Ankle-brachial index and arterial vascular events in systemic lupus erythematosus patients: a 5-year prospective cohort

J.-G. Erdozain[1], J.-I. Pijoan[2], I. Villar[3], J. Nieto[3], I. Ruiz-Arruza[1], G. Ruiz-Irastorza[1], A. Martinez-Berriotxoa[3]

[1]Autoimmune Diseases Research Unit, Department of Internal Medicine, Biocruces Health Research Institute, Hospital Universitario Cruces, University of The Basque Country, Bizkaia, Spain; [2]Clinical Epidemiology Unit-Hospital Universitario Cruces. Biocruces Health Research Institute. CIBER de Epidemiología y Salud Pública (CIBERESP). Madrid, Spain; [3]Department of Internal Medicine, Hospital Universitario Cruces, University of The Basque Country, Bizkaia, Spain.

Abstract

Objective

To determine the potential predictive value in patients with systemic lupus erythematous of the ankle-brachial index (ABI) for the occurrence of arterial vascular events.

Methods

216 lupus patients from a prospective clinical cohort were evaluated using the ABI at the start of the study and then followed up for 5 years. Abnormal ABI was defined as an index ≤0.9 or >1.4. Several potential vascular risk factors were also evaluated. Arterial vascular events (AVE): coronary events, cerebrovascular events, peripheral arterial disease and death related to vascular disease. Survival analysis was performed using a competitive risk regression approach, considering non-vascular death as a competitive event.

Results

18 arterial events and 14 deaths were identified. In the competitive risk regression analysis, independent predictors of higher risk were identified: family history of early AVE [subdistribution hazard ratio (SHR) 5.44, 95% confidence interval (CI) 1.69-17.50, p=0.004)], cumulative prednisone (grams) (SHR 1.01, 95% CI 1.01-1.03, p=0.007) and a personal history of arterial thrombosis (SHR 5.44, 95% CI 1.45-14.59, p=0.004). Female gender was a protective factor (SHR 0.22, 95% CI 0.07-0.77, p=0.017). A statistical trend was detected with abnormal ABI (SHR 2.65, 95% CI 0.86-8.14, p=0.089).

Conclusion

Male gender, exposure to high cumulative doses of prednisone, family history of early arterial vascular disease and occurrence of previous arterial thrombosis are independent risk predictors of arterial vascular events in patients with systemic lupus erythematosus. Abnormal ABI may be related to high risk for arterial vascular events.

Key words

systemic lupus erythematosus, cardiovascular disease, peripheral arterial disease, atherosclerosis, ankle brachial index

Jose-Gabriel Erdozain, MD
Jose-Ignacio Pijoan, MD, MSc
Irama Villar, MD
Javier Nieto, MD
Ioana Ruiz-Arruza, MD
Guillermo Ruiz-Irastorza, MD, PhD
Agustin Martinez-Berriotxoa, MD, PhD

Please address correspondence to:
Jose-Gabriel Erdozain,
Hospital Universitario Cruces,
Plaza de Cruces s/n,
48903 Barakaldo (Bizkaia), Spain.
E-mail: jgerdocas@gmail.com
jgerdocas@yahoo.es

Received on August 14, 2019; accepted in revised form on November 25, 2019.

Competing interests: none declared.

Introduction

Patients with systemic lupus erythematous (SLE) are known to be at increased risk for arterial vascular events (AVE), mainly ischaemic heart disease (IHD) and cerebrovascular disease (CVD) (1), but also peripheral arterial disease (PAD), either symptomatic or asymptomatic (2, 3). Such an increased risk is greatest among young patients (3-5). Early atherosclerosis has been demonstrated in lupus patients (6), with a prevalence of 41% in a recent Danish study that included the coronary, carotid, and lower-extremity territories (7). The premature atherosclerosis observed in SLE patients has been related to traditional cardiovascular risk factors, like arterial hypertension, diabetes, hypercholesterolaemia, tobacco use and obesity, however, some lupus-related factors, such as lupus activity itself, treatments (steroids, azathioprine) and inflammatory molecules may play an additional role (6).

