Accrual of atherosclerotic vascular events in a multicentre inception SLE cohort

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ACCRUAL OF ATHEROSCLEROTIC VASCULAR EVENTS IN A MULTICENTRE INCEPTION SLE COHORT

Short Title: **AVE in SLE**

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ABSTRACT

Background/Purpose: In previously published work, atherosclerotic vascular events (AVE) occurred in approximately 10% of patients with SLE. We aimed to investigate the annual occurrence and potential risk factors for AVE in a multinational, multiethnic inception cohort of patients with SLE.

Methods: A large 33-centre cohort of SLE patients was followed yearly between 1999-2017. AVEs were attributed to atherosclerosis on the basis of SLE being inactive at the time of the AVE, and typical atherosclerotic changes on imaging or pathology, and/or evidence of atherosclerosis elsewhere. Analysis included descriptive statistics, rate of AVE's per 1000 patient-years, and univariable and multivariable relative risk regression models.

Results: Of the 1848 patients enrolled in the cohort, 1710 had at least one follow up visit after enrolment, for a total of 13,666 patient-years. Of 1710, 3.6% had one or more AVEs attributed to atherosclerosis, for an event rate of 4.6 per 1000 patient-years. In multivariable analyses, lower AVE rates were associated with antimalarials (HR: 0.54[95% CI 0.32, 0.91]) while higher AVE rates were associated with any prior vascular event (VE) (HR: 4.00[1.55,10.30]) and body mass index (BMI) >40 (HR: 2.74[1.04,7.18]) A prior AVE increased the risk for subsequent AVE (HR 5.42[3.17,9.27], $p<0.001$).

Conclusion: The prevalence of AVE and rate of AVE accrual in this study is much lower than that seen in previously published data. This may be related to better control of both the disease activity and classic risk factors.

INTRODUCTION

Atherosclerotic disease has been recognized as a major cause of morbidity and mortality among patients with systemic lupus erythematosus (SLE)[1]. In previously published work, the fraction of patients with atherosclerotic vascular events (AVE) was approximately 10% in patients with SLE, after an average follow-up of 9 years[2]. Women with SLE have been observed to have a 5 to 50-fold increase in their risk of coronary artery disease (CAD)[3,4] compared to the general population. This has triggered a concentrated effort to identify and treat traditional cardiovascular risk factors[5,6], facilitated by the development of cholesterol-lowering medications and newer antihypertensive medications. Furthermore, the cardioprotective effect of antimalarial medications has been recognized in conjunction with their effect on prevention of disease flares, thrombosis, and damage accrual and improved survival[7,8,9,10], leading to increased use in patients with SLE[11]. This prompted us to reexamine the prevalence of AVE in the current era.

The Systemic Lupus International Collaborating Clinics (SLICC) group has developed an inception cohort of SLE patients to study atherosclerosis with the following specific objectives: 1. To determine the incidence, prevalence and nature of AVE in SLE; 2. To identify associated risk factors for the development of AVEs; 3. To develop interventional approaches to modify the identified risk factors[12,13,14].

We report on the prevalence, incidence rate, and risk factors for AVE in this multinational, multiethnic, inception cohort of patients with SLE, the SLICC inception cohort.

METHODS

Patients: An inception cohort of SLE patients has been assembled and followed according to a standardized protocol between October 1999-October 2017. Patients were enrolled in the cohort

within 15 months of SLE diagnosis (≥4 American College of Rheumatology (ACR) criteria)[15]. Clinical and laboratory features of SLE and comorbidities were recorded at yearly intervals[,12]. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K[16]). Accumulated damage was recorded according to the SLICC-ACR Damage Index (SDI)[17]. Data were entered and stored on an Oracle database. Patients who had at least one follow-up visit were included in analyses reported here.

The SLICC Registry Ethics approval with the University Health Network (UHN) Research Ethics Board (REB) is #00-0279-A under the title *The Systemic Lupus Collaborating Clinics Registry for Atherosclerosis in SLE.* All participating sites have their own local ethics approvals.

