

# Predisposing factors to nonfatal cardiovascular events in women with systemic lupus erythematosus. An observational, cross-sectional, multicenter study in Spain from the risk/systemic lupus erythematosus thematic network

Mar Fernández-Garcés, MD, PhD<sup>a,\*</sup>, Gonzalo Haro, MD, PhD<sup>b,c</sup>, María Luisa Micó, MD, PhD<sup>d</sup>

## Abstract

Very few studies have been published on cardiovascular morbidity in Spanish patients diagnosed with systemic lupus erythematosus (SLE). Moreover, knowledge of the predictive factors for the occurrence of nonfatal events in this group of patients is scarce.

This was a multicenter, observational, cross-sectional study designed to ascertain the prevalence of nonfatal cardiovascular risk factors and cardiovascular events (CVEs) in 335 Spanish women diagnosed with SLE between 2003 and 2013.

The average patient age was 36.0 years (range: 26.4–45.6); 35 patients (10.7%) experienced at least 1 CVE, which most frequently affected the brain, followed by the heart, and finally, the peripheral vasculature. Both the number of admissions because of SLE (95% confidence interval [CI] odds ratio [OR]=1.024–1.27,  $P=.017$ ) and the systemic lupus international collaborating clinics (SLICC) chronicity index score (95% CI OR=1.479–2.400,  $P=.000$ ) resulted in an increase in the OR of these patients presenting a CVE. Regarding the classic risk factors, only the interaction between hypertension (HT) and treatment with antihypertensive drugs influenced the presence of CVEs (95% CI OR=2.165–10.377,  $P=.000$ ). The presence of a family history of early cardiovascular disease was also related to CVEs (95% CI OR=2.355–40.544,  $P=.002$ ). Binary logistic regression including the above factors resulted in a model in which the 3 main variables in each group persisted, implying that they must be independent of each other. However, the weight of the interaction between the family history of early cardiovascular disease and the interaction between HT and the use of antihypertensives was higher than for the number of admissions for SLE.

The SLE disease activity over time (measured using the SLICC) and the number of hospital admissions due to the disease itself, both increase the risk of women with SLE presenting a CVE. Classic cardiovascular risk factors, especially HT and its treatment, as well as a family history of early CVEs, should be considered when assessing the risk of nonfatal CVEs in women with SLE.

**Abbreviations:** ACA = anticardiolipin antibody, ACR = American College of Rheumatology, ANA = antinuclear antibody, anti-dsDNA = anti-double stranded DNA, C3/C4 = compliment 3 or 4, CI = confidence interval, CRP = c reactive protein, CVE = cardiovascular event, CVRF = cardiovascular risk factor, DBP = diastolic blood pressure, DM = diabetes mellitus, HDL = high-density lipoprotein, HT = hypertension, LA = lupus anticoagulant, LDL = low-density lipoprotein, Lpa = lipoprotein a, LVH = left ventricular hypertrophy, OR = odds ratio, RR = relative risk, SD = standard deviation, SE = standard error, SLE = systemic lupus erythematosus, SLEDAI = systemic lupus erythematosus disease activity index, SLICC = systemic lupus international collaborating clinics (index), uCRP = ultrasensitive polymerase chain reaction for CRP.

**Keywords:** antihypertensive drugs, cardiovascular events, cardiovascular risk factors, hypertension, incidence, SLICC, systemic lupus erythematosus

Editor: Cassandra Ford.

The authors have no conflicts of interest to disclose.

<sup>a</sup> Internal Medicine Service, Hospital Universitario Dr. Peset, Valencia, <sup>b</sup> TXP Research Group, Department of Medicine, Universidad Cardenal Herrera-CEU, CEU Universities, Castellón, <sup>c</sup> Provincial Hospital of Castellón, <sup>d</sup> Internal Medicine Service, Hospital Universitario y Politécnico La Fe, Valencia, Spain.

\* Correspondence: Mar Fernández-Garcés, Servicio de Medicina Interna, Hospital Universitario Dr. Peset, Avenida Gaspar Aguilar, 90, CP46017 Valencia, Spain (e-mail: mar.fernandez.7823@gmail.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Fernández-Garcés M, Haro G, Micó ML. Predisposing factors to nonfatal cardiovascular events in women with systemic lupus erythematosus. An observational, cross-sectional, multicenter study in Spain from the risk/systemic lupus erythematosus thematic network. *Medicine* 2019;98:43(e17489).

Received: 6 June 2019 / Received in final form: 18 July 2019 / Accepted: 12 September 2019

<http://dx.doi.org/10.1097/MD.00000000000017489>

## 1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune and multisystemic disease with important gender differences: the disease predominantly affects women (in adults, the ratio varies from 7:1 to 15:1)<sup>[1,2]</sup> but has a worse prognosis in men. The prevalence of vascular damage is higher in patients with SLE than the general population, and these patients also present accelerated development of atherosclerosis which often leads to premature cardiovascular disease.<sup>[3,4]</sup> This is partly the result of the chronic activity of SLE and the side effects of its treatment.<sup>[5–10]</sup> Some comparative epidemiological studies indicate that the frequencies of classic cardiovascular risk factors (CVRFs) (hypertension [HT], dyslipidemia, diabetes mellitus [DM], smoking, obesity, sedentary lifestyle, and early menopause) are higher in patients with SLE.<sup>[11,12]</sup> The presence of antiphospholipid antibodies in up to 30% of SLE patients is also related to accelerated atherosclerosis and the lipid profile of SLE patients positive for anticardiolipin antibodies (IgM and IgG ACAs) tend to present even higher alterations.<sup>[13–15]</sup>

Some authors have come to consider SLE as a “coronary equivalent of DM,” meaning that its consideration by clinicians is very important, given its higher prevalence among young women who would normally be protected against arteriosclerosis during the most fertile stages of their lives.<sup>[16,17]</sup> Studies on the prevalence of cardiovascular morbidity and mortality are still scarce, and the predictive factors for the occurrence of cardiovascular events (CVEs) in Spanish patients with SLE are insufficiently understood.<sup>[18]</sup> Partly because of immunosuppressive treatments, SLE survival rates have improved in recent decades to more than 93% at 5 years and 85% to 93%<sup>[19,20]</sup> at 10 years. However, the quality of life of SLE patients is still lower than that of the general population,<sup>[21]</sup> and their risk of death is 2 to 3 times greater.<sup>[22–24]</sup> Some authors, such as Schoenfeld et al, now believe that young patients with SLE are at a 2 to 3-fold higher risk of death from cardiovascular disease than the general population,<sup>[25]</sup> making CVEs the most common cause of death not directly related to SLE in this population.<sup>[26]</sup>

In addition to the classic risk factors, whether modifiable or not, are “emerging” risk factors. These include serological and biochemical markers such as C-reactive protein (CRP), fibrinogen, vitamin D, homocysteine, plasma viscosity, or the presence of other dyslipidemias such as hypertriglyceridemia, increased lipoprotein a (Lpa) or elevated apolipoprotein B. Other emerging risk factors can be measured via imaging techniques and include left ventricular hypertrophy (LVH) and the intima-media thickness measured by carotid ultrasound imaging.<sup>[15,27]</sup>

The systems used to calculate the risk of cardiovascular disease, equivalent to the risk of experiencing a CVE in the subsequent 10 years, aim to identify high-risk patients who require medical attention and immediate intervention. The Framingham risk score-table stratifies the risk into low-risk: <10%, moderate-risk: 10% to 20%, and high-risk: >20%, with a risk >10% as a cut-off for recommending the initiation of therapy. Unlike other diseases such as rheumatoid arthritis, for which the European League Against Rheumatism recommended the use of the weighted systematic coronary risk evaluation in 2010.<sup>[28]</sup> No indices are currently available to quantify CVRFs in patients with SLE. This is because the risk tables used for SLE are strongly influenced by age, and most of these patients are young women (usually aged less than 35 years and very rarely older than 70 years) and so, they underestimate CVRFs among these patients.

