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Characteristics of Antiphospholipid Antibody Positive Patients in

AntiPhospholipid Syndrome Alliance for Clinical Trials and International Networking

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/acr.24468](https://doi.org/10.1002/acr.24468)

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Acknowledgement: Dr. Barbhaiya is supported by the Rheumatology Research Foundation Investigator Award. The Hopkins Lupus Cohort (MP) is supported by a grant from the NIH RO1 AR069572. Dr. Fortin is recipient of a tier 1 Canada Research Chair on Systemic Autoimmune Rheumatic Diseases. The APS ACTION registry was created using REDCAP provided by the Clinical and Translational Science Center at Weill Cornell Medical College (CTSC grant UL1 TR000457).

Conflict of interest: None

Key words: antiphospholipid syndrome, APS, antiphospholipid antibodies

ABSTRACT

Objective: To describe baseline characteristics of antiphospholipid antibody (aPL)-positive patients, overall and by clinical and laboratory subtypes, enrolled in an international registry.

Methods: AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking Registry includes persistently aPL-positive adults. We evaluated baseline sociodemographic and aPL-related (APS classification criteria and “non-criteria”) characteristics of patients overall and in subgroups (aPL-positive without APS, APS overall, thrombotic APS [TAPS] only, obstetric APS [OAPS] only, and both TAPS/OAPS). We assessed baseline characteristics of patients tested for three aPL (lupus anticoagulant test [LA], anticardiolipin antibody [aCL], and anti- β_2 -Glycoprotein-I [a β_2 GPI]) by aPL profiles (LA only, single, double, and triple aPL positivity).

Results: Of 804 aPL-positive patients (mean age: 45 ± 13 y; female: 74%; white 68%; other systemic autoimmune diseases: 36%), 80% were classified as APS (55% TAPS, 9% OAPS, and 15% TAPS/OAPS). In the overall cohort, 71% had vascular thrombosis, 50% with pregnancy history had obstetric morbidity, and 56% had at least one non-criteria manifestation. Among those with three aPL tested (n: 660), 42% were triple aPL positive. While single, double and triple aPL positive subgroups had similar frequencies of vascular, obstetric, and non-criteria events, these events were lowest in the single aPL subgroup consisting of aCL or a β_2 GPI only.

Conclusion: Our study demonstrates the heterogeneity of aPL-related clinical manifestations and laboratory profiles in a multicenter, international cohort. Within single aPL-positivity, LA may be a major contributor to clinical events. Future prospective analyses, using standardized core laboratory aPL tests, will help clarify aPL risk profiles and improve risk stratification.

Word count: 250

Significance and Innovations:

- Using the multi-center, international APS ACTION registry, we describe baseline clinical and laboratory characteristics of persistently aPL-positive patients, including 36% of patients with other systemic autoimmune disease.
- One-fifth of the registry patients do not fulfill clinical APS classification criteria; 71% have vascular events; one-fourth have aPL-related obstetric morbidity; and 56% have at least one other non-criteria clinical aPL manifestation, most commonly thrombocytopenia and central nervous system white matter lesions.
- Although single, double, and triple aPL positive subgroups had similar frequencies of vascular, pregnancy, and non-criteria events, these events were less common in the single aPL subgroup after excluding LA positive patients, suggesting the importance of LA positivity.
- Future prospective analyses, using standardized core laboratory aPL tests, will help clarify aPL risk profiles.

INTRODUCTION

Antiphospholipid syndrome (APS) is characterized as an autoimmune disease marked by thromboses and/or pregnancy morbidity with persistently positive antiphospholipid antibodies (aPL), (lupus anticoagulant test [LA], anticardiolipin antibodies [aCL], and/or anti- β_2 -glycoprotein-I antibodies [a β_2 GPI]), as defined by the 2006 Revised Sapporo Classification Criteria (1,2). Other well-recognized “non-criteria” clinical manifestations may occur in aPL-positive patients, including thrombocytopenia, autoimmune hemolytic anemia, livedo, aPL-associated nephropathy, cardiac valve disease, cognitive dysfunction, and skin ulcers (1,3). Antiphospholipid syndrome can occur in isolation (primary APS) or in association with other autoimmune diseases, most notably systemic lupus erythematosus (SLE) (4).

Antiphospholipid antibody positive patients can have heterogeneous clinical manifestations, including asymptomatic aPL positivity (no thrombosis or pregnancy morbidity), thrombotic APS (TAPS; characterized by venous, arterial, or microvascular involvement) and obstetric APS (OAPS; characterized by pregnancy complications such as fetal loss, recurrent early miscarriages, placental insufficiency, or preeclampsia). Furthermore, not every positive aPL is clinically significant, and transient low titer aPL positivity may occur in settings such as infection or malignancy (5,6). Despite accumulating data showing an important role for aPL laboratory profiles in APS assessment (7–9), the risk of aPL-related clinical events by aPL laboratory profile remains under investigation. Few large cohorts have estimated the prevalence of aPL-related clinical manifestations (10–12); furthermore, the distribution of demographic and

clinical factors by aPL-related clinical subtypes or laboratory profiles is not well established.

Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) is an international network established in 2010 to conduct large-scale, multicenter studies and clinical trials in persistently aPL-positive patients (2). 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. In this study, our primary objective was to retrospectively evaluate the baseline demographic and clinical characteristics of aPL-positive patients enrolled in the APS ACTION registry since 2010, overall and by clinical subtype (aPL positive without APS classification, thrombotic APS, and obstetric APS). Secondly, we also assessed the clinical characteristics of aPL-positive patients who were tested at baseline for all three “criteria” aPL (LA, aCL, and a β ₂GPI) and categorized by aPL profile (LA only, single, double, and triple aPL positivity).

METHODS

APS ACTION Registry and Data Collection

APS ACTION Registry inclusion criteria are: a) adults aged 18 to 60 years; and b) persistent (at least 12 weeks apart) aPL-positivity by the Revised Sapporo criteria (1), within 12 months prior to screening. Patients referred to APS ACTION sites were referred from hospital or outpatient settings and had aPL testing for a variety of reasons such as thrombosis, pregnancy morbidity, false positive serologic test for syphilis,

prolonged aPTT, thrombocytopenia, or concomitant systemic autoimmune diseases. As part of the registry entry criteria, patients must have had persistent aPL positivity prior to registry entry. Positivity for aCL and/or a β ₂GPI is defined as IgG/M/A (\geq 40 units, medium-to-high titer). LA activity was detected by coagulation assays according to the International Society on Thrombosis and Hemostasis guidelines (ISTH) (13).

An international web-based application, the REDCap (Research Electronic Data Capture) (14), is used to store and manage data on baseline sociodemographic information, aPL-related clinical events, pregnancy history, medications, and laboratory profile. Blood samples are also collected at registry entry for confirmation of aPL-positivity. Patients are followed every 12 ± 3 months with clinical data and blood collection, or at the time of a new aPL-related thrombosis and/or pregnancy morbidity.

Study Cohort

We included all persistently aPL-positive participants enrolled in APS ACTION registry between May 2010 to March 2019. We categorized patients into groups by clinical subtype at baseline: 1) “aPL without APS”[™]: patients fulfilling laboratory criteria for APS classification but not meeting the clinical Revised Sapporo criteria (1); and 2) “APS” (overall) patients fulfilling both laboratory and clinical criteria for definite APS. APS patients overall were further categorized into three mutually exclusive groups as follows: 1) TAPS: patients with a history of any vascular event (including any arterial thrombosis, venous thrombosis, or microvascular involvement, but excluding only superficial vascular thrombosis); 2) OAPS: patients with history of any pregnancy morbidity event

(defined by 2006 Revised Sapporo Classification) (1); and 3) TAPS/OAPS: patients with any vascular thrombosis event and any pregnancy morbidity event (Table 1).

Secondly, we evaluated the baseline laboratory profile of aPL-positive patients in the registry. We assessed the baseline clinical characteristics of aPL-positive patients with different laboratory profiles (single, double, and triple aPL positivity), among patients tested for all three aPL (LA, aCL, and a β_2 GPI). We also subcategorized the single aPL positivity subgroup, by separately evaluating those with LA only, and with single aPL positivity excluding LA (Table 2). For the purposes of this study, positivity for aCL IgG/M/A and a β_2 GPI IgG/M/A was defined as a titer of ≥ 40 units and the highest titer among all test results was taken into consideration during analysis.