AVE are one of the leading causes of increased morbidity and mortality in SLE patients (8) and detection of patients at high risk for cardiovascular disease is one of the priorities during follow-up, although these identification in clinical practice is sometimes not very adequate (9). In the general population, some specific actions could reduce the rate of AVE among high-risk patients (10). Likewise, preventing the occurrence of cardiovascular disease is one of the main objectives in SLE patients. A range of procedures have been developed for the early identification of subjects at increased vascular risk: duplex sonography of carotid arteries for the detection of plaques or to calculate intima/media thickening; coronary computed tomography to quantify coronary calcium burden; and ankle-brachial index (ABI) test.

Abnormal ABI, defined as ≤0.9 or >1.4, has been related with an increased morbidity and mortality in the general population, and ABI has been proposed to be a useful tool to identify a high cardiovascular risk population (11, 12).

SLE patients have been studied in many cross-sectional studies, even with control groups, with duplex sonography of carotid artery, detection of coronary calcium and the ABI test. A number of studies have shown an increased presence of carotid plaques, low ABI and increased coronary-calcium index in SLE patients (2, 13, 14). To date, there is only one published prospective follow-up study in patients with SLE using the carotid duplex sonography to identify patients at increased risk for AVE; in this study, the presence of carotid plaque was associated with an increased risk for coronary and cerebrovascular events (HR 4.67, 95% CI 1.41–15.53, p=0.001) (15).

Thus, we designed a prospective follow-up study of a SLE cohort with a baseline ABI previously reported (2) to determine its utility as a predictor of AVE. The secondary objective of our study was to analyse the relationship between other risk factors and the occurrence of AVE.

Material and methods

Study population

Follow-up data from 216 patients at the Autoimmune Diseases Unit, Department of Internal Medicine, Cruces University Hospital, a tertiary teaching centre in Baracaldo (Basque Country, Spain) associated with the University of the Basque Country. All patients fulfilled the 1997 classification criteria of the American College of Rheumatology and had participated in a previous cross-sectional study between January 2010 and June 2011 (2, 16).

Variables

The following variables were recorded at the time of enrolment for each patient:

1) Demographic characteristics: age, sex, race.
2) Clinical and immunological SLE variables: disease duration (years), SLE manifestations (lupus nephritis, antiphospholipid syndrome, neuropsychiatric lupus), autoantibody profile (anti-DNA, anti-Ro, anti-La, anti-RNP, anti-Sm, antiphospholipid), treatments received (corticosteroids, immunosuppressives, anti-malarials), the Systemic Lupus International Collaborating Clinics (SLICC) damage index (SDI) (17) and the SLE Disease Activity Index (SLEDAI) (18).
3) Cardiovascular (CV) risk factors:

age (defined as more than 55 and 65 years in men and women, respectively), arterial hypertension (HTN, defined as 2 consecutive measurements of at least 140/90 mmHg or antihypertensive therapy), diabetes mellitus (DM, defined as 2 consecutive fasting blood glucose determinations ≥126 mg/dl or treatment with antidiabetic drugs), hypercholesterolaemia (defined as total blood cholesterol fasting levels >200 mg/dl on 2 consecutive determinations or treatment with cholesterol-lowering drugs), metabolic syndrome according to the Adult Treatment Panel III definition (19), current or past smoking, degree of physical exercise (aerobic exercise 1 h/day, at least 3 days a week), and menopause in females. The size, weight, and waist and hip circumference were determined in each patient at the time of performing the ABI, along with calculation of the body mass index (BMI). We included in the study the levels of uric acid, vitamin D and fibrinogen at the time of the ABI.

4) Previous subclinical organ damage or CV events: left ventricular hypertrophy (LVH), microalbuminuria (presence in urine of albumin excretion between 30 and 300 mg/day, determined in spot urine sample), coronary disease, heart failure, cerebrovascular disease, chronic kidney disease, PAD, advanced retinopathy. CV events were defined as the presence of compatible clinical signs and symptoms and eventually confirmed by complementary tests: myocardial infarction was defined as typical chest pain with characteristic electrocardiographic features and elevated levels of creatine kinase (MB fraction) and/or T troponine; stroke by computed tomography (CT) scanning or magnetic resonance imaging; cerebral transient ischaemic attacks (TIA) were diagnosed in the setting of acute focal neurologic symptoms/signs lasting <24 h; chronic kidney disease is defined based on the presence of either kidney damage or decreased kidney function for three or more months, irrespective of cause; PAD, specifically atherosclerotic disease leading to peripheral artery obstruction, may be silent or present with a variety of symptoms and signs indicative of extremity ischaemia; advanced retinopathy is characterised by retinal haemorrhages, exudates, and papilloedema.
5) CV disease-related treatments received for at least 6 months: antiaggregants, statins, anticoagulants.
6) CV risk stratification was performed using the European Vascular Risk Systematic Coronary Risk Evaluation (SCORE) scale for the Mediterranean population (20).