The presence of arthritis and the use of corticosteroids in SLE patients can cause musculoskeletal alterations, meaning that they participate in less physical activity, another factor that contributes to sedentary lifestyles.<sup>[29]</sup> In addition, the use of corticosteroids can worsen HT, DM, obesity, and dyslipidemia. Several studies have shown that the risk of atherosclerosis and the use of corticosteroids is dose-dependent, such that doses higher than 10 mg/d are associated with altered lipid profiles.<sup>[30,31]</sup> In contrast, antimalarial drugs are now considered cardioprotective because they improve cardiovascular risk, lower levels of cholesterol and triglycerides, prevent the development of DM and metabolic syndrome, hinder the onset of thrombosis, and reduce the need for corticosteroids.<sup>[32,33]</sup> It is also important to remember the high frequency of early menopause among female patients with SLE. Moreover, some studies have related the increased rate of osteoporosis in this group (resulting from the use of corticosteroids) to the progression of arteriosclerotic disease because accelerated bone-mass loss in these patients would favor the progression of atherosclerotic calcification.<sup>[27,34]</sup>

Therefore, few studies have been published on cardiovascular morbidity in patients diagnosed with SLE, only 1 in the Spanish population. Although longitudinal studies are better for the evaluation of the predictive factors for the occurrence of fatal and nonfatal events, our transversal research could help to know the relative risk (RR) of some of the CVRFs. To this end, a cardiovascular profile and the prevalence of nonfatal CVE, the treatment and the degree of compliance with the therapeutic objectives are described in a significant sample of women diagnosed with SLE, as well as comparing 2 groups in the sample patients diagnosed with SLE, with or without previous CVE, trying to identify possible related factors.

## 2. Methods

### 2.1. Study design

This was an observational, cross-sectional, multicenter study, developed based on the risk/SLE Thematic Network; 31 specialists in internal medicine, rheumatology, and nephrology with experience in autoimmune diseases, from 9 homogeneously distributed Spanish hospitals, participated in the study. Every adult patient diagnosed with SLE and followed-up at one of these centers during the study period (February 2003–April 2013) was entered into a database and was consecutively followed up by their respective centers.

### 2.2. Patients

We carried out a nonprobabilistic opportunity sampling of adult patients diagnosed with SLE—who met at least 4 of the 11 American College of Rheumatology (ACR) criteria (according to the 1997 update of the 1982 ACR Revised Criteria for Classification of SLE) and who were being followed-up during the study period.<sup>[35,36]</sup> The only exclusion criterion was male sex (n=39). Thus, the final sample cohort comprised 335 women with SLE.

### 2.3. Definitions of variables

We recorded sociodemographic information, and clinical, SLE, laboratory, and treatment data. The clinical variables included the onset of SLE (when the patient first met 4 of the ACR SLE criteria), illness duration (time from diagnosis to the last visit or

death), cumulative ACR criteria met,<sup>[37]</sup> number of flare-ups (considered the reappearance of clinical activity at a specific time in a previously controlled patient),<sup>[38]</sup> the SLE disease activity (safety of estrogens in lupus national assessment–systemic lupus erythematosus disease activity index [SLEDAI]), the chronicity according to the SLE organic damage index (systemic lupus international collaborating clinics [SLICC] system) measured retrospectively based on the patient's last visit, hospitalizations (due to SLE or cardiovascular complications), SLE treatments with current or past medications, and treatment associated with cardiovascular pathologies (antihypertensive, antiplatelet, anticoagulant, or lipid-lowering drugs).

Comorbidities were also recorded: smoking, DM (previous diagnosis or  $\geq 2$  measurements of fasting serum glucose  $\geq 126$  mg/dL and/or use of antidiabetic medications), dyslipidemia (total cholesterol  $\geq 240$  mg/dL and/or low-density lipoprotein [LDL]  $> 150$  mg/dL and/or triglycerides  $\geq 150$  mg/dL and/or use of lipid-lowering medications), HT (systolic blood pressure  $> 140$  mm Hg and/or diastolic blood pressure [DBP]  $> 90$  mm Hg on  $\geq 2$  occasions and/or use of antihypertensive medications), peripheral arterial disease, ischemic heart disease, heart failure (clinical diagnosis and/or chest x-ray), thromboembolic disease and/or a cerebral vascular accident, and/or a family history of early cardiovascular disease (male first-degree relatives affected before the age 55 or female first-degree relatives affected before 65 years).

We included 4 subclinical arteriosclerotic disease variables: echocardiograms, carotid ultrasound imaging, ankle-brachial indices (pathological if  $\leq .9$ ), and bone densitometry (peripheral instantaneous X-ray imager method which measures the calcaneus, the bone-mass evaluation method recommended by the World Health Organization in 1994) which uses the following *T*-score criteria: normal  $> -1$  standard deviation (SD); osteopenia  $-1$  to  $-2.5$  SDs; osteoporosis  $< -2.5$  SDs; and severe or established osteoporosis  $< -2.5$  SDs with a history of at least 1 fragility fracture.

The complementary test data we recorded were basal glycemia, urea, creatinine, total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, LPa, hemoglobin, leukocytes, platelets, erythrocyte sedimentation rate, and the Framingham index (calculating the percentage according to Anderson).<sup>[39]</sup> In addition, proteinuria (considered positive if  $> 500$  mg/24 h), complement 3 (C3) fraction (positive if  $< 83$  mg/dL), complement 4 (C4) fraction (positive if  $< 15$  mg/dL), ACA IgG (positive if  $> 15$  GPL), ACA IgM (positive if  $> 13$  MPL), anticardiolipin antibody (lupus anticoagulant [LA]; positive or negative), and anti-beta 2 glycoprotein (positive or negative) data were also recorded.

To evaluate cardiovascular risk, the following variables were considered as emerging risk factors: viscosity (positive if  $> 1.33$  mPa/s), vitamin D3 (positive if  $< 15$  ng/mL), fibrinogen (positive if  $> 400$  mg/dL), homocysteine (positive if  $> 15$  mg/dL), and ultrasensitive polymerase chain reaction for CRP (uCRP; positive if  $> 1$  mg/L). The "classic" CVRFs variables we assessed were: HT (positive if arterial blood pressure while sitting was  $> 140/90$  in 2 separate measurements or if treatment for HT was used), DM (fasting glycemia  $\geq 126$  mg/dL or use of antidiabetic treatments), tobacco use (current smoker, or ex-smoker for less than 6 months), dyslipidemia (if triglycerides  $> 150$  mg/dL or LDL cholesterol  $> 150$  mg/dL), sedentary lifestyle (patient did not participate in regular physical exercise or at least walk for more than an hour a day), obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>), and early menopause (if it appeared before age 40).

Importantly, only CVEs that emerged after the diagnosis of SLE were considered; in patients with multiple CVEs, the different type combinations were recorded, defining them as follows:

- (1) ischemic heart disease including myocardial infarction, and/or angina pectoris (according to the clinical diagnosis, and/or electrocardiographic ischemic changes), and/or specific alterations in cardiac enzymes, and/or findings consistent with cardiovascular disease identified via cardiac catheterization;
- (2) cerebral vascular accident based on an unequivocal clinical diagnosis and/or supported by an imaging diagnosis using computed tomography angiography or magnetic resonance angiography; and
- (3) evidence of peripheral arterial disease from a well-established prior diagnosis or by the presence of clinical manifestations confirmed by an imaging procedure.

