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

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ABSTRACT. ***Objective.*** Systemic lupus erythematosus (SLE) is associated with an increased risk of cardiovascular disease (CVD). Thromboprophylaxis with low-dose aspirin (ASA) and hydroxychloroquine (HCQ) seems promising in SLE. We investigated the effects of HCQ cumulative dosages (c-HCQ) and the possible synergistic efficacy of ASA and HCQ in preventing a first CV event (CVE) in patients with SLE.

Methods. Patients consecutively admitted to our center who, at admission, satisfied the 1997 American College of Rheumatology and/or 2012 Systemic Lupus Collaborating Clinics classification criteria for SLE, and had not experienced any CVE, were enrolled. The occurrence of a thrombotic event, use of ASA, and c-HCQ were recorded. Kaplan-Meier analysis was performed to determine the c-HCQ associated with a lower incidence of CVE. Cox regression analysis served to identify factors associated with a first CVE.

Results. For the study, 189 patients with SLE were enrolled and monitored for 13 years (median). Ten CVE occurred during followup. At Kaplan-Meier analysis, the CVE-free rate was higher in ASA-treated patients administered a c-HCQ > 600 g (standard HCQ dose for at least 5 yrs) than in patients receiving ASA alone, or with a c-HCQ dose < 600 g (log-rank test chi-square = 4.01, p = 0.04). Multivariate analysis showed that antimalarials plus ASA protected against thrombosis (HR 0.041 and HR 0.047, respectively), while antiphospholipid antibodies (HR 17.965) and hypertension (HR 18.054) increased the risk of a first CVE.

Conclusion. Our results suggest that prolonged use of HCQ plus ASA is thromboprotective in SLE and provides additional evidence for its continued use in patients with SLE. (First Release May 15 2017; J Rheumatol 2017;44:1032–8; doi:10.3899/jrheum.161351)

Key Indexing Terms:
CARDIOVASCULAR RISK
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ASPIRIN

Accelerated atherosclerosis is one of the major causes of cardiovascular (CV) morbidity and mortality in patients with systemic lupus erythematosus (SLE). Consequently, efforts to identify treatments that can prevent thrombosis have become a priority in patients with SLE. Two drugs have been proposed to contrast accelerated atherosclerosis in SLE. Low-dose aspirin (ASA) is advocated for the primary prophylaxis of thrombosis in patients with SLE, especially in those with triple antiphospholipid antibody (aPL) positivity, lupus anticoagulant (LAC) positivity, or isolated persistent anticardiolipin antibodies (aCL) at medium–high titers[1,2], whereas hydroxychloroquine (HCQ) has been shown to reduce certain traditional CV risk factors (e.g., hyperlipidemia and diabetes)[3,4] and prevent thrombosis in patients with SLE[5,6,7,8]. However, it is not yet known when HCQ's thromboprotective effect starts and whether it is sustained over time. Further, the clinical implications of a potential synergistic effect of ASA and HCQ treatment in primary thromboprophylaxis in SLE have not yet been analyzed. We recently reported that ASA may be effective in the primary prevention of thrombosis in patients with SLE[9]. In that study, we did not detect any dose-independent protective effect of antimalarials. Our present analysis was performed to evaluate the role of HCQ cumulative dosages (c-HCQ) and the possible synergistic efficacy of ASA and HCQ therapies in the primary prevention of CV events (CVE) in patients with SLE.

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MATERIALS AND METHODS

Patients. From our database, we identified an inception cohort of patients attending the Rheumatology Unit of the Second University of Naples from November 1, 2000, to December 31, 2014, who at admission fulfilled the 1997 American College of Rheumatology (ACR) criteria for SLE[10] and/or the 2012 classification criteria of the Systemic Lupus International Collaborating Clinics group (SLICC)[11], and who had not experienced a CVE before their first clinical visit. A CVE was defined as the occurrence of angina or myocardial infarction (MI), heart failure, a transient ischemic attack (TIA), stroke, or atherosclerotic peripheral ischemia[12] identified by hospital discharge records and/or specific laboratory and radiologic tests [i.e., cerebral or myocardial imaging techniques, namely, central nervous system (CNS) computerized tomography, magnetic resonance, echocardiography, or myocardial scintigraphy]. Patients were subsequently assessed at intervals of 3–6 months, depending on their clinical condition. At each visit, any intervening CVE, as defined above[12], was recorded. The duration of followup was defined as the time from the first visit to the first CVE or to the last observation in patients without thrombosis. On June 30, 2016, each patient was contacted by telephone to ascertain vital status. Causes of death were identified from clinical records, hospital discharge, or when unavailable, by contacting the patient's relatives. The Ethics Committee of the Second University of Naples approved the study (CE1700/15).

