Thrombotic recurrences and bleeding events in APS vascular patients: a review from the literature and a comparison with the APS Piedmont Cohort.

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Abstract

In APS vascular patients, thrombotic recurrences are more frequent than in non-APS thrombotic patients. To better define this clinical setting, a systematic review of the literature after 1999 was performed: 8 cohort studies (including the recent APS Piedmont Cohort) and 6 intervention studies were selected and evaluated. Thrombotic recurrences, bleeding events, therapeutic strategies, antiphospholipid (aPL) profile, inherited and acquired risk factors (when present) were calculated and compared. Emerging risk factors for thrombotic recurrences include withdrawal of oral anticoagulant therapy (OAT), high intensity OAT (INR range 3–4), aPL profile (triple positivity, Miyakis types 1 and 2a profiles) and association with inherited or acquired pro-thrombotic risk factors. Moreover, there are evidences that high risk (mainly for aPL profile) APS vascular patients have a high recurrence rate in spite of correct OAT treatment. Clinical trials in this clinical setting are needed.

Keywords

Antiphospholipid syndrome; thrombosis; Thrombotic recurrences

1. Introduction

The antiphospholipid syndrome (APS) is a systemic, acquired, immuno-mediated syndrome, characterized by thrombotic events (venous, arterial or of the microcirculation) and/or by pregnancy morbidities and the persistent presence of circulating antiphospholipid antibodies. The clinical presentation of the syndrome may be “isolated” (idiopathic), or associated with other autoimmune diseases. Since Feinstein and Rapaport [1] used the term “lupus anticoagulant” for the first time in 1972, classification criteria for clinical and laboratory diagnosis have been proposed twice: i.e. Wilson et al. [2], in 1999 (the so-called “Sapporo” criteria), and the current ones, in 2006, by Miyakis et al. [3], (the “Sydney” criteria). These classification criteria have been formulated to allow a well-defined and shared picture of the syndrome. An in-depth review of APS classification criteria and therapeutic strategies, was recently published by Ruiz-Irastorza et al. [4].

A “seronegative” form of the syndrome has been described and recently revised [5]; management of these patients is still unclear.

Sydney classification criteria define the clinical characteristics of thrombotic (and obstetrical) events. Unlike the Sapporo criteria, superficial thrombophlebitis and TIAs have been excluded, as having all non-objectively or histologically documented events. Indeed, other clinical manifestations such as aPL positive thrombocytopenia, livedo reticularis and migraine, which are often associated to the syndrome [6] and [7], are actually considered non-criteria manifestations, and are followed separately. Laboratory diagnosis is now more standardized both for the LA test and for the cut-off values for aCL, and furthermore the anti-beta2glycoprotein I assay has been added. The time between the first test and the confirmation test has gone from 8 weeks to 12 weeks and the lag time between clinical symptoms (index event) and first positive

test must not be more than 5 years. The syndrome is considered present if at least one of the tests (LA, aCL or anti-beta2glycoprotein I) is positive, and is later confirmed.

An innovative aspect of the Sydney criteria consists in the fact that, for the first time, two adjunctive recommendations appear for the "researchers". The first concerns the non-exclusion of APS patients with inherited or acquired pro-thrombotic conditions, classified as a) the presence or b) the absence of such risk factors. The second is a thrombotic risk stratification in different categories according to laboratory tests: type 1 if more than one positivity is present (in any combination), type 2a, 2b and 2c, respectively if LA, aCL or anti-beta2glycoprotein I alone are positive. These recommendations have not always been applied in studies concerning APS patients.

There is strong evidence [8] concerning the fact that LA positivity alone correlates with higher thrombotic risk more than aCL or anti-beta2glycoprotein I positivity alone. Recently, the term "aPL profile" has replaced the term "category" of positivity, and good evidence has been published regarding the high predictive role of the "triple" positivity aPL profile, consisting in the simultaneous, persistent positivity for LA, aCL and anti-beta2glycoprotein I. APS patients with triple positivity, as well as asymptomatic patients with triple positivity are at higher risk of thrombosis and thrombotic recurrences [9] and [10].

Another very serious form of the syndrome, the so-called "catastrophics" APS, here is not considered, but has been recently revised [11].

This review only takes vascular APS into consideration, and in particular we focus on thrombotic recurrences. Nowadays the high frequency of thrombotic recurrences still represents a major clinical criticism and a yet unsolved therapeutic challenge. The aim of this paper was to evaluate the incidence of thrombotic recurrences, as well as the patients' risk factors, the aPL profile, and the bleeding events that have been reported in the literature, and to compare these data to the recent experience of the APS Piedmont Cohort [12].

