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Patients with antiphospholipid syndrome and a first venous or arterial thrombotic event: clinical characteristics, antibody profiles and estimate of the risk of recurrence

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Abstract

Objectives: Thrombosis in antiphospholipid syndrome (APS) involves in most cases the venous circulation. Why in some patients thrombotic APS affects the arterial circulation and in particular cerebral circulation is unknown. In previous studies, both patient characteristics and antiphospholipid antibody types and titers have been associated with arterial thrombosis. Aim of this study was to compare the clinical characteristics and laboratory findings of venous and arterial thrombotic APS from a large series of patients.
Methods: Data were retrieved from the Start 2 antiphospholipid, a multicenter prospective register of long-term collected data from Thrombosis Centers in Italy.
Results: Of 167 patients with thrombotic APS, 114 (68 %) had a venous and 53 (32 %) had an arterial event as first clinical manifestation. Several clinical characteristics and risk factors were different among groups in univariate analysis. Using logistic regression analysis, reduced creatinine clearance and hyperlipidemia were independent variable for the occurrence of arterial APS. Notably, no difference in antiphospholipid antibody profiles and aβ2-Glycoprotein I levels were found between groups. A higher adjusted global antiphospholipid syndrome score (aGAPSS) was found in arterial group indicating a possible high recurrence rate in arterial APS.
Conclusions: These data have pathophysiological and clinical implication since associated conditions might predispose patients to arterial rather than venous events and call to a close monitoring and treatment of arterial APS due to their increased tendency to recurrence.

Keywords: antiphospholipid syndrome; thrombosis; registries; classification

Introduction

Thrombotic antiphospholipid syndrome (APS) is an autoimmune condition in which both venous and arterial events are associated with a hypercoagulable state due to the persistent presence of circulating antiphospholipid antibodies (aPL) [1]. The reason why these antibodies promote thrombotic manifestations in different sites is unclear and the preference for cerebral arterial vessels has no explanation so far [2]. Despite the clinical and social impact of cerebral involvement [3], studies addressing the identification of risk factors or clinical characteristics leading to arterial thrombosis in APS have not been systematically investigated [2] and are often conflicting. Previous reports showed that APS patients with arterial thrombosis were significantly older than those with venous thromboembolism [4–6] and heart valve disease, hypertension, history of arterial thrombosis, smoking history and hyperhomocysteinaemia were the most cited risk factors in arterial thrombotic APS [6–8]. A review paper claimed that positivity for LA and aCL was significantly associated with an increased risk of arterial thrombosis in patients without SLE [7], while elevated anti-β2GPI IgM were associated with recurrent arterial events [6].

Aim of this study was to compare APS patients with arterial thrombosis with those with venous thrombosis in order to investigate peculiar characteristics and risk factors

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that may lead to one rather than the other type of thrombotic event. Mapping the characteristics of these patients may be clinically relevant in order to prevent potential recurrent events.

Materials and methods

The Survey on AnTicoAgulated Patients- RegisTry on antiPhosphoLipid antibodies (START-aPL) is a branch of the START-Register that was authorized by the Ethical Committee of the University Hospital 'S. Orsola-Malpighi', Bologna, Italy, in October 2011 (NCT02219984). START-aPL is a multicenter prospective register of long-term collected data from Centers for the Diagnosis of Thrombosis and Surveillance of Antithrombotic Therapies (FCSA) promoted by Arianna Foundation on Anticoagulation in Bologna, Italy. Approval was obtained from the Institutional Review Board or Ethics Committee at each participating center. All the patients signed an informed consent at time of enrollment in the Registry and the study was conducted according the ethical principles for medical research as set out in the Declaration of Helsinki. All participating centers have professional personnel qualified by education, training and experience to perform the required tasks. All data were gathered using an electronic clinical report form (e-CRF) developed for the START-aPL. Each participating center had access to the e-CRF by a specific account and password. All centers were invited to include patients consecutively in order to avoid a selection bias as much as possible.

Study population

Patients presenting with a first episode of venous or arterial thrombosis were recruited when testing positive for one or more criteria aPL tests [anti-cardiolipin (aCL) and anti β2-glycoprotein I (anti-β2GPI) antibodies IgG/IgM at any titer, lupus anticoagulant (LA)] and data were confirmed after 12 weeks. Demographic and clinical data (pregnancy complications, non-criteria clinical manifestations, systemic autoimmune disease, risk factors for venous and arterial thromboembolism and treatment) were entered in a web-based case report form.

