Seminars in Arthritis and Rheumatism 61 (2023) 152226

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Factors associated with cardiovascular events in systemic lupus erythematosus in a monocentric cohort with up to 40 years of follow-up

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ARTICLE INFO

Keywords:
Systemic lupus erythematosus
Cardiovascular disease
Glucocorticoid
Damage
Antiphospholipid antibodies

ABSTRACT

Objectives: Systemic lupus erythematosus (SLE) is associated with an increased cardiovascular risk. Several traditional and disease-specific risk factors have been shown to correlate with the occurrence of cardiovascular events (CVE) in patients with SLE. However, results of previous studies are diverse. The objectives of this study were to report number, type and those factors associated with CVE in patients with SLE in a large, single-center, ethnically diverse cohort with a long follow-up duration.

Methods: Medical records of patients treated at the Lupus Clinic at University College London Hospital (UCLH) between 1979 and 2020 were retrospectively reviewed. Data about CVE, traditional cardiovascular risk factors, demographic and disease features, and treatment history were collected. Only patients with complete available information were included in the study. Regression analyses were performed to identify factors associated with CVE.

Results: Four hundred and nineteen patients were included in the study. Maximum follow-up length was 40 years. Seventy-one (17%) patients had at least one CVE. Multivariable analysis showed that only antiphospholipid antibody positivity (p-*value*<0.001) was associated with CVE. When analysing different types of CVE, antiphospholipid antibodies were specifically associated with both venous thromboembolic events (p-*value*<0.001) and cerebrovascular events (p-*value*$=0.007$). Dedicated subanalyses revealed that cumulative glucocorticoid dose (p-*value*$=0.010$) and a diagnosis of SLE before 2000 (p-*value*<0.001) were significantly associated with CVE.

Conclusions: Cardiovascular disease is highly prevalent among patients with SLE and is associated with antiphospholipid antibodies, glucocorticoid therapy, and diagnosis before 2000.

Introduction

Cardiovascular events (CVE) occur more commonly in patients with SLE compared with age matched controls and are an important cause of mortality [1,2]. Young women with SLE are over 50 times more likely to have a myocardial infarction than healthy women of similar age [3]. Likewise, SLE is also associated with an increased incidence of stroke [4]. Traditional cardiovascular risk factors have been found to influence, to varying extents, the risk of CVE in patients with SLE [5–7] but do not entirely explain the association between SLE and CVE [8]. In addition, lupus-specific risk factors have been shown to contribute significantly to the increased cardiovascular burden in patients with SLE [9]. These disease-related factors include serological, clinical, and treatment features. However, results of the largest studies investigating factors associated with CVE in SLE are diverse, possibly due to differences in regard to study design, numbers of patients and centres included, and follow-up length [4–41]. Hence, the contribution of different factors to the overall risk of CVE remains unclear.

The objective of this study was to analyze the impact of traditional cardiovascular risk factors and SLE-specific disease features on the CVE risk in a large, single-center, ethnically diverse cohort of patients under careful long term follow-up.

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https://doi.org/10.1016/j.semarthrit.2023.152226

Available online 12 May 2023

Methods

Patients

We retrospectively reviewed medical records of patients treated at the Lupus Clinic at University College London Hospital (UCLH), established in 1978. All met the American College of Rheumatology revised classification criteria for SLE [42] or previous criteria extant at the time of entry into the cohort. Whenever a patient is enrolled into the UCLH cohort a specific paper copy research folder is started, in which clinical data are recorded at each clinic visit. In addition, a baseline serum sample is taken and stored. To establish accurate start date for follow-up one author (WL) reviewed all available research folders to find the earliest assessment and another (AR) reviewed the dates of the earliest sample in storage. Whichever was the earliest of these dates was taken as the start date for follow-up. From careful assessment of the medical records, we obtained the end-date of follow-up (death, loss to follow-up or ongoing follow-up in 2020).We also identified date and type of any CVE. In this study, to ensure accurate survival analysis, we included only patients for whom we had accurately established the start and end of follow-up, occurrence and year of CVE, as well as data regarding demographic and disease features, treatment history, and traditional cardiovascular risk factors. Patients for whom all of these data could not be retrieved (for example because of missing records) and those who experienced a CVE before the start of follow-up were excluded from the study.

This is an observational retrospective study of medical records collected over a period of over 30 years. All data were derived from normal clinical management and no patients underwent extra questionnaires or research procedures. No individualized or identifiable data are presented in this study. Therefore, ethical approval and informed consent were not required.

