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The incidence of cardiovascular events in Italian patients with systemic lupus erythematosus is lower than in North European and American cohorts: implication of disease-associated and traditional risk factors as emerged by a 16-year retrospective GIRRCS study

GIRRCS=Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale

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Abstract

Previous study from our group has pointed out a lower number of cardiovascular (CV) events in Italian patients with systemic lupus erythematosus (SLE) than in North European and American ones. This study aims to assess the incidence of the first CV event in a large, multicenter, Italian cohort of patients with SLE and search for differences in disease and traditional risk factors among distinct cohorts.

Clinical charts of SLE patients consecutively admitted to 5 Italian rheumatologic centers from November 1st 2000 to December 31st 2015 and free of CV events at baseline were retrospectively studied. CV cumulative incidence (ie, the proportion of patients who experienced a new CV event over the follow-up period) and CV incidence rate (ie, the number of events in the cohort divided by the total number of years at risk) were evaluated. The detected incidences were compared with those reported in SLE cohorts from other countries.

The median duration of follow-up was 6 years (IQR=3–11). During the observational period, 37 (cumulative incidence=7.2%) patients had a first episode of CV event with an incidence rate of 10.1/1000 person-years. The CV cumulative incidence and incidence rate detected in our Italian cohort were lower than those from most North European and American cohorts, characterized by a high impact of traditional risk factors. Nevertheless, the cumulative incidence was similar to that reported in a Spanish cohort with a high frequency of traditional risk factors (geographic impact), while the incidence rate was only slightly higher than that in the Baltimore cohort, which is characterized by a strict follow-up of patients (medical impact).

Our results confirmed that Italian lupus patients have a low incidence of CV events. Moreover, the geographic origin, traditional risk factors, and medical approach appear to have an impact on CV disease in SLE.

Abbreviations: ACR = American College of Rheumatology, aPL = antiphospholipid antibody, ASA = aspirin, CV = cardiovascular, HCQ = hydroxychloroquine, SCORE = Systematic COronary Risk Evaluation, SLE = systemic lupus erythematosus.

Keywords: cardiovascular events, incidence, systemic lupus erythematosus

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1. Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous chronic autoimmune disease that has an important impact on life expectancy.[1] Currently, effective management of active disease manifestations has improved the survival rate in patients with SLE. As a consequence, the mortality pattern has changed in recent years and, nowadays, cardiovascular (CV) disease is the leading cause of premature death among SLE patients.[2,3]

We have recently explored the role of traditional and disease-related CV risk factors and aspirin (ASA) ± hydroxychloroquine (HCQ) treatment in the occurrence of CV events in patients with SLE.[4–6] We detected that ASA treatment and HCQ use for more than 5 years were protective against thrombosis. Moreover, patients with a first CV event compared with those without any thrombotic events were antiphospholipid antibody (aPL) positive and had significantly higher disease damage, higher blood pressure, and hypercholesterolemia.

Looking at data from these studies, we were impressed by the low incidence of CV events in our SLE cohort. Over the last decades, several studies have analyzed the incidence of CV events in SLE patients. However, the majority of them have been conducted in American[7–9] and North European countries.[10,11] In that regard, geography and ethnic background might play a role. Actually, the only available study from Mediterranean countries[12] has pointed out a lower incidence of CV events in Spanish patients with respect to those from North Europe and America.

At the best of our knowledge, no studies have considered cumulative incidence and incidence rate of CV events in Italy. The present study is devoted to estimate the incidence of a first ever CV event in Italian lupus patients from 5 rheumatologic tertiary units from North, Centre, and South Italy.

2. Materials and methods

2.1. Patients and study design

Consecutive adult patients with SLE seen at the 5 Italian participating centers from November 1st 2000 to December 31st 2015 were considered for the study. Centers were widely distributed across the country (1 from North, 2 from Center, and 2 from South Italy). Patients were enrolled if, at admission, 1997 updated American College of Rheumatology (ACR) criteria for SLE[13] and/or the 2012 classification criteria of the Systemic Lupus International Collaborating Clinics group[14] were satisfied and no CV event had been previously experienced.