## 2.4. Statistical analysis

After the preliminary descriptive analysis of the data (SD, means, and percentages), we compared the SLE patient groups with or without a previous experience of a CVE. To compare the differences between the means we used Student *t* tests, expressed as the mean ( $\pm$  SD) and to compare the percentages Chi-square tests ( $\chi^2$ ) were used; possible correlations were identified using the Pearson test for parametric data or the Spearman test for nonparametric data. Finally, a binomial logistic regression model was created in which variables that presented correlations were considered independent, and group variables as dependent variables, according to the presence or absence of CVEs; *P*-values of less than .05 were considered significant in all our analyses. We used the SPSS statistical software (version 22.0, IBM Company, Armonk, NY) for all our analyses.

## 2.5. Ethical aspects

Scientific and ethical permission to carry out this study was obtained from the Medicinal Research Ethics Committee at the University and Polytechnic Hospital La Fe in Valencia (ref. 09/27/02), and this permit was approved by the other participating health centers. Informed consent was obtained from the patients for the purpose of publication.

## 3. Results

### 3.1. Sociodemographic characteristics

The average age of the sample was 36.0 years (SD=9.6); although all the sociodemographic data can be found in Table 1, it should be noted that 98.5% (n=330) of the women were Caucasian; 58.2% (n=167) were married; 44.3% (n=125) had completed secondary education; and 60.3% (n=158) were in active employment. It should be noted that 19.1% (n=64) had a recognized disability and the average level of disability was 52.6% (SD=17).

### 3.2. SLE disease characteristics

The mean length of time patients had had a SLE diagnosis was 98 months (SD=81.3; range: 0–389) and a mean of 5.32 ACR criteria was satisfied (SD=1.24; range: 4–10). Regarding clinical information, the most frequent ACR criterion was positive

**Table 1**  
Sociodemographic characteristics of patients with systemic lupus erythematosus.

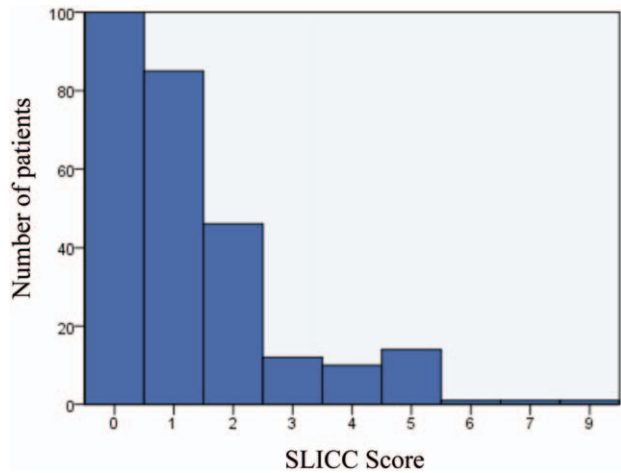
	%	n
Ethnicity		
Caucasian	98.5	327
Other ancestry	1.5	5
Civil status		
Married	58.2	167
Single	28.6	82
Divorcee	7.7	22
Widow	5.6	16
Education		
Primary education	44.3	125
Secondary education	33.0	93
Higher education	17.7	50
Incomplete primary education	5.0	14
Employment		
Active	60.3	158
Unemployment	13.4	35
Permanent incapacity	11.1	29
Retired	9.2	24
Temporal incapacity	6.1	16
Recognized disability	19.1	64

antinuclear antibody (ANA) (89%, n=298), followed by nonerosive arthritis (81.8%, n=274) (Table 2). The mean number of hospital admissions due to SLE was 1.6 (SD=3.1; range: 0–25), while the mean number of hospital admissions due to cardiovascular complications was .08 (SD=.35; range: 0–3); the patients had presented an average of 2.8 flare-ups from the time of the onset of their illness (SD=3.0; range: 0–25). The mean SLICC chronicity index score was 1.3 (SD=1.5; range: 0–9; Fig. 1) and the mean SLEDAI disease activity score was 6.0 (SD=5.5; range: 0–29; Fig. 2).

Regarding the rest of the autoimmunity markers, anti-double stranded DNA (anti-dsDNA) was expressed in 49.4% (n=77) of the SLE patients. Of the other SLE disease-activity marker data recorded, C4 and C3 expression were reduced in 49.6% (n=60) and 36.4% (n=44) of the cohort, respectively. Regarding the remaining autoimmunity markers, anti-Smith antibody was present in 34.2% (n=53) of the sample, ACA IgG was observed in 18.2% (n=20), and ACA IgM was registered in 17.3% (n=19); 45.5% (n=70) of patients tested positive for LA, while 38.5% (n=10) were positive for anti-beta-2 glycoprotein. The

**Table 2**  
Prevalence of the American College of Rheumatology criterion (1997) for systemic lupus erythematosus.

	%	n
1. Malar rash	61.5	206
2. Discoid rash	8.4	28
3. Photosensitivity	49.6	166
4. Oral ulcers	42.4	142
5. Nonerosive arthritis	81.8	274
6. Pleuritis or pericarditis	21.5	72
7. Renal disorder	34.6	116
8. Neurologic disorder	11.0	37
9. Hematologic disorder	60.3	202
10. Immunologic disorder	71.9	241
11. Positive antinuclear antibody	89.0	298



**Figure 1.** Distribution of the SLICC chronicity index scores. SLICC=systemic lupus international collaborating clinics.

mean results of the physical examination and complementary tests are shown in Table 3.

**3.3. Cardiovascular risk factors**

Regarding the classic CVE risk factors, 38.3% of the sample had 1 risk factor, 23.5% had 2, 21.7% had 3, and only 8.7% had no risk factors; 50.6% (n=159) were sedentary; 33.3% (n=106) were smokers; 30.4% (n=100) had dyslipidemia; 23.8% (n=79) were hypertensive; 15.5% (n=18) were obese; and 4.2% (n=14) were diabetic. Only 4.8% (n=16) of women with SLE suffered early menopause; 17.3% (n=58) of the patients were menopausal; the average age of the appearance of menopause was 42.7 years.

In terms of the emerging CVRFs, it is important to consider that between 66.9% and 75.5% of the participating specialist clinicians involved in this study did not use the established cut-off points for an increased risk of CVEs at their hospitals. Thus, 65.7% (n=23) of the patients presented altered vitamin D levels; uCRP was altered in 58.5% (n=38); plasma viscosity was changed in 30.55% (n=25); fibrinogen was altered in 24.3% (n=27); and homocysteine levels were affected in 14.3% (n=12) of the sample.

**3.4. CVEs and subclinical cardiovascular disease**

At least 1 CVE was presented in 10.7% (n=35) of the patients; the most frequently affected area was the brain (51.4%; n=18), followed by the heart (31.4%; n=11), and then by the peripheral vascular system (11.4%; n=4); 1 patient was affected by both cardiac and peripheral disease and another presented cardiac and cerebral CVEs. Regarding the detection of subclinical cardiovascular disease, echocardiography and carotid ultrasound imaging highlighted pathological disease in 36.2% and 20.7% of cases, respectively. The ankle-brachial index indicated the presence of subclinical cardiovascular disease in 9.2% (n=7) patients.