Laboratory data

APL profiles were classified as triple, double and single positive test. LA was defined as positive when screening, mixing and confirmatory tests of diluted Russell Viper Venom Time (dRVVT) and/or LA-sensitive activated partial thromboplastin time LA-PTT were above the cut off value provided by the manufacturers (Werfen group, Milan Italy; Stago, Asnières sur Seine, France; Siemens Healthcare GmbH, Erlangen, Germany). LA was considered positive when at least one of the two tests was positive and confirmed 12 weeks apart. In patients on warfarin, Lupus Anticoagulant was performed when the INR was less than 3.0 [8, 9].

Accordingly, the immunological tests were deemed positive when reported values were above the cut-off indicated by the manufacturers (Werfen, Milan, Italy; Stago, Asnières sur Seine, France; Phadia AB, Uppsala, Sweden). To get a rough estimate of antibody titers, we reported a composite of Units obtained with different methods. Around two third of centers used ELISA (GPL and MPL Units) for immunological determinations and one third used automated assays. The distribution of the assays among VTE and ATE patients was the same (VTE 69 % ELISA and ATE 68 % ELISA). We thus combined the results that were expressed as Units'.

Risk of recurrence

To determine the risk of recurrence in APS patients with a first venous or arterial events we used the aGAPSS score [5]. The score assigns each of the variables identified as independent risk factors for recurrent thrombosis a number of points that was proportional to its regression coefficient. The aGAPSS assigns three points for hyperlipidemia, one point for Hypertension, five point for positive aCL IgG/IgM, four points for positive aβ2GPI IgG/IgM and four points for the presence of LA. The maximum score for each patient is thus 17. aPS/PT antibodies were present in the original GAPSS score [10] but were excluded in aGAPSS as these antibodies are not yet present in the APS classification criteria [11] or used in the routine clinical setting.

Statistical analysis

Data are described as mean value ± SD for continuous variables and as proportions for categorical variables. Differences between continuous values were assessed using the unpaired t-test, and categorical variables were compared by the chi-squared test or Fisher exact test, as appropriate. Mann-Whitney test was used for nonparametric values. Logistic regression analysis was used to calculate odds ratios and their 95 % confidence intervals (95 % CI) as a measure of the relative risk for each cardiovascular risk factor. Variables selection by backward Wald method. An attempt to correct for the most significant interactions between the independent variables (Age/Creatinine Clearance, Gender/Hemoglobin, BMI/Creatinine Clearance, and Hypertension/Hyperlipidemia) was done. Significance was set at $p<0.05$.

Results

As of July 2023, 184 patients with thrombotic APS were enrolled in the START Antiphospholipid register. Of these, 114 (68 %) had a venous and 53 (32 %) had an arterial event as first clinical manifestation. 17 patients with both venous and arterial thrombosis were not considered for this study. Sites of venous and arterial thromboembolism are depicted in Table 1. Most venous events were deep vein thrombosis of the lower limbs with associated PE in 31 % of cases, 3 of which with hemodynamic impairment. Few cases were isolated PE and the remaining cases involved other sites of venous circulation. Most arterial events involved cerebral circulation while other sites were less represented.

Clinical characteristics

Table 2 compares the clinical characteristics of patients with venous and arterial thrombosis. Patients with arterial

Table 1: Sites of venous and arterial thrombosis in 167 APS patients.

Venous thromboembolism n, %	**114(68)**	**Arterial thromboembolism n (%)**	**53(32)**
Sites	**n (%)**	**Sites**	**n (%)**
Lower limb[a]	92 (81)	Cerebral	44 (83)
Proximal	72	Ischemic stroke	34
Distal	20	TIA	10
Isolated PE	7 (6)	Coronary	2 (4)
Cerebral	4 (3)	Splenic	2 (4)
Retinal	4 (3)	Retinal	2 (4)
Inferior caval vein	3 (3)	Other	3 (5)
Jugular	2 (2)		
Other	2 (2)		

[a]Associated PE n=29; PE, pulmonary embolism; TIA, transient ischemic attack.

thrombosis are significantly older and more frequently females. They have more frequently an associated autoimmune disease, hypertension, hyperlipidemia, valvular heart disease, cognitive disorders, reduced hemoglobin level and reduced creatinine clearance. No significant difference in pregnancy morbidity and risk factors for venous thromboembolism.