Data Collection for Baseline Characteristics

Demographic characteristics collected included mean age, race (White, Latin American Mestizos, Asian, Black, or other), ethnicity (Non-Latin American or Latin American [for United States, Canada, Europe], Afro-descendent, Mestizo, or Caucasian [for South America], Afro-descendent [for South Africa], or “Other”), and region of residence (Europe, North America [for United States and Canada], Latin-America, and Asia-Pacific). Clinical manifestations were subgrouped into vascular events (arterial thrombosis, venous thrombosis, microvascular involvement), catastrophic APS [CAPS]), pregnancy morbidity, and “other”. Other clinical manifestations included livedo reticularis/racemosa, persistent thrombocytopenia defined as a platelet count $< 100,000$ per microliter tested twice at least 12 weeks apart, autoimmune hemolytic anemia,

echocardiography proven cardiac valve disease, aPL-nephropathy, skin ulcers, chorea, seizure disorder, radiographic white matter lesions (only identified in those patients who had an MRI performed), and neuro-psychiatric test-proven cognitive dysfunction (Supplementary Table). Catastrophic APS was defined (definite or probable) based on the international classification criteria (15). Past and current medications, including aspirin, warfarin, low-molecular-weight heparin (LMWH), direct oral anticoagulants, corticosteroids, hydroxychloroquine (HCQ), intravenous immunoglobulin, rituximab, azathioprine, cyclophosphamide, cyclosporine, methotrexate, and mycophenolate mofetil, were collected at registry entry.

Study Design and Statistical Analysis

Data from APS ACTION Registry were locked in March 2019. First, we evaluated the baseline demographic and clinical characteristics of aPL-positive patients overall, and by clinical subtype: aPL without APS; APS (overall); OAPS, TAPS, and TAPS/OAPS. We also classified aPL-positive patients (overall and by aPL-related clinical subtypes) as having primary aPL/APS or aPL/APS with other systemic auto-immune disease (SAID) (including SLE, rheumatoid arthritis, mixed connective tissue disease, Sjogren's syndrome, systemic sclerosis, inflammatory muscle disease, and vasculitis).

Secondly, we assessed the clinical characteristics of aPL-positive patients with different baseline laboratory profiles (LA only, single, single after excluding LA, double, and triple positivity), among patients tested for all three aPL. Descriptive statistics were used to

describe continuous variables (mean, standard deviation, minimum, median, and maximum).

RESULTS

Baseline Characteristics in Overall Cohort

As of March 2019, 804 persistently aPL-positive patients were enrolled from 26 centers worldwide (mean age at entry: 45 ± 13 y; female: 594 [74%]; White: 546 [68%]; Latin American Mestizos: 87 [11%]; Europe: 387 [48%], North America: 232 [29%]). Table 1 shows the baseline demographic and clinical characteristics of aPL-positive patients at registry entry, overall and by clinical subtype. In the study cohort, 642 (80%) patients met clinical criteria for definite APS; among these patients, 74 (12%) had OAPS only, 446 (69%) had TAPS only, and 122 (19%) had both OAPS and TAPS. 162 patients (20%) did not meet clinical criteria for definite APS; among these “aPL without APS” patients, 76 (47%) had one or more other (non-criteria) clinical manifestations associated with aPL and 86 (53%) were asymptomatic. Thirty-six percent of the overall cohort had at least one concomitant SAID (SLE: 30%, Sjogren`s syndrome: 2%, mixed connective tissue disease: 2%, rheumatoid arthritis: 1%, vasculitis: 1%, systemic sclerosis: 1%, and other: 4%); the frequency of SAID was slightly higher in “aPL without APS” group (45%), compared to APS patients (33%).

Among the 804 registry participants, 568 (71%) had at least one vascular (arterial thrombosis, venous thrombosis, or microvascular involvement) event, and 28% had recurrent vascular events. Venous thrombosis occurred more frequently than arterial

thrombosis (43% vs 37%, both 11%) in the overall cohort; 12% had microvascular involvement and 1% had CAPS. Among those with arterial thrombosis, strokes (21%) occurred much more frequently than cardiac events (4%); lower extremity events were the most common type of venous thrombosis (27%). Of the 393 women in the registry with pregnancy history, 50% had a pregnancy morbidity event, most commonly due to unexplained fetal death ≥ 10 weeks (69%). Over half (56%) of the overall cohort had at least one non-criteria manifestation; among these, the most common were central nervous system white matter lesions and persistent thrombocytopenia.

In terms of medications currently used at registry entry, 62% of aPL-positive patients were on anticoagulation (warfarin [54%], LMWH [6%], factor Xa inhibitor [3%]); other commonly used medications were aspirin (46%), hydroxychloroquine (45%), and statins (24%).

Baseline Characteristics by Clinical Subtype

When comparing characteristics by aPL-related clinical subtypes (Table 1), concomitant SAID was highest in “aPL without APS” (45%) and lowest in OAPS (26%) patients; a similar pattern was reflected in aPL-positive patients with concomitant SLE specifically (37% in “aPL without APS” versus 20% in OAPS). Mean age was lowest in OAPS (41.47 ± 11 years) and highest in TAPS (46.69 ± 14 years). The majority of patients in each clinical subtype were White; there were very few Blacks, and the highest percent of Latin American Mestizos were in the TAPS/OAPS group (Table 1). Approximately 50% of cases in each clinical subtype were recruited from Europe, except TAPS/OAPS

which occurred less frequently in European patients (37%). Approximately 30% of TAPS/OAPS cases were recruited from Latin America, which was the most common clinical subtype recruited from this region.

While we observed similar frequencies of arterial (54% vs. 50%) and venous thrombotic events (60% vs. 64%) within the TAPS versus TAPS/OAPS groups, lower extremity venous thrombosis events were slightly higher in TAPS patients (40% vs. 33%) (Table 1). We also observed a similar rate of microvascular involvement (15% vs. 17%) and catastrophic APS (2% vs. 2%) between the TAPS and TAPS/OAPS groups. Comparing pregnancy morbidity in those with OAPS versus TAPS/OAPS, we found similar frequencies of unexplained death ≥ 10 th week (69% vs. 70%), premature birth < 34 th week due to eclampsia, pre-eclampsia or placental insufficiency (34% vs 35%), and at least three unexplained spontaneous abortions < 10 weeks gestation (15% vs. 19%).

Compared to the overall cohort, “aPL without APS” patients had a slightly lower rate of other clinical manifestations (47% vs 58%). Other clinical manifestations were highest in the TAPS/OAPS group (66%) and lowest in OAPS patients (41%); in particular, TAPS/OAPS had substantially higher rates of livedo reticularis/racemosa, persistent thrombocytopenia, cardiac valve disease, skin ulcer, and cognitive dysfunction compared to the other subtypes and the overall cohort (Table 1). TAPS patients also had a higher rate of other clinical manifestations (59%) compared to OAPS (41%).

The “aPL without APS” patients had higher rates of current aspirin (67% vs 40%) and hydroxychloroquine (56% vs 43%) use, and lower rates of anticoagulation, statin, and anti-hypertensive use compared to the APS patients at the time of registry entry. Aspirin use was highest in patients with a history of OAPS (70%) compared to thrombotic APS (38%) or TAPS/OAPS (31%). A majority of APS patients currently received anticoagulation with warfarin (66%) at registry entry; any current anticoagulation use (warfarin, LMWH, Factor Xa inhibitor, Thrombin inhibitor) was highest in TAPS (83%) compared to aPL without APS (11%). A similar pattern of medication use was observed for “ever” use at the time of registry entry among the aPL-related clinical subgroups (Table 1).

Baseline Characteristics by aPL Profile

Of the 804 aPL-positive patients, 660 (83%) were tested for all three aPL (LA, aCL, and a β ₂GPI), and 42% were triple aPL positive. We excluded eight patients who were tested for three aPL but had low titer (20-39U) aPL ELISA with negative LA test. Approximately one-fifth of patients (17%) were missing at least one aPL test; in this group, the proportion with single positivity was similar to that with double positivity (50% vs. 46%). Among those without three aPL tested, with single positivity only (50%), LA positivity was most common (37%); the combination of LA plus aCL positivity was more common than aCL plus a β ₂GPI in those with double aPL positivity (Figure 1).

While similar frequencies of vascular thrombosis, pregnancy morbidity, and other clinical manifestations were observed across single, double, and triple aPL positive

subgroups, the single aPL positivity subgroup excluding the patients with only LA positivity had substantially lower frequencies of all three event types (Table 2).

Compared to the other aPL profile subgroups, triple aPL positivity had the highest proportion of patients with at least one preterm delivery before 34 weeks of gestation, persistent thrombocytopenia, aPL nephropathy, and cardiac valve disease. Within the single aPL-positive group, LA only positivity had the highest proportion of patients with any vascular events, pregnancy morbidity, and other clinical manifestations (Table 2).