Ankle-brachial index

ABI was performed in both legs of each patient in ad hoc scheduled visits, from January 2010 to June 2011. The MD2/SD2 Dopplex High Sensitivity Pocket Doppler was used for our study and all ABI were performed by the same 2 trained physicians working together with each patient. In every patient, 1 ABI was calculated for each leg. For the purposes of this study, the ABI variable was coded as abnormal ABI: ≤0.9 or >1.4, according to the previously mentioned evidences (11, 12).

Follow-up

A 5-year follow-up was planned for all study participants. Patients were routinely assessed every 3 to 6 months, unless clinical status demanded more frequent visits. Lupus flares (defined as any clinical manifestation of lupus that involves the use of high doses of corticosteroids, use of a new immunosuppressant or increasing the dose of some immunosuppressant previously used) were recorded. Arterial vascular events (AVE) were systematically investigated at each visit through a standardised interview. The AVE were defined as coronary events (angina pectoris, acute myocardial infarction, coronary revascularisation by angioplasty or surgery), cerebrovascular events (transient ischaemic attack, ischaemic or haemorrhagic stroke), PAD (symptomatic intermittent claudication, distal ischaemia, revascularisation by angioplasty or surgery), and vascular death. Follow-up ended when the patient attended the 5-year follow-up visit or due to death. The cause of death was established for all patients who deceased during the follow-up period.

Statistical analysis

Continuous data were described using mean and standard deviation (SD) or median and range, if it does not present a normal distribution; categorical variables with relative frequencies and percentages. The normality of the continuous variables analysed was confirmed with the appropriate statistical studies.

To identify associations with AVE, the following independent variables were tested against the dependent variable "incidence of AVE", using chi-square with Yates' correction or Student *t*-test: age at SLE diagnosis, age at the time of ABI, disease duration, sex, age as a vascular risk factor, abdominal obesity, metabolic syndrome, DM, HTN, hypercholesterolaemia, smoking (current or past), any vascular risk factor (DM or HTN or hypercholesterolaemia or current/past smoking), exercise, alcohol consumption, family history of premature CV disease, BMI, menopause, previous subclinical organ damage (LVH and microalbuminuria), previous CV events [ischaemic heart disease and/or heart failure (IHD/HF), stroke, PAD], chronic kidney disease, previous arterial thrombosis (stroke or IHD/HF or PAD), uric acid levels, vitamin D levels, previous lupus nephritis, previous antiphospholipid syndrome (APS), previous neuropsychiatric lupus (NPSLE), lupus flares during follow-up, anti-DNA, anti-Ro, anti-La, anti-U1RNP, anti-Sm, and antiphospholipid antibodies (aPL; lupus anticoagulant and/or anticardiolipin antibodies at medium-high levels on at least 2 different determinations 12 weeks apart), SLEDAI, SDI value (categorised: 0 *vs.* ≥1), prednisone (cumulative dose in grams and maximum dose ever received), hydroxychloroquine (yes/no and total dose), cyclophosphamide (cumulative dose), low-dose aspirin (number of months on treatment), anticoagulants (number of months taking treatment), or statins (number of months taking treatment) and fibrinogen levels (continuous variable).

Given the fact that the probability of occurrence of the outcomes of interest

(AVE) was influenced by other alternative events (non-vascular death) a competing risk regression (CRR) approach was adopted to obtain more accurate estimates of the 5-year cumulative risk of AVE (21). The model proposed by Fine *et al*. (22) was implemented, as it does not depend upon the independence between both the competing event and the event of interest. Accordingly, subdistribution hazard ratios (SHR) were obtained as estimates of the relative effect of a putative risk factor on the occurrence of the AVE, and subdistribution cumulative hazard functions as estimates of the adjusted 5-year risks. Ninety five percent confidence intervals were also provided.

Those variables with a p-value <0.1 in the univariate analysis were subsequently included as potential predictors of AVE: sex, age at the time of ABI, disease duration in years, family history of premature CV disease, HTN, hypercholesterolemia, SDI value, APS, fibrinogen levels at the time of the ABI, previous arterial thrombosis, prednisone cumulative dose at baseline and abnormal ABI.