Outcome: The diagnosis of AVE was confirmed using standard clinical criteria, relevant laboratory data and imaging and includes (1) Myocardial infarction, defined as one of: definite electrocardiographic (ECG) abnormalities; typical symptoms with probable ECG abnormalities and abnormal enzymes (> 2X upper limit of normal). (2) Angina, defined as severe pain or discomfort over the upper or lower sternum or anterior left chest and left arm, of short duration, relieved by rest or vasodilators. (3) Transient ischemic attack (TIA), defined as a brief episode of neurological dysfunction without residua. (4) Stroke, defined as an abrupt onset of neurological dysfunction resulting in neurological damage. (5) Congestive heart failure due to ischemic heart disease requiring treatment. (6) Bradyarrhythmia due to ischemic heart disease requiring pacemaker insertion. (7) Peripheral vascular disease (based on the presence of intermittent claudication). Attribution of vascular events to atherosclerosis was based on SLE being inactive (clinical SLEDAI-2K of 0) at the time of the event, and the presence of typical atherosclerotic changes on imaging or pathology and/or evidence of atherosclerosis elsewhere. Only vascular events that occurred after enrolment into the cohort were included. All required information for an

AVE diagnosis was recorded by the local SLE clinical investigator on a standardized data retrieval form. Information was obtained from the attending physician and recorded on the data retrieval form. Each event had an event date associated with it which was not necessarily the same as the annual follow up date and the assessment of lack of disease activity occurred at the time of the event.

The following variables were recorded: baseline demographics, classic cardiovascular risk factors (smoking, hypertension [>140/90], high cholesterol, random glucose levels, body mass index (BMI), alcohol use, family history of cardiovascular disease), disease-related (SLEDAI-2K, SDI, antiphospholipid antibodies [anticardiolipin antibody (aCL) and/or lupus anticoagulant (LA)] ever in those who were tested), previous non-atherosclerotic vascular events (VEs), and SLE treatment (glucocorticosteroids, antimalarials, immunosuppressive agents).

Statistical Analysis: We calculated the incidence rate per 1000 patient-years for AVEs. Demographic information was summarized with mean and standard deviations (SD) for normally distributed data and count (percentage) for categorical data. For missing values for patients' weight, height, and family history of cardiovascular disease, carried-forward imputations were used.

Kaplan-Meier curves were calculated for time-to-event outcomes. Demographic information at enrolment was used to define time-fixed covariates in Cox relative risk regression models while clinical, treatment, and classic AVE risk factor information were updated at the time of each visit[18]. The primary outcome of interest was the time to the first AVE. Other patients were deemed to be event-free until the date of their last visit. The time scale used for analysis was age, to provide the most general adjustment for age, with the time of entry into follow-up defined as the age at the enrolment visit. We carried out univariable and multivariable time-dependent Cox regressions for time to first AVE, with all analyses adjusted for the prior occurrence of non-AVEs. Because aCL

and/or LA tests were not performed in 23% of the patients, we initially performed these analyses on all patients but excluded antiphospholipid antibodies as a risk factor. We then repeated the analyses in the 77% of the patients who had these antibodies tested. Multivariable models were developed based on univariable results and the fitting of models with the most relevant clinical variables. Additional analyses incorporated recurrent AVEs and were based on relative risk modelling with stratification by previous AVE[19].

The analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina), and the program coxph in R[20].

RESULTS

Of the 1848 patients in the cohort, 1710 patients had at least one follow-up visit for a total of 13,366 patient years, and constitute the study population. The 138 patients excluded from the study were not different in terms of initial visit information from the 1710 patients who formed this study cohort. This is an early, multicenter, multiethnic inception cohort followed for a mean of 8.3 and standard deviation of 4.3 years. **Table 1** illustrates the demographics, clinical, and therapeutic features of this cohort. Of the 1710 patients enrolled, 85 have died, giving a crude mortality of 5.0% (85/1710) or 6.4 per thousand person years (85/13366). Three hundred and fifty-seven patients were lost to follow-up giving a crude rate of 20.9%).

One hundred and seventy vascular events were identified in 113 patients after their enrolment visit. Of these, 86 were attributed to AVE, and 84 were VEs not attributed to atherosclerosis. Of these 84, 53 were attributed to SLE, and 31 were attributed to other causes, including vasospasm, trauma, fluid-overload associated with chronic renal disease, vascular malformations, and sepsis. Since the purpose of our study was to identify and determine risk factors for AVEs, we focused our analyses on AVEs. Of the 86 AVEs, 61 were first events and 25 were recurrent events (**Table 2**).

Sixty-one (3.57%) of the 1710 patients had at least one AVE. The mean (SD) duration from diagnosis to the first event was 6 (3.9) years. The total number of patient-years of follow-up among these patients from entry into the cohort to AVE, last visit or death was 13,366 years providing an incidence rate of 4.56 per 1000 patient-years (95% confidence interval, CI 3.6 -5.9). **Figure 1** presents Kaplan-Meier estimates of the probability of being event free from first AVEs.