Clinical and laboratory data. Our database contains information about each patient from admission to followup, and includes 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[13] and disease damage by the SLICC/ACR Damage Index (SDI)[14]. Antinuclear and anti-dsDNA antibodies were detected by immunofluorescence using HEp-2 cells and *Crithidia luciliae* as substrate[15]. Positive aPL was defined when at least 1 of the following was detected on 2 or more occasions at least 12 weeks apart: LAC, aCL immunoglobulin G (IgG) and IgM, and anti-β2 glycoprotein I antibodies (IgG and IgM). Traditional CV risk factors [hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, hypertension (HTN), smoking, and obesity] were present if they were observed at any time during the followup period[16]. Attempts were made to modify risk factors; patients with diabetes were treated with insulin or oral hypoglycemic agents, while those having HTN received antihypertensive therapy. We also recorded treatments with statins.

Statistical analysis. Continuous variables are presented as the mean ± SD if normally distributed or as median and quartiles if distribution was skewed. Kaplan-Meier curves and the log-rank test were used to analyze differences in event-free survival. Comparisons between groups were performed using the chi-square or Fisher's exact test for categorical variables, and using the Wilcoxon Mann-Whitney test or unpaired Student t test for continuous variables, as appropriate. Univariate Cox regression analysis served to identify factors associated with the occurrence of a CVE in the overall cohort. The factors found to be significant in univariate analysis were entered in the multivariable Cox regression model. A p value < 0.05 was considered significant. Analyses were performed with SPSS software, version 12.0.1 (SPSS Inc.).

RESULTS

Baseline data. A total of 230 consecutive patients with SLE (227 white, 1 Hispanic, 1 African descendant, and 1 Asian) were admitted to our unit from November 1, 2000, to December 31, 2014. Of these, 41 had a history of CVE and were therefore excluded; thus, 189 patients with SLE (175 women and 14 men) were included in our study. The median age at the first visit was 31 years [interquartile range (IQR) 24–39]. The main epidemiological, serological, and clinical features of the cohort at baseline are listed in Table 1. At study entry, 43 patients were aPL-positive (22.7%). In detail, a triple-positive aPL profile was found in 6 patients (3.1%) and double positivity in 15 (7.9%). Regarding traditional thrombosis risk factors at baseline, 23 patients had dyslipidemia (10 patients hypertriglyceridemia, 2 hypercholesterolemia, and 11 had both conditions), 84 patients were smokers, 49 had HTN, 8 had diabetes, and 15 had a body mass index > 30 kg/m^2. Patients were subdivided into severe and mild disease according to the ACR guidelines for the referral and management of SLE[17]. Patients with glomerulonephritis, CNS involvement, heart and lung parenchymal manifestations, and hemolytic or aplastic anemia were subclassified as having severe SLE, whereas patients with other manifestations were subclassified as having mild SLE.

Table 1. Demographic, serological, clinical, and clinometric characteristics of patients with SLE at baseline. Values are n (%) unless otherwise specified.