Regarding the model selection, we followed a manual backward procedure, starting with the full model and removing variables based on the lack of statistically significant association using likelihood ratio tests, until all the remaining variables were statistically significant. The proportionality of risks assumption was assessed through the introduction of time-dependent covariates and the use of graphical tools. As abnormal ABI was the factor of main interest, it was kept in all the models. Departures from linearity in the log-odds for continuous variables were assessed creating and statistically testing squared and cubic terms.

Stata 14.2 for Windows was used for all analyses (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Ethics

The Ethics Committee for Clinical Research at Cruces University Hospital approved the study protocol in accordance with the Helsinki Declaration (CEIC E09/07). All patients signed an informed consent at the time of enrolment.

Table I. Baseline variables.

Female	200	(92%)
Race	Caucasian: 209	(96%)
Afro-Caribbeans:	3	(1.3%)
Hispanic:	2	(0.9%)
Arabic:	2	(0.9%)
Age at ABI	49	(15) years.
SLE duration at ABI	11	(0-37) years.
APS	21	(9.7%)
Lupus nephritis	60	(27.6%)
NPSLE	5	(2.3%)
Lupus flares	39	(18.3%)
SLEDAI at ABI	0: 104	(48.1%)
	1-5: 91	(42.2%)
	≥6: 21	(9.7%)
SDI at ABI	0: 98	(45.2%)
	1: 53	(24.4%)
	>1: 65	(30.4%)
Use of prednisone	191	(88.4%)
Maximum dose of prednisone	30.8	(25.9) mg
Average daily dose of prednisone	5.6	(8.2) mg
Cumulative dose of prednisone: mean (SD)	18.7	(57) g
Cumulative dose of prednisone: median (IQR)	7.32	(0-177.6) g
Hydroxychloroquine	193	(89.3%)
Cyclophosphamide	52	(24%)
Mycophenolate	34	(15.7%)
Azathioprine	64	(29.7%)
Family history of early vascular disease	25	(11.5%)
Current smoking at ABI	65	(30%)
Smoking (ever)	109	(50.2%)
Diabetes mellitus	7	(3.2%)
Hypertension	71	(32.7%)
Hypercholesterolaemia	74	(34.1%)
Statins	72	(33.3%)
Antiaggregants	103	(47.7%)
Anticoagulants	26	(12%)
Body mass index	Low-normal weight: 106	(49.1%)
	Overweight-obesity: 110	(50.9%)
SCORE	0-4: 205	(95%)
	≥5: 11	(5%)
Previous vascular disease	IHD: 6	(2.8%)
	CVD: 19	(8.8%)
	PAD: 3	(1.4%)

ABI: ankle-brachial index; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; NPSLE: neuropsychiatric lupus; SDI: SLICC Damage Index; IHD: ischaemic heart disease; CVD: cerebrovascular disease; PAD: peripheral arterial disease.

Results

Baseline demographic variables

Two hundred sixteen patients started the follow-up. One hundred ninety-nine (92%) were women. Two hundred nine patients (96%) were white, with the remaining consisting of 3 Afro-Caribbeans, 2 Hispanics, and 2 Arabic. The age at baseline was 49 (15) years, and the follow-up after SLE diagnosis was 11 (0–37) years (Table I).

Cardiovascular risk factors

Traditional CV risk factors were frequent in our cohort, with 162 (74.7%) patients presenting at least one CVRF: HTN 32.7%, hypercholesterolaemia 34.1%, tobacco use 50.2%, overweight-obesity 50.9%, family history of premature CV disease 11.5%, DM 3.2%. 205 patients (95%) had a SCORE between 0 and 4 and 11 patients (5%) had a SCORE ≥5. Previous CV events were present in 26 (12%) patients: CVD in 19 (8.8%), IHD in 6 (2.8%) and PAD in 3 (1.4%). Two patients suffered two or more CV events: one with PAD and CVD and another with IHD and CVD; 72 (33.3%) patients had been treated with statins, 103 (47.7%) with antiaggregants and 26 (12%) with anticoagulants (Table I).