We analyzed individually the predictors for first AVE. **Table 3** summarizes these analyses, all adjusted for prior other VEs which is highly significant as a predictor itself (HR[95%CI]: 4.13[1.61,10.6]). Missing values in the predictors led to fewer events in some analyses but with the exception of aCL/LA information, this was minimal. There was some evidence that female sex, antimalarial treatment and never having smoked were protective and a high BMI and ever having a positive aCL/LA conferred increased risk. The coding for BMI was influenced by non-parametric estimation of the effect of BMI which indicated that only very high values of BMI (>40) were associated with a higher risk of AVEs (not statistically significant). Similarly, there was a trend for average steroid dose to be associated with increased risk of AVE.

Table 4 presents results from two multivariable models including the predictors with significant effects in the single factor analyses, one, Model (a), without the aCL/LA variable and one, Model (b), with this variable. The inclusion of aCL/LA led to the exclusion of 405 patients, of whom 7 had AVEs, for whom this variable was missing. In addition to the predictive effect associated with prior other VEs, high BMI was also predictive of first AVE while only antimalarial therapy demonstrated a highly significant protective effect, [HR (95%CI): 0.54 (0.32, 0.91)], after adjustment for the other factors in the model. While 67.8% of all patients took antimalarials at enrolment, 86.7% were using antimalarials during the course of follow-up. The other effects were broadly consistent with the single factor analyses although the estimated effects were generally

smaller in multivariable models with the exception of the increased risk associated with very high BMI (>40) which is somewhat more significant in these models.

We performed a univariable analysis to determine whether previous AVE was a risk for recurrent AVE. Previous AVE was found to increase the risk of subsequent AVEs [HR(95% CI): 5.42(3.17,9.27), p<0.001].

Table 5 presents an additional multivariable analysis when recurrent AVEs are included in the analysis, with time dependent stratification on prior occurrence of an AVE. Initial investigations (results not shown) indicated that there was some evidence of differential effects for first AVEs and recurrent AVEs for female sex and anti-malarial therapy. Both variables appear to have protective effect only for first AVEs (although not significant for female sex). This is reflected in Table 5 by presenting separate effects for these variables in the two strata. Broadly speaking, the estimated effects associated with other variables are consistent with those found in analyses of first AVEs, although the effect of never smoking is somewhat more marked. A stratified analysis of all AVEs including the aCL/LA variable is not presented as there was insufficient data for some variables to allow reliable estimation. The results for other variables were consistent with the results shown in **Table 5**.

DISCUSSION

Atherosclerotic cardiovascular events have been recognized as a major comorbidity in SLE. Initial estimates of clinical prevalence of AVE in SLE were 6.7-10%[2,3,21].

The SLICC inception cohort was established in 1999 initially to determine the incidence, prevalence and nature of AVEs in SLE. Patient accrual to this cohort continued until 2011 when 1848 patients had been recruited. Patients continue to be followed to the present time. Thus, identification and prevalence of AVEs in the SLICC inception cohort represents the modern era.

The prevalence of AVE in this study is much lower than in previously published data. In the Toronto Cohort, reported in 2007 (followed from 1970 to 2004), 10% of the patients in both the prevalent and inception cohorts had the AVEs[2]. In the current study, only 3.6% of patients had an AVE. Furthermore, the rate of AVEs in the Hopkins Cohort reported in 2012, which included the period 1987 to 2010, was 14.1/1000 patient-years[22]. It should be noted that in the Baltimore study, VEs in patients with and without active SLE were both counted whereas our analysis excluded VEs in patients with SLEDAI > 0. Thus one must be cautious in comparing event rates between the two studies. However, this is similar to AVE rate in the Toronto Lupus Cohort followed from 1975 to 1999, which was 19/1000 patient-years[23]. In the SLICC cohort including patients from 1999 to 2017 the incidence rate was 4.56 per 1000 patient-years, similar to the incidence of 4.4/1000 seen in the Toronto cohort followed during the same period both using similar definitions for AVEs[23]. Taking out the Toronto patients from the SLICC cohort provided the same frequency. This decline in rate of AVEs mirrors the declining incidence of AVEs noted in the general population[24,25]. The decline in AVEs in the SLICC cohort may also be due to better control of lupus disease activity, more judicious use of glucocorticosteroids[26] as well as improvements in the treatment of cardiac risk factors in the modern era[23].