Characteristic	Value
Patients, n	189
Sex	
Female	175 (92.5)
Male	14 (7.4)
Age at diagnosis, yrs, median (IQR)	31 (24–39)
Autoantibody profile	
Anti-dsDNA	105 (55.5)
Anti-Sm	30 (15.8)
aPL	43 (22.7)
Severe SLE	116 (61.3)
Ever smokers	84 (44.4)
Obesity	15 (7.9)
Hypertension	49 (25.9)
Dyslipidemia	23 (12.1)
Diabetes	8 (4.2)
SELENA-SLEDAI, mean ± SD	7 ± 4.1
SDI, median (range)	0 (0–3)

SLE: systemic lupus erythematosus; IQR: interquartile range; aPL: antiphospholipid antibodies; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Followup data. Followup visits were planned every 3–6 months, depending on the patient's clinical condition. The median duration of followup was 13 years (IQR 7–16 yrs). On June 30, 2016, 12 patients (6.3%) were lost to followup. Nonlethal thrombotic manifestations occurred in 10 patients (5.2%; stroke in 1 patient, TIA in 5 patients, and acute MI in 4 patients). The median time to the occurrence of the first CVE was 5 years. Of the 189 patients, 4 (2.1%) died during the study. Cancer was the cause of death in 2 cases (1 died of lung cancer at age 61, and the other of brain cancer at age 39). Another patient died of hepatic cirrhosis at age 61. The remaining patient died of kidney failure at age 72. No deaths attributable to CV complications were observed. During followup, aPL were detected in 5 patients (2.6%), who were negative at enrollment.

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Regarding medications, 52 patients (27.5%) had been treated with high-dose steroids (cumulative dose prednisone equivalent ≥ 40 g, reported to be associated with atherosclerosis in SLE)[18]. A total of 155 patients (82%) were prescribed HCQ at a dose of 6 mg/kg of actual body weight per day (maximum daily dose prescribed: 400 mg). The median treatment duration was 5 years (IQR 2–12 yrs). A total of 164 patients (86.7%) were treated with ASA; 136 patients (71.9%) received both ASA and HCQ, whereas 28 (14.8%) received ASA alone. Nineteen patients (10%) were treated with HCQ alone and 6 (3.1%) received neither ASA nor HCQ. Patients did not receive HCQ because of retinopathy (9 patients) or because of the occurrence of side effects (7 had allergic cutaneous manifestations, 2 had myopathy associated with loss of weight, and 1 had hypertransaminasemia), whereas 15 patients failed to adhere to treatment. Regarding ASA, 15 patients did not take any dose for personal reasons and 6 patients discontinued ASA because of menorrhagia and 4 because of thrombocytopenia.

Kaplan-Meier analysis revealed a significant difference in CVE-free rates among the 4 subgroups of patients (chi-square = 14.08, p = 0.002; Figure 1). The CVE-free rate did not differ between the 136 patients treated with both ASA and HCQ and the 28 patients treated with ASA alone (Figure 2). At the Kaplan-Meier analysis performed to determine the c-HCQ associated with a lower incidence of CVE, we found a higher CVE-free rate in the 85 patients treated with ASA-HCQ who had reached a c-HCQ dosage > 600 g (which corresponded to a standard daily dose for at least 5 yrs) than in the 28 patients treated with either ASA alone or the 51 patients treated with ASA and c-HCQ < 600 g (chi-square = 4.01, p = 0.045; Figure 3). No differences in traditional and SLE-specific CV risk factors or medications (statins, high-dose steroids) were found among the 3 patient groups (Table 2).

Predictors of CVE. Features predictive of CVE at univariate analysis were reported in Supplementary Table 1 (available with the online version of this article). Patients with a CVE had significantly higher blood pressure and aPL positivity versus patients without a CVE. ASA and longterm HCQ treatment were found to be protective against CVE. All other variables examined were not associated, either positively or negatively, with the occurrence of thrombotic events: traditional CV risk factors (diabetes, smoking, obesity, hypercholesterolemia, hypertriglyceridemia), disease activity, disease damage, severe manifestations, and other medications (immunosuppressive agents, high steroids dose, antimalarials, statins).

At multivariate analysis (Supplementary Table 2, available with the online version of this article), use of HCQ for at least 5 years (HR 0.04, 95% CI 0.004–0.48) and ASA treatment (HR 0.04, 95% CI 0.003–0.54) remained significant. Moreover, aPL positivity (HR 17.96, 95% CI 1.48–217.61) and ever having HTN (HR 18.05, 95% CI 1.64–198.76) were identified as being associated with an increased risk of thrombosis.