Baseline SLE-related variables and lupus flares

At baseline, 21 (9.7%) patients had an SLEDAI ≥6 and 104 (48.1%) were inactive with a SLEDAI score of 0. APS was diagnosed in 21 (9.7%) patients. 60 (27.6%) patients had been diagnosed of lupus nephritis (in 6 patients, lupus nephritis was active at the time of inclusion in the study). 5 (2.3%) patients had been previously diagnosed of NPSLE. The baseline SDI was 0 in 98 (45.2%) patients, 53 (24.4%) patients had a SDI index of 1 and 65 (30.4%) patients had a SDI >1. Thirty-nine patients suffered at least one lupus flare during follow-up (range 1 to 4 lupus flares).

Regarding SLE treatments, 191 (88.4%) patients had received prednisone with a mean maximum dose ever received 30.8 (25.9) mg/d, mean daily dose at baseline 5.6 (8.2) mg/d and median cumulative prednisone dose 7.32 (0–177.6) g. Hydroxychloroquine was used in 193 (89.3%), cyclophosphamide in 52 (24%), mycophenolate in 34 (15.7%) and azathioprine in 64 (29.7%) (Table I).

Cardiovascular events and mortality

Follow-up data were available for 212 (98.1%) patients, with 1016 patient/year observation; 4 patients discontinued follow-up. Among them, 186 (88%) patients survived during the whole follow-up period without suffering any AVE. 18 AVE were identified in 17 patients: 11 cerebrovascular events, 4 coronary events, 2 peripheral arterial disease events and 1 sudden death, with one patient presenting two angina pectoris episodes requiring percutaneous coronary interventions during follow-up. Fourteen patients died during the follow-up: 6 because of AVE or their sequelae, 4 due to cancer and 4 due to cardio-respiratory failure (Table II). The age at the time of death was 74 (14) years, and the age at the time of the AVE was 66 (16) years (Table II).

Ankle-brachial index

The baseline prevalence of abnormal ABI was 24.1%, being more prevalent in males (6/17, 35.3%) than females (46/199, 23.1%). In patients who suffered AVE during follow-up, 41.2% had a normal ABI while 58.8% had an abnormal ABI. In patients who remained free of AVE during follow-up, 79% had a normal ABI while 21% had an abnormal ABI. In the analysis structured by the type of AVE we observe the following findings: in patients with IHD and sudden death 100% had an abnormal ABI; in patients with CVD 54.5% had a normal ABI and 45.5% had an abnormal ABI; and in patients with PAD 50% had a normal ABI and 50% had an abnormal ABI (Table III).

Table II. Mortality causes.

Death causes	n (%)	Types
Arterial vascular events	6	4 cerebrovascular events 1 acute myocardial infarction 1 sudden death
Malignant neoplasm	4	2 lung cancer 1 gastrointestinal cancer 1 lymphoma
Other causes	4	1 interstitial lung disease 1 pulmonary hypertension 1 disseminated infection 1 multiple organ failure (at 90 years of age)

Table III. Arterial vascular events and ABI.

	Patients	Normal ABI	Abnormal ABI
All vascular events	17/212 (8.01%)	7/17 (41.2%)	10/17 (58.8%)
Cerebrovascular event: - Cerebrovascular accident (10) - Transient ischaemic attack (1)	11/212 (5.18%)	6/11 (54.5%)	5/11 (45.5%)
Coronary events (3 patients) - Acute myocardial infarction (2) - Angina pectoris with angioplasty (2)	4/212 (1.88%)	0/3 (0%)	3/3 (100%)
Peripheral arterial disease	2/212 (0.94%)	1/2 (50%)	1/2 (50%)
Sudden death	1/212 (0.47%)	0/1 (0%)	1/1 (100%)
No vascular event during follow-up	**195/212 (91.98%)**	**154/195 (79%)**	**41/195 (21%)**

Table IV. Competing risk regression: abnormal ABI.

Variable	SHR	*p*-value	95% CI
Female	0.22	0.017	0.07-0.77
Family history of early thrombosis	5.44	0.004	1.69-17.51
Previous thrombosis	5.01	0.007	1.55-16.19
Cumulative dose of prednisone	1.01	0.007	1.005-1.031
Abnormal ABI	2.65	0.089	0.86-8.14

SHR: subdistribution hazard ratio; ABI: ankle-brachial index.