DISCUSSION

Based on our multi-center international aPL-positive cohort, one-fifth of patients meeting the entry criteria do not fulfill clinical APS classification criteria, 71% have vascular events, 50% of those with pregnancy history have aPL-related obstetric morbidity, and 56% have at least one non-criteria clinical aPL manifestation, most commonly thrombocytopenia and white matter lesions. Non-criteria clinical manifestations were highest in the TAPS/OAPS group versus TAPS or OAPS only. APS patients overall had higher current anticoagulation and statin use, but lower aspirin and hydroxychloroquine use than “aPL without APS” patients at registry entry. Compared to single, double, and triple aPL positive subgroups, the single aPL positivity subgroup excluding LA only had substantially lower frequencies of vascular, pregnancy morbidity, and other clinical events; this suggests that LA positivity appears to be a major contributor to aPL-related clinical features.

Our study adds to prior work demonstrating the clinical heterogeneity of aPL, which can result in a broad spectrum of clinical manifestations. Although the current (Revised Sapporo) APS classification criteria incorporates vascular events and pregnancy morbidity, various “non-criteria” manifestations, known to occur frequently in aPL-positive patients were not included (16–18). Since then, various systematic reviews and meta-analyses in SLE patients have aimed to better characterize the role of aPL-related “non-criteria” manifestations, demonstrating an increased likelihood of cardiac valve disease, pulmonary hypertension, livedo reticularis, thrombocytopenia, hemolytic anemia, and renal impairment in aPL-positive SLE patients compared to aPL-negative SLE patients (11,19). Others have assessed these manifestations in APS patients with and without concomitant SAID and demonstrated increased rates of cognitive dysfunction, white matter lesions, aPL-nephropathy, thrombocytopenia, and livedo reticularis (10,20). The current study adds to this literature by demonstrating that non-criteria manifestations, most commonly white matter lesions and thrombocytopenia, occurred in the majority (56%) of international aPL-positive patients, and were more likely to occur in TAPS/OAPS patients (66%), suggesting that non-criteria manifestations are prevalent in aPL-positive patients and potentially associated with more severe disease (20,21). In fact, efforts are underway using cluster analysis methodology, a data-driven method which groups patients by combinations of aPL profiles and clinical features, to further identify clinical phenotypes and distinct “clusters” of APS ACTION patients (22,23).

Assessment of clinical phenotypes, along with better understanding of the role of aPL laboratory profile, may play a critical role in risk stratification of aPL-positive patients (24). Although the definition of a “clinically significant” and “high-risk” aPL profile has not been clearly defined, different aPL profiles appear to confer different thrombosis risks (7,25–27). Positive LA (compared to aCL or a β_2 GPI ELISA tests), moderate-to-high titer (≥ 40 U) aCL or a β_2 GPI (compared to lower titers), IgG isotype (compared to IgM and IgA isotype), and triple aPL-positivity (compared to single or dual aPL positivity) correlate better with aPL-related clinical events (28–30). However, there is ongoing debate about the clinical significance of isolated LA positivity and whether it is as important as triple aPL positivity. Additionally, one recent study demonstrated that aCL IgG but not IgM, and LA test positivity are associated with higher rates of thromboses in SLE patients (31). Our cross-sectional analysis, demonstrating a relatively similar frequency of aPL-related clinical events in single, double, and triple aPL positivity, and a substantially lower frequency in single positive aPL patients without LA, supports the association of clinical events with LA positivity. Furthermore, while accumulating data show that LA positivity may be a stronger risk factor for thrombosis and pregnancy morbidity than positivity for either aCL or a β_2 GPI (1,32), standardization of laboratory testing and cut-off thresholds are still needed (1). Prospective studies will determine the association between laboratory study levels and clinically relevant disease.

While anticoagulation is the mainstay of treatment of aPL-related clinical events in thrombotic APS (33), alternative treatments are required in patients with refractory disease or microvascular APS (24,34–39). Although the majority of APS patients overall

received anticoagulation, less than half received aspirin or immunosuppression and few received other treatments such as intravenous immunoglobulin, plasma exchange, or rituximab. This finding may reflect an inherently low rate of refractory/microvascular APS or selection bias in our cohort. While data regarding treatment of obstetric APS are controversial regarding the need for prophylactic low dose aspirin versus the addition of unfractionated heparin to low-dose aspirin (40–44), the majority of OAPS only patients in our cohort received aspirin (ever and at registry entry) and LMWH (ever).

Furthermore, no clear consensus exists on primary prevention management of persistently aPL-positive patients (45), including use of aspirin, hydroxychloroquine or anticoagulation, although recent European League Against Rheumatism (EULAR) guidelines suggest that low dose aspirin may be beneficial for various aPL-positive patients (46). Our registry data show that the majority of “aPL without APS” patients were treated with aspirin (67%) and HCQ (56%), which may be driven by use of these medications for prevention of thrombosis, underlying concomitant systemic autoimmune disease, (45% of aPL without APS patients), or other comorbid medical disease including cardiovascular risk factors. aPL patients without APS had the highest percentage of concomitant SLE, which may have prompted aPL testing in this group.

Although we previously reported that LA positivity, livedo, and cognitive dysfunction are more common in patients recruited from Brazil compared to those recruited from other parts of the world (47), the current study did not investigate specific clinical and laboratory differences by geographic region as a comprehensive regional analysis of the

registry is underway. Additionally, the low rate of black patients (3-4%) in the registry may reflect selection bias (e.g. half of the patients were recruited from Europe), or disparities in access to care and would be worth investigation in future studies.

While our study was limited in its retrospective, cross-sectional study design, we used data from a large, multi-center international patient cohort enriched with granular sociodemographic, clinical, laboratory, and medication information. Epidemiologic studies focusing on APS are limited; few large APS cohorts inclusive of different genders, races and geographic regions are available to estimate the distribution of APS across clinical and laboratory subtypes. As data collection is ongoing in our registry, our data represents an interim assessment of baseline characteristics; future analyses will use statistical testing and APS ACTION core laboratory aPL test results to evaluate significant differences between subgroups. Selection bias could be a factor in the low percentage of “other” clinical manifestations and SAID in the OAPS group, as some patients in this group are recruited from obstetrics clinics. Our future prospective study will assess the risk of incident SAID development after the diagnosis of primary OAPS. Although selection and referral bias to APS “experts” should be considered in interpretation of our registry data, our study demonstrated a low rate of CAPS or use of medications suggestive of refractory disease. Additionally, given that the aPL profile was not necessarily collected at the time of the clinical event, our results should be confirmed in prospective studies. Additionally, while other “non-criteria” aPL tests, such as anti-phosphatidyl serine-prothrombin and anti-Domain I antibodies, are increasingly shown to contribute to APS diagnosis and risk assessment for thrombosis (48,49), our

study did not evaluate these laboratory tests as they are not currently standardized or widely commercially available. Lastly, although we did not stratify our cohort by those with or without an SAID, in a previous analysis of APS ACTION registry patients, the frequencies of thrombosis and pregnancy morbidity were similar in aPL-positive patients with or without concomitant SLE, however SLE in patients with persistent aPL positivity was associated with increased frequency of thrombocytopenia, hemolytic anemia, low complement, and positive IgA anti- β_2 GPI antibodies (50).

In conclusion, our study demonstrates the heterogeneity of aPL-related clinical manifestations and laboratory profiles in a multi-center, international aPL-positive cohort. Identification of APS patients by different clinical phenotypes and aPL profiles may improve risk stratification and help physicians and researchers better characterize the disease and understand clinical outcomes. Future prospective analyses, using standardized core laboratory aPL tests, will help clarify the role of aPL risk profiles.