The follow-up started at the first visit and ended at the time of the first CV event, or death or at the last observation in patients who did not experience any thrombotic event. Written informed consent was obtained by each patient. The study was approved by local Ethics Committees (CE 278\17).

2.2. Clinical and laboratory data collection

Data recorded included demographics, clinical features, exposure to drugs, and serologic investigations carried out to assess disease activity by the Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index[15] and disease damage by the Systemic Lupus International Collaborating Clinics group/ACR damage Index (SDI).[16] Antinuclear and anti-dsDNA antibodies were detected by immunofluorescence using HEp-2 cells and *Crithidia luciliae* as substrate[17]; aPL positivity was defined when at least one of the following was detected at medium-high titers on 2 or more occasions at least 12 weeks apart: lupus anticoagulant, anticardiolipin, and anti-β2 glycoprotein I antibodies (IgG and IgM).

The following traditional CV risk factors were registered: smoking status, dyslipidemia (low-density lipoprotein >120 mg/dL and/or triglycerides >150 mg/dL and/or intake of lipid-lowering drugs), diabetes (2 fasting serum glucose levels >126 mg/dL and/or antidiabetic drugs), arterial hypertension (blood pressure ≥130 e/o 85 mm Hg on 2 occasions and/or intake of antihypertensive drugs), and obesity (BMI > 30) and were considered to be present if they were observed at any time during the follow-up period.[17] Systematic COronary Risk Evaluation (SCORE), using the charts of low risk European countries, was assessed to assign patients to the appropriate 10 year-risk category at baseline.[18]

According to the ACR guidelines for referral and management of SLE,[19] each patient was subclassified as severe if any of the following conditions had occurred at baseline: peripheral or central nervous system disease (eg, psychosis, confusion, disorientation, paresthesias, seizure, cognitive dysfunction, severe unremitting headache, and retinal vasculitis), glomerulonephritis, heart and lung parenchymal manifestations, hemolytic, or aplastic anemia. Moreover, treatments with ASA, HCQ, and/or statins were recorded.

2.3. Outcome variables

Patients were assessed every 6 months, unless requiring more frequent visits for their clinical condition. At each visit, any intervening CV event was recorded.

A CV event was defined as the presence of at least one of the following[20]:

(1) Ischemic heart disease, including angina pectoris (confirmed by exercise stress test) or MI (confirmed by electrocardiography and cardiac enzymes).
(2) Ischemic cerebrovascular disease, including transient ischemic attack or stroke supported by an imaging procedure (ie, computed tomography angiography or magnetic resonance angiography).
(3) Ischemic peripheral vascular disease: intermitted claudication or peripheral arterial thrombosis, confirmed by an imaging procedure (angiography or Doppler flow studies).

Patients with any CV event occurred prior to the first visit were excluded.

2.4. CV event incidence

Cumulative incidence (ie, the proportion of patients who experienced a new CV event over the follow-up period) and incidence rates (ie, the number of events observed divided by the total number of person-years at risk, expressed as n/1000 person-years of observation) of all and each CV event were calculated. Data from the Italian registry Progetto Cuore[21] were used to compare the incidence of ischemic coronary and cerebral events observed with those of the Italian general population. Moreover, the detected incidences were compared with those reported in other European (Spanish and Swedish)[10–12] and American (from Maryland, Alabama, and Wisconsin)[7–9] SLE cohorts in which the respective item had been evaluated. In addition, baseline characteristics and traditional risk-factors between patients with and without CV events and among the distinct cohorts were compared.

2.5. Statistical analysis

Continuous variables are presented as the mean ± SD if normally distributed or as median and quartiles (IQR) if distribution was skewed. Continuous variables were analyzed with Student unpaired *t* test or with the Mann–Whitney *U* test as appropriate. The Chi-square test or Fisher exact test was applied for categorical variables. Cox regression analysis was carried out to identify factors independently associated with CV event occurrence. A *P* value <.05 was considered significant. MedCalc software, version 15.4, was used for all analyses.