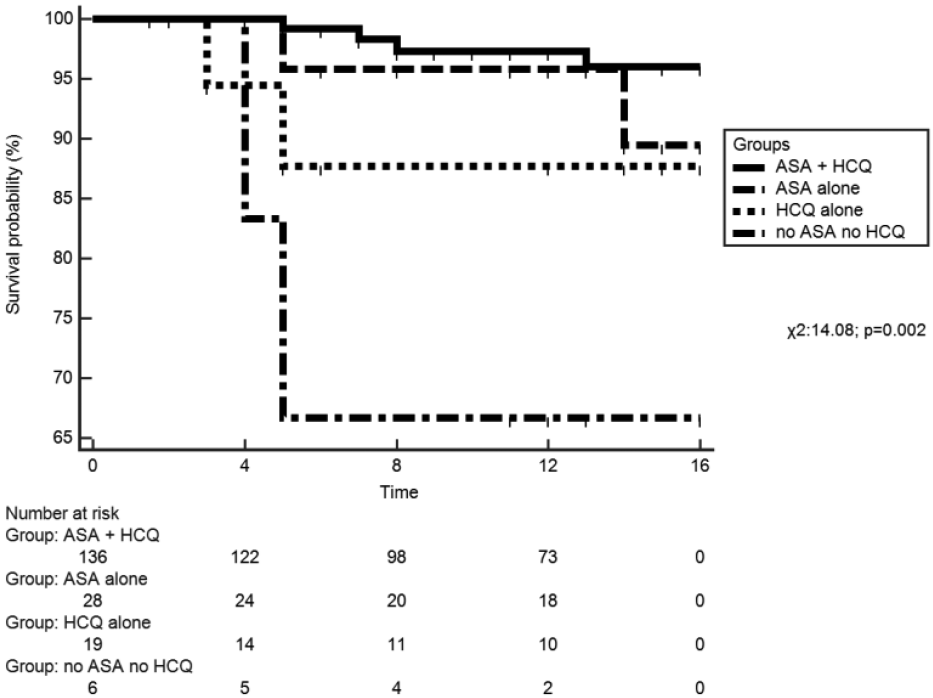

Figure 1. Kaplan-Meier survival curves by treatment groups. ASA: low-dose aspirin; HCQ: hydroxychloroquine.

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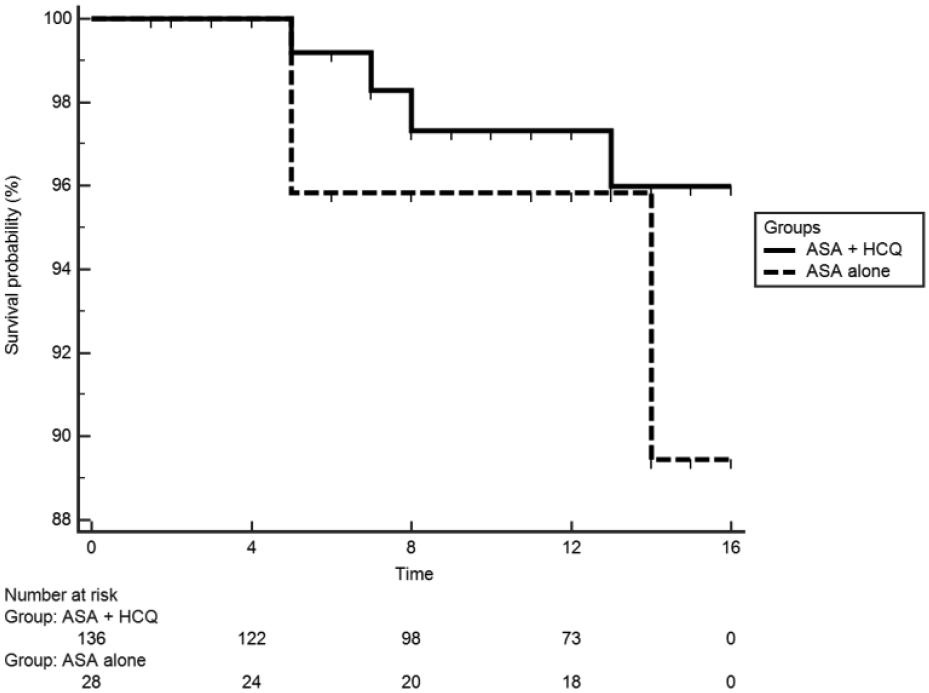

Figure 2. Rate of cardiovascular events over time in patients treated with ASA combined or not with HCQ. ASA: low-dose aspirin; HCQ: hydroxychloroquine.