Multivariate analysis

In the final model, the risk factors associated to cardiovascular events were family history of early thrombosis (SHR 5.44 [1.69-17.51]; p=0.004), personal history of previous arterial thrombosis (SHR 5.01 [1.55-16.19]; p=0.007) and cumulative dose of corticosteroids (in prednisone gram equivalents) (SHR 1.01 [1.005-1.031]; p=0.007). An abnormal baseline ABI showed a SHR 2.65 [95% confidence interval 0.86-8.14]; p=0.089. As a protective factor we identify the female sex (SHR 0.22 [0.07-0.77]; p=0.017) (Table IV).

Discussion

In the main objective of the study, we have found a clear statistical trend but not an association between abnormal ABI and risk of AVE. As secondary objectives of the study, we identified a set of risk factors to suffer AVE in SLE patients: family history of premature AVE, previous cardiovascular disease, male gender and higher cumulative glucocorticoids dose.

Although the results do not conclusively confirm the utility of the ABI as a predictor of AVE, we think that this

clear statistical trend observed should be taken into consideration, bearing in mind the relatively low power of the study, due to the small number of patients included in the study and the small number of events occurring during the 5-year follow-up time. In the studies that found association in the general population between the abnormal ABI and the risk of AVE, the number of participants was much higher, including thousands of patients, and with a longer follow-up, as can be seen in different cohorts or systematic reviews (23-26). For all these reasons we can neither confirm nor rule out a possible association between an abnormal ABI and a higher risk of AVE in SLE patients.

In the lupus population, only one study had, to our knowledge, a similar design. In a prospective cohort study, Kao *et al*. (15) investigated the association between the presence of carotid plaque, detected by using B-model ultrasound, and incident cardiovascular events: myocardial infarction, coronary angioplasty, coronary artery bypass graft, fatal cardiac arrest and cerebrovascular accident. All patients were women without previous cardiovascular disease, unlike our study cohort. The presence of carotid plaque (HR 4.67, 95% CI 1.41–15.53, p=0.01) and the duration of corticosteroid use (HR 1.08, 95% CI 1.03–1.13, p<0.01) were both associated with an increased risk for vascular events. The family history of AVE was analysed but was found non-significant.

In Schoenfeld's systematic review, only 9/20 of the studies took into account family history of premature AVE (1), and only in one of them a statistically significant association with IHD was shown in the multivariable analysis (26). In our cohort, family history of premature AVE was actually the predictor with the highest SHR. This is in keeping with large cohorts studies in the general population, in which this variable has been related to an increased risk of arterial events; indeed, family history of premature cardiovascular disease has been used for the stratification of total cardiovascular risk in the 2013 European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) guidelines for the management of arterial hypertension (27).

In many studies designed to identify risk factors for AVE in SLE patients, patients with previous vascular disease have been excluded, whilst in the general population a history of arterial thrombosis conferred a very high cardiovascular risk (27). Patients with previous thrombosis had a 5-fold higher risk of AVE in the final model of our study.

Also, male gender was independently associated with an increased risk of arterial events. This finding is not reported in many of the studies of vascular disease in SLE because have been conducted in exclusively female populations (1), but is consistent with the results obtained in some SLE cohort and population-based studies (28-30), in the general population (31) and in other inflammatory rheumatic diseases (32).

The effect of glucocorticoids on the cardiovascular risk of SLE patients is complex. On the one hand, glucocorticoids can control lupus activity, which is a cause of premature atherosclerosis. On the other hand, the metabolic side effects of glucocorticoid can themselves increase cardiovascular risk (33), taking into account that the dose/toxicity gradient is not linear: damage risk increases with doses of prednisone over 7.5 mg/d, reaching maximum levels with doses over 30 mg/d (34). Thus, it is not surprising that studies analysing the relation of glucocorticoid therapy with cardiovascular disease have yielded heterogeneous results (1). In this study we built three different variables to model the effect of glucocorticoids on AVE: the maximum dose received during the follow-up, the average daily dose and the total cumulative dose. Only the cumulative total dose was identified as a risk factor, with each increase of 10 g over the mean of the whole cohort, 18.7g, resulting in an increased risk for AVE of around 2%. This is in keeping with a recent study from our cohort, in which a reduced dose glucocorticoid regime resulted in a significant decrease in cardiovascular damage after 5 years of follow-up (35). More recently, a longitudinal cohort study in Chinese SLE patients from Hong-Kong has shown that those receiving doses of prednisone ≥0.6 mg/kg/day for 4 weeks or longer were 14-fold more likely to die during the follow-up (36).