3. Results

3.1. Baseline data

Table 1 lists the main epidemiological, serological, and clinical features of the 507 patients considered in the present study. Most (92.8%) were women, with a median (IQR) age at study entry of 39 (31–49) years, a median SLEDAI of 2 (IQR 0–4), and a median SDI of 0 (IQR 0–0). High levels of total serum cholesterol and triglycerides were observed in 74 (14.5%) and 37 (7.2%) patients, respectively. Fifty-nine patients (11.6%) had a body mass index >30 and 135 (26.6%) had smoked before their entry into the study. Arterial hypertension was detected in 101 (19.9%) patients, while type II diabetes mellitus in 16 (3.1%) patients. Two hundred and forty-six patients (48.5%) had a severe disease and 137 (27%) were aPL positive. Median SCORE index was 0% (0–1). A total of 302 (59.5%) patients was treated with ASA: 258 (50.8%) patients received both ASA and HCQ, whereas 44 (8.6%) received ASA alone. A total of 173 (34.1%) patients were treated with HCQ alone and 32 (6.3%) patients received neither ASA nor HCQ.

3.2. CV events

The median duration of follow-up was 6 years (IQR = 3–11) with a total of 3659 person-years. Thirty-seven patients (cumulative incidence = 7.2%) had a first CV event with an incidence rate of 10.1/1000 person-years. No difference was detected in the cumulative incidence neither in the incidence rate of the first CV events among patients from North, Centre, and South Italy. Therefore, patients were collectively analyzed.

The average (±SD) age at the first CV event was 47 (±13) years and the event occurred after a median follow-up of 5.6 years. Ischemic heart disease was the most frequent CV event (21/37; 56.7%) with an incidence rate of 5.7/1000 person-years, followed by ischemic cerebrovascular disease (11/37; 29.7%; 3.0/1000 person-years) and ischemic peripheral vascular disease (5/37; 13.5%; 1.3/1000 person-years).

3.3. Predictors of CV events

Table 1 also shows the characteristics of SLE patients who had CV events compared with all other patients. Subjects who developed a first CV event were mostly male, had a higher prevalence of arterial hypertension, high cholesterol levels,

Table 1

Baseline characteristics of patients (values in bold are statistically significant at an alpha of .05).

	All patients N = 507	Patients who developed a CV event N = 37	Patients free of CV events N = 470	*P*
Traditional risk factors				
Male gender (n, %)	36 (7.1%)	6 (16.2%)	30 (6.3%)	**.025**
Age, y (median, IQR)	39 (31–49)	45 (35–53)	39 (31–49)	>.05
Smokers (n, %)	135 (26.6%)	14 (37.8%)	121 (25.7%)	>.05
Obesity (n,%)	59 (11.6%)	7 (18.9%)	52 (11.0%)	>.05
Hypertension (n, %)	101 (19.9%)	20 (54.0%)	81 (17.2%)	**<.0001**
Hypercholesterolemia (n, %)	74 (14.5%)	12 (32.4%)	62 (13.1%)	**.001**
Hypertriglyceridemia (n, %)	37 (7.2%)	5 (13.5%)	32 (6.8%)	>.05
Diabetes (n, %)	16 (3.1%)	2 (5.4%)	14 (2.9%)	>.05
SCORE (median, IQR)	0 (0–1)	0 (0–1)	0 (0–1)	>.05
Lupus manifestations				
Severe SLE (n, %)	174 (34.3%)	13 (35.1%)	161 (34.2%)	>.05
Nephritis (n, %)	106 (20.9%)	6 (16.1%)	100 (21.2%)	>.05
Neurological disorders (n, %)	49 (9.6%)	8 (21.6%)	41 (8.7%)	**.010**
Lung involvement (n, %)	13 (2.5%)	2 (5.4%)	11 (2.3%)	>.05
Haemolytic anaemia (n, %)	49 (9.6%)	4 (10.8%)	45 (9.5%)	>.05
SELENA-SLEDAI (median, IQR)	2 (0–4)	2 (0–4)	2 (0–4)	>.05
SDI, (median, IQR)	0 (0-0)	0 (0-0)	0 (0-0)	>.05
Autoantibody profile				
Any aPL (n, %)	137 (27.0%)	16 (43.2%)	121 (25.7%)	**.021**
CL IgG–IgM (n, %)	104 (20.5%)	12 (32.4%)	92 (19.5%)	>.05
β2GP-1IgG–IgM (n, %)	75 (14.7%)	9 (24.3%)	66 (14.0%)	>.05
LAC (n, %)	81 (15.9%)	12 (32.4%)	69 (14.6%)	**.004**
dsDNA (n, %)	225 (44.3%)	15 (40.5%)	210 (44.6%)	>.05
Sm (n, %)	61 (12.0%)	3 (8.1%)	58 (12.3%)	>.05
Treatments				
Hydroxychloroquine (n, %)	431 (85.0%)	26 (70.2%)	405 (86.1%)	**.009**
Aspirin (n, %)	302 (59.5%)	17 (45.9%)	285 (60.6%)	.07
Statins (n, %)	60 (11.8%)	3 (8.1%)	57 (12.1%)	>.05