Demographic, disease, and cardiovascular profile features

The following data were retrieved for each patient (definitions are detailed in the *Supplementary Material*):

- Demographic features: gender and ethnicity (Caucasian, South Asian, African/Caribbean or Other);
- Disease clinical features: age at start of follow-up, history of lupus nephritis, Systemic Lupus International Collaborating Clinics Damage Index score (SDI - points due to items related to CVE were deducted from the total score to avoid a biasing effect) [43].; For the 71 patients who had a CVE, the SDI from just before the CVE was used. For the other 348 patients, SDI were calculated in 2017 for 121 patients and in 2022 for the other 227.
- Disease serological features: decreased levels of C3, positivity of anti-double-stranded DNA antibodies, and positivity of aPL at any time;
- Treatment history: use of hydroxychloroquine ever and cumulative glucocorticoid dose;
- Traditional cardiovascular risk factors: raised body mass index (>25 kg/m^2), smoking status, diabetes mellitus, hypertension, and hypercholesterolemia.

Cardiovascular events

Clinical information on CVE was obtained from patient records and from interviews with patients (for those still alive and under follow-up in the clinic and with subsequent confirmation from clinical records) with informed consent and with ethics approval from the London Hampstead Research Ethics Committee (*Reference Number 12/LO/0373*). Only CVE that occurred after the diagnosis of SLE and enrolment to our cohort were considered for the purpose of this study. Observed CVE were classified in the following categories (definitions are detailed in the *Supplementary Material*):

- Venous thromboembolic events (VTE): deep venous thrombosis, pulmonary embolism, and catastrophic antiphospholipid syndrome;
- Cerebrovascular attacks (CVA): stroke and transient ischemic attack;
- Coronary artery disease (CAD): acute and chronic coronary syndrome.

Statistical analysis

Continuous variables are reported as median values (interquartile range [IQR]), according to their distribution as tested with Skewness and Kurtosis test. Categorical variables are reported as absolute numbers and percentages. A comparison between patients who had a CVE and those who did not was performed using Mann-Whitney test and chi-squared statistics for continuous and categorical variables, respectively. All demographic, disease, and cardiovascular profile features were compared. Inferential analysis was then performed to find potential factors associated with CVE among these features. Initially, univariable analysis with the Cox proportional hazards model was used to test the association of all variables with CVE. Survival curves were also estimated for each categorical variable with the Kaplan-Meier method and then compared with the log-rank test of equality. Variables that were associated with CVE in univariable analysis with a *p-value*<0.15 were subsequently included as covariates in a multivariable Cox proportional hazards model. Covariates also included *a priori* ever-smoking, hypertension and sex as these are generally recognised to affect cardiovascular risk. We performed the Proportional Hazard assumption test based on Schoenfeld residuals and confirmed that this requirement was met for all variables and models.

Additional analyses were performed to determine which variables were specifically associated with different types of CVE.The same sequential univariable - multivariable Cox regression model used for the previous analysis was used in this case, and we considered VTE and CVA as outcomes (we did not consider CAD in light of the small number of these events).

A further sequential Proportional Hazard regression analysis was conducted only on the subgroup of 212 patients for whom data regarding the cumulative dose of glucocorticoids were available to assess the role of this variable in relation to CVE.

Finally, we studied the impact of the year of SLE diagnosis on the risk of CVE. To do so, we chose year 2000 as a cut-off since the use of innovative therapies (e.g., mycophenolate mofetil and rituximab) started to be more extensive subsequently. We considered the diagnosis before or after that year as a new categorical covariate in a final Cox model to assess its association with CVE. We only included the first 20 years of follow-up i.e. the longest possible observation period for patients who were diagnosed after 2000, in order that the maximum follow-up for both the two groups would be the same.

Analyses were performed using statistical package Stata 17.0 (StataCorp LLC).

Results

Characteristics of study participants

Complete information was available for 419 individuals, who were accordingly included in the current study. Median follow-up duration was 13 (IQR 9–18) years, with a maximum of 40 years. Disease characteristics and cardiovascular risk factors of the study population are shown in detail in Table 1. We obtained this set of 419 patients from a total population of 527 patients with SLE for whom we had clinical information on presence or absence of CVE. The 107 patients excluded comprised 18 for whom either start or end of follow-up was not known, 29 in whom the CVE occurred before the diagnosis of SLE and 60 for whom information on traditional cardiovascular risk factors was incomplete.Of the excluded patients 97/107 (91%) were female and 73/107 (68%) were Caucasian.

Table 1
Descriptive comparative analysis of demographic and disease features between patients who had and patients who did not have a cardiovascular event. Continuous and categorical variables are reported as median (interquartile range) and absolute frequency (percentage), respectively. Age is expressed in years.

