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Article type : Original Article

The Impact of Systemic Lupus Erythematosus on the Clinical Phenotype of Antiphospholipid Antibody Positive Patients: Results from AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Clinical Database and Repository

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Key Words:

Antiphospholipid Syndrome – Systemic Lupus Erythematosus – APS ACTION – Cardiovascular Disease - Hydroxychloroquine

Financial Disclosure:

The study was partially supported by New York Community Trust.

Michael H. Belmont, MD is a consultant to Exagen Diagnostics, Inc.

Doruk Erkan, MD received research grants from New York Community Trust, Hospital for Special Surgery Medical Education Academy, Lupus Clinical Trials Consortium, and NHLBI; is a clinical trial investigator for EMD Serono, GSK, and Xencor; and is a consultant for Ablynx.

Remaining authors do not have any financial disclosures.

Abstract:

Objective: Although systemic lupus erythematosus (SLE) is the most common autoimmune disease associated with antiphospholipid antibodies (aPL), limited data exist on the impact of SLE on the clinical phenotype of aPL-positive patients. The primary objective was to compare the clinical, laboratory, and treatment characteristics of aPL-positive patients with or without SLE.

Methods: A secure web-based data capture system stores patient demographics, and aPL-related clinical and laboratory characteristics. Inclusion criteria include aPL positivity according to the Updated Sapporo Classification Criteria. Patients fulfilling the SLE Classification Criteria and those with no other autoimmune diseases were included in the analysis.

Results: 672 aPL-positive patients were recruited from 24 international centers; 426 were without other autoimmune diseases and 197 with SLE. The aPL with SLE group had higher rates of thrombocytopenia, hemolytic anemia, low complements, and IgA anti-β_2 glycoprotein-I antibodies (aβ_2GPI), whereas the aPL only group had higher rates of cognitive dysfunction and IgG aβ_2GPI. The frequency of arterial and venous thromboses (including recurrent) as well as the pregnancy morbidity were similar between the groups. The prevalence of cardiovascular disease risk factors at the registry entry did not differ between the two groups, except current smoking, which was more frequent in aPL with SLE group.

Conclusions: Although the frequencies of thrombosis and pregnancy morbidity are similar between aPL-positive patients with or without SLE, the diagnosis of SLE in persistently aPL-positive patients is associated with an increased frequency of thrombocytopenia, hemolytic anemia, low complements, and IgA aβ_2GPI positivity.

Significance and Innovation:

- Although systemic lupus erythematosus (SLE) is the most common autoimmune disease associated with aPL, limited data exist on the impact of SLE on the clinical phenotype of antiphospholipid antibody (aPL)-positive patients.
- Based on the analysis of a large scale international registry, our study demonstrates that concomitant SLE diagnosis in persistently aPL-positive patients does not increase the frequencies of thrombosis (including recurrent) and pregnancy morbidity. However, aPL-positive patients with SLE have increased frequency of thrombocytopenia, hemolytic anemia, low complement levels, and IgA aβ_2GPI positivity compared to aPL-positive patients without other autoimmune diseases.
- Additionally, aPL-positive patients with SLE had significantly higher frequency of current smoking, while aPL-positive patients without other autoimmune disease had an increased prevalence of cognitive dysfunction.
- Although hydroxychloroquine (HCQ) use was more common in aPL-positive patients with SLE, 40% of aPL-positive patients with no other autoimmune diseases also received HCQ, especially those with lupus-related clinical and serologic manifestations.

Introduction:

Antiphospholipid syndrome (APS) is characterized by thromboses and/or pregnancy morbidity associated with persistently positive antiphospholipid antibodies (aPL) (lupus anticoagulant [LA] test, anticardiolipin antibodies [aCL], and/or anti-β_2 glycoprotein-I antibodies [aβ_2GPI]) (1). Thrombocytopenia, autoimmune hemolytic anemia, livedo, aPL-associated nephropathy, cardiac valve disease, cognitive dysfunction, and skin ulcers can also occur in aPL-positive patients (1, 2), characterized as non-criteria APS manifestations.

