DM, hypertension, hyperlipidemia, COPD, HF, CAD, stroke, asthma, and smoking.

* $P < 0.05$.

*** $P < 0.001$.

TABLE 4. Trends of Peripheral Arterial Occlusive Disease Stratified According to Follow-Up Years

	Control Subjects			SLE			Compared to SLE	
Follow Time, Yr	**Event**	**PY**	**Rate**	**Event**	**PY**	**Rate**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
≤1	14	10,080	1.39	378	9180	41.2	29.3 (17.2, 49.9)***	32.0 (18.7, 54.5)***
1–3	27	17,778	1.52	244	14,995	16.3	10.7 (7.19, 15.9)***	10.8 (7.25, 16.1)***
4–5	31	13,822	2.24	127	11,492	11.1	4.93 (3.33, 7.30)***	4.99 (3.37, 7.39)***
>5	38	19,664	1.93	120	17,312	6.93	3.59 (2.49, 5.17)***	3.59 (2.49, 5.18)***

Rate: incidence rate, per 1000 person-years. Adjusted HR: multivariable analysis including age and the comorbidities of DM, hypertension, hyperlipidemia, COPD, HF, CAD, stroke, asthma, smoking, and medication of steroid use, and warfarin.
*** $P < 0.001$.

risk of myocardial infarction or stroke in the SLE population was 1.27-fold higher than that in the general population, but among patients with SLE who were aged 40 to 49 years, this risk was 8-fold higher during a 7-year follow-up period.[8] Ward determined that in18 to 44-year-old patients with SLE, the risk of stroke was 1.75 times higher than that in age-matched controls. Moreover, Manzi et al demonstrated that the incidence of myocardial infarction in 35 to 44-year-old female patients with lupus was >50 times higher than that in females of a similar age from a population-based sample.[27]

Our study showed that PAOD was also strongly associated with traditional cardiovascular risk factors such as COPD and CAD. The inflammatory milieu of SLE leads to a dysregulation of lipid metabolism pathways, thus contributing to an increased risk of atherosclerotic disease among patients with SLE.[29,30] A Framingham Heart Study cohort showed an association with hyperlipidemia, but not with other traditional cardiovascular risk factors.[27] In a Spanish study, the final model revealed that only age was an independent variable of PAOD, although other cardiovascular risk factors such as DM, hypertension, hypercholesterolemia, or current smoking also tended to be present.[22] Bhatt et al identified a relationship between PAOD and dyslipidemia, but not age, DM, or hypertension.[31] Our results showed that the PAOD risk was higher in female patients with SLE than in male patients with the disease. In 2 large cohort studies, male patients with SLE had a 4-fold higher risk of developing CVD compared with female patients[10,32]; however, in both studies, nearly 90% of the patients with SLE were female. Nevertheless, in previous studies, sex showed nostatistically significant difference between groups in relation to PAOD occurrence among patients with SLE.[18–20,22]

Our results showed that the risk of developing PAOD was highest in the first year of follow-up and then decreased over time. A nationwide study indicated that the risk of CAD among patients with SLE decreased over time and was highest in the first year of follow-up (standardized incidence ratio (SIR) = 4.94, 95% CI 4.15–5.83).[33] Furthermore, the risk of hemorrhagic stroke among patients with SLE was highest in the first year and then decreased (SIR = 8.65 in the first year, 95% CI 3.92–16.5; SIR = 2.89 after 1–5 years, 95% CI 1.53–4.95).[5]

TABLE 5. Incidence, Crude and Adjusted Hazard Ratio of Peripheral Arterial Occlusive Disease Compared Among SLE Patients With and Without Various Biologic Therapies Treatment and Non-SLE Controls

Variables	**N**	**Event**	**PY**	**Rate**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
Non-SLE controls	10,144	110	61,344	1.79	1 (reference)	1 (Reference)		
SLE without various biologic therapies (including azathioprine, cyclosporin, immunoglobulin, mycophenolate, and tacrolimus)	5044	484	24,426	19.8	10.7 (8.69, 13.1)***	10.6 (8.63, 13.1)***	1 (Reference)	1 (Reference)
SLE with various biologic therapies (including azathioprine, cyclosporin, immunoglobulin, mycophenolate, and tacrolimus)	5100	385	28,552	13.5	7.50 (6.07, 9.27)***	8.10 (6.54, 10.0)***	0.71 (0.62, 0.81)***	0.74 (0.64, 0.86)***

Rate: incidence rate, per 1000 person-years. Adjusted HR: multivariable analysis including age and the comorbidities of DM, hypertension, hyperlipidemia, COPD, HF, CAD, stroke, asthma, smoking, and medication of steroid use, and warfarin.
*** $P < 0.001$.