We decided to systemically evaluate the literature reports after 1999; although the literature prior to 1999 contains a wealth of important studies concerning APS, comparison with recent ones is not possible, since the former lack information on classification criteria of the syndrome. Fourteen studies were chosen and in-depth evaluation was carried out. These studies were divided into two groups based on their methodological approach: cohort studies, usually retrospective or ambispective, which report the index event and recurrences, and intervention studies, retrospective or prospective, some of which were randomized, containing comparisons of thrombotic recurrences (and sometimes bleeding events) in patients treated with different therapeutic strategies.

2. The APS Piedmont Consortium

Is a group of volunteer physicians and biologists coming from different specialties, working in the Piedmont Region, which is in north-western Italy, an area of about 5 million people. The activity of the Consortium began in 2004. The aims of the Consortium are: 1) to diagnose, treat and follow up APS patients, and to record data at diagnosis in the Regional Registry for Rare Diseases (National Health Service) 2) to improve knowledge of the syndrome, and to share up-to-date diagnostic and therapeutic strategies; and 3) to discuss controversial clinical cases and to support clinical and laboratory research. The APS Piedmont Cohort study is an ambispective study that includes 217 consecutive APS patients, selected from a broader group of about 400 suspected cases [12]. Enrolled patients strictly met the ongoing clinical and laboratory classification criteria, and APS diagnosis was confirmed by a centralized board. All the diagnoses that were

made before 2006 were revised afterwards on the basis of the Sydney criteria. Patients were anonymously entered into a database program (Excel). The characteristics that were reported include: sex, race, age, age at diagnosis, underlying autoimmune disease, if any, clinical manifestations at onset (defined as index event), aPL profile, inherited thrombophilia and cardiovascular risk factors. Ongoing therapy, before and after thrombosis diagnosis or recurrence was also recorded. The study was performed according to the principles of the Declaration of Helsinki and informed consent was signed by each patient at diagnosis, when they entered in the Interregional Registry of Rare Diseases – National Health Service. All thrombotic events were objectively documented and patients were treated according to current recommendations at the time of diagnosis [13], [14], [15], [16] and [17].

3. Cohort studies

Eight cohort studies were chosen and evaluated (see Table 2).

In 2002 Ruiz Irastorza et al. [18] studied 66 vascular APS patients who had been diagnosed according to the Sapporo criteria. It is an observational, retrospective cohort study in which all patients were treated with oral anticoagulant treatment (OAT), and INR target 3.5. The followup period lasted 12 months. The recurrence rate of thrombosis was 9.1% patients per year, while the recurrence of bleeding events was 6%. Patients spent 37% of their time in the INR range 3‐4. The relatively short followup period and the low adherence to the target INR do not allow to get strong clinical messages.

Turiel et al. [19] prospectively followed-up 56 patients with primary APS for 5 years. Sapporo criteria were used for diagnosis. The observed thrombosis recurrence rate was 5.4% patients per year. A high aCL level (> 40 GPL-U) was shown to be a risk factor for thrombotic recurrences. The treatment for venous thrombosis was OAT for 6 months, and 12 months in the case of pulmonary embolism, while therapy for arterial thrombosis consisted of either OAT or antiaggregants. In this study a relatively high incidence of thrombotic events may have been related to the early discontinuation of OAT (6 or 12 months).

In the study by Forastiero et al. [20], 194 patients with persistent LA and/or aCL were followed up for a median of 45 months, regardless of whether they had had a previous thrombotic event or not. Half of the patients (n = 97) had had a thrombotic event at diagnosis (these were APS patients), and some patients were thrombocytopenic or had had a TIA, or had had obstetrical manifestations. Overall incidence of thrombosis was 5.6% patients per year. The calculated recurrence rate (28 patients out of 97 in 3.7 years) was 7.8% patients per year in APS patients. Ten out of 28 patients with recurrence had a venous thrombosis during OAT. An inherited pro-thrombotic condition was searched in 12 out of 21 patients with venous thrombosis, and 3 patients (25%) were positive (had protein C deficit and 2 had prothrombin G20210 mutations). The Authors found that the highest incidence of thrombosis in “LA patients” was related to the presence of both anti-beta2glycoprotein I and anti-prothrombin antibodies. Male gender and a previous thrombosis also independently correlated with thrombotic risk.

Wittosky et al. [21] studied 36 APS patients diagnosed according to the Sapporo criteria and compared them to a matched cohort of 36 thrombotic patients in OAT without APS. It is a retrospective observational study. INR range was 2‐3 for both groups. Recurrence rate was 9.6% patients per year in the APS group versus 0% in non-APS. Bleeding rates were 3.2% and 3.1%, respectively. In this small study, standard OAT treatment seems to be less effective in APS patients compared to thrombotic non-APS patients.