Variable	All patients (n = 419)	Patients who did not have CVE (n = 348)	Patients who had CVE (n = 71)	*p-value*
Age at diagnosis	31 (23–40)	30 (22–39)	33 (25–41)	0.076
Female sex	381 (91%)	319 (92%)	62 (87%)	0.246
Caucasian ethnicity	239 (57%)	192 (55%)	47 (66%)	0.087
South Asian ethnicity	73 (18%)	63 (18%)	10 (14%)	0.415
African/Caribbean ethnicity	94 (22%)	83 (24%)	11 (16%)	0.123
Other (including East Asian and Mixed Ethnicity)	13 (3%)	10 (3%)	3 (4%)	0.549
Raised BMI (>25 kg/m^2)	196 (47%)	160 (46%)	36 (51%)	0.462
Ever smoker	123 (29%)	98 (28%)	25 (35%)	0.240
Hypertension	145 (35%)	117 (34%)	28 (39%)	0.306
Hypercholesterolemia	128 (31%)	99 (28%)	29 (41%)	**0.035**
Diabetes	20 (5%)	13 (4%)	7 (10%)	**0.027**
Lupus nephritis ever	142 (34%)	115 (33%)	27 (38%)	0.428
Anti-dsDNA positivity ever	267 (64%)	220 (53%)	47 (66%)	0.653
Decreased C3 ever	191 (47%)	157 (45%)	34 (48%)	0.714
aPL positivity ever	134 (32%)	93 (27%)	41 (58%)	**<0.001**
Use of hydroxychloroquine ever	366 (87%)	309 (89%)	57 (80%)	**0.049**
SDI	0 (0–1)	0 (0–1)	1 (0–2)	0.123

Anti-dsDNA, anti-double-stranded DNA antibodies; aPL, antiphospholipid antibodies; CVE, cardiovascular event; SDI, Systemic Lupus International Collaborating Clinics Damage Index score; SLE, systemic lupus erythematosus.

Factors associated with cardiovascular events

Seventy-one (17%) patients had at least one CVE, whereas two different CVE were observed in nine (2%) cases. Forty (50%) events were VTE, 26 (32.5%) were CVA, and 14 (17.5%) were CAD. Mean age at CVE was 44 (SD 12) years, while mean disease duration was 10 (SD 7) years. Median time from diagnosis to CVE was 8 (IQR 4–15) years, and the survival curve is shown in Fig. 1. There was no significant difference between median times to different types of CVE (*p-value*=0.141). Five patients died of CV causes; one with stroke, two with MI and two with heart failure.

Descriptive comparative analysis showed an increased prevalence of hypercholesterolemia, diabetes, and aPL positivity among patients with CVE (Table 1). Furthermore, these patients were treated less frequently with hydroxychloroquine. However, univariable Cox proportional hazards analysis revealed that only aPL positivity was significantly associated with the occurrence of CVE (Table 2, 1st section).

When considering different aPL, the presence of either lupus anticoagulant (n = 70, 22%) or anti-cardiolipin antibodies (n = 100, 26%) was associated with CVE (*p-value*<0.001). On the contrary, the positivity of anti-beta-2-glycoprotein I antibodies (n = 31, 7%) was not significantly related to the outcome (*p-value*=0.129).

Log-rank test highlighted an additional association with diabetes (Fig. 2) though it must be acknowledged that this was based on a very

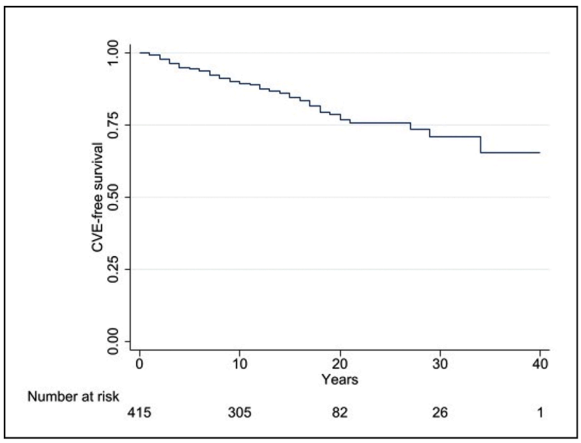

Fig. 1. Survival curve for cardiovascular events in our study population. CVE, cardiovascular event.

Table 2
Univariable (*1st section*) and multivariable (*2nd section*) Cox regression analysis to evaluate the association between independent variables and cardiovascular events in the whole study population.