With regards to predictors of first AVEs, in the total cohort we demonstrated that prior other VE and BMI >40 were predictive of AVEs while antimalarial treatment was protective. These results were consistent whether the whole cohort or the sub-cohort that included only patients tested for aCL/LA were analyzed. Although aCL/LA, never having smoked and female sex were predictive in univariable analyses they were less marked in the multivariable analysis. In a study of 182 patients from Sweden, published in 2009, any aCL was predictive of first cardiovascular event[27], and another study performed in Northern Sweden including 277 patients also identified aCL as a

prognostic factor for cardiovascular events[28]. Also, in a study from Baltimore including 1874 patients with SLE, a history of LA was predictive of cardiovascular events[22]. These reports did not provide information on the attribution of AVEs to aCL.

When we analyzed multiple AVEs we found that a prior AVE was predictive of a recurrent AVE and a multivariable analysis also demonstrated that a prior other vascular events was predictive for recurrent events, never having smoked was protective for all events and antimalarial treatment was protective for first AVEs.

Hanly et al.[29] investigated cerebrovascular events in the SLICC cohort and found that 94% were due to SLE. Moreover, 40% of events were identified at the enrollment visit, and the remainder over the mean follow-up of 6.6 years, almost 2 years shorter than the current study. These early events due to SLE are in contrast to the events described here that are later in onset and attributed to atherosclerosis.

The strength of the study is that it is based on a multinational multiethnic large inception cohort followed over 18 years with an average follow-up of 8 years. Definitions for AVE were specified a priori and known risk factors for AVE were collected prospectively.

There are a number of limitations for the study. The adjudication of AVEs vs non-atherosclerotic VEs was subject to potential inaccuracy as it was determined by each local SLE expert/site investigator although attempts were made for standardization of this procedure by using clear definitions of each AVE and SLE disease activity was taken into account. Silent atherosclerotic events might have been missed but those ascertainment criteria are similar to those used in the general population. As well, more AVEs may accrue with further follow-up. Another possible limitation is the fact that the study was designed as yearly evaluation and the exact timing of possible discontinuation of therapies could not be analyzed. However, the time dependent analyses

do inform on the effect of taking a medication prior to the event. Since SLE activity was tied into the outcome definition, it may have impacted the observed association with potential predictors that may also be associated with SLE disease activity, although antimalarials are generally continued regardless of disease activity.

With regards to the SLICC atherosclerosis registry aims, we have now demonstrated that the incidence of AVEs in the current era is lower than expected. While it was anticipated that there would be both classic risk factors (e.g. smoking) and disease related risk factors, we were unable to establish clear relationships between AVEs and many of the variables studied. We hypothesize that more effective control of lupus disease activity and treatment of classic atherosclerotic risk factors may have both contributed to controlling AVEs in this inception cohort. However, in all our analyses we found that antimalarial treatment was protective for AVE emphasizing the importance of this therapy in the management of SLE.

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FIGURE LEGEND

Figure 1. Kaplan Meier survival curve for first AVE in 1710 SLE patients including 95% confidence intervals.

Table 1: Characteristics of SLE population N=1710	
Mean Age at SLE Diagnosis (years)*	34.7 ± 13.4
Mean disease duration at enrolment (months)*	5.7 ± 4.2
Females	1515 (88.6%)
Race (%) Caucasian / African descendant / Hispanic / Asian / Other	49.4 / 16.4 / 15.5/ 15.0 / 3.7
Mean duration of follow-up (yrs)*	8.3 ± 4.3
Mean SLEDAI-2K at first visit*	5.4 ± 5.4
SLICC Damage Index at year 1* SLICC Damage Index at year 1 for those SDI >0* (N = 314)	0.3 ± 0.8 1.5 ± 0.8
Glucocorticosteroid treatment at enrolment	1186 (69.4%)
Average daily glucocorticosteroid dose at enrolment (of those treated with glucocorticosteroids)*mg/day	23.9 ± 16.5
Antimalarial treatment at enrolment	1159 (67.8%)
Immunosuppressive treatment at enrolment	692(40.5%)
SBP>140 or DBP>90 mmHg at enrolment BP treatment	204 (11.9%) 505 (29.5%)
Abnormal total cholesterol regardless of treatment Statins treatment at enrolment	517 (30.2%) 155 (9.1%)
BMI at enrolment BMI > 40	25.3 ± 5.8 38 (2.2%)

Smoking (currently or prior) at enrolment	598 (35.0%)
Alcohol consumption Yes (%) Units per week in those consumed	470 (27.5%) 3.7 ± 4.9
Family history of sudden death, MI, angina or stroke at enrolment	512 (29.9%)
Ever ACL/LA positive ever (N = 1305) Anticoagulants treatment at enrolment Aspirin treatment at enrolment	469 (35.9%) 92 (5.4%) 287 (16.8%)
*Mean and standard deviation (SD)	