**3.5. SLE and cardiovascular disease treatment**

Regarding the treatment of the whole sample, 91.3% (n=303) received at least 1 drug specifically for SLE: 15.9% (n=48) received pulses of cyclophosphamide and 9.5% (n=27) received

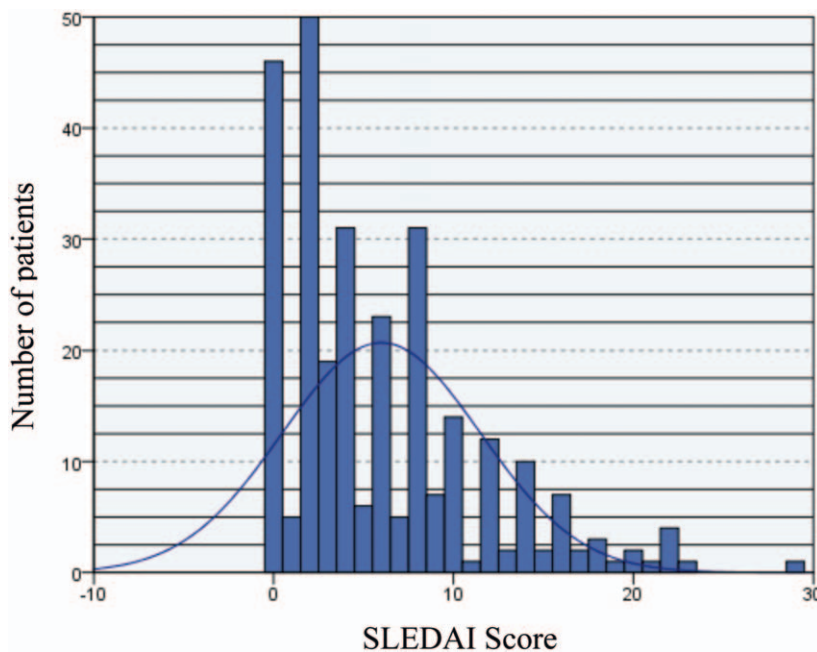


Figure 2. Distribution of the SLEDAI scores. SLEDAI=systemic lupus erythematosus disease activity index.

pulses of corticosteroids. In turn, 50.8% (n=166) received at least 1 specific cardiovascular treatment: 22.2% (n=71) antiplatelet therapy, 17.8 (n=57) antihypertensives, 8.8% (n=28) anticoagulants, and 8.2% (n=26) lipid-lowering agents.

### 3.6. Comparative analysis, correlations, and binomial logistic regression

Table 4 shows the quantitative variables which were significantly different between the SLE patient groups with or without CVEs.

**Table 3**  
Physical examination and complementary test results of patients with systemic lupus erythematosus.

	Mean	Minimum	Maximum	SD
Ankle brachial index	1.03	.77	1.38	.12
BMI, kg/m <sup>2</sup>	24.56	15.61	55.00	5.68
Waist circumference, cm	80.67	60	119	13.57
SBP, mm Hg	120.69	90	165	15.84
DBP, mm Hg	76.02	50	108	11.18
SBP/DBP difference	45.17	25	93	11.62
Glycemia, mg/dL	92.33	63	371	37.21
Urea, mg/dL	39.85	14	346	35.10
Creatinine, mg/dL	.94	.30	5.00	.64
Cholesterol, mg/dL	188.02	113	417	45.29
CLDL, mg/dL	109.21	46	181	31.12
CHDL, mg/dL	54.46	21	100	14.75
Triglycerides, mg/dL	128.48	27	587	87.53
Leukocytes, × 10 <sup>3</sup> /mm <sup>3</sup>	6.21	2	14	2.59
Platelets, × 10 <sup>3</sup> /mm <sup>3</sup>	222.05	1	481	93.02
ESR, mm/Hg	31.36	5	109	22.59
Framingham index* (%)	4.14	0	27.93	5.98

BMI=body mass index, CHDL=cholesterol high-density lipoproteins, CLDL=cholesterol low-density lipoproteins, DBP=diastolic blood pressure, ESR=erythrocyte sedimentation rate, SBP=systolic blood pressure, SD=standard deviation.

\*The Framingham index was only calculated in patients without cardiovascular events.

Of note, the SLE patients with at least 1 CVE were 3.7 years older, had been diagnosed with SLE for 5 years longer, and had had almost 3 more hospital admissions resulting from SLE and .5 more for cardiovascular complications, than the SLE patients without CVEs. In addition, patients with SLE and CVEs had an average of 2 more disease flare-ups and higher DBPs and SLICC scale scores. The percentage of patients with a family history of early CVEs ( $\chi^2=9.67, P=.002$ ) was higher in patients with SLE who had experienced a CVE. In terms of the classic risk factors, there were differences in the frequency of women with HT ( $\chi^2=14.0, P=.000$ ) and dyslipidemia ( $\chi^2=4.67, P=.031$ ) CVEs, but the differences in sedentary lifestyle, smoking, obesity, or DM were not significant. Physical examination revealed a greater presence of heart murmurs ( $\chi^2=4.97, P=.026$ ) and carotid murmurs ( $\chi^2=18.47, P=.000$ ), as well as in the presence of LVH ( $\chi^2=6.45, P=.011$ ) in electrocardiograms of these patients. No statistically significant differences were found in relation to the prevalence of heart failure. With respect to subclinical arteriosclerotic disease, there were more alterations in the carotid ultrasound imaging ( $\chi^2=4.97, P=.026$ ) and ankle-brachial index ( $\chi^2=5.02, P=.025$ ) in patients with CVEs. From the complementary tests, only the autoimmune marker ACA IgM ( $\chi^2=5.61, P=.018$ ), as well as LA positivity ( $\chi^2=5.45, P=.020$ ), was higher amounts in patients with CVEs. None of the emerging risk factors were differentially altered between patients with or without CVEs.

Differential proportional analysis showed that patients with CVEs most frequently received treatment with corticosteroid ( $\chi^2=8.9; P=.003$ ) or cyclophosphamide ( $\chi^2=10.0; P=.002$ ) pulses or cardiovascular associated treatments ( $\chi^2=21.7; P=.000$ ). Regarding the associated treatments, the greatest difference was found in anticoagulant treatments ( $\chi^2=32.36, P=.000$ ), but the use of antihypertensive agents ( $\chi^2=14.18, P=.000$ ), antiplatelet agents ( $\chi^2=5.89, P=.000$ ), and lipid-lowering drugs ( $\chi^2=4.33, P=.037$ ) was also more common among patients presenting CVEs. Table 5 shows the results from

**Table 4**  
**Significant differences in the mean variables, as measured with Student *t* tests, based on the presentation of cardiovascular events.**

	Significance (bilateral)	No CVEs	CVEs	Difference in the means	Standard error of the difference	95% confidence interval	
Age	.031	35.48	39.17	3.69	1.70	.34	7.04
Length of disease diagnosis in months	.000	91.02	152.74	61.72	14.96	32.27	91.16
Admissions for SLE	.003	1.30	4.17	2.86	.90	1.02	4.70
Admissions for CVEs	.000	.03	.56	.53	.13	.26	.81
Number of flare-ups	.028	2.62	4.52	1.90	.82	.22	3.58
SLICC	.000	1.07	2.97	1.89	.39	1.09	2.69
DBP, mm Hg	.021	75.20	82.77	7.57	3.23	1.17	13.96

CVE = cardiovascular event, DBP = diastolic blood pressure, SLE = systemic lupus erythematosus, SLICC = systemic lupus international collaborating clinics.

the analysis of correlations between variables with mean differences related to the presence or absence of CVEs.

We carried out several logistic regression analyses to determine the odds ratio (OR) of a CVE for each of the individual variables; we then grouped the significant ones according to the concept they referred to as a whole and used these conditionally in the subsequent experiments. After analysis of the SLE variables, the number of hospital admissions was the only variable that influenced the presentation of CVEs (95% confidence interval [CI] OR = 1.024–1.270;  $P = .017$ ). Because many ACA IgM and LA values were lost, only 26% of the sample was used, and so we repeated the logistic regression excluding these markers. Thus, the SLICC scale scores became the only predictor of CVEs (95% CI OR = 1.479–2.400;  $P = .000$ ). When the treatment variables with pulses of corticoids or cyclophosphamide were introduced into the equation, neither of them improved admissions or the SLICC score, and so these treatments were omitted and their ORs were lost. None of the logical interactions increased the OR.

The classical risk factors were also individually included in the logistic regression trials; when all the variables of this group were included in the conditional procedure, only the interaction between HT and antihypertensive treatments influenced the presence of CVE (95% CI OR = 2.165–10.377;  $P = .001$ ). Among the variables directly related to CVE, the presence of a family history of early CVE and the number of admissions due to cardiovascular complications stand out. The number of admissions for cardiovascular complications variable was excluded from the multivariate analyses because of its obvious relationship to the presence of CVEs. Thus, we obtained a logistic regression in which the importance of a family history of early CVEs increased when subclinical cardiovascular disease factors were considered (95% CI OR = 2.355–40.544;  $P = .002$ ).