	Covariate	Hazard Ratio	95% Confidence Interval	*p-value*
UNIVARIABLE ANALYSIS	Age at diagnosis	1.012	0.994 - 1.031	0.178
	Female sex	0.619	0.307 - 1.250	0.182
	Caucasian ethnicity	1.379	0.834 - 2.281	0.210
	Raised BMI (>25 kg/m^2)	0.948	0.579 - 1.553	0.834
	Ever smoker	1.177	0.713 - 1.942	0.522
	Hypertension	1.098	0.670 - 1.801	0.708
	Hypercholesterolemia	1.496	0.921 - 2.429	0.103
	Diabetes	2.165	0.988 - 4.746	0.054
	Lupus nephritis	1.132	0.693 - 1.847	0.619
	adsDNA positivity	1.208	0.724 - 2.014	0.468
	Decreased C3	1.217	0.755 - 1.960	0.419
	aPL positivity	3.205	1.975 - 5.201	< **0.001**
	Use of hydroxychloroquine	0.632	0.350 - 1.143	0.129
	SDI	0.986	0.788 - 1.235	0.907
MULTIVARIABLE ANALYSIS	Female sex	0.593	0.278 - 1.274	0.181
	Ever smoker	0.915	0.535 - 1.563	0.746
	Hypertension	1.116	0.676 - 1.844	0.677
	Hypercholesterolemia	1.446	0.877 - 2.385	0.148
	Diabetes	1.611	0.695 - 3.739	0.266
	aPL positivity	3.009	1.828 - 4.953	< **0.001**
	Use of hydroxychloroquine	0.659	0.357 - 1.218	0.184

aPL, antiphospholipid antibodies; BMI, body mass index; SDI, Systemic Lupus International Collaborating Clinics Damage Index score.

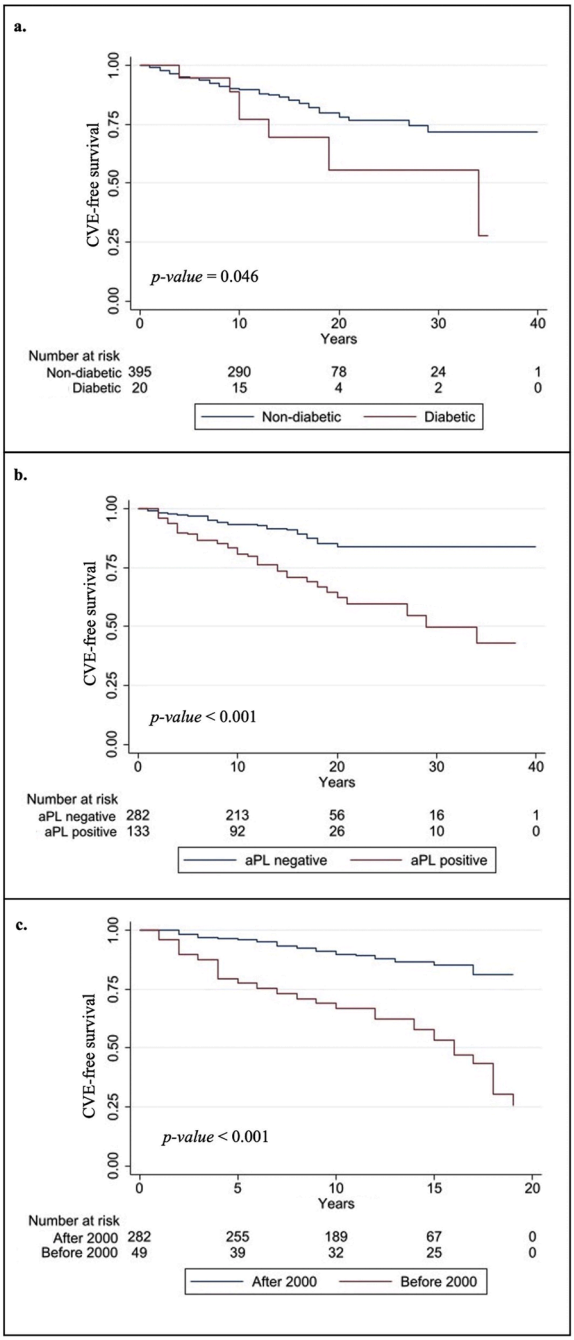

Fig. 2. Survival curves for cardiovascular events according to the presence of diabetes (**a**), antiphospholipid antibodies (**b**), and year of diagnosis (**c**). aPL, antiphospholipid antibodies; CVE, cardiovascular events.

small number of patients.

The final multivariable Cox proportional hazards model confirmed aPL positivity as the only factor associated with CVE (Table 2, 2nd section).

Factors associated with specific types of cardiovascular events

As reported in Table 3, multivariable Cox regression dedicated analyses showed that only aPL positivity was associated with the occurrence of both VTE and CVA.

Table 3
Multivariable Cox regression analysis to evaluate the association of independent variables with different types of cardiovascular events in the whole study population: venous thromboembolic events and cerebrovascular attacks.