Antiphospholipid syndrome can occur in individuals without an underlying systemic autoimmune disease (primary APS) or in the context of other systemic autoimmune diseases, with systemic lupus erythematosus (SLE) being the most common (30-50%) (3). Variable clinical features ranging from mild joint and skin involvement to life-threatening renal, hematologic, and/or central nervous system manifestations can occur in SLE. (4). Thirty-to-forty percent of SLE patients are positive for aPL (5); the prevalence of a "clinically significant" aPL profile (positive LA test based on the guidelines of International Society of Thrombosis and Haemostasis [ISTH] (6), aCL IgG/IgM greater than or equal to 40 GPL/MPL, and/or aβ_2GPI IgG/IgM greater than or equal to 40 GPL/MPL, tested twice at least 12 weeks apart) is approximately 30% (7). Although aPL-positivity has an impact on the clinical presentation and prognosis of SLE patients (5), there are limited number of studies analyzing the impact of SLE on the clinical phenotype and prognosis of aPL-positive patients (8).

Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) is an international network created to design and conduct large-scale, multicenter

studies and clinical trials in persistently aPL-positive patients (9). The APS ACTION clinical database and repository ("registry") was created to study the natural course of persistently aPL-positive patients with or without autoimmune disorders over at least 10 years; the registry allows us to perform cross-sectional and prospective analyses.

In this international multicenter study, our primary objective was to compare the clinical, laboratory, and treatment characteristic of aPL-positive patients with and without SLE. Secondly, we analyzed: a) the frequencies of traditional CVD risk factors in aPL-positive patients with and without SLE; and b) the pattern of hydroxychloroquine (HCQ) use, an immunoregulatory agent with anti-thrombotic effects, among aPL-positive patients with no other autoimmune diseases. We hypothesized that aPL-positive patients with SLE have increased rates of aPL-related clinical manifestations, traditional cardiovascular disease (CVD) risk factors, lupus-related antibodies, and immunosuppressive use (including HCQ), compared to those without SLE.

Methods:

APS ACTION Registry and Data Collection:

An international web-based application, the REDCap (Research Electronic Data Capture) (10), captures data on patient demographics, aPL-related clinical and laboratory characteristics, and medications. Data are collected once a year and at the time of a new aPL-related thrombosis or pregnancy morbidity. The inclusion criteria are: a) age between 18 and 60 years; and b) persistent (at least 12 weeks apart) aPL-positivity within 12 months prior to screening; positivity is defined as aCL IgG/M/A ($\geq$ 40 GPL/MPL/APL, medium-to-high titer, and/or greater than the 99th percentile), and/or aβ_2GPI IgG/M/A ($\geq$ 40 GPL/MPL/APL, medium-to-high titer, and/or greater than the 99th percentile), and/or positive LA test based on ISTH guidelines (6). Patients

are followed every 12 ± 3 months with clinical data and blood collection; they also receive advice on CVD and thrombosis prevention at each visit.

Study Cohort:

Although APS ACTION registry captures data from patients with a variety of autoimmune diseases, for the purpose of this analysis, patients with autoimmune diseases other than SLE were excluded. Thus, two mutually exclusive groups were included: a) aPL-positive patients with no other systemic autoimmune diseases ("aPL-only"); and b) aPL-positive patients who also met the American College of Rheumatology (ACR) SLE Classification Criteria ("aPL with SLE'') (11).

Covariates:

We evaluated demographic characteristics at time of cohort entry, including mean age, race (White, Latin American Mestizos, Asian, Black, American Indian or Alaskan, Native American, "Other"), ethnicity (Non-Latin American or Latin American [for United States, Canada, Europe], Afro-descendent, Mestizo, or Caucasian [for South America], Aboriginal or Non-Aboriginal [for Australia], or "Other"). Clinical data retrieved were history of arterial and venous thrombosis, biopsy proven microthrombosis (pulmonary, skin, kidney, and "other"), pregnancy morbidity based on the Updated Sapporo Classification Criteria, catastrophic APS based on the preliminary classification criteria (12), livedo reticularis/racemosa, persistent thrombocytopenia defined as platelets<100,000 tested twice at least 12 weeks apart, autoimmune hemolytic anemia, echocardiography proven cardiac valve disease, biopsy proven aPL-nephropathy, skin ulcers, and neuro-psychiatric test proven cognitive dysfunction. Laboratory data retrieved at baseline