Finally, exploration of binary logistic regression which included the main factors from each group, except those directly related to CVE, resulted in a model in which the 3 main variables in each group persisted, implying that they must be independent of each other. However, the weight of the interaction between the “family history of early cardiovascular disease” and the interaction between HT and the use of antihypertensives drugs was higher than the number of admissions for SLE (Table 6).

#### 4. Discussion

This study included a sample of 335 young women diagnosed with SLE; men ( $n = 39$ ) were excluded from the analysis because being male itself is a CVE risk factor. Moreover, the frequency of CVEs among men in the general population is higher with respect to women<sup>[40]</sup> and SLE predominantly affects women. However,

in this discussion, we also consider our data in the context of studies that included men.<sup>[18,41,42]</sup> The patients included in this study had at least moderate disease activity, with an average SLEDAI index score of  $6 \pm 5.5$ . Notwithstanding, more than half (60.3%) of these women were actively employed. This level of disease activity is similar to that reported by Urowitz et al<sup>[43]</sup> ( $5.5 \pm 5.6$  points) but is higher than cited in most cardiovascular risk studies (1.4–2.8 points)<sup>[18,44,45]</sup> and is lower than reported for a study conducted in Asia ( $13.8 \pm 6.9$ ).<sup>[46]</sup> However, the SLICC index we found was medium-low ( $1.3 \pm 1.5$  points; range: 0–9) and so chronicity in our study was low. This meant that there was less accumulated structural damage that, a priori, resulted in less inflammation and the presence of fewer CVEs. This latter finding is comparable to those from other studies; for example, Relesser et al, Pons-Estel et al, and Bengtsson et al reported a mean SLICC score of 1.0, 1.6, and 2.0, respectively.<sup>[18,44,47]</sup>

The autoimmunity markers (such as ANA and anti-dsDNA) used in the diagnosis of CVEs were present in similar percentages to the prevalence described for SLE.<sup>[48]</sup> In our study, the disease activity was moderate according to the SLEDAI index. However, the fact that 36.4% and 49.6% of our patients respectively presented positive C3 and C4 fractions is evidence that they had poor disease control and therefore, their compliance with therapeutic objectives was low. Nonetheless, disease activity cannot be reduced exclusively to the interpretation of serological results. In this sense, the consensus on the use of biological therapies for SLE states that clinical manifestations are the main indicator of activity, which is why it is considered a quiescent clinical disease when only immunological markers are altered.<sup>[49]</sup> Thus, we cannot affirm that compliance with the therapeutic objectives of the patient cohorts from other studies (such as that by Relesser et al) was worse, even though more of them (76.3%) had lower complement percentages.<sup>[18]</sup>

Traditional CVRFs are higher in patients with SLE than in the general population,<sup>[11,12]</sup> the most frequent being a sedentary lifestyle (present in up to 50.6% of patients), followed by tobacco use and very closely after, by dyslipidemia, present in 33.3% and 30.4% of patients, respectively. Somewhat less of risks are HT, obesity, early menopause, and lastly, diabetes, with the latter presenting in 4.2% of the population. As in other studies,<sup>[18,43,44]</sup> we found that diabetes was not usually very prevalent in patients with SLE (2.4%–5.2%); however, it is a very important factor because patients with DM present similar proportions of CVEs as patients with SLE.<sup>[17]</sup> Of note, only 8.7% of our patients were free of classical CVRFs; most presented 1 CVRF (38.3%), 23.5% had 2, and 21.7% had 3. In the study by Urowitz et al the most prevalent CVRFs were dyslipidemia and tobacco use (37.4% and 36.6%, respectively), while in the Relesser study, these were the

**Table 5**

**Correlations between the variables with differences in the means or proportions according to the presence or absence of CVEs, assessed with the Spearman coefficient.**

	CVEs	Age	Length of SLE diagnosis	Admissions for SLE	Admissions for CVEs	Number of flare-ups	Family clinical history	Arterial hypertension	Diastolic blood pressure	Dyslipidemia	Heart murmur	Carotid murmur	Carotid ultrasound	Ankle brachial index	ACA IgM	Corticosteroid pulses	Cyclophosphamide pulses	Cardiovascular treatment	Lipid-lowering drugs	Antihypertensives	Antiaggregant		
Age	.12*																						
Length of SLE diagnosis	.20†	.36†																					
Admissions for SLE	.21†	n.s.	.32†																				
Admissions for CVEs	.50*	n.s.	.12*	.18†																			
Number of flare-ups	.17†	.14*	.31†	.38†	n.s.	.35†																	
SUCC	.34†	.25†	.30†	.40†	.23†	n.s.	n.s.																
Family clinical history	.18†	n.s.	n.s.	.18†	n.s.	.29†	.20†																
Arterial hypertension	.21†	.14*	.21†	.21†	n.s.	n.s.	n.s.	.37†															
Diastolic blood pressure	.20*	n.s.	n.s.	.21*	n.s.	n.s.	n.s.	n.s.															
Dyslipidemia	.12*	n.s.	n.s.	.12*	n.s.	.24†	.20†	.36†	.18*														
Heart murmur	.20*	n.s.	n.s.	.23†	.18*	n.s.	.24*	.19*	n.s.	n.s.													
Carotid murmur	.39†	n.s.	n.s.	.19*	n.s.	n.s.	n.s.	n.s.	.20*	n.s.	n.s.												
LVH	.23*	n.s.	n.s.	.20*	n.s.	n.s.	n.s.	.20*	n.s.	n.s.	.32†	.20*											
Carotid ultrasound imaging	.20*	.21*	.22*	.19*	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	.22*	n.s.	n.s.										
Ankle brachial index	.26*	n.s.	.31†	n.s.	.35†	n.s.	n.s.	n.s.	-.27†	n.s.	n.s.	n.s.	n.s.										
ACA IgM	.23*	n.s.	n.s.	.20*	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.									
LA	.20*	n.s.	.19*	n.s.	n.s.	n.s.	n.s.	.18*	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.								
Corticosteroid pulses	.18†	n.s.	n.s.	.34†	n.s.	.12*	.16*	.24†	n.s.	.14*	n.s.	n.s.	n.s.	n.s.	n.s.								
Cyclophosphamide pulses	.18†	n.s.	n.s.	n.s.	n.s.	.23†	.13*	.30†	n.s.	.27†	n.s.	n.s.	n.s.	n.s.	n.s.	.23†	.52†						
Cardiovascular treatment	.26†	n.s.	.19†	.14*	.20†	.21†	.26†	.39†	n.s.	.22†	n.s.	n.s.	n.s.	n.s.	.30†	.25†	.13*	.26†					
Lipid-lowering drugs	.12*	n.s.	n.s.	.21†	n.s.	.14*	n.s.	.30†	.27†	.45†	n.s.	n.s.	n.s.	n.s.	n.s.	.13*	n.s.	.29†					
Antihypertensives	.21*	n.s.	.17†	.31†	.13*	.20†	.21†	.68†	n.s.	.16†	n.s.	n.s.	n.s.	n.s.	n.s.	.16†	n.s.	.45†	.26†				
Antiaggregant	.14*	n.s.	.14*	n.s.	.12*	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	.32*	n.s.	n.s.	.51†	n.s.	n.s.			
Anticoagulant	.32†	n.s.	n.s.	n.s.	.34†	n.s.	.27†	n.s.	n.s.	n.s.	.26†	.37†	n.s.	n.s.	.22*	n.s.	n.s.	.30†	n.s.	n.s.	n.s.		