	Covariate	Hazard ratio	95% Confidence interval	*p-value*
VTE	Age at diagnosis	1.020	0.994 - 1.047	0.124
	Female sex	0.675	0.232 - 1.966	0.472
	Ever smoker	1.023	0.517 - 2.027	0.947
	Hypertension	0.762	0.377 - 1.538	0.448
	Diabetes	1.315	0.435 - 3.978	0.627
	aPL positivity	4.019	2.027 - 7.969	< **0.001**
	Use of hydroxychloroquine	0.619	0.279 - 1.374	0.239
CVA	Ever smoker	0.614	0.229 - 1.646	0.344
	Hypertension	1.900	0.854 - 4.224	0.115
	Decreased C3	1.786	0.797 - 4.001	0.158
	aPL positivity	3.010	1.348 - 6.721	**0.007**
	Use of hydroxychloroquine	0.720	0.279 - 1.855	0.497

CVA, cerebrovascular attack; VTE, venous thromboembolic event; aPL, antiphospholipid antibodies.

The role of glucocorticoids and year of diagnosis

Detailed information regarding cumulative dose of glucocorticoids was available for 212 patients, having been collected previously for a separate study on fracture risk in patients with SLE [44]. The median total prednisolone-equivalent dose was 23,210 (IQR 12,935–34,858) mg. Patients with CVE were exposed to higher total doses than patients without CVE (29,515 [IQR 25,101–39,223] mg vs 21,605 [IQR 10, 745–33,016] mg; *p-value* = 0.001). In this subgroup of 212 patients, Cox regression analysis pinpointed glucocorticoid cumulative dose as a factor associated with CVE (Hazard Ratio [HR] per 1000 mg =1.029, 95% Confidence Interval [CI] 1.008–1.050, *p-value*=0.006).

Likewise, the analysis focusing on the impact of the year of SLE diagnosis showed that being diagnosed before 2000 was significantly associated with CVE (HR=4.39, 95% CI 2.64–7.28, *p-value*<0.001). Survival curves are shown in Fig. 2.

Discussion

Our study shows that the prevalence of cardiovascular disease is high among patients with SLE, as almost one in five of our patients had at least one CVE. We also found aPL positivity and glucocorticoid therapy to be associated with the occurrence of a CVE. In contrast, even though traditional cardiovascular risk factors were common in our cohort, they were not significantly associated with CVE in multivariable analysis. There was a possible association with diabetes, but this was based on very small numbers.

Although several studies investigated this topic prior to our current study, their findings are highly variable [4-6,8–41,45]. Results of the largest studies published to date are summarised in Table 4. Discrepancies are evident both in terms of prevalence of cardiovascular disease and potential predictors of CVE. Various factors may have contributed to this diversity of findings, including differences in CVE definition, ethnicity, world region, numbers of patients and centres involved, and follow-up duration. When compared to previous reports, our analysis relies on the largest number of patients from a monocentric cohort in Europe and is the most ethnically diverse from this region. Furthermore, our patients were followed for up to 40 years, which is - to our knowledge - the longest follow-up in Europe and the second longest in the world [11]. It is thus important to analyze in detail the results of our study and compare them to previous reports.

The prevalence of cardiovascular disease in our cohort is approximately in the middle of the range reported by previous studies. More specifically, analyses cumulatively investigating - like ours - the

Table 4
Studies evaluating prevalence and factors associated with cardiovascular events in more than 400 patients with systemic lupus erythematosus. Where multiple studies have described a single cohort with the same methods in more than one paper over time, only the most recent study is included.