Risk factors in logistic regression model

Logistic regression model was performed with ATE vs. VTE as the dependent variable and Age, Gender, BMI, Hb, Creatinine Clearance, Associated autoimmune diseases, Diabetes, Hypertension, Smoke, and Hyperlipidemia as independent variables. Results are shown in Table 2. A reduced creatinine clearance and the presence of hyperlipemia are significant independent risk factors for arterial thrombosis in patients with APS. Despite not reaching statistical significance, a role in arterial thrombosis can be attributed to female sex and autoimmune disorders. The attempt to correct for the most significant interactions

Table 2: Characteristics of APS patients with venous or arterial events[a].

	VTE n=114	**ATE n=53**	**Univariate comparison p-Value**	**Logistic regression OR (95 %CI)**	**p-Value**
Age, years	54.7 ± 16.4	61.0 ± 14.5	0.02	–	–
Male sex	48 (42)	13 (25)	0.038	0.47 (0.2–1.0)	0.057
Caucasian ethnicity	110 (96)	52 (98)	–	–	–
Current or past smoker	15 (13)	12 (23)	–	–	–
BMI	26.4 ± 5.2	25.5 ± 5.0	–	–	–
Associated autoimmune diseases	33 (29)	25 (47)	0.024	2.02 (0.9–4.2)	0.06
SLE	18	7			
Other diseases	16	18			
VTE risk factors	17 (14.9)	4 (7.5)	–	–	–
Congenital thrombophilia	6	2			
Estroprogestinic	5	1			
Family history	4	0			
Pregnancy	2	1			
Hypertension	35 (31)	27 (51)	0.016	–	–
Hyperlipidemia[b]	12 (10)	20 (38)	<0.0001	4.2 (1.8–9.8)	0.001
Diabetes	6 (5.3)	5 (9.4)	–	–	–
Valvular heart disease	1 (0.9)	6 (11.3)	0.004	–	–
Cognitive disorders	2 (1.8)	7 (13)	0.005	–	–
Pregnancy loss	13/66 (20)	12/40 (30)	–	–	–
Early	8	5			
Late	4	5			
Other pregnancy complications	1	2			
RBC × 10^6/μL	4.7 ± 0.7	4.4 ± 0.5	–	–	–
Hb g/dL	13.4 ± 1.8	12.8 ± 1.5	0.04	–	–
WBC × 10^3/μL	6.9 ± 2.8	6.2 ± 2.0	–	–	–
Platelet count × 10^3/μL	226 ± 84	227 ± 82	–	–	–
ALT, U/L	24.9 ± 10.9	20.4 ± 7.4	–	–	–
AST, U/L	27.0 ± 19.0	21.2 ± 7.6	–		
Creatinine clearance mL/min	98 ± 52	76.6 ± 29	0.003	0.98 (0.97–9.99)	0.02

[a]Plus–minus values are means ± SD; n (%) are number of cases (percent); VTE, venous and ATR, arterial thromboembolism; "–"denotes non-significant findings; [b]primary driven by hypercholesterolemia. Count based on the assumption of specific drugs (statins). RBC, red blood cells; Hb, haemoglobin; WBC, white blood cells; ALT and AST, alanine and aspartate transaminase.

between the independent variables (age/creatinine clearance, gender/hemoglobin, BMI/creatinine clearance, and hypertension/hyperlipidemia) did not change the model because they were not significant.

Antiphospholipid antibody profiles

Based on test results exploring the presence of antiphospholipid antibodies, patients were classified as triple, double or single positive. There was no difference between venous and arterial APS in each of the classification groups (Table 3).

Antibody titre

We analyzed the titer of aβ2GPI in VTE and ATE using available values of triple (n=72) and double (33) positive patients. Median and interquartile range (IQR) of aβ2GPI IgG was 37 (IQR 10–157) in venous and 57 (IQR 21–176) in arterial thrombotic APS (p=0.2) as shown in Figure 1. Likewise, median (IQR) of aβ2GPI IgM in venous and arterial APS were 10 U (1.8–40) and 12.5 U (4.1–73.0). As shown in Figure 2, there was no difference between the two groups (p=0.3).