Table 2: Nature and attribution of vascular event		
Event name	Attributed to atherosclerosis	Non Atherosclerotic
Myocardial infarction	21	4
Angina	23	4
TIA	5	13
Stroke	10	30
CHF	12	19
Pacemaker insertion	5	4
Peripheral vascular disease	10	10
Total number of events	86	84

Table 3. Cox relative risk regression for the outcome first AVE, adjusted for prior other VEs			
	Univariate		
Predictor	**# events***	**HR (95% CI)**	**p value**
Age at SLE diagnosis (years)	61	1.03(0.95,1.11)	0.47
Female vs. Male	61	0.53(0.29,0.97)	0.04
Caucasian vs. Non-Caucasian	61	1.36(0.76,2.44)	0.30
SLEDAI score	61	1.03(0.97,1.10)	0.30
Adjusted mean SLEDAI	61	1.05(0.99,1.13)	0.13
Smoking: Never vs. ever smoked	61	0.46(0.22,0.95)	0.04
Ex-smoker vs. current-smoker		0.69(0.31,1.50)	0.35
Elevated random glucose compared to normal	61	0.97(0.45,2.07)	0.94
SBP >140 or diastolic > DBP 90 regardless of treatment	61	0.91(0.49,1.72)	0.77
Elevated cholesterol regardless of treatment vs. normal	61	1.17(0.66,2.08)	0.59
Body Mass Index: 30-40	60	0.82(0.42,1.61)	0.57
>40		2.51(0.97,6.47)	0.06
Alcohol consumption (yes/no)	56	0.76 0.42-1.37)	0.36
Family history of sudden death, MI, angina or stroke	59	1.26(0.72,2.21)	0.43
Average oral steroid dose (mg/day)	61	1.02(1.00,1.04)	0.08
Antimalarials treated vs. not treated	61	0.51(0.30,0.87)	0.01
Immunosuppressives treated vs. not treated	61	0.99(0.59,1.68)	0.97
Ever ACL/LA positive	54	2.09(1.18,3.71)	0.01
SBP – systolic blood pressure, DBP – diastolic blood pressure. Except age, sex, and Caucasian variables, which were time-fixed, the remaining variables were time-dependent. *. Missing values in the predictors led to fewer events in some analyses.			

Table 4: Multivariate Models. *Outcome: first AVE*					
	Model (a) [60 events]*			Model (b) [53 events]*	
Predictor	HR(95%CI)	p-value		HR(95%CI)	p-value
Prior other VEs	4.00(1.55,10.3)	0.004		4.76(1.80,12.60)	0.002
Female	0.60(0.32,1.24)	0.12		0.57(0.28,1.13)	0.11
Never vs ever smoked Ex-smoker vs current smoker	0.51(0.24,1.06) 0.67(0.30,1.48)	0.07 0.33		0.48(0.23,1.03) 0.53 (0.23,1.21)	0.06 0.13
Anti-malarials	0.54(0.32,0.91)	0.02		0.52(0.29,0.92)	0.02
BMI 30-40 ≥ 40	0.95(0.48,1.88) 2.74(1.04,7.18)	0.89 0.04		0.88(0.42,1.87) 3.10(1.17,8,23)	0.74 0.02
aCL/LA ever				1.73(0.95,3.12)	0.07
*Two multivariable models including the predictors with significant effects in the single factor analyses: Model (a), without the aCL/LA variable and, Model (b), with this variable. Missing values in the predictors led to fewer events in some analyses. BMI – body mass index; aCL/LA – anticardiolipin/lupus anticoagulant; VEs – vascular events					

Table 5: Multivariable model including first and recurrent AVEs in 82 events with stratification on prior AVE

Predictor	HR(95%CI)	p-value
Prior other VEs	2.85(1.20,6.78)	0.02
Female (no prior AVE)	0.63(0.34,1.21)	0.16
Females (with prior AVE)	1.25(0.39,4.00)	0.70
Never vs ever smoked	0.40(0.21,0.76)	0.005
Ex-smokers vs current smokers	0.63(0.32,1.25)	0.19
Antimalarials (no prior AVE)	0.53(0.31,0.91)	0.02
Antimalarials (with prior AVE)	1.90(0.67,5.35)	0.23
BMI 30-40	1.00(0.55,1.80)	0.99
BMI >=40	1.96(0.75,5.14)	0.17

* Missing values in the predictors led to fewer events in some analyses. BMI – body mass index; aCL/LA – anticardiolipin/lupus anticoagulant; VEs – vascular events