Authors and year	N. of patients	Region	Most prevalent ethnicity	Average Age and sex	Follow-up duration	Types of CVE	Study design	N. of CVE/ 100 patients	Factors associated with CVE
Mok et al. 2009, [12]	490	Asia	*NR*	33 years, 92% F	Up to 8 years	CVA	Retrospective cohort study	4	Younger age
Mok et al., 2010 [13]	516	Asia	100% A	32 years, 91% F	Up to 10 years	VTE	Retrospective cohort study	2.7	Younger age, aPL positivity
Wang et al., 2012 [14]	1072	Asia	100% A	32 years, 87% F	Up to 2 years	CAD, CVA	Cross-sectional	6.6	Older age, hypertension, lupus nephritis/CKD, longer GC use
Chiu et al., 2012 [5]	11,637	Asia	100% A	41 years, 89% F	Up to 7 years	CVA	Retrospective cohort study	2.2	Older age, male sex, hypertension, diabetes
Lin et al., 2014 [15]	1207	Asia	*NR*	*NR* 82% F	Up to 8 years	CAD	Retrospective cohort study	1.6	Female sex, SLE-related hospitalizations
Fernandez-Nebro et al., 2015 [16]	3658	Europe	97% C	55 years, 86% F	Up to 24 years	CAD, CVA	Cross-sectional	7.4	Older age, hypertension, smoking, diabetes, dyslipidemia, NPSLE, serositis, aPL positivity, C3 reduction, azathioprine
Fasano et al., 2018 [17]	507	Europe	*NR*	39 years, 93% F	Up to 11 years	CAD, CVA	Retrospective cohort study	7.3	Hypertension, smoking, aPL positivity, non-use of ASA and HCQ
Haugaard et al., 2021 [18]	1616	Europe	*NR*	45 years, 87% F	Up to 20 years	CAD, CVA	Retrospective cohort study	18.8	Non-use of HCQ
Watad et al., 2017 [19]	5018	Middle East	*NR*	50 years, 82% F	*NR*	CAD	Case-control study	11.3	Female sex
Gladman et al., 1987 [20]	507	North America	*NR*	43 years, *NR*	*NR*	CAD	Retrospective cohort study	8.9	Peri-myocarditis, hypercholesterolemia, diabetes
Manzi et al., 1997 [3]	498	North America	76% C	34 years, 100% F	Up to 14 years	CAD	Retrospective cohort study	6.6	Older age, hypercholesterolemia, longer SLE duration
Ward, 1999 [6]	8742	North America	56% C	49 years, 100% F	*NR*	CAD, CVA	Case-control study	Up to 13 *	Hypertension, diabetes, CKD
Somers et al., 2002 [21]	678	North America	54% C	*NR*, 93% F	Up to 14 years	VTE	Prospective cohort study	5.2	Male sex, hypercholesterolemia, aPL positivity
Toloza et al., 2004 [22]	546	North America	28% C	37 years, 90% F	Up to 9 years	CAD, CVA	Prospective cohort study	6.2	Older age, smoking, CRP, aPL positivity, azathioprine
Calvo-Alen et al., 2005 [23]	570	North America	28% C	37 years, 90% F	Up to 8 years	VTE	Prospective cohort study	8.9	Older age, smoking, shorter SLE duration, SLE activity, aPL positivity, GC dose
Fernandez et al., 2005 [24]	518	North America	13% C	36 years, 100% F	Up to 6 years	CAD, CVA, VTE	Prospective cohort study	8.5	Older age, smoking, longer SLE duration, GC dose
Ho et al., 2005 [25]	442	North America	31% AA	*NR*	Up to 8 years	CAD, CVA, VTE	Prospective cohort study	10.4	Smoking, SLE activity, SLE-related damage
Urowitz et al., 2007 [26]	1087	North America	79% C	32 years, 96% F	Up to 17 years	CAD, CVA	Retrospectivecohort study	10.9	Framingham risk score, smoking, NPSLE, vasculitis
Pons-Estel et al., 2009 [27]	637	North America	28% C	37 years, 90% F	*NR*	CAD	Prospective cohort study	6.8	Older age, male sex, SLE-related damage, CRP, fewer education years
Bertoli et al., 2009 [28]	1333	North America	46% C	36 years, 90% F	Up to 11 years	CAD, CVA	Prospective cohort study	9.8	Older age, smoking, anemia, NPSLE
Nikpour et al., 2011 [29]	991	North America	70% C	37 years, 89% F	Up to 13 years	CAD	Prospective cohort study	8.6	Older age, male sex, GC use, hypertension, hypercholesterolemia, SLE activity, non-use of HCQ
Magder et al., 2012 [30]	1874	North America	56% C	37 years, 93% F	Up to 23 years	CAD, CVA	Retrospective cohort study	7.2	Older age, male sex, hypertension, dyslipidemia, diagnosis before 1993, aPL positivity, SLE activity, anti-dsDNA titer, higher GC dose
Maynard et al., 2012 [31]	1752	North America	60% C	29 years, 92% F	Up to 24 years	CAD, CVA	Retrospectivecohort study	14	Low income
Avina-Zubieta et al., 2017 [4]	4863	North America	*NR*	49 years, 86% F	Up to 14 years	CAD, CVA	Retrospective cohort study	4.1	Shorter SLE duration

(*continued on next page*)

Table 4 (*continued*)

Authors and year	N. of patients	Region	Most prevalent ethnicity	Average Age and sex	Follow-up duration	Types of CVE	Study design	N. of CVE/ 100 patients	Factors associated with CVE
Barbhaiya et al., 2017 [32]	65,788	North America	42% AA	41 years, 93% F	Up to 7 years	CAD, CVA	Retrospective cohort study	3.4	African American and Hispanic ethnicities
Mok et al., 2005 [33]	625	AmericaAsia	41% A	36 years, 89% F	Up to 9 years	CAD, CVA, VTE	Prospective cohort study	13.2	Female sex, Chinese ethnicity, dyslipidemia, diabetes, raised BMI, oral ulcers, leukopenia, anemia, serositis, nephritis, aPL positivity
Hanly et al., 2018 [10]	1826	AmericaEuropeAsia	49% C	35 years, 89% F	Up to 11 years	CVA	Prospective cohort study	4.5	African American ethnicity, SLE-related damage, aPL positivity
Urowitz et al., 2020 [7]	1710	AmericaEurope Asia	49% C	35 years, 89% F	Up to 18 years	CAD, CVA	Prospective cohort study	6.6	BMI > 40 kg/m^2, prior CVE, non-use of HCQ