aPL = antiphospholipid antibody, CL = cardiolipin, CV = cardiovascular, dsDNA = doublestranded DNA, β2GP-1 = beta2glykoprotein-1, IQR = interquartile range, LAC = lupus anticoagulant test, SCORE = Systematic COronary Risk Evaluation, SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, SELENA-SLEDAI = SLE Disease Activity Index (Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index), SLE = systemic lupus erythematosus, Sm = Smith.

Table 2

Incidence rates (per 1000 person-years) and rates ratio for CV events stratified by sex and age.

	Male				Female			
	CV events/ person-years, n	Incidence rate (95% CI)	Incidence rate ratio general population (95% CI)	*P*	CV events/ person-years, n	Incidence rate (95% CI)	Incidence rate ratio general population (95% CI)	*P*
<45 y	1/89	11.3 (0.2–63.2)	2.9 (2.0–4.4)	<.001	14/1516	9.2 (5.0–15.4)	11.5 (5.5–27.4)	<.001
45–54 y	1/52	19.6 (2.8–36.1)	3.1 (2.3–4.2)	<.001	9/988	9.1 (5.7–10.8)	5.0 (3.0–8.9)	<.001
>55 y	4/102	39.0 (10.6–99.8)	2.6 (2.2–3.2)	<.001	7/822	8.5 (3.4–17.5)	1.6 (1.1–2.4)	.003

CI = confidence interval, CV = cardiovascular.

neuropsychiatric involvement, and aPLs positivity. Moreover, patients treated with ASA and HCQ had a lower incidence of CV events. At stratified analyses, there was statistically significant effect modification by sex and age. Although the absolute rate was highest among the oldest males (for age group >55 years), the relative incidence rate was highest for females <45 years old compared with the general population matched for age and sex (Table 2). At univariate analysis (Table 3), patients with a first CV event compared with those without any thrombotic events were smokers, had significantly higher blood pressure, higher SCORE index, and BMI ($P = .026$, $P = .001$, $P < .0001$, an $P = .049$, respectively). Of SLE manifestations, aPL positivity, higher disease damage at last visit, and neurolupus were more frequently observed in patients with CV disease ($P = .005$, $P = .01$, and $P = .005$, respectively). Moreover, ASA treatment ($P = .038$) and HCQ use ($P = .001$) were negative predictors. All other variables examined, including statins, hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, disease activity at first and last visit, baseline disease damage, other severe SLE manifestations, were not associated, either positively or negatively, with the occurrence of CV events. At a multivariable Cox regression model (Table 4), aPL positivity (HR 4.77, 95% CI 2.26–10.08), smoking (HR 2.49, 95% CI 1.23–5.01), and hypertension (HR 2.50, 95% CI 1.16–5.37) were independent predictors of the first CV event, while taking ASA and HCQ was protective against thrombosis (HR 0.28, 95% CI 0.13–0.57, and HR 0.23, 95% CI 0.11–0.50, respectively).

Table 3

Factors predicting the occurrence of a first cardiovascular event during follow-up in univariate analysis (values in bold are statistically significant at an alpha of .05).