In the study by Tarr et al., [22] 272 lupus patients were enrolled and followed-up for 5 years. Lupus patients were then divided into three groups, aPL negative, aPL positive and APS (84 patients who met the Sapporo

criteria, afterwards revised according to Sydney). Recurrence rate in the APS patient group was 1.7% patients per year. Cut off values for aCL positivity was 22 GPL or 16 MPL, and 14.6 SGU/ml or 3 U/ml for IgM anti-beta2glycoprotein I. Only 21.2% of patients had LA positivity, while 10% had triple positivity. No trigger event was evident in any of the thrombotic events that were observed in the followup period. About half of the APS patients were treated with OAT (± ASA). In this paper, aPL profile, previous thrombosis and oral anticoagulant treatment were the risk factors influencing thrombotic risk. The rate of bleeding events was not reported.

The paper by Cervera et al. [23] reports the results of the largest APS cohort ever studied. It is a prospective, multicenter study. Sapporo diagnostic classification criteria were used and the drop out rate was 15%. 16.6% of patients had a recurrent thrombotic event, with a calculated recurrence rate of 3.3% patients per year. OAT was used in 420 patients, but more than half of the recurrences presented during OAT. The bleeding rate was 1.5% patients per year. Important clinical considerations from this study are that in the "real world" a significant proportion (23%) of APS patients do not receive either OAT or antiaggregant treatment, and that many patients had recurrences in spite of OAT. On the other hand, serious or lethal bleeding complications were not negligible. Data concerning general cardiovascular risk factors or inherited thrombophilia are not available.

The study by Pengo et al. [9] is an ambispective, multicenter study. Laboratory criteria for enrollment were confirmed triple positivity for aPL tests. This is the first study concerning "high risk" APS patients selected for aPL profile at diagnosis. The followup period was more than 5 years, and the recurrence rate was 5.2% patients per year, with the highest rate (12.2%) being observed in the first year. The recurrence rate was significantly higher in patients not on OAT. Furthermore, OAT was the only predictor of thrombotic events during the followup. Bleeding rate was 0.8% patients per year. The index event at diagnosis (arterial or venous) did not predict the site of recurrence.

4. The APS Piedmont Cohort study

It is an ambispective, multicenter study. Sydney classification criteria were used for diagnosis. One hundred seventy-seven patients were enrolled (the clinical characteristics of the cohort are summarized in Table 1). The qualifying event at diagnosis was VTE in 100 cases (57%) and arterial thrombosis in 77 cases (43%). Miyakis types 1 and 2a aPL profiles (compared to 2b and 2c) were very highly represented (96%) in our cohort. Twenty-six percent of our patients had "triple" aPL positivity. Thrombotic recurrences in the followup period were 54: 24% patients were under OAT, 28% on low dose aspirin, 46% were off therapy, and 2% were under OAT plus aspirin. The thrombotic recurrence rate was 6% patients per year. There were 12 major bleeding events, eight of which occurred in patients on oral anticoagulants (1.6% patients per year). No differences in aPL profile were observed between patients with arterial and venous events. The same aPL profile (Miyakis types 1 and 2a) was observed in patients with or without recurrences. Diabetes ($p < 0.01$; OR 10) and thrombophilia ($p < 0.0078$; OR 4) were independent risk factors for recurrence. To our knowledge, this is the first study in which enrollment of consecutive APS patients was strictly performed according to the Sydney criteria, and in a well defined geographical area. Moreover, laboratories performed periodic external quality assessment (EQA), and clinical events and laboratory tests were evaluated by a central board. Generic cardiovascular risk factors and inherited thrombophilia were also evaluated, and both thrombotic recurrences and bleeding events were calculated.

5. Intervention studies

Six intervention studies have been selected and evaluated (see Table 3).

The study by Crowther et al. [24] was a prospective, randomized one on APS patients enrolled according to the Sapporo criteria. Patients were assigned to two different intensities of anticoagulation groups: INR 2-3 versus 3-4. Recurrence rate was 1.3% patients per year in standard and 3.2 in high intensity INR treatment. Bleeding rates were 2.2% and 3.6%, respectively. The Authors underline the fact that in the high intensity INR group, patients spent in the correct INR range only in 40% of the time. As for the WASP study, the small sample size and low adherence to target INR do not allow us to come to definitive conclusions.

Giron-Gonzales et al. [25] followed-up 404 patients that were divided into two groups: 1) 226 patients with primary or secondary APS according to the Sapporo criteria; 2) 178 asymptomatic aPL carriers. A total of 176 vascular APS patients were treated with OAT, range 2.5-3.5. Those in group 2 did not receive continuous treatment, but were given thromboprophylaxis in high risk periods. The follow-up period was 3 years. Eighteen patients died within the first 3 months of follow-up.

The recurrence rate was 0.5% patients per year in group 1. Recurrent thrombosis were related to insufficient anticoagulation. Bleeding was 0.6%. The high death rate and the low recurrence rate make this study poorly comparable to other literature reports.