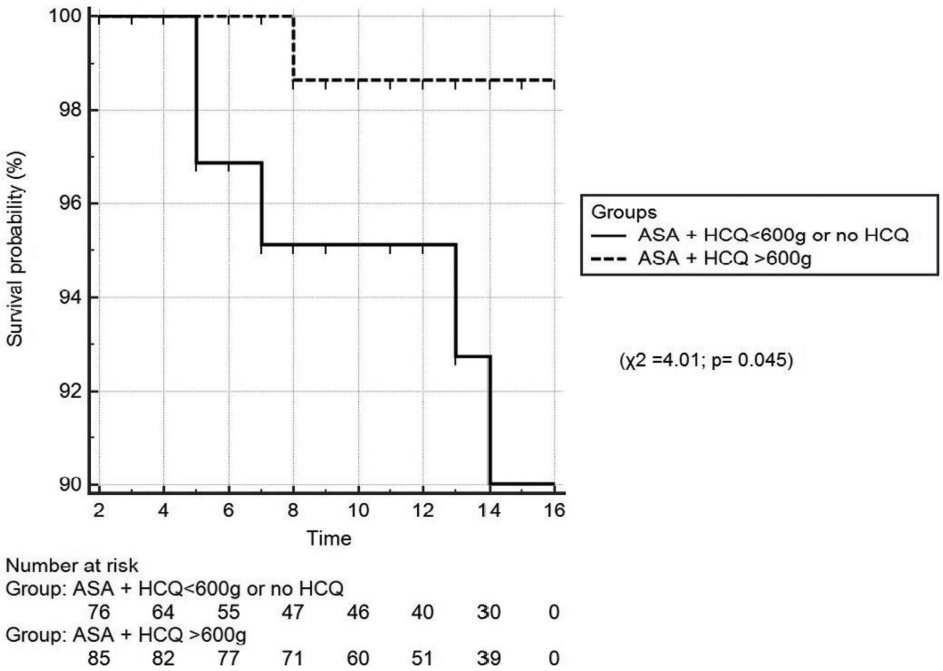

Figure 3. Rate of cardiovascular events over time in patients treated with ASA combined or not with cumulative HCQ dose more than 600 g. ASA: low-dose aspirin; HCQ: hydroxychloroquine.

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Table 2. Characteristics of the 3 subgroups of patients with SLE. Values are n (%).

Characteristics	ASA + HCQ > 600 g, n = 85	ASA + HCQ < 600 g or no HCQ, n = 79	HCQ Alone, n = 19	p*
Hypercholesterolemia	11 (12.9)	13 (16.4)	1 (5.2)	0.428
Hypertriglyceridemia	9 (10.5)	9 (11.3)	1(5.2)	0.731
Hypertension	17 (20)	24 (30.3)	8 (42.1)	0.091
Diabetes	4 (4.7)	3 (3.7)	1 (5.2)	0.941
Obesity	6 (7)	7 (8.8)	1 (5.2)	0.835
aPL positivity	25 (29.4)	23 (29.1)	3 (15.7)	0.462
Ever smokers	43 (50.5)	30 (37.9)	7 (36.8)	0.217
Severe SLE	52 (61.1)	50 (63.2)	11 (57)	0.899
High-dose steroids, cumulative dose prednisone equivalent > 40 g	23 (27)	22 (27.8)	6 (31.5)	0.924
Statins	10 (11.7)	9 (11.3)	1 (5.2)	0.702
Basal SDI ≥ 1	11 (12.9)	18 (22.7)	2 (10.5)	0.179
Basal SELENA-SLEDAI ≥ 6	56 (65.8)	53 (67)	11 (57.8)	0.748