Features	*P* value	Hazard ratio	95% CI
High cumulative steroids dose	.203	1.52	0.79–2.92
Hypertension (ever)	**.001**	**3.04**	**1.52–6.06**
aPL positivity (ever)	**.005**	**2.54**	**1.31–4.89**
CL IgG–IgM	**.0009**	**2.98**	**1.56–5.70**
β2GP-1 IgG–IgM	**.002**	**2.84**	**1.46–5.52**
LAC	**.003**	**2.66**	**1.39–5.08**
Cumulative damage at first visit	.411	0.90	0.69–1.15
Cumulative damage at last visit	**.010**	**1.40**	**1.08–1.83**
Smoke (ever)	**.026**	**2.04**	**1.08–3.86**
Hypercholesterolemia (ever)	.092	1.74	0.91–3.32
Obesity (ever)	**.049**	**1.99**	**1.01–3.98**
Hypertriglyceridaemia (ever)	.087	1.92	0.90–4.08
Diabetes mellitus (ever)	.198	1.97	0.69–5.58
Severe SLE (ever)	.800	1.08	0.56–2.08
Haemolytic anaemia	.318	1.52	0.66–3.46
Neurological disorders	**.005**	**2.59**	**1.32–5.10**
Lung involvement	.827	0.85	0.20–3.54
Nephritis	.274	0.67	0.33–1.36
SLEDAI first visit	.081	1.05	0.99–1.12
SLEDAI last visit	.427	1.03	0.94–1.12
SCORE index	**<.0001**	**1.89**	**1.39–2.56**
Aspirin	**.038**	**0.50**	**0.26–0.96**
Hydroxychloroquine	**.001**	**0.32**	**0.16–0.66**
Statins	.336	0.56	0.17–1.82

aPL = antiphospholipid antibody, CL = cardiolipin, β2GP-1 = beta2glykoprotein-1, LAC = lupus anticoagulant test, SCORE = Systematic COronary Risk Evaluation, SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, SELENA-SLEDAI = SLE Disease Activity Index (Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index), SLE = systemic lupus erythematosus.

3.4. Comparison with general population

To compare the CV ischemic morbidity in our cohort with that expected in a sample of the Italian population matched for age and traditional risk factors, we calculated the expected 10-year incidence rate of CV events in our patients according to the risk score from Progetto Cuore.[21] Rate of ischemic events observed in our SLE cohort was 12-fold higher than that expected in the age and sex-matched Italian population (0.8/1000 person-years; $P < .0001$).

3.5. Comparison with other lupus cohorts

We compared baseline characteristics, CV cumulative incidence, and incidence rates detected in our cohort with those from other European (Spanish and Swedish)[10–12] and American (from Maryland, Alabama, and Wisconsin)[7–9] cohorts (Table 5). Significant differences were detected in the prevalences of males, smokers, hypertensive, and hypercholesterolemic patients. In particular, cohorts from Spain and Sweden had a high prevalence of smoking ($P < .0001$), hypertension ($P < .0001$), and dyslipidemia ($P = .0002$). Patients from Wisconsin cohort were more likely to smoke ($P < .0001$), while patients from Alabama cohort were more likely to present hypertension ($P < .0001$). Males were

Table 4

Factors predicting the occurrence of a first cardiovascular event during follow-up in multivariable analysis (values in bold are statistically significant at an alpha of .05).

Features	*P*	Hazard ratio	95% CI
Hypertension	**.018**	**2.50**	**1.16–5.37**
aPL positivity	**<.0001**	**4.77**	**2.26–10.08**
Cumulative damage at last visit	.375	1.15	0.83–1.60
Smoke	**.010**	**2.49**	**1.23–5.01**
Obesity	.966	0.96	0.45–2.07
Neurolupus	.067	1.96	0.95–4.03
SCORE index at baseline	.29	0.73	0.41–1.29
Aspirin	**.0005**	**0.28**	**0.13–0.57**
Hydroxychloroquine	**.0002**	**0.23**	**0.11–0.50**

aPL = antiphospholipid antibodies, CI = confidence interval, SCORE = Systematic COronary Risk Evaluation.

Table 5

Comparison of characteristics among patients from different SLE cohorts (values in bold are statistically significant at an alpha of .05).