Word Count: 3,448

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TABLES AND FIGURES

Table 1: Baseline Demographic and Clinical Characteristics of Antiphospholipid Antibody (aPL) Positive Patients Between Different Groups of aPL-positive Patients Included in the AntiPhospholipid Syndrome (APS) Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Based on aPL-related Clinical Phenotype (2010-2019)

Number (%)	All Patients 804	aPL Without APS 162 (20)	APS (Overall) 642 (80)	OAPS Only 74 (9)	TAPS Only 446 (55)	TAPS + OAPS 122 (15)
Primary aPL/APS	516 (64)	89 (55)	427 (67)	55 (74)	295 (66)	77 (63)
Concomitant Systemic Autoimmune Disease¹	288 (36)	73 (45)	215 (33)	19 (26)	151 (34)	45 (37)
Systemic Lupus Erythematosus	242 (30)	60 (37)	182 (28)	15 (20)	129 (29)	38 (31)
Sociodemographic						
Age at Registry Entry (mean ± SD years)	45.12 ± 13	43.80 ± 13	45.45 ± 13	41.47 ± 11	46.69 ± 14	43.34 ± 12
Gender						
Female	594 (74)	127 (78)	467 (73)	74 (100)	271 (61)	122 (100)
Race²						
White	546 (68)	118 (73)	428 (67)	52 (70)	305 (68)	71 (58)
Latin American Mestizos	87 (11)	6 (4)	81 (13)	6 (8)	47 (11)	28 (23)
Asian	56 (7)	17 (10)	39 (6)	8 (11)	24 (5)	7 (8)
Black	26 (3)	7 (4)	19 (3)	2 (3)	12 (3)	5 (4)
American Indian or Alaskan	2	1 (1)	1	0	1	0
Native American	0	0	0	0	0	0
Reported as "Other" ³	14 (2)	2 (1)	12 (2)	1 (1)	9 (2)	2 (2)
Ethnicity⁴						
United States, Canada, Europe	377 (47)	92 (57)	285 (44)	43 (58)	201 (45)	41 (34)
Non-Hispanic	356 (44)	88 (54)	268 (42)	38 (51)	194 (43)	36 (30)
Hispanic	21 (3)	4 (2)	17 (3)	5 (7)	7 (2)	5 (4)
South America	137 (17)	8 (5)	129 (20)	8 (11)	82 (18)	39 (32)
Mestizos	72 (9)	2 (1)	70 (11)	4 (5)	42 (9)	24 (20)
Caucasian	47 (6)	4 (2)	43 (7)	2 (3)	31 (7)	10 (8)
Afro-descendent	18 (2)	2 (1)	16 (2)	2 (3)	9 (2)	5 (4)
Other ⁵	135 (17)	35 (22)	100 (16)	16 (22)	65 (15)	19 (16)
Australia	4 (1)	0	4 (1)	0	2	2 (2)
Not Aboriginal	4 (1)	0	4 (1)	0	2	2 (2)
Aboriginal	0	0	0	0	0	0

Region of Residence						
Europe	387 (48)	84 (52)	303 (47)	37 (50)	221 (50)	45 (37)
North America	232 (29)	60 (37)	172 (27)	23 (31)	117 (26)	32 (26)
USA	201 (25)	56 (35)	145 (23)	21 (28)	95 (21)	29 (24)
Canada	31 (4)	4 (2)	27 (4)	2 (3)	22 (5)	3 (4)
Latin America	131 (16)	6 (4)	125 (19)	7 (9)	83 (19)	35 (29)
Asia-Pacific	54 (7)	12 (7)	42 (7)	7 (9)	25 (6)	10 (8)
Clinical Manifestations						
Any Vascular Event	568 (71)	0	568 (71)	0	446 (100)	122 (100)
Any Arterial Thrombosis	300 (37)	0	300 (37)	0	239 (54)	61 (50)
Stroke	165 (21)	0	165 (26)	0	127 (28)	38 (31)
Transient Ischemic Attacks	69 (9)	0	69 (11)	0	50 (11)	19 (16)
Myocardial Infarction	31 (4)	0	31 (5)	0	29 (7)	2 (2)
Intracardiac Thrombus	3	0	3	0	2	1 (1)
Peripheral Artery ⁶	30 (4)	0	30 (5)	0	27 (6)	3 (3)
Visceral	10 (1)	0	10 (2)	0	9 (2)	1 (1)
Retinal	5 (1)	0	5 (1)	0	3 (1)	2 (2)
Any Venous Thrombosis	347 (43)	0	347 (54)	0	269 (60)	78 (64)
Central Venous Sinus	13 (2)	0	13 (2)	0	12 (3)	1 (1)
Pulmonary Embolism	76 (9)	0	76 (12)	0	64 (14)	12 (10)
Upper Extremity	7 (1)	0	7 (1)	0	7 (2)	0
Lower Extremity	217 (27)	0	217 (34)	0	177 (40)	40 (33)
Visceral	8 (1)	0	8 (1)	0	4 (1)	4 (3)
Retinal	6 (1)	0	6 (1)	0	5 (1)	1
Any Microvascular Involvement	93 (12)	3 (2)	90 (14)	2 (3)	67 (15)	21 (17)
Biopsy Proven	32 (4)	0	32 (5)	0	26 (6)	6 (5)
Kidney	15 (2)	0	15 (2)	0	11 (2)	4 (3)
Skin	9 (1)	0	9 (1)	0	9 (2)	0
Pulmonary	3	0	3	0	3 (1)	0
Other	5 (1)	0	5 (1)	0	3 (1)	2 (2)
Clinical Suspicion, No Biopsy	61 (8)	3 (2)	58 (9)	2 (3)	41 (9)	15 (12)
Kidney	14 (2)	0	14 (2)	2 (3)	10 (2)	2 (2)
Skin	37 (5)	3 (2)	34 (5)	0	24 (5)	10 (8)
Pulmonary	2	0	2	0	2	0
Other	8 (1)	0	8 (1)	0	5 (1)	3 (2)