ACA IgM = anticardiolipin IgM antibodies; CVE = cardiovascular event; LA = lupus anticoagulant (positive or negative); LVH = left ventricular hypertrophy; n.s. = not significant; SLE = systemic lupus erythematosus; SUCC = systemic lupus international collaborating clinics.

\*  $P < .05$ .

†  $P < .001$ .

**Table 6**  
**Logistic regression of the main factors that influence cardiovascular events in systemic lupus erythematosus patients.**

	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>df</i>	<i>Sig.</i>	<i>Exp (B)</i>	95% <i>CI</i> for <i>Exp (B)</i>	
							Lower	Upper
Step 1								
Admissions for SLE	.167	.049	11.436	1	.001	1.182	1.073	1.303
Step 2								
Admissions for SLE	.171	.050	11.692	1	.001	1.187	1.076	1.309
Family clinical history	1.360	.444	9.372	1	.002	3.898	1.631	9.312
Step 3								
Antihypertensives and HTA	1.107	.451	6.030	1	.014	3.024	1.250	7.314
Admissions for SLE	.135	.053	6.576	1	.010	1.144	1.032	1.269
Family clinical history	1.379	.450	9.397	1	.002	3.971	1.644	9.588

*B* = *B* statistic, *CI* = confidence interval, *df* = degrees of freedom, *Exp (B)* = exponent of *B* (ie, the odds ratio), *SE* = standard error, *Sig.* = probability of significance (*P*).

prevalence of smoking followed by dyslipidemia (37.0% and 30.1%, respectively).<sup>[18,43]</sup>

Finally, there was a high prevalence of nonfatal CVEs in our patients with SLE (10.7%) compared to another series in Spain which reported a prevalence of 7.4%.<sup>[18]</sup> However, this prevalence is within the expected range if we also take European, American, and Asian studies into account, which report a prevalence of CVEs between 5.8% and 19%.<sup>[29,43,44,47,50–53]</sup> The differences between these studies are mainly methodological because not all of them included fatal events and so retrospective studies tend to underestimate their frequency.<sup>[18]</sup> As in other studies, our results indicate that most of the events in our patients affected the region of the brain (51.4%), followed by the heart (31.4%), and finally, the peripheral vascular system (11.4%).<sup>[15,18,43,50,54]</sup>

The therapeutic objectives we considered were the minimum tolerable activity, avoiding the appearance of new flare-ups, and the involvement of newly affected organs.<sup>[49]</sup> Therefore, we consider an increase in admissions for SLE, flare-ups, and SLICC scores to be direct indicators of poor compliance with these objectives. In our study, these direct indicators were related to an increased risk of presenting a CVE (OR: 1.20, 1.15, and 1.87, respectively). These results are novel because previous studies have related only the SLICC score to CVRFs (OR: 1.03–2.48<sup>[44,47]</sup> and RR: 1.05–1.22<sup>[50]</sup>). However, previous studies have found different therapeutic objectives noncompliance indicators, including the presence of valvular heart disease (RR: 2.12, OR: 2.44), psychosis (RR: 2.76, OR: 2.42), seizures (RR: 1.93), serositis (OR: 1.54), nephritis (OR: 2.08), and anemia (RR: 1.97).<sup>[18,43,46,50]</sup> Regarding the SLEDAI, other studies did not (or barely) related it to noncompliance (OR: 1.04–1.15)<sup>[44–46,49,55]</sup>; Schoenfeld et al justify this because the SLEDAI does not capture arteriosclerosis-related systemic inflammation with a high degree of sensitivity.<sup>[25]</sup> Finally, only the study by Fernández-Nebro et al related low levels of complement (C3 or C4) to CVE (OR: 1.81).<sup>[18]</sup>

In our study, when we grouped all the variables related to SLE into a multivariate logistic regression model to evaluate their relationship with CVEs, only the SLICC index and the number of admissions for SLE remained significant (ORs: 1.88 and 1.14, respectively). Other variables such as age or SLE disease duration, as well as immunological markers including ACA IgM and LA lost their influence in the model in favor of these aforementioned factors. However, other studies did find that variables related to SLE influenced the risk of CVEs. We found that disease duration was significantly related to CVE risk, but that the probability of

presenting a CVE was very low (OR: 1.01). Indeed, most studies show that the duration of SLE is not a factor related to the presentation of CVEs, but when the relationship is significant, as in our study, the increase in probability is very low (ORs: 1.04 and 1.10).<sup>[44,46]</sup>

As touched upon in the introduction, antiphospholipid antibodies are especially relevant in SLE because they are related to the risk of atherothrombosis.<sup>[25]</sup> In this line, our data indicate the importance of the presence of ACA IgM and LA in patients presenting CVEs because, when studied individually, higher ORs were obtained for these markers (4.29 and 3.25, respectively). Another study has also corroborated the importance of LA (OR: 3.08),<sup>[44]</sup> while others consider it a protective factor (OR: .37).<sup>[46]</sup> However, still others indicate that the type of antiphospholipid antibodies is not important, but rather, that the presence of any of them increases the risk of patients with SLE presenting a CVE (OR: 1.57–4.90).<sup>[18,56]</sup> Some authors, including Bultink et al, propose that these markers are even more important than the classic risk factors among patients with SLE.<sup>[57]</sup> Finally, regarding variables related to SLE activity, only 1 article shows that the presence of anti-dsDNA increases the risk of presenting a CVE (OR: 1.56).

Our study did not include men, and so only provides analytical data for women. However, other studies have confirmed that male sex is a risk factor for the presentation of a CVE (OR: 1.56–3.67),<sup>[25,43,45,47]</sup> and studies that tried to find differences between the sexes did not find significant ORs in their multivariate analyses.<sup>[50]</sup> In turn, some authors place so much importance on age that they adjusted all the variables according to the patient ages.<sup>[44]</sup> Like other articles (OR: 1.03–1.08),<sup>[18,43,44,47,50]</sup> the importance of patient age was low in our study (OR: 1.04). Only publications that separately evaluated older patients found a greater influence for age,<sup>[45]</sup> reporting an OR of 7.72 for patients aged over 60 years.<sup>[46]</sup> In our case, it is important to remember that only the number of admissions for SLE and the SLICC index increased the probability of presenting a CVE, and that age was secondary. As in other reports in the literature, apart from years of education – which seem to behave as a protective factor (OR: .85),<sup>[47]</sup> none of the other sociodemographic variables we studied significantly affected the appearance of CVEs in our cohort.

Regarding whether there are differences in the cardiovascular profile of patients diagnosed with SLE according to whether or not they have previously presented a CVE, our results suggest the importance of HT (OR: 3.71) and its related variables, DBP (OR: 1.06) and the use of antihypertensive drugs (OR: 3.97). These findings coincide with those obtained by other authors, who



found increases in the risk of CVEs in patients with HT (OR: 1.71–3.78).<sup>[18,25,46,50]</sup> As in our study, blood pressure data does not appear to be as important factor in these patients (OR: 1.03–1.17)<sup>[45]</sup> as their treatment with antihypertensives (OR: 3.41).<sup>[44]</sup> In our study, the interaction between the use of antihypertensive drugs and a diagnosis of HT had the greatest predictive power (OR: 4.74). This may be because hypertensive patients have a higher risk of poor disease control, even when receiving treatment with antihypertensives. This agrees with the hypothesis that patients who do not meet their therapeutic objectives either for SLE or for avoiding classic CVRFs have a greater risk of CVEs.