	Our cohort N = 507	Spain[12] N = 3649	Sweden[10] N = 182	Maryland[7] N = 1874	Alabama[8] N = 1333	Wisconsin [9] N = 70
Male gender (n, %)	36 (7.1%)	353 (9.7%)	18 (10%)	136 (7.2%)	127 (9.6%)	**13 (18.5%)**
Age, y						
(median, IQR)	39 (31–49)	45 (35–56)	45 (31–53)	–	–	**52**
(mean, SD)	45, 12.6	–	–	37,12	35.7,12.3	–
Etnicity						
White European (n, %)	507	3300 (90.4%)	171 (94%)		0	0
White Americans (n, %)	0	185 (5.1%)	0		640 (46.5%)	68 (97%)
Black n, %)	0	8 (0.2%)	0		472 (35.6%)	0
Asians (n, %)	0	21 (0.6%)	11 (6%)		0	0
Hispanics (n, %)	0	0	0		241 (18.1%)	0
Other (n, %)	0	29 (0.8%)	0		0	2 (3%)
Smokers (n, %)	135 (26.6%)	**1350 (37%)**	**92 (51%)**		**215 (16.1%)**	**37 (52.9%)**
Hypertension (n, %)	101 (19.9%)	**1061 (29.1%)**	**54 (30%)**		**687 (51.5%)**	17 (24%)
Dyslipidemia (n, %)	111 (21.8%)	**1100 (30.1%)**	–		–	9 (13%)
Diabetes (n, %)	16 (3.1%)	**1086 (29.8%)**	4 (2%)		–	5 (7%)
HCQ (n, %)	431 (85%)	**2878 (78.9%)**	**52 (29%)**	–	**1075 (80%)**	**52 (75%)**
Aspirin (n, %)	302 (59.5%)	**1091 (29.9%)**	**34 (19%)**	–	**382 (28.6%)**	–
Events (n, %)	37 (7%)	269 (7.4%)	**24 (13%)**	134 (7%)	**123 (9.8%)**	**17 (24%)**
First CV event	Yes	Yes	Yes	Yes	Yes	No
Mean follow-up, y	6	–	8.3	–	6.4	7.7
Person-years	3659	–	–	9485	–	540
Incidence rate (1000 py)	10.1	–	–	**14.1**	–	**31.4**

CV = cardiovascular, HCQ = hydroxychloroquine, IQR = interquartile range, SD = standard deviation, SLE = systemic lupus erythematosus.

more frequent in Wisconsin cohort ($P = .001$). Moreover, in our cohort the majority of patients were treated with HCQ and ASA ($P < .0001$).

As far as the incidence rate, because of the unavailability of person-years follow-up in Spanish, Swedish, and Alabama cohort, the comparison was only feasible with cohorts from Maryland and Wisconsin. The incidence rate ratio resulted to be significantly higher in the Wisconsin cohort (31.4/1000 person-years; ratio = 3.11; IC95% 1.64–5.66; $P < .0001$) and nearly significantly higher in the Maryland cohort (14.1/1000 person-years; ratio = 1.39; IC95% 0.96–2.06; P.070) with respect to our cohort (10.1/1000 person-years).

4. Discussion

The present study is mainly devoted to investigate the incidence of CV events in Italian SLE patients, to compare it with those registered in SLE cohorts from other countries, and to search for features associated with and potentially causative of the detected differences.

We were moved to undergo this study by the low incidence of CV events detected in our 3 previous studies.[4–6] Since these studies had been mostly based on SLE cohorts from South Italy, we enrolled patients from North, Center, and South Italy. The present report confirms the results from our previous studies, that is, arterial hypertension and hypercholesterolemia among traditional risk factors, aPL positivity, and neurological involvement as disease-related factor are more frequent in patients undergoing a first CV event; ASA and HCQ play a preventative role. Moreover, no difference emerged in the cumulative incidence and incidence rates of CV events among the 3 subgroups. Therefore, we think that our results are generalizable to the Italian SLE population seen in outpatient care in the last decades.

The cumulative incidence of CV events detected in our cohort resulted to be 7.2%, which is similar to that reported in previous studies published in other Mediterranean countries[12] and in the Maryland cohort,[7] but lower than those registered in other European and American SLE cohorts,[8–10] which ranged from 9.8% to 24%. Although some differences could be due to the varying clinical definitions used for CV events and study design, our incidence still remained low. These disparities could be ascribed to the differences in the prevalences of traditional risk factors (namely, smoking, hypertension, and hypercholesterolemia) among the distinct cohorts and on the use in a high percentage of our patients of ASA and HCQ. Nevertheless, geographic and local medical factors deserve to be considered.