were aPL-related (LA, aCL IgG/IgM/IgA, and aβ_2GPI IgG/IgM/IgA) and lupus-related [antinuclear antibody [ANA], anti-double-strand-DNA antibody [dsDNA], anti-smith antibody [anti-Sm], and complement component 3 [C3] and 4 [C4]). Cardiovascular risk factors assessed at the time of registry entry were hypertension, diabetes, and hyperlipidemia requiring treatment, current and past smoking, estrogen use, obesity, family history of CVD, and sedentary lifestyle. Medications (low-dose aspirin, warfarin, direct oral anticoagulants, corticosteroids, HCQ, intravenous immunoglobulin, rituximab, azathioprine, cyclophosphamide, cyclosporine, methotrexate, and mycophenolate mofetil) were included in the analysis as "ever" or "never" used.

Statistical Analysis:

Data from APS ACTION registry were locked in February 2017. We compared the prevalence of covariates (historical or baseline) in "aPL-only" and "aPL with SLE" patients using chi-square test for categorical variables. One-way ANOVA test was used to test the differences in means between multiple independent groups, and a Student's t test was used for two group comparisons. The statistical software used was SPSS 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). We calculated two-sided p-values to determine the significance of all findings, with a significance level set at $p<0.05$.

Results:

As of February 2017, 672 aPL-positive patients were recruited from 24 centers; 43 (6%) patients were excluded due to underlying autoimmune diseases other than SLE and 6 (1%) due to missing data. Of the remaining 623 patients, 426 were without other autoimmune diseases ("aPL only")

and 197 with SLE ("aPL with SLE"). Fifty-nine patients of the "aPL only" group had SLE-like disease (3 of 11 ACR SLE Classification Criteria met) (11).

Table 1 demonstrates the clinical, laboratory, and treatment characteristics collected at registry entry. The mean age (± SD) at entry was 44.2 ± 12.8 years with the majority of patients being categorized as white (74%). Three hundred and thirty-eight of 426 (79%) of "aPL only" group, and 137/426 (70%) of "aPL with SLE" group were classified as APS based on the Updated Sapporo Classification Criteria (1). Overall 422 of 623 (68%) patients had history of thrombotic APS and 57 (9%) had obstetric APS only. The mean disease duration (± SD) (time from the first available positive aPL test result to the enrollment date) was similar; 5.6 ± 4.9 years in the "aPL only" group and 6.3 ± 5.1 years in the "aPL with SLE "group (p = 0.1).

Antiphospholipid antibody-positive patients with SLE had higher rates of persistent thrombocytopenia, autoimmune hemolytic anemia, low complement component 3 (C3) and 4 (C4), and IgA aβ_2GPI positivity, whereas the "aPL only" group had significantly higher rates of cognitive dysfunction and IgG aβ_2GPI positivity. Corticosteroids, HCQ, azathioprine, cyclophosphamide, methotrexate, and mycophenolate mofetil were more frequently used in the "aPL with SLE" group.

The prevalence of traditional CVD risk factors at the time of the registry entry did not differ between two groups, except current smoking, which was more frequent in SLE patients (9% vs 15%, p = 0.03) (Table 2). In the "aPL only" group, 262 (62%) patients were never treated with HCQ, 133 (31%) were current users (200–400mg daily), and 31 (7%) were past users; 74% (99/133) of current users and 84% (26/31) of past users were classified as APS. Patients with

lupus-related clinical manifestations, low complement C4, and lupus-related autoantibodies were more likely to be treated with HCQ (Table 3). After excluding patients with SLE-like disease (3 of 11 ACR SLE Classification Criteria met) (n: 59), when we analyzed 367 patients in the "aPL only" group, we found a higher frequency of HCQ treatment in patients with low complement C4 and lupus-related autoantibodies.