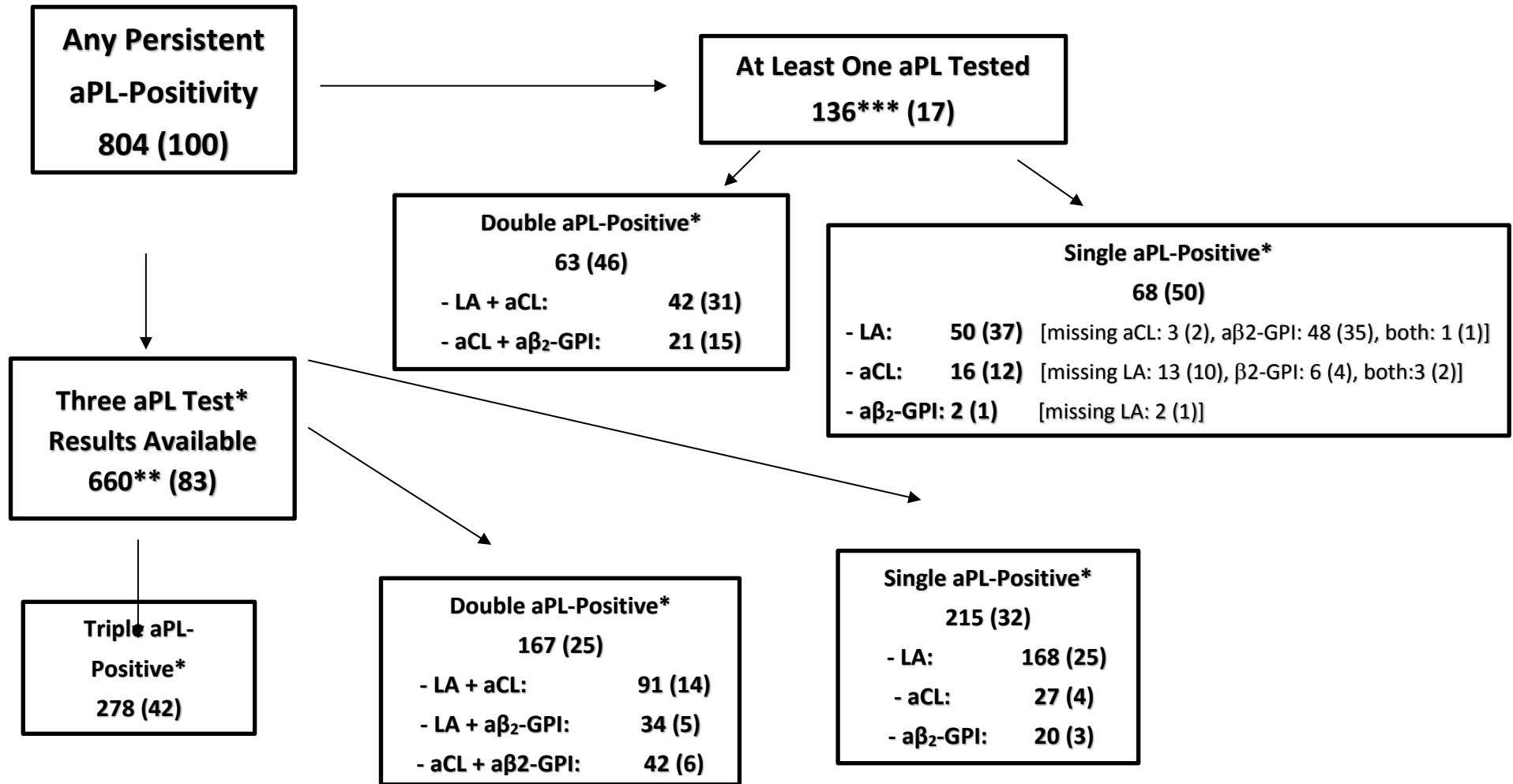
Both Arterial and Venous Thrombosis	92 (11)	0	92 (14)	0	72 (16)	20 (16)
Recurrent Vascular Events⁷	225 (28)	0	225 (35)	0	173 (39)	52 (43)
Catastrophic APS⁸	9 (1)	0	9 (1)	0	7 (2)	2 (2)
History of Pregnancy	393/594 (66)	70/127 (55)	323 (50)	74 (100)	127/271 (47)	122 (100)
Pregnancy Morbidity	196/393 (50)	0	196/323 (61)	74 (100)	0	122 (100)
Unexplained Death ≥10th week	136/196 (69)	0	136/196 (69)	51/74 (69)	0	85/122 (70)
Premature Birth <34th week Due to Eclampsia, Preeclampsia or Placental Insufficiency	68/196 (35)	0	68/196 (35)	25/74 (34)	0	43/122 (35)
≥3 Unexplained Spontaneous Abortion < 10th Week	34/196 (17)	0	34/196 (17)	11/74 (15)	0	23/122 (19)
Three Consecutive Unexplained Spontaneous Abortions <10th week	29/196 (15)	0	29/196 (15)	9/74 (12)	0	20/122 (16)
Other Clinical Manifestations⁹	451 (56)	76 (47)	375 (58)	30 (41)	264 (59)	81 (66)
Livedo Reticularis/Racemosa	100 (12)	10 (6)	90 (14)	8 (11)	56 (13)	26 (21)
Persistent Thrombocytopenia (platelet count <100,000/μL)	151 (19)	32 (20)	119 (19)	14 (19)	75 (17)	30 (25)
Autoimmune Hemolytic Anemia	40 (5)	9 (6)	31 (5)	4 (5)	22 (5)	5 (4)
Cardiac Valve Disease	65 / 688 (9)	10/142 (7)	56/546 (10)	2/52 (4)	34/391 (9)	20/103 (19)
Skin Ulcer	50 (5)	3 (2)	47 (6)	0	36 (6)	11 (7)
aPL-Associated Nephropathy	29/755 (4)	0/156 (0)	29/599 (5)	2/69 (3)	21/414 (5)	6/116 (5)
Neurologic Presentations						
Cognitive Dysfunction	85 (11)	11 (7)	74 (12)	3 (4)	53 (12)	18 (15)
MS-like disease	6 (1)	1 (1)	5 (1)	0	5 (1)	0
Chorea	13 (2)	2 (1)	11 (2)	0	7 (2)	4 (3)
Seizure Disorder	67 (8)	8 (5)	59 (9)	3 (4)	42 (9)	14 (11)
White Matter lesions	136 / 549 (25)	17/103 (17)	119/446 (27)	6/35 (17)	90/326 (28)	23/85 (27)
Medications (Registry Entry)						
Any Anticoagulation	497 (62)	18 (11)	479 (75)	9 (12)	372 (83)	98 (80)
Warfarin	434 (54)	13 (8)	421 (66)	4 (5)	328 (74)	89 (73)
Low-Molecular-Weight-Heparin	48 (6)	4 (2)	44 (7)	5 (7)	30 (7)	9 (7)
Factor Xa Inhibitor	28 (3)	1 (1)	27 (4)	0	26 (6)	1 (1)
Thrombin Inhibitor	0	0	0	0	0	0
Acetylsalicylic Acid (Aspirin)	366 (46)	108 (67)	258 (40)	52 (70)	168 (38)	38 (31)
Clopidogrel	29 (4)	2 (1)	27 (4)	1 (1)	21 (5)	5 (4)
Hydroxychloroquine	364 (45)	90 (56)	274 (43)	31 (44)	189 (42)	54 (44)

Statins	191 (24)	16 (10)	175 (27)	9 (12)	143 (32)	23 (19)
Angiotensin-Converting Enzyme Inhibitor/ Angiotensin Receptor Blocker	163 (20)	21 (13)	142 (22)	9 (12)	106 (24)	27 (22)
Intravenous Immunoglobulin	5 (1)	0	5 (1)	0	5 (1)	0
Plasma exchange	1	0	1	0	0	1 (1)
Rituximab	16 (2)	3 (2)	13 (2)	0	12 (3)	1 (1)
Other Immunosuppression ¹⁰	202 (25)	42 (26)	160 (25)	10 (14)	116 (26)	34 (28)
No medications	28 (3)	16 (10)	12 (2)	9 (12)	2	1 (1)
Medications (Ever)						
Any Anticoagulation	763 (95)	37 (23)	566 (88)	43 (58)	407 (91)	116 (95)
Warfarin	526 (65)	20 (12)	506 (79)	10 (14)	388 (87)	108 (89)
Low-Molecular-Weight-Heparin	340 (42)	21 (13)	319 (50)	41 (55)	200 (45)	78 (64)
Factor Xa Inhibitor	43 (5)	2 (1)	41 (6)	1 (1)	37 (8)	3 (3)
Thrombin Inhibitor	4 (1)	0	0	0	4 (1)	0
Acetylsalicylic Acid (Aspirin)	516 (64)	121 (75)	395 (62)	63 (85)	250 (56)	82 (67)
Clopidogrel	50 (6)	3 (2)	47 (7)	1 (1)	38 (9)	8 (7)
Hydroxychloroquine	428 (53)	101 (62)	327 (51)	34 (46)	223 (50)	70 (57)
Statins	210 (26)	20 (12)	190 (30)	9 (12)	153 (34)	28 (23)
Angiotensin-Converting Enzyme Inhibitor/ Angiotensin Receptor Blocker	192 (24)	23 (14)	169 (26)	11 (15)	121 (27)	37 (30)
Intravenous Immunoglobulin	57 (7)	11 (7)	46 (7)	4 (5)	35 (8)	7 (6)
Plasma exchange	16 (2)	1 (1)	15 (2)	2 (3)	8 (2)	5 (4)
Rituximab	48 (6)	9 (6)	39 (6)	1(1)	34 (8)	4 (3)
Other Immunosuppression ¹⁰	297 (37)	57 (35)	240 (37)	18 (24)	174 (39)	48 (39)
No medications	11 (1)	9 (6)	2	2	0	0

Missing data and other categories are not included. APS: Antiphospholipid Syndrome; TAPS: Thrombotic APS; OAPS: Obstetric APS.

¹ Systemic autoimmune diseases included SLE, rheumatoid arthritis, mixed connective tissue disease, Sjogren's syndrome, systemic sclerosis, inflammatory muscle disease, and vasculitis. ² Races were allowed to be collected in a total of 731 patients (aPL only: 162, OAPS: 69, TAPS: 403, TAPS+OAPS: 97). Latin American Mestizo: refers to a person of combined European and Indigenous American descent. ³ Includes American Indian or Alaskan; Native Hawaiian or Pacific Islander; and other unspecified races as indicated by the patient. ⁴ Ethnicities were allowed to be collected in a total of 653 patients (aPL only: 146, OAPS: 65, TAPS: 354, TAPS+OAPS: 88). ⁵ Other unspecified ethnicities as indicated by the patient. ⁶ Consists of the arteries not in the chest or abdomen (i.e. in the arms, hands, legs and feet). ⁷ Arterial and/or venous. ⁸ Catastrophic APS (CAPS): was diagnosed when all four criteria of the CAPS Classification Criteria (1). ⁹ Livedo reticularis/racemosa, persistent thrombocytopenia, and autoimmune hemolytic anemia, patients were considered as ever or never having had these findings at the time of registry entry; μ L: microliter. ¹⁰ Other immunosuppression includes: Azathioprine, Corticosteroids, Cyclophosphamide, Cyclosporine, Methotrexate, Mycophenolate Mofetil and others

Figure 1: Baseline Antiphospholipid Antibody (aPL) Profile Among Persistently Positive Antiphospholipid Patients Included in the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking Registry (n: 804)



aPL: Antiphospholipid Antibodies;

*: LA: Lupus anticoagulant; aCL: Anticardiolipin Antibody; a β ₂GPI: Anti- β ₂ Glycoprotein-I Antibody;

** : Additional 8 patients (1%), tested for three aPL, but were excluded due to low titer (20-39U) aPL ELISA with negative LA test.

***Of 804 patients, 136 (17%) had missing data for antiphospholipid antibody profile; LA: 38 (5%), aCL: 3, and a β ₂-GPI: 100 (12%).