As far as the former, the cumulative incidence of CV events detected in our patients was very similar to that detected in the Spanish cohort, despite the higher frequency of traditional risk factors and the lower prevalence of ASA-HCQ use in that cohort. Fernández-Nebro et al[12] ascribed their results to yet undefined racial-geographical factors collectively referred to as the "Mediterranean paradox," by which the incidence of CV events is dissociated from CV risk factors compared with other industrialized countries. Such a hypothesis may, at least in part, be consistent with our data. Actually, Mediterranean diet has been reported to be associated with a lower incidence of CV events in the general population.[24] Nevertheless, factors associated with and potentially causative of the so called "Mediterranean Paradox" in SLE patients await to be explained.

The influence of the racial background on the disease pattern in patients with SLE has been already reported.[22] Reasons for such significant differences are not clear but American Black and Hispanic patients have been shown to have an early age and aggressive disease at onset of SLE. In addition, the risk of CV disease was reported to be elevated among blacks, compared to whites.[23] These aspects have been ascribed to socioeconomic status, but race-related factors might play a role.

The lower incidence of CV events in our SLE series mirrors the lower incidence of CV disease in the general population as compared with Northern Europe and United States.[24,25]

Nevertheless, our lupus patients were 12.5-fold more likely to have a CV event compared with the general population, confirming the increased CV risk in SLE. In particular, the average age at the first CV event was 47 years, whereas in the non-SLE population this occurred later.[26] Interestingly, although younger SLE patients were at higher relative risk of CV events compared with healthy controls, the highest rate of CV events was observed in older male patients, suggesting that prevention of CV complications would be important in every SLE age group.

As far as local medical factors are concerned, the incidence rate detected by us (10.1/1000 person-years) was only nearly significantly lower than that in Maryland cohort. Unlike other cohorts, patients from Maryland undergo a strict follow-up.[7] Actually they are examined every 3 months, which might ensue in a better control of the main traditional risk factors and of disease activity. However, even if disease activity indicates on-going inflammation which is known to be a CV risk factor,[27] at multivariable analysis, SLE Disease Activity Index was not significantly associated with CV events rates in our cohort and only mildly associated in the Maryland cohort, after adjusting for medication use. This is consistent with most of the previous studies, suggesting that an isolated assessment is not enough to identify patients at risk. However, the relatively low disease activity at baseline in our cohort might have resulted in a limited ability to detect the association between disease activity and the risk of CV events.

The strengths of the present study include the homogeneity in the ethnic composition and the large size of our sample, the long follow-up period, the multicentric design, and the use of hard endpoints. Moreover, no difference was detected in the incidence of CV events among patients from North, Center, and South Italy. This evidence suggests that the results detected in our multicenter series reflect the features of the SLE Italian patient population.

However, some limitations should be taken into account, the main one being the retrospective design of our study, which not allow addressing more detailed questions. In particular, this study was not able to exclude the impact of other factors when analyzing both the comparisons between patients with and without CV disease and among the cohorts from different countries. Moreover, the risk estimation from the European CV risk algorithm SCORE, which was developed for use in the general population, deviated from the observed risk, underestimating the risk of future CV events in these patients. An explanation for the results found may be that, by design, the SCORE is unlikely to identify young women as having a significant risk of CV disease. Actually, of all variables evaluated, age and sex have an important contribution to the total risk score. A further limitation is that, as the aPL positivity increased the CV risk, it is possible that not all CV events recorded in our cohort were due to atherosclerosis. However, in daily clinical practice, sometimes it is not possible to define the etiology of each CV event.

In conclusion, the geographic (ie, Mediterranean) origin, the lower prevalence of traditional risk factors and the high frequency of ASA-HCQ intake might be associated with the low incidence rate of CV event in Italy. On the other hand, the slight difference detected between our series and Maryland cohort underlines the need of a strict follow-up of the SLE patient to identify early and treat aggressively traditional risk factors, control SLE-related risk factors and disease activity. Prospective studies are needed to confirm our findings.