Discussion:

Based on the analysis of a large scale international registry of persistently aPL-positive patients, our study demonstrates that the frequencies of thrombosis (including recurrent) and pregnancy morbidity are similar between aPL-positive patients with or without SLE. However, concomitant SLE diagnosis in persistently aPL-positive patients is associated with an increased frequency of thrombocytopenia, hemolytic anemia, low complement levels, and IgA aβ_2GPI positivity compared to aPL-positive patients without other autoimmune diseases. Additionally, aPL-positive patients with SLE had significantly higher frequency of current smoking, while aPL-positive patients without other autoimmune disease had an increased prevalence of cognitive dysfunction. Although HCQ use was more common in "aPL with SLE" group, 40% of "aPL only group" also received HCQ, especially those with lupus-related clinical and serologic manifestations.

Although the impact of aPL on SLE is well studied (5, 7), limited data exist regarding the impact of SLE on the clinical phenotype of persistently aPL-positive patients. In a European multicenter cohort of 1,000 mainly Caucasian patients with APS, patients with concomitant SLE had higher prevalence of livedo reticularis, thrombocytopenia, arthritis, and leukopenia (13). Our multiethnic study also showed an increased frequency of thrombocytopenia and autoimmune

hemolytic anemia in aPL-positive patients with SLE compared to those without, but except for cognitive dysfunction, similar frequencies of the criteria or other non-criteria aPL manifestations, namely livedo reticularis, cardiac valve disease, and aPL-associated nephropathy. Given that our SLE patients were classified based on the ACR SLE Classification Criteria (11), which incorporates thrombocytopenia and autoimmune hemolytic anemia, the increased frequency of these hematological abnormalities in aPL-positive patients with SLE was not unexpected.

Cognitive dysfunction is common in APS and SLE, frequently associated with livedo reticularis and white matter lesions on brain magnetic resonance imaging in APS patients. Tektonidou et al. found no difference in cognitive performance assessed by a three-hour battery of neurocognitive tests among patients with primary APS and those with SLE/APS (14). Kozora et al. demonstrated that 12 of 20 (60%) of the SLE and 8/20 (40%) of the aPL-positive non-SLE patients had global cognitive impairment on ACR-SLE cognitive impairment index (CII), a validated neuropsychological instrument; there were no group differences on CII or on individual measures (15). Our study included persistently aPL-positive patients with and without APS classification (1), and still found that neuro-psychiatric test-proven cognitive dysfunction was more common in aPL-positive patients without SLE. These findings further support the importance of cognitive dysfunction research and clinical assessment in aPL-positive patients without other systemic autoimmune diseases.

The Updated Sapporo APS Classification Criteria do not include IgA aCL and aβ_2GPI. Although IgA isotype is common in African American SLE patients (16) and now it is included in the new Systemic Lupus Collaborating Clinics (SLICC) SLE Classification Criteria (17), the prevalence and clinical significance have been controversial (18). We found that although aPL types and

isotypes as well as the double or triple aPL-positivity were generally comparable between two groups, aPL-positive patients with SLE had more frequently IgA aβ_2GPI, while IgG aβ_2GPI was more frequent in those without SLE. Although it remains unknown why patients develop different isotypes of aPL, our findings support previous studies (19) demonstrating a potential diagnostic and clinical significance of IgA isotype in lupus patients, compared to those without lupus.

Traditional CVD risk factors, including diabetes and smoking, increase the risk of thrombosis in aPL-positive patients (20). Systemic lupus erythematosus itself is an independent risk factor for CVD, which still remains the major cause of mortality in SLE patients (21). It is not well studied whether CVD risk factors differ among aPL positive patients with or without SLE; our study demonstrates that the prevalence of CVD risk factors was similar between aPL-positive patients with or without SLE except current smoking. In addition, although the role of smoking in the development of aPL, APS, and/or SLE is not well-established (22), smoking is associated with worse outcomes and venous thrombosis in SLE as well as the development of SLE subtypes, defined by autoantibody status (23). All these findings support the importance of similar diligence in CVD risk assessment and management measures in both aPL-positive with or without SLE.