A, Asian; AA, African-American; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; ASA; aspirin; C, Caucasian; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CRP, C-reactive protein; CVA, cerebrovascular attack; CVE, cardiovascular events; F, female; GC, glucocorticoid; HCQ, hydroxychloroquine; NPSLE, neuropsychiatric systemic lupius erythematosus; NR, not reported; VTE, venous thromboembolic event; SLE, systemic lupus erythematosus.

* Population prevalence ratio between patients with systemic lupus erythematosus and those without.

epidemiology of CAD, CVA, and VTE, found a prevalence ranging from 7.8% up to 26% [9,11,24,25,33,34]. Such a wide range may be partially explained by differences in follow-up length. Most of the studies reporting a prevalence lower than ours encompassed a shorter follow-up duration. However, McVeigh et al. - whose study spanned over 41 years - found that only 7.8% of their patients had a CVE, although their study involved fewer patients than ours and this might have influenced their results [11]. On the contrary, both Becker-Merok and Gustafsson reported that 26% of their patients had a CVE, despite a shorter follow-up when compared to our study [9,34]. Differences in terms of ethnicity - more than 90% of their patients were Caucasian - may have influenced the results. Ethnicity is known to influence the levels of disease activity in patients with SLE [46], and African, Caucasian, and Chinese ethnicities have been separately suggested as predictors of CVE in previous studies [10,32,33,37]. However, the role of ethnicity is not straightforward, and it did not influence the occurrence of events either in our patients or in other large-scale studies [26,27,31].

In spite of this variability, our study and previous studies clearly show that patients with SLE have a high prevalence of CVE, which is increased when compared to the general population [3,6].

Our study also evaluated, in detail, the relationship between traditional and lupus-specific risk factors and the occurrence of CVE, both cumulatively and according to different types of events. As stated above, the role of such factors is not straightforward based on results of previous reports. Indeed, some studies have shown that features typically associated with CVE in the general population, such as smoking, hypertension, diabetes, and dyslipidemia, may also be associated with CVE in patients with SLE [5,6,8,9,14,16,20-26,28–30,33,35,36]. However, other authors did not find any association between these traditional risk factors and CVE when they specifically looked for it [11,13,26,27]. Our study did not find any association between hypertension, smoking, or raised BMI and CVE. Though the prevalence of hypercholesterolemia was higher in patients with a history of CVE, inferential statistics did not find this feature to be significantly associated with CVE. Similarly, while diabetes was significantly associated with the outcome in univariable analysis, this association became non-significant in the final multivariable model.

We found that a diagnosis of SLE before 2000 was strongly associated with a worse cardiovascular outcome, and Fig. 1 also shows a flattening of the survival curve in more recent years. These results suggest that accrual of CVE in patients with SLE may be slowing over time. This finding is in line with what has been previously shown in North American patients [30]. Urowitz et al., in a multi-center study of 1710 patients from the SLICC inception cohort recruited from 1999 onwards reported that the prevalence of atherosclerotic vascular events was lower than in earlier studies and posited that this might be due to better control of disease activity and of cardiovascular risk factors [7].

Lupus-specific features are known to contribute to the cardiovascular risk in patients with SLE as well [9]. Of note, our study shows a strong association between aPL positivity and CVE, both CVA and VTE. Prior to this study, other groups also highlighted this finding [9,10,16,17,21-23,30,33,35,37,38]. Although most of them defined aPL positivity as the persistent presence of aPL, some authors - like us - did not require aPL presence to be confirmed at a second time-point to define patients as aPL positive [21,35]. Indeed, this method increases the sensitivity in determining the impact of any aPL ever detected on the risk of CVE. To our knowledge, our study is the first to have shown the effect of aPL on CVE over 40 years follow-up. Furthermore, it involved the largest European monocentric study population to date. New assays for aPL are being developed, one of which is a test for antibodies to Domain I of beta2-glycoprotein I (anti-DI). In a separate study, currently in press [47], we looked at a group of 400 patients for whom the earliest available serum sample had been tested in our research laboratory for IgG antibodies to cardiolipin, beta2glycoprotein I and DI. Although 154 patients were positive for at least one of these antibodies at this early point in their disease, 86 of these were positive only for IgG anti-DI, which would not have been detected by any of the standard clinical assays. Nevertheless, early positivity for any of these three IgG aPL, and particularly positivity for any two or three simultaneously, was associated with increased risk of subsequent vascular events.