Table 2: Clinical Characteristics of Antiphospholipid Antibody Positive Patients in the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Registry (2010-2019) Tested for Three aPL Antibodies*, Categorized by aPL Profile (n: 660)**

<u>Number (%)</u>	LA only Positivity 168 (25)	Any Single*** aPL Positivity 215 (32)	Single aPL (excluding LA only) 47 (7)	Double*** aPL Positivity 167 (25)	Triple*** aPL Positivity 278 (42%)
<u>Any Vascular Events</u>	127 (73)	148 (67)	21 (45)	118 (68)	195 (70)
Arterial thrombosis	61 (36)	73 (34)	12 (26)	68 (41)	96 (35)
Venous Thrombosis	81 (48)	92 (43)	11 (23)	66 (40)	132 (47)
Microvascular Thrombosis	10 (6)	12 (6)	2 (4)	9 (5)	16 (6)
Transient Ischemic Attacks	11 (7)	13 (6)	2 (4)	19 (11)	20 (7)
<u>Any Pregnancy Morbidity</u>	43/84 (51)	53/108 (49)	10/24 (42)	41/86 (48)	62/117 (53)
>1 Fetal Death ≥10th week	31 (51)	39 (52)	8 (57)	29 (53)	43 (56)
>1 Preterm Delivery <34th week	12 (20)	13 (17)	1 (7)	14 (25)	29 (38)
≥3 Pre-Emb/Emb Loss <10th week	9 (15)	14 (19)	5 (36)	6 (11)	6 (8)
<u>Any Other Clinical Manifestation</u>	93 (55)	107 (50)	14 (30)	104 (62)	158 (57)
Livedo Reticularis/Racemosa	27 (16)	28 (13)	1 (2)	24 (14)	32 (12)
Persistent Thrombocytopenia	26 (15)	30 (14)	4 (9)	29 (17)	70 (25)
Hemolytic Anemia	9 (5)	10 (5)	1 (2)	7 (4)	16 (6)
Cardiac Valve Disease	11/146 (8)	12/188 (6)	1/42 (2)	12/142 (8)	32/234 (14)
Skin Ulcers	6 (4)	7 (3)	1 (2)	7 (4)	10 (4)
aPL-associated Nephropathy	4/157 (3)	4/201 (2)	0	5/160 (3)	11/256 (4)
Cognitive Dysfunction	14 (8)	17 (8)	3 (6)	20 (12)	33 (12)
Multiple Sclerosis-like disease	2 (1)	3 (1)	1 (2)	3 (2)	0
Chorea	2 (1)	2 (1)	0	4 (2)	6 (2)
Seizure	17 (10)	21 (10)	4 (9)	13 (8)	23 (8)
White Matter Lesions	33/120 (28)	40/155 (26)	7/35 (20)	33/116 (28)	45/190 (24)

*Patients in this analysis were tested for three aPL (lupus anticoagulant [LA], anticardiolipin antibody [aCL], and anti-β₂-Glycoprotein-I [aβ₂GPI]). --Single aPL Positivity was defined as positivity for one of the three aPL tests. Double positivity included 2/3 and triple included 3/3 aPL positive tests)

**Additional 8 patients, tested for three aPL, had low titer (20-39U) aPL ELISA with negative LA test; thus they were excluded

***: 40U cut-off for aCL and a β 2GPI IgG/M/A positivity

All groups except LA only and single aPL were mutually exclusive.

Only 5/660 (0.8%) of patients had isolated aCL/a β 2GPI IgA positivity with negative LA and aCL/a β 2GPI IgG/M.

In total 6 patients had Catastrophic APS, distributed between double and triple aPL positive groups.

Persistent thrombocytopenia was defined as a platelet count of <100,000 per microliter tested twice at least 12 weeks apart.

Autoimmune hemolytic anemia was defined as anemia in the presence of antibodies directed against red blood cells, evidenced by either direct or indirect Coombs tests.

Abbreviations: aPL: Antiphospholipid Antibodies; APS: Antiphospholipid Syndrome; MS: Multiple Sclerosis

TABLES AND FIGURES

Table 1: Baseline Demographic and Clinical Characteristics of Antiphospholipid Antibody (aPL) Positive Patients Between Different Groups of aPL-positive Patients Included in the AntiPhospholipid Syndrome (APS) Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Based on aPL-related Clinical Phenotype (2010-2019)

Number (%)	All Patients 804	aPL Without APS 162 (20)	APS (Overall) 642 (80)	OAPS Only 74 (9)	TAPS Only 446 (55)	TAPS + OAPS 122 (15)
Primary aPL/APS	516 (64)	89 (55)	427 (67)	55 (74)	295 (66)	77 (63)
Concomitant Systemic Autoimmune Disease¹	288 (36)	73 (45)	215 (33)	19 (26)	151 (34)	45 (37)
Systemic Lupus Erythematosus	242 (30)	60 (37)	182 (28)	15 (20)	129 (29)	38 (31)
Sociodemographic						
Age at Registry Entry (mean ± SD years)	45.12 ± 13	43.80 ± 13	45.45 ± 13	41.47 ± 11	46.69 ± 14	43.34 ± 12
Gender						
Female	594 (74)	127 (78)	467 (73)	74 (100)	271 (61)	122 (100)
Race²						
White	546 (68)	118 (73)	428 (67)	52 (70)	305 (68)	71 (58)
Latin American Mestizos	87 (11)	6 (4)	81 (13)	6 (8)	47 (11)	28 (23)
Asian	56 (7)	17 (10)	39 (6)	8 (11)	24 (5)	7 (8)
Black	26 (3)	7 (4)	19 (3)	2 (3)	12 (3)	5 (4)
American Indian or Alaskan	2	1 (1)	1	0	1	0
Native American	0	0	0	0	0	0
Reported as "Other" ³	14 (2)	2 (1)	12 (2)	1 (1)	9 (2)	2 (2)
Ethnicity⁴						
United States, Canada, Europe	377 (47)	92 (57)	285 (44)	43 (58)	201 (45)	41 (34)
Non-Hispanic	356 (44)	88 (54)	268 (42)	38 (51)	194 (43)	36 (30)
Hispanic	21 (3)	4 (2)	17 (3)	5 (7)	7 (2)	5 (4)
South America	137 (17)	8 (5)	129 (20)	8 (11)	82 (18)	39 (32)
Mestizos	72 (9)	2 (1)	70 (11)	4 (5)	42 (9)	24 (20)
Caucasian	47 (6)	4 (2)	43 (7)	2 (3)	31 (7)	10 (8)
Afro-descendent	18 (2)	2 (1)	16 (2)	2 (3)	9 (2)	5 (4)
Other ⁵	135 (17)	35 (22)	100 (16)	16 (22)	65 (15)	19 (16)
Australia	4 (1)	0	4 (1)	0	2	2 (2)
Not Aboriginal	4 (1)	0	4 (1)	0	2	2 (2)
Aboriginal	0	0	0	0	0	0

Region of Residence						
Europe	387 (48)	84 (52)	303 (47)	37 (50)	221 (50)	45 (37)
North America	232 (29)	60 (37)	172 (27)	23 (31)	117 (26)	32 (26)
USA	201 (25)	56 (35)	145 (23)	21 (28)	95 (21)	29 (24)
Canada	31 (4)	4 (2)	27 (4)	2 (3)	22 (5)	3 (4)
Latin America	131 (16)	6 (4)	125 (19)	7 (9)	83 (19)	35 (29)
Asia-Pacific	54 (7)	12 (7)	42 (7)	7 (9)	25 (6)	10 (8)
Clinical Manifestations						
Any Vascular Event	568 (71)	0	568 (71)	0	446 (100)	122 (100)
Any Arterial Thrombosis	300 (37)	0	300 (37)	0	239 (54)	61 (50)
Stroke	165 (21)	0	165 (26)	0	127 (28)	38 (31)
Transient Ischemic Attacks	69 (9)	0	69 (11)	0	50 (11)	19 (16)
Myocardial Infarction	31 (4)	0	31 (5)	0	29 (7)	2 (2)
Intracardiac Thrombus	3	0	3	0	2	1 (1)
Peripheral Artery ⁶	30 (4)	0	30 (5)	0	27 (6)	3 (3)
Visceral	10 (1)	0	10 (2)	0	9 (2)	1 (1)
Retinal	5 (1)	0	5 (1)	0	3 (1)	2 (2)
Any Venous Thrombosis	347 (43)	0	347 (54)	0	269 (60)	78 (64)
Central Venous Sinus	13 (2)	0	13 (2)	0	12 (3)	1 (1)
Pulmonary Embolism	76 (9)	0	76 (12)	0	64 (14)	12 (10)
Upper Extremity	7 (1)	0	7 (1)	0	7 (2)	0
Lower Extremity	217 (27)	0	217 (34)	0	177 (40)	40 (33)
Visceral	8 (1)	0	8 (1)	0	4 (1)	4 (3)
Retinal	6 (1)	0	6 (1)	0	5 (1)	1
Any Microvascular Involvement	93 (12)	3 (2)	90 (14)	2 (3)	67 (15)	21 (17)
Biopsy Proven	32 (4)	0	32 (5)	0	26 (6)	6 (5)
Kidney	15 (2)	0	15 (2)	0	11 (2)	4 (3)
Skin	9 (1)	0	9 (1)	0	9 (2)	0
Pulmonary	3	0	3	0	3 (1)	0
Other	5 (1)	0	5 (1)	0	3 (1)	2 (2)
Clinical Suspicion, No Biopsy	61 (8)	3 (2)	58 (9)	2 (3)	41 (9)	15 (12)
Kidney	14 (2)	0	14 (2)	2 (3)	10 (2)	2 (2)
Skin	37 (5)	3 (2)	34 (5)	0	24 (5)	10 (8)
Pulmonary	2	0	2	0	2	0
Other	8 (1)	0	8 (1)	0	5 (1)	3 (2)