In our analysis, corticosteroids, HCQ, azathioprine, cyclophosphamide, methotrexate, and mycophenolate mofetil were more frequently used in aPL-positive patients with SLE versus those without, at the time of cohort entry. Hydroxychloroquine use is well established in SLE; however, no strong clinical data exist to recommend HCQ for aPL-positive patients without other systemic autoimmune diseases. Given animal and in vitro studies showing that HCQ has a

potential antithrombotic role in addition to its immunoregulatory and metabolic effects (24-29), HCQ has been used by some centers to prevent thrombosis in aPL-positive patients without other systemic autoimmune disease (30-32). An international effort to determine the effectiveness against thrombosis in asymptomatic aPL-positive patients was terminated early due to logistical reasons (33). Approximately 40% of aPL-positive patients without other systemic autoimmune disease reported HCQ use in our study, with higher frequency of serological features of SLE among aPL-positive patients using HCQ. Our study was not designed to determine the prophylactic role of HCQ; however, we believe that prospective follow-up of our registry patients will provide further valuable data on outcomes in HCQ-treated aPL-positive patients.

Although our study was limited in its retrospective, cross-sectional study design, we used large, multi-center international patient cohort. Our dataset is enriched with granular sociodemographic, clinical, laboratory, and medication data. However, data for CVD risk factors were collected at the time of the patient's enrollment and not at the time of the thrombotic events, which may have resulted in inaccurate CVD prevalence estimates in different groups of aPL-positive patients.

In conclusion, our analysis of a multicenter international cohort of persistently aPL-positive patients demonstrates increased frequency of thrombocytopenia, hemolytic anemia, low complement levels, and IgA aβ_2GPI positivity, but not the risk of thrombotic, obstetric, and non-criteria APS manifestations (except cognitive dysfunction) among aPL-positive patients with concomitant SLE diagnosis compared to those without SLE. Our exploratory study provides pilot data for future risk-stratified prospective data analyses of APS ACTION registry, which will better determine the clinical impact of SLE on the presentation of aPL-positive patients.

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Acknowledgments:

We want to thank: Joann Vega, CCRC for her research/administrative assistance including patient recruitment and data monitoring. Data management was performed using REDCAP provided by the Clinical and Translational Science Center at Weill Cornell Medicine (CTSC grant UL1 TR000457).

Table 1: Clinical and Laboratory Characteristics (historically and/or at registry entry) of Persistently Antiphospholipid Antibody (aPL)-positive Patients (overall and stratified by systemic lupus erythematosus [SLE])

Variables n(%) unless listed differently	**All aPL-positive Patients (n=623)**	**"aPL Only" Patients (n=426)**	**"aPL with SLE" Patients (n=197)**	**p**
Demographics				
Age at Registry Entry (mean ± SD)	44.2 ± 12.8	44.58 ± 12.9	43.24 ± 12.5	0.22
Female	459 (74%)	307 (72%)	152 (77%)	0.18
Race[1]				
White	397 (71%)	274 (71%)	123 (71%)	
Latin American Mestizos	81 (15%)	66 (17%)	15 (9%)	
Asian	48 (9%)	28 (7%)	20 (12%)	
Black	21(4%)	10 (3%)	11 (6%)	
American Indian or Alaskan	1 (0.2%)	0	1 (0.6%)	
Native American	0	0	0	
Reported as "Other"	12 (2%)	9 (2%)	3 (2%)	
Ethnicity[2]				
United States, Canada, Europe	261 (51%)	183 (50%)	78 (55%)	
Non-Latin American	242 (48%)	168 (46%)	74 (48%)	
Latin American	19 (4%)	15 (4%)	4 (3%)	
South America	124 (24%)	96 (26%)	28 (20%)	
Afro-descendent	16 (3%)	8 (2%)	8 (6%)	
Mestizo	67 (13%)	54 (15%)	13 (9%)	
Caucasian	41 (8%)	34 (9%)	7 (5%)	