Our study has some limitations. When interpreting our results it must be taken into account the fact that our population was mainly constituted by Caucasians living in a country with a low general cardiovascular risk. Almost 90% of our patients received treatment with hydroxychloroquine, and the doses of prednisone were low compared with other cohorts (33). In probable relation with all this, the absolute number of AVE was low, a fact that could have reduced the study power to identify risk factors for arterial events. Another limitation is the number of patients included and the time of follow-up. Probably these two factors also limit the study power.

Among the strengths of our study, it should be emphasised the use of detailed information on clinical and immunological SLE variables, treatments administered and internationally agreed upon cardiovascular risk factors. Follow-up data were available for more than 98% of the 216 patients included in the original study. The statistical analysis was performed using the CRR approach, which substantially reduces bias associated with unreliable assumptions about the censoring profiles common in classical survival studies.

Of course, the findings obtained should be confirmed by other cohorts. A longer follow-up of this cohort can give us a future answer to the question of the prognostic utility of ABI for AVE in patients with SLE.

In summary, we have found that male gender, higher cumulative prednisone dose, family history of early vascular disease and personal history of arterial vascular disease are related to a higher risk for AVE in SLE patients. Regarding the ABI, we can consider carrying out this test, because could be useful to identify patients with SLE with a possible higher risk of AVE. In patients who present the previous factors, a more aggressive control of modifiable cardiovascular risk factors should be accomplished.