* None of the p values are significant (significant $p < 0.05$). SLE: systemic lupus erythematosus; ASA: low-dose aspirin; HCQ: hydroxychloroquine; HCQ > 600 g: cumulative HCQ dose > 600 g; HCQ < 600 g: cumulative HCQ dose < 600 g; aPL: antiphospholipid antibodies; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

DISCUSSION

To our knowledge, this is the first longterm study to investigate the c-HCQ–related effects in the primary thromboprophylaxis in patients with SLE, and to assess whether exposure to antimalarial drugs has an additional antithrombotic effect that may be synergistic with ASA treatment. After years of empirical use, many studies have established that prolonged use of HCQ for the treatment of SLE has a relatively safe profile and may help patients with SLE to keep their disease under remission, thereby improving survival rates[19,20]. Several cohort studies have suggested that antimalarials have also beneficial influence on lipid profile[21] and risk of thrombosis in patients with SLE[5,6,7,22]. However, the results are controversial. An antithrombotic effect of HCQ was not confirmed in a multivariate analysis conducted in the large prospective cohort study by the LUpus in MInorities, NAture versus nurture Study Group[23]. Moreover, Tektonidou, *et al*[22] reported that ASA may protect against thrombosis in aPL-positive patients with SLE, while HCQ did not seem to have any protective effect ($p = 0.30$); however, in a multi-adjusted analysis, they found that prolonged use of HCQ was associated with a borderline lower incidence of thrombotic complications ($p = 0.05$). In this scenario, we carried out a retrospective analysis of the rate of CVE in 189 patients with SLE without a history of thrombosis and followed for 16 years. At Kaplan-Meier analysis, patients taking HCQ together with ASA for at least 5 years had a lower incidence of CVE than those who had not taken c-HCQ > 600 g. At multivariate analysis, c-HCQ > 600 g independently and significantly reduced the incidence of CVE. This protective effect could be related to the immune-modulatory properties (e.g., reduction of the formation of aPL–β2-glycoprotein I complexes to phospholipid bilayers and inhibition of oxidative stress) that HCQ exerts in the endothelial microenvironment[24,25,26].

There are several limitations in our study. First, the incidence of CVE is lower in our cohort than in previous studies[26,27]. However, it is noteworthy that the rate of ischemic events observed in our SLE cohort was 5-fold higher than that expected in the Italian population matched for age and sex as reported in "Progetto Cuore," an Italian register of ischemic diseases[28]. Although a multivariate analysis could be biased by the low number of events, we addressed it to further confirm the significant results from the Kaplan-Meier analyses. Second, this is an observational cohort study and an association between treatment and results might be influenced by treatment indications, i.e., skin and joint disease. However, no difference in disease pattern was detected between HCQ-treated and -untreated patients (Table 2). Another limitation of our study is that it relies on patient-reported adherence to treatment and poor adherence to therapeutic regimens is a common issue in patients with SLE[29,30,31]. However, this limitation would affect the outcomes in both treatment groups (patients with a c-HCQ respectively higher and lower than 600 g). Last, most of our patients were white and these results may not be generalizable. In fact, SLE can have a more severe course in African-descendant patients[32], even though data on CV disease incidence in different ethnic groups have been questioned[33,34].

Despite these limitations, our data increase awareness of the high CV risk in patients with SLE. Although rigorous management of all potential risk factors for thrombosis is warranted in patients with SLE[35], given the lack of evidence-based recommendations, most patients with SLE without previous thrombotic manifestations do not receive

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any prophylactic treatment. Noninvasive assessment of carotid intima-media thickness and plaque should be used to predict CVE in asymptomatic patients with SLE, and studies are required to analyze effects of treatment on subclinical atherosclerosis. HCQ appears to protect against thrombosis, particularly in the longterm, and the HCQ-ASA combination seems to synergistically reduce further the CV risk in patients with SLE. Our results support the prolonged use of HCQ in all patients with SLE, as previously advocated[35]. Nevertheless, larger, controlled, prospective studies are needed to better define the involvement of HCQ in primary CV prevention in patients with SLE.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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