Australia	3 (0.6%)	2 (0.5%)	1 (0.7%)	
Aboriginal	0	0	0	
Not Aboriginal	3 (0.6%)	2 (0.5%)	1 (0.7%)	
Other	121 (24%)	85 (23%)	36 (24%)	
Clinical Manifestations				
Arterial Thrombosis (AT)	193 (31%)	139 (33%)	54 (27%)	0.26
Venous Thrombosis (VT)	272 (44%)	185 (43%)	87 (44%)	0.13
Microthrombosis (MT)	37 (6%)	27 (6%)	10 (5%)	0.23
Any Vascular Event (AT/VT/MT)	422 (68%)	297 (70%)	125 (64%)	0.12
Recurrent Vascular Event	198/422 (47%)	163/297 (55%)	61/125 (49%)	0.25
Pregnancy History (ever)	318 (51%)	221(52%)	97 (49%)	0.06
Pregnancy Morbidity	210 (34%)	154 (36%)	56 (28%)	0.1
• ≥1 Fetal Death ≥ 10th Week of Gestation	110 (18%)	76 (18%)	34 (17%)	0.15
• ≥1 Premature Birth < 34th Week of Gestation	54 (9%)	43 (10%)	11 (6%)	0.09
• ≥3 Consecutive Unexplained Spontaneous Abortions < 10th Week of Gestation	23 (4%)	19 (5%)	4 (2%)	0.1
Catastrophic APS	6 (1%)	4 (1%)	2 (1%)	0.24
Livedo Reticularis/Racemosa	80 (13%)	52 (12%)	28 (14%)	0.48
Persistent Thrombocytopenia	124 (20%)	69 (16%)	55 (28%)	0.001
Autoimmune Hemolytic Anemia	32 (5%)	9 (2%)	23 (12%)	<0.001
Echocardiography Proven Cardiac Valve Disease	50/518 (10%)	30/349 (9%)	20/169 (12%)	0.31

Biopsy Proven aPL-associated Nephropathy	19/577 (3%)	11/397 (3%)	8/180 (4%)	0.30
Skin Ulcers	32 (5%)	21 (5%)	11 (6%)	0.12
Cognitive Dysfunction	19/148 (13%)	14/90 (16%)	5/58 (9%)	<0.001
Complement Levels				
Low Complement C3	93/240 (39%)	29/126 (23%)	64/114 (56%)	<0.001
Low Complement C4	92/240 (38%)	30/126 (24%)	62/114 (54%)	<0.001
Antiphospholipid Antibodies				
Lupus Anticoagulant (LA)	417 (67%)	288 (68%)	129 (66%)	0.6
Anticardiolipin Antibodies (aCL)				
IgG (cut-off 20 GPL)*	357 (57%)	245 (58%)	112 (57%)	0.87
IgG (cut-off 40 GPL)**	280 (45%)	202 (47%)	78 (40%)	0.07
IgM (cut-off 20 MPL)*	223 (36%)	154 (36%)	69 (35%)	0.79
IgM (cut-off 40 MPL)**	139 (22%)	96 (23%)	43 (22%)	0.84
IgA (cut-off 20 APL)*	41/149 (28%)	24/89 (27%)	17/60 (28%)	0.85
IgA (cut-off 40 APL)**	26/149 (17%)	15/89 (17%)	11/60 (18%)	0.81
Anti-β_2GPI Antibodies (aβ_2GPI)				
IgG (cut-off 20 GPL)*	265 (43%)	194 (46%)	71 (36%)	0.03
IgG (cut-off 40 GPL)**	208 (33%)	157 (37%)	51 (26%)	0.01
IgM (cut-off 20 GPL)*	173 (28%)	124 (29%)	49 (25%)	0.27
IgM (cut-off 40 GPL)**	114 (18%)	81 (19%)	33 (17%)	0.5
IgA (cut-off 20 GPL)*	58/160 (36%)	30/104 (29%)	28/56 (50%)	0.02