Risk of recurrence

The aGAPSS score was calculated in each patient and results in venous vs. arterial thrombotic APS were compared. As shown in Figure 3, mean aGAPSS score in venous thrombotic APS was 10.2 ± 3.9 while that in arterial thrombotic APS was 11.6 ± 3.7 and the difference was statistically significant (p=0.03).

Table 3: Antiphospholipid profile in venous and arterial APS[a].

	VTE n=114	ATE n=53
Triple positive	56 (49)	26 (49)
Double positive	28 (25)	15 (28)
Single positive LAC	23 (20)	8 (15)
Single positive aCL	6 (5)	3 (6)
Single positive aβ2GPI	1 (1)	1 (1)

[a]Values are presented as n (%): non-significant differences between groups.

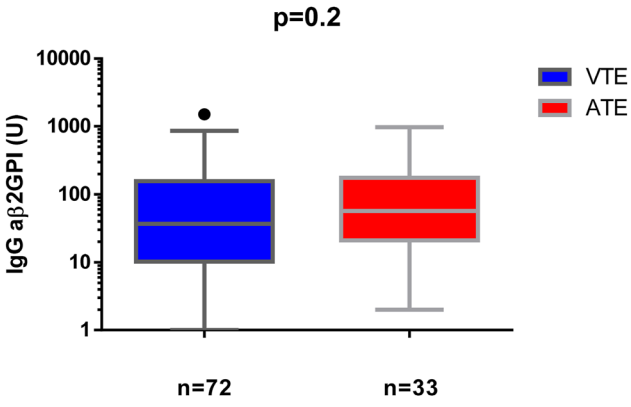

Figure 1: Box and Whisker plot shows the mean, upper and lower quartiles of IgG aβ2GPI titers in triple or double positive patients with venous (VTE) and arterial (ATE) thrombotic antiphospholipid syndrome. Data are shown in logarithmic scale. To get a rough estimate of antibody titers, we reported a composite of Units obtained with different methods (two-third of centers used ELISA and one-third automated assays and the proportion (ELISA/automated assays) was the same among VTE and ATE patients). Data refer to available values.

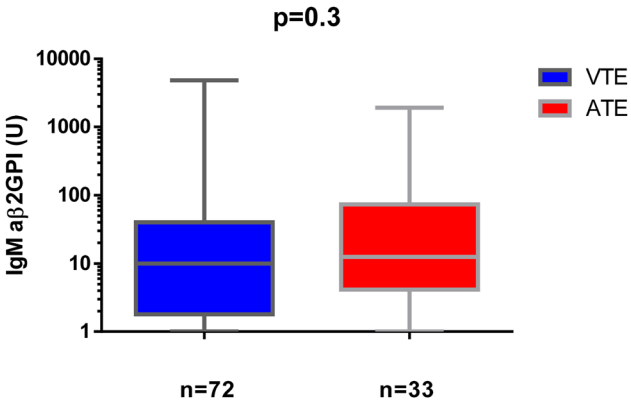

Figure 2: Box and Whisker plot shows the mean, upper and lower quartiles of IgM aβ2GPI titer in triple or double positive patients with venous (VTE) and arterial (ATE) thrombotic antiphospholipid syndrome. Data are shown in logarithmic scale. To get a rough estimate of antibody titers, we reported a composite of Units obtained with different methods (two-third of centers used ELISA and one-third automated assays and the proportion (ELISA/automated assays) was the same among VTE and ATE patients). Data refer to available values.

Discussion

Venous and arterial thrombotic manifestations in APS are different disorders with different pathogenesis and different risk factors [12]. A clear identification of such risk factors is not available so far with many of them being reported [6, 12–15]. Data from the START 2 Antiphospholipid Registry show that the presence of cardiovascular risk factors is more