Author contributions

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References

[1] Lee YH, Choi SJ, Ji JD, et al. Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. Lupus 2016;25:727–34.
[2] Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) 2003;82:299–308.
[3] Bernatsky S, Boivin J-F, Joseph L, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006;54:2550–7.
[4] Iudici M, Fasano S, Gabriele Falcone L, et al. Low-dose aspirin as primary prophylaxis for cardiovascular events in systemic lupus erythematosus: a long-term retrospective cohort study. Rheumatol Oxf Engl 2016;55:1623–30.
[5] Fasano S, Pierro L, Pantano I, et al. Longterm hydroxychloroquine therapy and low-dose aspirin may have an additive effectiveness in the primary prevention of cardiovascular events in patients with systemic lupus erythematosus. J Rheumatol 2017;44:1032–8.
[6] Fasano S, Margiotta DP, Navarini L, et al. Primary prevention of cardiovascular disease in patients with systemic lupus erythematosus: case series and literature review. Lupus 2017;26:1463–72.
[7] 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.
[8] Bertoli AM, Vilá LM, Alarcón GS, et al. Factors associated with arterial vascular events in PROFILE: a Multiethnic Lupus Cohort. Lupus 2009;18:958–65.
[9] Bartels CM, Buhr KA, Goldberg JW, et al. Mortality and cardiovascular burden of systemic lupus erythematosus in a US population-based cohort. J Rheumatol 2014;41:680–7.
[10] 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.
[11] Hermansen M-L, Lindhardsen J, Torp-Pedersen C, et al. The risk of cardiovascular morbidity and cardiovascular mortality in systemic lupus erythematosus and lupus nephritis: a Danish nationwide population-based cohort study. Rheumatol Oxf Engl 2017;56:709–15.
[12] Fernández-Nebro A, Rúa-Figueroa Í, López-Longo FJ, et al. Cardiovascular events in systemic lupus erythematosus: a nationwide study in Spain From the RELESSER Registry. Medicine (Baltimore) 2015;94: e1183.
[13] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
[14] Petri M, Orbai A-M, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64:2677–86.
[15] Buyon JP, Petri MA, Kim MY, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med 2005;142:953–62.
[16] 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.

[17] Palmieri V, Migliaresi P, Orefice M, et al. High prevalence of subclinical cardiovascular abnormalities in patients with systemic lupus erythematosus in spite of a very low clinical damage index. Nutr Metab Cardiovasc Dis 2009;19:234–40.
[18] Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987–1003.
[19] American College of Rheumatology ad hoc committee on Systemic Lupus Erythematosus guidelinesGuidelines for referral and management of systemic lupus erythematosus in adults. Arthritis Rheum 1999; 42:1785–96.
[20] Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156: 871–81.
[21] http://www.cuore.iss.it/eng/default.asp. Accessed May 6, 2017.
[22] Reveille JD, Bartolucci A, Alarcón GS. Prognosis in systemic lupus erythematosus. Negative impact of increasing age at onset, black race, and thrombocytopenia, as well as causes of death. Arthritis Rheum 1990;33:37–48.
[23] Scalzi LV, Hollenbeak CS, Wang L. Racial disparities in age at time of cardiovascular events and cardiovascular-related death in patients with systemic lupus erythematosus. Arthritis Rheum 2010; 62:2767–75.
[24] Verschuren WM, Jacobs DR, Bloemberg BP, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. JAMA 1995;274:131–6.
[25] Palmieri L, Donfrancesco C, Giampaoli S, et al. Favorable cardiovascular risk profile and 10-year coronary heart disease incidence in women and men: results from the Progetto CUORE. Eur J Cardiovasc Prev Rehabil 2006;13:562–70.
[26] Tragni E, Filippi A, Casula M, et al. Risk factors distribution and cardiovascular disease prevalence in the Italian population: The CHECK study. Open Journal of Epidemiology 2012;2:90–1.
[27] McMahon M, Hahn BH, Skaggs BJ. Systemic lupus erythematosus and cardiovascular disease: prediction and potential for therapeutic intervention. Expert Rev Clin Immunol 2011;7:227–41.