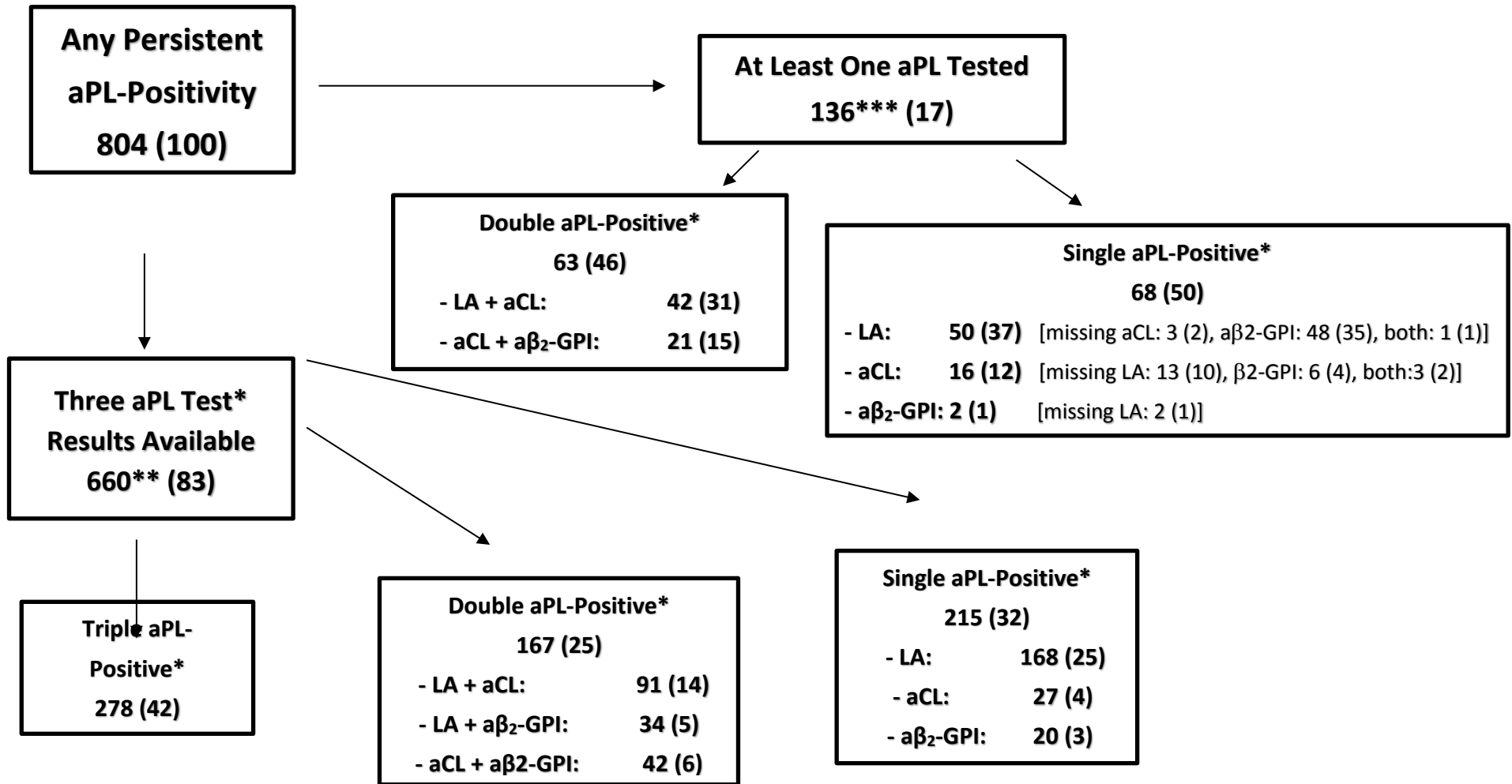
Both Arterial and Venous Thrombosis	92 (11)	0	92 (14)	0	72 (16)	20 (16)
Recurrent Vascular Events⁷	225 (28)	0	225 (35)	0	173 (39)	52 (43)
Catastrophic APS⁸	9 (1)	0	9 (1)	0	7 (2)	2 (2)
History of Pregnancy	393/594 (66)	70/127 (55)	323 (50)	74 (100)	127/271 (47)	122 (100)
Pregnancy Morbidity	196/393 (50)	0	196/323 (61)	74 (100)	0	122 (100)
Unexplained Death ≥10th week	136/196 (69)	0	136/196 (69)	51/74 (69)	0	85/122 (70)
Premature Birth <34th week Due to Eclampsia, Preeclampsia or Placental Insufficiency	68/196 (35)	0	68/196 (35)	25/74 (34)	0	43/122 (35)
≥3 Unexplained Spontaneous Abortion < 10th Week	34/196 (17)	0	34/196 (17)	11/74 (15)	0	23/122 (19)
Three Consecutive Unexplained Spontaneous Abortions <10th week	29/196 (15)	0	29/196 (15)	9/74 (12)	0	20/122 (16)
Other Clinical Manifestations⁹	451 (56)	76 (47)	375 (58)	30 (41)	264 (59)	81 (66)
Livedo Reticularis/Racemosa	100 (12)	10 (6)	90 (14)	8 (11)	56 (13)	26 (21)
Persistent Thrombocytopenia (platelet count <100,000/μL)	151 (19)	32 (20)	119 (19)	14 (19)	75 (17)	30 (25)
Autoimmune Hemolytic Anemia	40 (5)	9 (6)	31 (5)	4 (5)	22 (5)	5 (4)
Cardiac Valve Disease	65 / 688 (9)	10/142 (7)	56/546 (10)	2/52 (4)	34/391 (9)	20/103 (19)
Skin Ulcer	50 (5)	3 (2)	47 (6)	0	36 (6)	11 (7)
aPL-Associated Nephropathy	29/755 (4)	0/156 (0)	29/599 (5)	2/69 (3)	21/414 (5)	6/116 (5)
Neurologic Presentations						
Cognitive Dysfunction	85 (11)	11 (7)	74 (12)	3 (4)	53 (12)	18 (15)
MS-like disease	6 (1)	1 (1)	5 (1)	0	5 (1)	0
Chorea	13 (2)	2 (1)	11 (2)	0	7 (2)	4 (3)
Seizure Disorder	67 (8)	8 (5)	59 (9)	3 (4)	42 (9)	14 (11)
White Matter lesions	136 / 549 (25)	17/103 (17)	119/446 (27)	6/35 (17)	90/326 (28)	23/85 (27)
Medications (Registry Entry)						
Any Anticoagulation	497 (62)	18 (11)	479 (75)	9 (12)	372 (83)	98 (80)
Warfarin	434 (54)	13 (8)	421 (66)	4 (5)	328 (74)	89 (73)
Low-Molecular-Weight-Heparin	48 (6)	4 (2)	44 (7)	5 (7)	30 (7)	9 (7)
Factor Xa Inhibitor	28 (3)	1 (1)	27 (4)	0	26 (6)	1 (1)
Thrombin Inhibitor	0	0	0	0	0	0
Acetylsalicylic Acid (Aspirin)	366 (46)	108 (67)	258 (40)	52 (70)	168 (38)	38 (31)
Clopidogrel	29 (4)	2 (1)	27 (4)	1 (1)	21 (5)	5 (4)
Hydroxychloroquine	364 (45)	90 (56)	274 (43)	31 (44)	189 (42)	54 (44)