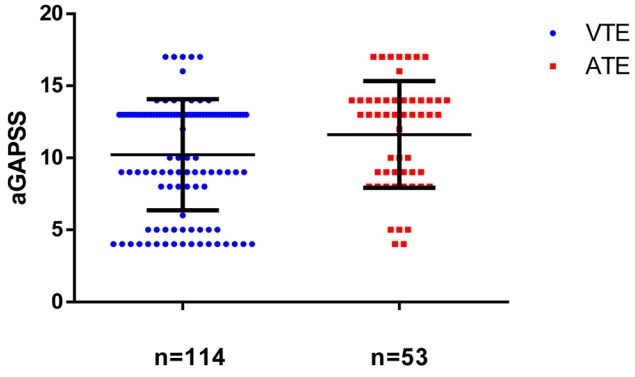

Figure 3: The aGAPSS score was calculated and compared between patients with venous and arterial thrombotic APS.

frequent in individuals with APS and arterial thrombosis than in those with venous thrombosis. Noteworthy, a reduced creatinine clearance and hyperlipidemia were independent risk factors for arterial thrombosis. It was previously shown that APS patients suffering from hypertension and hypercholesterolemia were at the increased risk of arterial thrombosis [16–20] and those with APS and metabolic syndrome that includes raised blood pressure and dyslipidemia had associated arterial thrombosis [21]. At variance with the previous report we did not find a difference in the rate of diabetes among APS patients with arterial thrombosis [22]. Concerning dyslipidemia, a study showed that it is insufficiently treated in antiphospholipid syndrome patients [23]. Another study found a suboptimal cardiovascular risk factor target achievement in APS, especially in high/very high-risk patients [24], highlighting the need for accurate cardiovascular risk factors management strategies. Since a slightly increased frequency of IgG anticardiolipin antibodies (ACL) in the arterial thrombosis group was previously observed [16], we focused our attention on aPL antibodies. We found no difference in the antibody profiles (triple, double and single positivity) between venous and arterial APS nor in the amount of circulating aβ2GPI antibodies [4]. These data underpin the hypothesis that cardiovascular risk factors rather than the hypercoagulable state induced by aPL are major determinants of arterial thrombosis in APS [25]. Independent risk factors for arterial thrombosis in our study were a reduced creatinine clearance and the presence of hyperlipidemia. Declining kidney function causes a systemic, chronic proinflammatory state contributing to an accelerated aging of the cardiovascular system leading an increased risk of cardiovascular events [26]. In addition, hyperlipidemia is a potent risk factor for cardiovascular disease even in early adulthood [27, 28]. Although not classified as an independent risk factor for arterial thrombosis in the logistic regression model, associated autoimmune diseases represent a further factor increasing the risk of cardiovascular events [29].

Positive cardiovascular risk factors result in a significant increase in the aGAPPS score in the arterial group predicting a higher risk of thrombotic events in the arterial thrombotic APS patients in the follow up period. Among other prediction scores, aGAPSS had the best discrimination to predict arterial thrombosis [12] indicating that these patients will probably develop recurrent events [5, 30]. As a consequence, particular attention at reducing cardiovascular risk factors in APS patients with arterial thrombosis in addition to appropriate antithrombotic therapy should be paid.

Limitations of the study

Other potential risk factors for thrombosis in APS were not considered in this study. Among them, previous cancer, infections or trauma although no patients had active cancer at time of inclusion in the registry and infections or trauma were not mentioned in the general notes. Other biomarkers possibly linked to arterial thrombosis such as IgG anti High Density Lipoprotein [31] or mean platelet volume [32] were not available in the registry. Finally, recent new classification criteria [11] may change the type of patients enrolled in the START-aPL registry.

In conclusion, data from this study show that some clinical features (reduced creatinine clearance and hyperlipidemia) distinguish APS patients with arterial from those with venous thrombosis. Instead, type of aPL profile and aPL concentration are similar in the two groups indicating that a different hypercoagulable state does not determine the site of thrombosis in these patients. These data have clinical implications calling for accurate treatment of associated conditions that predict recurrent arterial events.

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Research ethics: The study was conducted according to the ethical principles for medical research as set out in the Declaration of Helsinki.

Informed consent: All the patients signed an informed consent at the time of enrollment in the Registry.

Author contributions: VP gave a substantial contribution to concept and design of the study and wrote the first draft of the manuscript. LS, EA, SDA, EB, GD contributed to analyze and interpret the data. DP, GP gave a substantial contribution to collect data, critical writing and revising the intellectual content. All Authors approved the final version.

Competing interests: Prof. V. Pengo recieved lecture fees from Werfen (Milan, Italy). All other authors state no conflict of interest.

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Data availability: Data are available upon reasonable request.

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