Cardiovascular disease is known to be also influenced by other SLE-specific factors, such as disease activity [15,23,25,29,30,34,35,37,39]. SLE-related damage - which represents the final effect of persistent disease activity over time [43] - has also been associated with a worse cardiovascular outcome in previous studies [27,35]. However, this factor was not associated with CVE in our cohort. Fasano et al. also did not observe an association between SDI scores and CVE in their study [17]. We specifically computed SDI scores just before the occurrence of CVE for patients who suffered from them whereas different approaches have been used in other studies (e.g. baseline SDI at the start of monitoring). Not every previous study that found an association between SDI and CVE included in its methods the exclusion of CVE-related items from the calculation of SDI scores [25]. These methodological differences may have contributed to the fact that different studies reached different conclusions.

Lupus nephritis, which has been previously shown to correlate with a

increased cardiovascular risk in some studies [14,33], but not in others [16,34], was not associated with the occurrence of CVE in our cohort.

Treatment also plays a pivotal role in determining the cardiovascular profile risk in patients with SLE. Though glucocorticoids represent a very effective therapeutic strategy in SLE, they are undoubtedly associated with a significant toxicity burden [30]. Their use has been previously shown to increase cardiovascular risk [11,14,23,24,29,30,36], and we confirmed this association in our large cohort and with a very long follow-up. On the contrary, hydroxychloroquine was shown to improve cardiovascular outcome in previous European studies [34,38,39], though this beneficial effect was not evident in a large Asian study [40]. We found that patients with CVE were less frequently treated with antimalarials, but this protective property of hydroxychloroquine was not confirmed in the multivariable model, perhaps because such a high proportion of both the CVE and non-CVE groups received this drug.

Our study has some limitations. The retrospective design means that we can only detect associations and do not claim to have identified predictors of CVE. It is possible that the high number of patients excluded due to lack of full information could introduce a bias in terms of disease severity and occurrence of cardiovascular disease. Furthermore most patients had mild to moderate disease. We used the results of univariable analyses to guide the multivariable analysis, though other approaches are possible that may reduce risk of missing effects of some factors. Small subgroup sizes for some events such as CAD and CVA limited the analyses of these outcomes.We did not have data about some potentially relevant factors that could affect risk of CVE, such as physical exercise. Data about cumulative dose of glucocorticoid could not be obtained in all patients, but only in a subgroup. Nonetheless, available data were sufficient to estimate a significant role for this variable. We do not have information about the exact time when particular variables were measured in each patient so cannot assess them as time-dependent covariates. Finally, we cannot exclude the possibility that patients with persistent aPL positivity have different risk to those who are positive only once.

The implications of our findings are important, as the most appropriate management of cardiovascular risk in patients with SLE is currently unclear. Available guidelines from the European League against Rheumatism recommend a careful and regular assessment of traditional risk factors in patients with SLE [1,2]. The management of glucocorticoid therapy is also pivotal in the determination of the cardiovascular risk of patients with SLE. Our results support the existing recommendation regarding the use of glucocorticoid at the lowest dose possible [2]. Guidelines also advise preventive treatment with antiplatelets to be considered based on the individual cardiovascular risk profile of patients, though specific indications are not given [2]. Low-dose aspirin - in light of its association with a reduced risk of CVE in patients with SLE [38,41] - is recommended in the presence of high-profile aPL-risk (i.e., lupus anticoagulant, anti-cardiolipin antibodies > 40 units, or double/triple aPL positivity), though the indication for its use in other circumstances of aPL positivity is not clear [1].

In summary, our study confirms that prevalence of CVE is high among patients with SLE and shows that CVE are strongly associated with aPL positivity and the cumulative dose of glucocorticoids. Though others have previously shown these associations, our study involved a large number of ethnically diverse patients over a follow-up period of up to 40 years. Our study showed that aPL positivity is associated with a significantly increased cardiovascular risk regardless of the specific detected aPL, number of concomitant antibodies, and titer. This hints at the possibility that an earlier and more extended use of aspirin in patients with aPL might be implemented in clinical practice. However, randomised clinical trials are mandatory to explore and validate this hypothesis. On the other hand, frequent assessment for the presence of aPL in previously negative patients might be of use in identifying these biomarkers and accordingly in assessing and managing the cardiovascular risk profile. Our results also add to the growing consensus that reducing use of corticosteroids in patients with SLE is a key goal for the future.

Authorship contributions

All authors collected data. NF carried out formal analysis. NF and AR wrote the final manuscript. All authors contributed to critical analysis of the manuscript and approved the final version.

Data availability

Data are available on request to the authors.

Declaration of Competing Interest

None of the authors has any competing interests to declare.

Funding

This work was carried out at a center supported by the National Institute for Health Research University College London Hospitals Biomedical Research Center.

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