IgA (cut-off 40 GPL)**	37/160 (23%)	19/104 (18%)	18/56 (32%)	0.04
Double aPL-Positivity (LA + aCL, LA + aβ_2GPI, or aCL + aβ_2GPI)	187 (30%)	121 (28%)	66 (34%)	0.1
Triple aPL Positivity (LA + aCL + aβ_2GPI)	209 (34%)	158 (37%)	51 (26%)	0.1
Medications* **				
Low-dose Aspirin	273 (44%)	183 (43%)	90 (44%)	0.52
Warfarin	344 (55%)	245 (58%)	99 (50%)	0.09
Direct Oral Anticoagulants	15 (2%)	10 (2%)	5 (3%)	0.89
Corticosteroids	111 (18%)	39 (9%)	72 (37%)	<0.001
Hydroxychloroquine	276 (44%)	133 (31%)	143 (72%)	<0.001
Immunosuppressive Agents				
Intravenous Immunoglobulin	2 (0.3%)	1 (0.2%)	1 (1%)	0.58
Rituximab	7 (1%)	3 (1%)	4 (2%)	0.14
Azathioprine	46 (7%)	11 (3%)	35 (18%)	<0.001
Cyclophosphamide	8 (1%)	2 (1%)	6 (3%)	0.008
Cyclosporine	4 (1%)	2 (1%)	2 (1%)	0.43
Methotrexate	17 (3%)	4 (1%)	13 (7%)	<0.001
Mycophenolate Mofetil	45 (7%)	11 (3%)	34 (17%)	<0.001

*more than low titer; ** more than moderate titer; *** at the time of registry entry.

[1] Races were allowed to be collected in a total of 560 patients (387 in “aPL only” group and 173 in “aPL with SLE” group). [2] Ethnicities were allowed to be collected in a total of 509 patients (366 in “aPL only” group, 143 in “aPL with SLE” group).

Table 2: Prevalence of Cardiovascular Disease (CVD) and Thrombosis Risk Factors (upon registry entry) Among Persistently Antiphospholipid Antibody (aPL)-positive Patients, Stratified by Systemic Lupus Erythematosus (SLE)

Variables n (%)	aPL only (n=426)	aPL with SLE (n=197)	p
Hypertension	118 (28%)	66 (34%)	0.14
Diabetes	22 (5%)	8 (4%)	0.55
Hyperlipidemia	103 (24%)	36 (18%)	0.1
Smoking ever	116 (27%)	49 (25%)	0.65
Current Smoking	40 (9%)	30 (15%)	0.03
Estrogen Use	3 (1%)	3 (2%)	0.54
Obesity	107 (25%)	59 (30%)	0.37
Family History of CVD	67 (16%)	21 (11%)	0.18
Sedentary Lifestyle	197 (46%)	94 (48%)	0.73

Table 3: Analysis of 426 Antiphospholipid Antibody (aPL)-positive Patients Without Other Systemic Autoimmune Diseases, Stratified by Hydroxychloroquine (HCQ) Use

Variables, n (%)	HCQ Users (n:164)	HCQ Non-users (n:262)	p
Clinical Profile			
Thrombotic APS	89 (54%)	148 (57%)	0.65
• Arterial Thrombosis	52 (32%)	87 (33%)	0.84
• Venous Thrombosis	75 (46%)	110 (42%)	0.3
• Mictothrombosis	11 (7%)	16 (6%)	0.74
Obstetric APS	16 (10%)	28 (11%)	0.76
Thrombotic and Obstetric APS	21 (13%)	37 (14%)	0.70
3 out of 11 ACR SLE criteria	42 (26%)	17 (7%)	<0.001
Laboratory Profile			
Persistent Triple aPL-positive	60 (37%)	98 (37%)	0.87
Persistent Double aPL-positive	54 (33%)	67 (26%)	0.1
Persistent Single aPL-positive	50 (30%)	97 (27%)	0.16
ANA Positive*	102 (62%)	86 (33%)	<0.001
Anti-dsDNA Positive*	30 (18%)	10 (4%)	<0.001
Anti-Sm Positive*	5 (3%)	0 (0%)	0.008
Low Complement C3**	17/66 (26%)	12/60 (20%)	0.44
Low Complement C4**	20/66 (30%)	10/60 (17%)	0.02

* Patients were considered positive for ANA, anti-dsDNA, or anti-Sm antibodies if they were ever tested positive for these antibodies. ** "Low complement C3/C4" was determined based on: a) the levels below normal; and b) the most recent C3/4 tests before the registry entry.