Previous studies have demonstrated that immunosuppressive treatment reduced endothelial damage and improved patient condition in atherosclerosis.[34,35] This finding agrees with our result showing that the PAOD risk was higher in SLE patients without immunosuppressive treatment than in SLE patients with various treatments. Thus, we hypothesized that suppression of inflammation and disease control might reduce cardiovascular risk in patients with SLE.

The present study has several strengths. First, this is the first population-based study to analyze the association between SLE and PAOD. Second, we examined the incidence and risk factors for PAOD in patients with SLE in comparison with controls from the general population. Third, we adjusted for these confounding factors: DM, hypertension, hyperlipidemia, COPD, heart failure, CAD, stroke, asthma, smoking, and medication of steroid use, and warfarin. Despite possessing these strengths, our study had some limitations. First, the NHIRD cannot provide the individual SLE patient's laboratory data (such as disease activity in SLE and autoantibody of lupus anticoagulant). Therefore, we cannot do the further study about the potential relationship of lupus anticoagulant and peripheral artery occlusive disease. This is one of the study limitations. Second, we could have underestimated the incidence of PAOD because patients who exhibited no symptoms or presented with mild PAOD symptoms might have been overlooked. Finally, from the NHIRD, we could not obtain data related to cardiovascular risk factors including smoking habits, dietary habits, body mass index, and the extent of daily activity. To minimize the influence from smoking, we have used an alternative way and adjusted for smoking-related diseases (including chronic obstructive pulmonary disease, coronary artery disease, stroke, asthma) in our analysis. In addition, less than 5% women are smoker in Taiwan, the PAOD risk associated with SLE was greater for women.

In conclusion, the risk of PAOD is increased in patients with SLE, and SLE per se is an independent risk factor for PAOD. Attention must be devoted to the risk of PAOD among young patients with SLE because this risk is markedly elevated. Additional studies on disease screening and early intervention are necessary to prevent subsequent complications of PAOD in patients with SLE.