From among the remaining classic CVRFs, we found that only the presence of dyslipidemia (OR: 2.18) and the use of lipid-lowering agents (OR: 2.76) were significant. However, this influence was nullified in our multivariate study because of the influence of the interaction between HT and the use of antihypertensives, as already discussed. Other studies also point to the importance of dyslipidemia, which increases the risk of presenting a CVE<sup>[18,35–45,51]</sup> by effect size from 1.04 to 3.35, as well as the protective role of HDL (OR: .25).<sup>[46]</sup> The articles we reviewed also showed that the other classic risk factor of smoking increased the risk of patients with SLE experiencing a CVE by 1.14–2.78.<sup>[18,44,47,50]</sup> Finally, we did not find any articles that demonstrate that a sedentary lifestyle or obesity influence the presentation of CVEs in patients with SLE, although the study by Fernández-Nebro et al obtained an OR of 2.22 in the presence of DM<sup>[18]</sup> and Manzi et al reported a RR of .77 for menopause.<sup>[51]</sup>

None of the emerging risk factors we analyzed (plasma viscosity, vitamin D, fibrinogen, homocysteine, and uCRP) were differentially altered in patients with CVEs compared to those without CVEs in our sample of women with SLE. Although these markers seemed promising when we started this study a decade ago, our review of the recent literature shows that uCRP is not a useful predictor of CVE (OR: 1.01–2.63),<sup>[46,47]</sup> but fibrinogen and homocysteine do appear to have some predictive value (ORs: 1.72 and 2.44, respectively).<sup>[56,58]</sup> Our results show that the presence of a family history of CVE was the strongest predictive factor (OR: 9.77) from among the variables directly related to CVE. Our multivariate analysis positioned this variable above other initially important variables such as the number of admissions for CVE (OR: 12.30). In this regard, a 2016 study also highlighted the importance of detecting subclinical atherosclerosis in SLE patients by studying the thickness of the intima-media.<sup>[59]</sup> Other studies did not consider these variables, perhaps because their relationship has already been demonstrated in patients without SLE. However, the only study that did take the family history of CVE into account, did not demonstrate its significance in this context.<sup>[51]</sup>

In terms of the potential differences in the therapeutic objectives of patients diagnosed with SLE according to their prior presentation of CVEs, both the number of admissions for SLE and the SLICC index score were more important in the multivariate analyses than specific treatment either with corticoids or cyclophosphamide pulses. In contrast, our patient cohort had a higher risk of CVEs when they had received pluses of corticoids (OR: 4.04) or cyclophosphamide (OR: 3.51). However, the disease chronicity and number of admissions for SLE were higher in the patients in our sample compared to those who had received similar cycles of treatments in other studies.<sup>[25]</sup> As already mentioned in the introduction, treatments with corticosteroids are one of the factors most strongly related to CVEs.<sup>[55]</sup> Specifically, treatment with doses exceeding 20 mg/d

(OR: 2.54)<sup>[45]</sup> and longer treatment periods (RR: .98)<sup>[51]</sup> have been related to an increased risk of CVEs. Like our results for the use of pulsed treatments, 2 other studies found that treatment with azathioprine resulted in an increased risk of presenting a CVE (OR: 1.47–1.53).<sup>[18,50]</sup> This may be because azathioprine is used only in more chronic patients with SLE because it allows less overall steroid use in these groups. Finally, although hydroxychloroquine effectively controls lipids and glycemia in patients with SLE, its efficacy in preventing CVE is less clear.<sup>[25]</sup>

Lastly, this study did have some methodological limitations, including its cross-sectional design and that some of our parameters could not be obtained in some patients. Regarding the former, we were able to supplement our findings with longitudinal studies<sup>[47]</sup> and results from other comparable studies in similar settings in Spain.<sup>[18]</sup> In terms of the latter, C3 and C4 and antiphospholipid antibody determination data were only available for about a third of our patients (36.1% and 32.8%, respectively), and anti-β2 glycoprotein data were only available in 7.8% of patients because this test was not widely available until well after the study commenced in 2003. There was also a similar problem for the emerging CVRFs: uCRP, plasma viscosity, fibrinogen, homocysteine, and vitamin D. Nonetheless, studies conducted 8 years later in our setting incorporated these tests into periodic clinical assessments, allowing these authors to obtain these data for more than 95% of patients.<sup>[18]</sup> Moreover, a study undertaken in the United States 6 years later also highlighted the same limitations as we have.<sup>[50]</sup> However, the authors want to emphasize that the lack of some determinations in part of the sample recommends that the results and their interpretation should be taken with caution.

## 5. Conclusions

This study demonstrates that the best predictor of the presentation of CVEs in patients with SLE is long-term disease activity, especially when it is measured via the SLICC chronicity index and the number of hospital admissions for SLE. Higher SLE disease activity results in higher inflammatory activity and an increased risk of suffering a CVE. Therefore, the therapeutic objective of clinicians must be to minimize disease activity among patients with SLE as far as possible in order to prevent them from presenting cardiovascular complications. Furthermore, to stratify the risk of CVEs, classic CVRFs, especially arterial HT and its treatment, should be another of the main targets in the prevention of CVRFs in patients with SLE. Finally, emerging CVRFs are not such an important factor in the CVE risk-stratification.

## Acknowledgments

ML, the principal investigator of the study, thanks the 31 medical specialists who participated in the selection of patients with SLE for Risk/SLE Thematic Network.

HG and FGM thank Ana Benito from Universidad Cardenal Herrera-CEU, CEU Universities, who reviewed the manuscript as statistical expert. María Ledran from EFL Scientific Editing translated the manuscript and helped with the editing.

## Author contributions

**Conceptualization:** María Luisa Micó.

**Data curation:** Mar Fernández-Garcés, María Luisa Micó.

**Formal analysis:** Mar Fernández-Garcés, María Luisa Micó, Gonzalo Haro.  
**Funding acquisition:** María Luisa Micó, Mar Fernández-Garcés.  
**Investigation:** Mar Fernández-Garcés, María Luisa Micó.  
**Methodology:** Mar Fernández-Garcés, Gonzalo Haro, María Luisa Micó.  
**Project administration:** María Luisa Micó.  
**Resources:** María Luisa Micó.  
**Software:** María Luisa Micó, Gonzalo Haro.  
**Supervision:** Gonzalo Haro, María Luisa Micó.  
**Validation:** María Luisa Micó.  
**Visualization:** Mar Fernández-Garcés, Gonzalo Haro.  
**Writing – original draft:** Mar Fernández-Garcés, Gonzalo Haro, María Luisa Micó.  
**Writing – review and editing:** Mar Fernández-Garcés, Gonzalo Haro, María Luisa Micó.  
 Gonzalo Haro orcid: 0000-0002-1299-9611.