Statins	191 (24)	16 (10)	175 (27)	9 (12)	143 (32)	23 (19)
Angiotensin-Converting Enzyme Inhibitor/ Angiotensin Receptor Blocker	163 (20)	21 (13)	142 (22)	9 (12)	106 (24)	27 (22)
Intravenous Immunoglobulin	5 (1)	0	5 (1)	0	5 (1)	0
Plasma exchange	1	0	1	0	0	1 (1)
Rituximab	16 (2)	3 (2)	13 (2)	0	12 (3)	1 (1)
Other Immunosuppression ¹⁰	202 (25)	42 (26)	160 (25)	10 (14)	116 (26)	34 (28)
No medications	28 (3)	16 (10)	12 (2)	9 (12)	2	1 (1)
Medications (Ever)						
Any Anticoagulation	763 (95)	37 (23)	566 (88)	43 (58)	407 (91)	116 (95)
Warfarin	526 (65)	20 (12)	506 (79)	10 (14)	388 (87)	108 (89)
Low-Molecular-Weight-Heparin	340 (42)	21 (13)	319 (50)	41 (55)	200 (45)	78 (64)
Factor Xa Inhibitor	43 (5)	2 (1)	41 (6)	1 (1)	37 (8)	3 (3)
Thrombin Inhibitor	4 (1)	0	0	0	4 (1)	0
Acetylsalicylic Acid (Aspirin)	516 (64)	121 (75)	395 (62)	63 (85)	250 (56)	82 (67)
Clopidogrel	50 (6)	3 (2)	47 (7)	1 (1)	38 (9)	8 (7)
Hydroxychloroquine	428 (53)	101 (62)	327 (51)	34 (46)	223 (50)	70 (57)
Statins	210 (26)	20 (12)	190 (30)	9 (12)	153 (34)	28 (23)
Angiotensin-Converting Enzyme Inhibitor/ Angiotensin Receptor Blocker	192 (24)	23 (14)	169 (26)	11 (15)	121 (27)	37 (30)
Intravenous Immunoglobulin	57 (7)	11 (7)	46 (7)	4 (5)	35 (8)	7 (6)
Plasma exchange	16 (2)	1 (1)	15 (2)	2 (3)	8 (2)	5 (4)
Rituximab	48 (6)	9 (6)	39 (6)	1(1)	34 (8)	4 (3)
Other Immunosuppression ¹⁰	297 (37)	57 (35)	240 (37)	18 (24)	174 (39)	48 (39)
No medications	11 (1)	9 (6)	2	2	0	0

Missing data and other categories are not included. APS: Antiphospholipid Syndrome; TAPS: Thrombotic APS; OAPS: Obstetric APS.

¹ Systemic autoimmune diseases included SLE, rheumatoid arthritis, mixed connective tissue disease, Sjogren's syndrome, systemic sclerosis, inflammatory muscle disease, and vasculitis. ² Races were allowed to be collected in a total of 731 patients (aPL only: 162, OAPS: 69, TAPS: 403, TAPS+OAPS: 97). Latin American Mestizo: refers to a person of combined European and Indigenous American descent. ³ Includes American Indian or Alaskan; Native Hawaiian or Pacific Islander; and other unspecified races as indicated by the patient. ⁴ Ethnicities were allowed to be collected in a total of 653 patients (aPL only: 146, OAPS: 65, TAPS: 354, TAPS+OAPS: 88). ⁵ Other unspecified ethnicities as indicated by the patient. ⁶ Consists of the arteries not in the chest or abdomen (i.e. in the arms, hands, legs and feet). ⁷ Arterial and/or venous. ⁸ Catastrophic APS (CAPS): was diagnosed when all four criteria of the CAPS Classification Criteria (1). ⁹ Livedo reticularis/racemosa, persistent thrombocytopenia, and autoimmune hemolytic anemia, patients were considered as ever or never having had these findings at the time of registry entry; μ L: microliter. ¹⁰ Other immunosuppression includes: Azathioprine, Corticosteroids, Cyclophosphamide, Cyclosporine, Methotrexate, Mycophenolate Mofetil and others

Figure 1: Baseline Antiphospholipid Antibody (aPL) Profile Among Persistently Positive Antiphospholipid Patients Included in the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking Registry (n: 804)



aPL: Antiphospholipid Antibodies;

*: LA: Lupus anticoagulant; aCL: Anticardiolipin Antibody; a β ₂GPI: Anti- β ₂ Glycoprotein-I Antibody;

** : Additional 8 patients (1%), tested for three aPL, but were excluded due to low titer (20-39U) aPL ELISA with negative LA test.

***Of 804 patients, 136 (17%) had missing data for antiphospholipid antibody profile; LA: 38 (5%), aCL: 3, and a β ₂-GPI: 100 (12%).

Table 2: Clinical Characteristics of Antiphospholipid Antibody Positive Patients in the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Registry (2010-2019) Tested for Three aPL Antibodies*, Categorized by aPL Profile (n: 660)**

<u>Number (%)</u>	LA only Positivity 168 (25)	Any Single*** aPL Positivity 215 (32)	Single aPL (excluding LA only) 47 (7)	Double*** aPL Positivity 167 (25)	Triple*** aPL Positivity 278 (42%)
<u>Any Vascular Events</u>	127 (73)	148 (67)	21 (45)	118 (68)	195 (70)
Arterial thrombosis	61 (36)	73 (34)	12 (26)	68 (41)	96 (35)
Venous Thrombosis	81 (48)	92 (43)	11 (23)	66 (40)	132 (47)
Microvascular Thrombosis	10 (6)	12 (6)	2 (4)	9 (5)	16 (6)
Transient Ischemic Attacks	11 (7)	13 (6)	2 (4)	19 (11)	20 (7)
<u>Any Pregnancy Morbidity</u>	43/84 (51)	53/108 (49)	10/24 (42)	41/86 (48)	62/117 (53)
>1 Fetal Death ≥10th week	31 (51)	39 (52)	8 (57)	29 (53)	43 (56)
>1 Preterm Delivery <34th week	12 (20)	13 (17)	1 (7)	14 (25)	29 (38)
≥3 Pre-Emb/Emb Loss <10th week	9 (15)	14 (19)	5 (36)	6 (11)	6 (8)
<u>Any Other Clinical Manifestation</u>	93 (55)	107 (50)	14 (30)	104 (62)	158 (57)
Livedo Reticularis/Racemosa	27 (16)	28 (13)	1 (2)	24 (14)	32 (12)
Persistent Thrombocytopenia	26 (15)	30 (14)	4 (9)	29 (17)	70 (25)
Hemolytic Anemia	9 (5)	10 (5)	1 (2)	7 (4)	16 (6)
Cardiac Valve Disease	11/146 (8)	12/188 (6)	1/42 (2)	12/142 (8)	32/234 (14)
Skin Ulcers	6 (4)	7 (3)	1 (2)	7 (4)	10 (4)
aPL-associated Nephropathy	4/157 (3)	4/201 (2)	0	5/160 (3)	11/256 (4)
Cognitive Dysfunction	14 (8)	17 (8)	3 (6)	20 (12)	33 (12)
Multiple Sclerosis-like disease	2 (1)	3 (1)	1 (2)	3 (2)	0
Chorea	2 (1)	2 (1)	0	4 (2)	6 (2)
Seizure	17 (10)	21 (10)	4 (9)	13 (8)	23 (8)
White Matter Lesions	33/120 (28)	40/155 (26)	7/35 (20)	33/116 (28)	45/190 (24)

*Patients in this analysis were tested for three aPL (lupus anticoagulant [LA], anticardiolipin antibody [aCL], and anti-β₂-Glycoprotein-I [aβ₂GPI]). --Single aPL Positivity was defined as positivity for one of the three aPL tests. Double positivity included 2/3 and triple included 3/3 aPL positive tests)

**Additional 8 patients, tested for three aPL, had low titer (20-39U) aPL ELISA with negative LA test; thus they were excluded

***: 40U cut-off for aCL and a β 2GPI IgG/M/A positivity
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Only 5/660 (0.8%) of patients had isolated aCL/a β 2GPI IgA positivity with negative LA and aCL/a β 2GPI IgG/M.
In total 6 patients had Catastrophic APS, distributed between double and triple aPL positive groups.
Persistent thrombocytopenia was defined as a platelet count of <100,000 per microliter tested twice at least 12 weeks apart.
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