REFERENCES

1. Zhang CY, Lu LJ, Li FH, et al. Evaluation of risk factors that contribute to high prevalence of premature atherosclerosis in Chinese premenopausal systemic lupus erythematosus patients. *J Clin Rheumatol.* 2009;15:111–116.
2. Roman MJ, Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med.* 2003;349:2399–2406.
3. Shang Q, Tam LS, Li EK, et al. Increased arterial stiffness correlated with disease activity in systemic lupus erythematosus. *Lupus.* 2008;17:1096–1102.
4. Sacre K, Escoubet B, Pasquet B, et al. Increased arterial stiffness in systemic lupus erythematosus (SLE) patients at low risk for cardiovascular disease: a cross-sectional controlled study. *PLoS One.* 2014;9:e94511.
5. Zöller B, Li X, Sundquist J, et al. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. *BMC Neurol.* 2012;12:41.
6. Fischer LM, Schlienger RG, Matter C, et al. Effect of rheumatoid arthritis or systemic lupus erythematosus on the risk of first-time acute myocardial infarction. *Am J Cardiol.* 2004;93:198–200.
7. Hak AE, Karlson EW, Feskanich D, et al. Systemic lupus erythematosus and the risk of cardiovascular disease: results from the nurses' health study. *Arthritis Rheum.* 2009;61:1396–1402.
8. Bengtsson C, Ohman ML, Nived O, et al. Cardiovascular event in systemic lupus erythematosus in northern Sweden: incidence and predictors in a 7-year follow-up study. *Lupus.* 2012;21:452–459.
9. Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum.* 1999;42:338–346.
10. Pons-Estel GJ, González LA, Zhang J, et al. Predictors of cardiovascular damage in patients with systemic lupus erythematosus: data from LUMINA (LXVIII), a multiethnic US cohort. *Rheumatology.* 2009;48:817–822.
11. Toloza SM, Uribe AG, McGwin G Jr et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXIII. Baseline predictors of vascular events. *Arthritis Rheum.* 2004;50:3947–3957.
12. Fernández-Nebro A, Rúa-Figueroa Í, López-Longo FJ, et al. Cardiovascular Events in Systemic Lupus Erythematosus: A Nationwide Study in Spain From the RELESSER Registry. *Medicine.* 2015;94:e1183.
13. Lee AB, Godfrey T, Rowley KG, et al. Traditional risk factor assessment does not capture the extent of cardiovascular risk in systemic lupus erythematosus. *Intern Med J.* 2006;36:237–243.
14. Koenig KF, Ribi C, Radosavac M, et al. Prevalence of vascular disease in systemic lupus erythematosus compared with type-1 diabetes mellitus: a cross-sectional study of two cohorts. *Lupus.* 2015;24:58–65.
15. Goldberg RJ, Urowitz MB, Ibañez D, et al. Risk factors for development of coronary artery disease in women with systemic lupus erythematosus. *J Rheumatol.* 2009;36:2454–2461.
16. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med.* 1992;326:381–386.
17. Morillas P, Quiles J, Cordero A, et al. Impact of clinical and subclinical peripheral arterial disease in mid-term prognosis of patients with acute coronary syndrome. *Am J Cardiol.* 2009;104:1494–1498.
18. Hassan AA, Habib HM, Eissa AA. Peripheral arterial disease in patients with systemic lupus erythematosus: a prospective controlled study. *Int J Rheum Dis.* 2013;16:319–324.
19. June RR, Scalzi LV. Peripheral vascular disease in systemic lupus patients. *J Clin Rheumatol.* 2013;19:367–372.
20. Burgos PI, Vilá LM, Reveille JD, et al. Peripheral vascular damage in systemic lupus erythematosus: data from LUMINA, a large multiethnic U.S. cohort (LXIX). *Lupus.* 2009;18:1303–1308.
21. McDonald J, Stewart J, Urowitz MB, et al. Peripheral vascular disease in patients with systemic lupus erythematosus. *Ann Rheum Dis.* 1992;51:56–60.
22. Erdozain JG, Villar I, Nieto J, et al. Peripheral arterial disease in systemic lupus erythematosus: prevalence and risk factors. *J Rheumatol.* 2014;41:310–317.
23. Shen CH, Lin TY, Huang WY, et al. Pneumoconiosis increases the risk of peripheral arterial disease: a nationwide population-based study. *Medicine (Baltimore).* 2015;94:e911.
24. Chou TY, Su TW, Jou HJ, et al. Increased risk of peripheral arterial disease after hip replacement: an 11-year retrospective population-based cohort study. *Medicine (Baltimore).* 2015;94:e870.
25. Chou CH, Lin CL, Chang SN, et al. A nationwide population-based retrospective cohort study: increased risk of acute myocardial infarction in systemic lupus erythematous patients. *Int J Cardiol.* 2014;174:751–753.

26. Chung WS, Lin CL, Chang SN. Systemic lupus erythematosus increases the risks of deep vein thrombosis and pulmonary embolism: a nationwide cohort study. *J Thromb Haemost.* 2014;12:452–458.
27. Manzi S, Meilahn EN, Rairie JE, 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;145:408–415.
28. Schoenfeld SR, Kasturi S, Costenbader KH. The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: a systematic review. *Semin Arthritis Rheum.* 2013;43:77–95.
29. McMahon M, Grossman J, Skaggs B, et al. Dysfunctional proinflammatory high-density lipoproteins confer increased risk of atherosclerosis in women with systemic lupus erythematosus. *Arthritis Rheum.* 2009;60:2428–2437.
30. McMahon M, Skaggs BJ, Sahakian L, et al. High plasma leptin levels confer increased risk of atherosclerosis in women with systemic lupus erythematosus, and are associated with inflammatory oxidised lipids. *Ann Rheum Dis.* 2011;70:1619–1624.
31. Bhatt SP, Handa R, Gulati GS, et al. Peripheral vascular disease in systemic lupus erythematosus. *Lupus.* 2007;16:720–723.
32. Urowitz MB, Gladman D, Ibañez D, et al. Atherosclerotic vascular events in a multinational inception cohort of systemic lupus erythematosus. *Arthritis Care Res.* 2010;62:881–887.
33. Zöller B, Li X, Sundquist J, et al. Risk of subsequent coronary heart disease in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. *PLoS One.* 2012;7:e33442.
34. Kisiel B, Kruszewski R, Juszkiewicz A, et al. Systemic lupus erythematosus: the influence of disease-related and classical risk factors on intima media thickness and prevalence of atherosclerotic plaques—a preliminary report. Beneficial effect of immunosuppressive treatment on carotid intima media thickness. *Acta Cardiol.* 2015;70:169–175.
35. Parker B, Al-Husain A, Pemberton P, et al. Suppression of inflammation reduces endothelial microparticles in active systemic lupus erythematosus. *Ann Rheum Dis.* 2014;73:1144–1150.