## References

- [1] Lahita RG. The role of sex hormones in systemic lupus erythematosus. *Curr Opin Rheumatol* 1999;11:352–6.
- [2] ChaKravarty EF, Bush TM, Manzi S, et al. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. *Arthritis Rheum* 2007;56:2092–4.
- [3] Asanuma Y, Oeser A, Shintani AK, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349:2407–15.
- [4] Roman MJ, Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349:2399–406.
- [5] Doria A, Shoenfeld Y, Wu R, et al. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis* 2003;62:1071–7.
- [6] Fangtham M, Petri M. 2013 update: Hopkins lupus cohort. *Curr Rheumatol Rep* 2013;15:360.
- [7] El-Magadmi M, Bodill H, Ahmad Y, et al. Systemic lupus erythematosus: an independent risk factor for endothelial dysfunction in women. *Circulation* 2004;110:399–404.
- [8] Seavy LM, Grosel JM. Accelerated cardiovascular disease in patients with lupus: a review. *JAAPA* 2012;25:28–32.
- [9] Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001;44:2331–7.
- [10] Shang Q, Tam LS, Li EK, et al. Increased arterial stiffness correlated with disease activity in systemic lupus erythematosus. *Lupus* 2008;17:1096–102.
- [11] Bruce IN, Urowitz MB, Gladman DD, et al. Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. *Arthritis Rheum* 2003;48:3159–67.
- [12] Urowitz MB, Ibanez D, Gladman DD. Atherosclerotic vascular events in a single large lupus cohort: prevalence and risk factors. *J Rheumatol* 2007;34:70–5.
- [13] George J, Afek A, Gilburd B, et al. Autoimmunity in atherosclerosis: lessons from experimental models. *Lupus* 2000;9:223–7.
- [14] Zampieri S, Iaccarino L, Ghirardello A, et al. Systemic lupus erythematosus, atherosclerosis, and autoantibodies. *Ann N Y Acad Sci* 2005;1051:351–61.
- [15] Ahmad Y, Shelmerdine J, Bodill H, et al. Subclinical atherosclerosis in systemic lupus erythematosus (SLE): the relative contribution of classic risk factors and the lupus phenotype. *Rheumatology* 2007;46:983–8.
- [16] Bruce IN. Cardiovascular disease in lupus patients: should all patients be treated with statins and aspirin? *Best Pract Res Clin Rheumatol* 2005;19:823–38.
- [17] Koenig KF, Ribic 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.
- [18] Fernández-Nebro A, Rúa-Figueroa I, López-Longo FJ, et al. Cardiovascular events in systemic lupus erythematosus: a nationwide study in Spain from the RELESSER registry. *Medicine (Baltimore)* 2015;94:e1183.
- [19] Cervera R, Khamashta MA, Hughes GRV. The euro-lupus project: epidemiology of systemic lupus erythematosus in Europe. *Lupus* 2009;18:869–74.
- [20] Ruiz E, Ramalle-Gomara E, Elena A, et al. Trends in systemic lupus erythematosus mortality in Spain from 1981 to 2010. *Lupus* 2014;23:431–5.
- [21] McElhone K. A review of health related quality of life in systemic lupus erythematosus. *Lupus* 2006;15:633–43.
- [22] Rúa-Figueroa I, Erausquin C. Factores asociados a la mortalidad del lupus eritematoso sistémico. *Semin Fund Esp Reumatol* 2008;9:219–34.
- [23] Yurkovich M, Vostretsova K, Chen W, et al. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. *Arthritis Care Res (Hoboken)* 2014;66:608–16.
- [24] Urowitz MB, Bookman A, Koehler B, et al. The bimodal mortality pattern of systemic lupus erythematosus. *Am J Med* 1976;60:221–5.
- [25] 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.
- [26] Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum* 2006;54:2550–7.
- [27] Svenungsson E, Jensen-Urstad K, Heimbürger M, et al. Risk factors for cardiovascular disease in systemic lupus erythematosus. *Circulation* 2001;104:1887–93.
- [28] Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325–31.
- [29] Petri M, Perez-Gutthann S, Spence D, et al. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med* 1992;93:513–9.
- [30] Petri M, Spence D, Bone LR, et al. Coronary artery disease risk factors in the Johns Hopkins Lupus Cohort: prevalence, recognition by patients, and preventive practices. *Medicine (Baltimore)* 1992;71:291–302.
- [31] MacGregor AJ, Dhillon VB, Binder A, et al. Fasting lipids and anticardiolipin antibodies as risk factors for vascular disease in systemic lupus erythematosus. *Ann Rheum Dis* 1992;51:152–5.
- [32] Bertsias G, Ioannidis JP, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis* 2008;67:195–205.
- [33] Jung H, Bobba R, Su J, et al. The protective effect of antimalarial drugs on thrombovascular events in systemic lupus erythematosus. *Arthritis Rheum* 2010;62:863–8.
- [34] Hak AE, Pols HA, van Hemert AM, et al. Progression of aortic calcification is associated with metacarpal bone loss during menopause: a population-based longitudinal study. *Arterioscler Thromb Vasc Biol* 2000;20:1926–31.
- [35] Hochberg MC. Updating the American College of Rheumatology. Revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
- [36] Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677–86.
- [37] American College of Rheumatology ad hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;42:599–608.
- [38] Ruperto N, Hanrahan LM, Alarcón GS, et al. Lupus Foundation of America, Inc. International consensus for a definition of disease flare in lupus. *Lupus* 2011;20:453–62.
- [39] Anderson KM, Odell PM, Wilson PWF, et al. Cardiovascular disease risk profiles. *Am Heart J* 1991;121:293–8.
- [40] Alonso MD, Martínez-Vázquez F, Riancho-Zarrabeitia L, et al. Sex differences in patients with systemic lupus erythematosus from Northwest Spain. *Rheumatol Int* 2014;34:11–24.
- [41] George C, Tsokos MD. Systemic lupus erythematosus. *N Engl J Med* 2011;365:2110–21.
- [42] Rúa-Figueroa I, Lopez-Longo FJ, Calvo-Alen J, et al. National registry of patients with systemic lupus erythematosus of the Spanish Society of Rheumatology: objectives and methodology. *Reumatol Clin* 2014;10:17–24.
- [43] Urowitz MB, Gladman DD, Ibanez D, et al. Atherosclerotic vascular events in a multinational inception cohort of systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2010;62:881–7.

- [44] Bengtsson C, Öhman 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;21:452–9.
- [45] Magder LS, Petri M. Incidence of and risk factors for adverse cardiovascular events among patients with systemic lupus erythematosus. *Am J Epidemiol* 2012;176:708–19.
- [46] Wand XY, Tang XQ, Huang YJ, et al. Frequency of established cardiovascular disease and its risk factors in Chinese patients with systemic lupus erythematosus. *Clin Rheumatol* 2012;31:669–75.
- [47] Pons-Estel GJ, Gonzalez LA, Zhang J, et al. Predictors of cardiovascular damage in patients with systemic lupus erythematosus: data from LUMINA (LXVIII), a multiethnic US cohort. *Rheumatology (Oxford)* 2009;48:817–22.
- [48] Hahn BH, Kasper DL, Fauci AS, Hauser SL, et al. Systemic lupus erythematosus. *Harrison's. Principles of medicine 19th edition USA: Mc Graw-Hill Medical*; 2016;2124–33.
- [49] Calvo-Alén J, Silva-Fernández L, Úcar-Angulo E, et al. Spanish Society of Reumatology consensus for biological therapy in systemic lupus erythematosus [Spanish]. *Reumatol Clin* 2013;5:281–96.
- [50] Bertoli AM, Vilá LM, Alarcon GS, et al. Factors associated with arterial vascular events in PROFILE: a multiethnic lupus cohort. *Lupus* 2009;18:958–65.
- [51] 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;145:408–15.
- [52] Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42:338–46.
- [53] Becker-Merok A, Nossent J. Prevalence, predictors and outcome of vascular damage in systemic lupus erythematosus. *Lupus* 2009;18:508–15.
- [54] Burgos PI, Vila LM, Reveille JD, et al. Peripheral vascular damage in systemic lupus erythematosus: data from LUMINA, a large multi-ethnic U.S. cohort (LXIX). *Lupus* 2009;18:1303–8.
- [55] Karp I, Abrahamowicz M, Fortin PR, et al. Recent corticosteroid use and recent disease activity: independent determinants of coronary heart disease risk factors in systemic lupus erythematosus? *Arthritis Rheum* 2008;59:169–75.
- [56] Gustafsson J, Gunnarsson I, Börjesson O, et al. Predictors of the first cardiovascular event in patients with systemic lupus erythematosus – a prospective cohort study. *Arthritis Res Ther* 2009;11:R186.
- [57] Bultink IEM. Prospective cohort studies on risk factors for cardiovascular events in systemic lupus erythematosus: a major challenge. *Arthritis Res Ther* 2010;12:107.
- [58] Petri M, Roubenoff R, Dallal GD, et al. Plasma homocysteine as a risk factor for atherothrombotic events in systemic lupus erythematosus. *Lancet* 1996;348:1120–4.
- [59] Wu GC, Liu HR, Leng RX, et al. Subclinical atherosclerosis in patients with systemic lupus erythematosus: a systemic review and meta-analysis. *Autoimmun Rev* 2016;15:22–37.