References

1. 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.
2. ERDOZAIN JG, VILLAR I, NIETO J, RUIZ-IRASTORZA G: Peripheral arterial disease in systemic lupus erythematosus: prevalence and risk factors. *J Rheumatol* 2014; 41: 310-17.
3. CHUANG YW, YU MC, LIN CL, YU TM, SHU KH, KAO CH: Risk of peripheral arterial occlusive disease in patients with systemic lupus erythematosus: a nationwide population-based cohort study. *Medicine* (Baltimore) 2015; 94: e2121.
4. 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.
5. WARD MM: Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum* 1999; 42: 338-46.
6. MCMAHON M, SKAGGS B: Pathogenesis and treatment of atherosclerosis in lupus. *Rheum Dis Clin North Am* 2014; 40: 475-95
7. KAY SD, POULSEN MK, DIEDERICHSEN AC, VOSS A: Coronary, carotid, and lower-extremity atherosclerosis and their interrelationship in Danish patients with systemic lupus erythematosus. *J Rheumatol* 2016; 43: 315-22
8. YURKOVICH M, VOSTRETSOVA K, CHEN W, AVIÑA-ZUBIETA JA: 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.
9. ESMAEILBEIGI F, POPE JE: Appropriate cardiovascular disease risk assessment in systemic lupus erythematosus may be lacking in rheumatology practice. *Clin Exp Rheumatol* 2018; 36: 526-32.
10. GAEDE P, VEDEL P, LARSEN N, JENSEN GV, PARVING HH, PEDERSEN O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348 383-93.
11. ANKLE BRACHIAL INDEX COLLABORATION: FOWKES FG, MURRAY GD, BUTCHER I *et al*.: Ankle Brachial Index combined with Framingham risk score to predict cardiovascular events and mortality. A meta-analysis. *JAMA* 2008; 300: 197-208
12. ABOYANS V, CRIQUI MH, ABRAHAM P *et al*.; AMERICAN HEART ASSOCIATION COUNCIL ON PERIPHERAL VASCULAR DISEASE, COUNCIL ON EPIDEMIOLOGY AND PREVENTION, COUNCIL ON CLINICAL CARDIOLOGY, COUNCIL ON CARDIOVASCULAR NURSING, COUNCIL ON CARDIOVASCULAR RADIOLOGY AND INTERVENTION, AND COUNCIL ON CARDIOVASCULAR SURGERY AND ANESTHESIA. MEASUREMENT AND INTERPRETATION OF THE ANKLE-BRACHIAL INDEX: A Scientific Statement From the American Heart Association. *Circulation* 2012; 126: 2890-909.
13. ROMAN MJ, SHANKER BA, DAVIS A *et al*.: Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *NEJM* 2003; 349: 2399-406
14. ASANUMA Y, OESER A, SHINTANI AK *et al*.: Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *NEJM* 2003; 349: 2407-15
15. KAO AH, LERTRATANAKUL A, ELLIOTT JR *et al*.: Relation of carotid intima-media thickness and plaque with incident cardiovascular events in women with systemic lupus erythematosus. *Am J Cardiol* 2013; 112: 1025-32.
16. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (letter). *Arthritis Rheum* 1997; 40: 1725.
17. GLADMAN D, GINZLER E, GOLDSMITH C *et al*.: The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996; 39: 363-9.
18. GLADMAN DD, IBAÑEZ D, UROWITZ MB: SLE Disease Activity Index 2000. *J Rheumatol* 2002; 29: 288-91.
19. NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP): Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106: 3143-421.
20. CONROY RM, PYÖRÄLÄ K, FITZGERALD AP *et al*.; SCORE PROJECT GROUP: Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE Project. *Eur Heart J* 2003; 24: 987-1003.
21. LAU B, COLE SR, GANGE SJ: Competing risk regression models for epidemiologic data. *Am J Epidemiol* 2009; 170: 244-56.
22. FINE JP, GRAY RJ: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94: 496-509.
23. O'HARE AM, KATZ R, SHLIPAK MG, CUSHMAN M, NEWMAN AB: Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. *Circulation* 2006; 113: 388-93.
24. DOOBAY AV, ANAND SS: Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. *Arterioscler Thromb Vasc Biol* 2005; 25: 1463-9.
25. LIN JS, OLSON CM, JOHNSON ES, WHITLOCK EP: The ankle-brachial index for peripheral artery disease screening and cardiovascular disease prediction among asymptomatic adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013; 159: 333-41.
26. HAQUE S, GORDON C, ISENBERG D *et al*.: Risk factors for clinical coronary heart disease in systemic lupus erythematosus: the lupus and atherosclerosis evaluation of risk (LASER) study. *J Rheumatol* 2010; 37: 322-29.
27. MANCIA G, FAGARD R, NARKIEWICZ K *et al*.: 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34: 2159-219.
28. UROWITZ MB, GLADMAN D, IBAÑEZ D *et al*.; FOR THE SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS: Atherosclerotic vascular events in a multinational inception cohort of systemic lupus erythematosus. *Arthritis Care Res* (Hoboken) 2010; 62: 881-87.
29. NIKPOUR M, UROWITZ MB, IBANEZ D, HARVEY PJ, GLADMAN DD: Importance of cumulative exposure to elevated cholesterol and blood pressure in development of atherosclerotic coronary artery disease in systemic lupus erythematosus: a prospective proof-of-concept cohort study. *Arthritis Res Ther* 2011; 13: R156.
30. PONS-ESTEL GJ, GONZÁLEZ LA, ZHANG J *et al*.: Predictors of cardiovascular damage in patients with systemic lupus erythematosus: data from LUMINA (LXVIII), a multiethnic US cohort. *Rheumatology* (Oxford) 2009; 48: 817-22.
31. PIEPOLI MF, HOES AW, AGEWALL S *et al*.; AUTHORS/TASK FORCE MEMBERS: 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; 37: 2315-81.
32. MARTÍN-MARTÍNEZ MA, CASTAÑEDA S, GONZÁLEZ-JUANATEY C *et al*.: Incidence of first cardiovascular event in Spanish patients with inflammatory rheumatic diseases: prospective data from the CARMA project. *Clin Exp Rheumatol* 2019; 37: 731-39
33. PARKER B, UROWITZ MB, GLADMAN DD *et al*.: Clinical associations of the metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort. *Ann Rheum Dis* 2013; 72: 1308-14.
34. RUIZ-ARRUZA I, UGARTE A, CABEZAS-RODRIGUEZ I, MEDINA JA, MORAN MA, RUIZ-IRASTORZA G: Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. *Rheumatology* (Oxford) 2014; 53: 1470-76.
35. RUIZ-ARRUZA I, LOZANO J, CABEZAS-RODRIGUEZ I *et al*.: Restrictive use of oral glucocorticoids in systemic lupus erythematosus and prevention of damage without worsening long-term disease control: an observational study. *Arthritis Care Res* 2018; 70: 582-91.
36. MOK CC, TSE SM, CHAN KL, HO LY: Effect of immunosuppressive therapies on survival of systemic lupus erythematosus: a propensity score analysis of a longitudinal cohort. *Lupus* 2018; 27: 722-27.