The APASS study [26] is a prospective, randomized study of stroke patients (not APS patients) who received either warfarin with INR range of 1.4-2.8, or aspirin of 325 mg/die. Recurrence rate was 13% patients per year under OAT and 11% under aspirin. Bleeding events are not reported. The Authors report observing no differences between the results of the two treatments, nor that aPL status predicted vascular occlusive events. There was a great deal of criticisms concerning the study design, and some comments are summarized in JAMA, June 2004 [27] by Cabral et al., Ruiz Irastorza et al., Wahl et al. In summary, the mean age of patients was high, no confirmation tests were performed, only 0.2% patients had elevated aCL levels, and many patients were aPL positive (41%), leading to doubts concerning the specificity of the test, and the INR therapeutic target range was unusual and lower than the standard, most often recommended one [2] and [3]. More recently, the risk of ischaemic stroke and of myocardial infarction, has been shown to be very high in young women with lupus anticoagulant, in the RATIO study [28].

Ames et al. [29] enrolled 67 patients with primary APS according to the Sapporo criteria, 24 patients with a mitral valve replacement and 89 patients with inherited thrombophilia. All patients were under OAT; the followup period was 3.3 years. All patients were randomized to two different intensity regimens of OAT: 2-3 versus 3-4 INR ranges. APS patients had 4% recurrence per year in the standard and 10.5% in the high intensity OAT regimen. Bleeding rate was higher in the high intensity INR range i.e. 10.5% versus 0.6%. Only 10% of APS patients spent their time in 3-4 INR range, while 84% were in 2-3 INR range. Even in this case, the small number of patients and the low adherence to the target INR do not allow us to come to any firm conclusions.

The WAPS study [30] is a prospective, randomized study of APS patients. One hundred and nine patients were enrolled according to the Sapporo criteria and were randomized to different OAT intensity treatments: INR 2-3 versus 3-4.5. The Authors show that high intensity warfarin was not superior to standard treatment: recurrence rate was 1.6% patients per year for INR 2-3, and 3.1% for higher intensity OAT. Bleeding rates were 1.6% for standard INR and 1% for high intensity INR, respectively. The results do not appear so rational, and could, at least in part, be explained by the relatively small sample size. Furthermore adherence to the high intensity treatment was suboptimal.

Okuma et al. [31] enrolled 20 APS stroke patients according to the Sydney criteria. They were randomized to receive aspirin 100 mg or aspirin 100 mg associated to OAT, with INR 2–3. The recurrence rate in the former group was 16.2% patients per year versus 2.5% in the latter group. This small study suggests that aspirin alone is less effective than OAT plus aspirin in the clinical subset of APS stroke patients.

6. Conclusions and comments

The recurrence rate of venous thromboembolism in the general population (non-APS patients) was quite well defined in 1996 by Prandoni et al. [32] who showed a 30% cumulative incidence of recurrence after 8 years of followup (i.e. 3.75% patients per year, in subjects off therapy). Similar results were obtained by Hansson et al. in 2000 [33], who reported a recurrence rate of 20% at 6 years, i.e. 3.33% patients per year after OAT withdrawal. The WODIT study by Agnelli et al. [34] demonstrated that, regardless of the duration of OAT treatment, a "cluster" of recurrences occurs in the first months after OAT discontinuation.

A direct comparison of the calculation of thrombotic (both venous and arterial) recurrence rates in studies concerning APS patients is quite difficult, because of the different classification criteria, laboratory cut off values, and the different therapeutic strategies [35]. However, an approximate thrombosis recurrence rate can be deduced from the above mentioned studies. If we rule out the studies with the shorter followup period (about 1 year) (see Table 2: 18,21) due to the higher recurrence rate in the first year, and a small study concerning only APS stroke patients (see Table 3: 30), resulting thrombotic recurrences range between 2 and 10% patients per year. It must be underlined that a great deal of these patients was under OAT, and the higher the INR intensity, the higher the recurrence rate. Thrombotic recurrences are generally higher (when calculated) in the first year of followup [9], [12], [18] and [21].

Moreover, if bleedings are difficult to calculate by an objective method, bleeding rates in APS studies were different and scattered with respect to the rates observed in the general population under OAT. In the ISCOAT study [36], the bleeding rate (for major bleedings) among the general population under OAT was about 1% patients per year. In the studies we analyzed, the annual bleeding rate ranges from 0.6 to 10%, but if more recent studies in which INR range was 2–3 are considered separately (see Table 2: 9,23,12; see Table 3: 29), bleedings drop from 0.8 to 1.6%, similar to those of the ISCOAT study.

On the basis of the above mentioned studies, which include about two thousands patients as a whole, some conclusions may be drawn. First, the absence of OAT (or OAT under-treatment) is often a significant, independent (sometimes the only one) risk factor for thrombotic recurrence. In clinical practice, a missed APS diagnosis, or early OAT withdrawal, must be considered as the cause of thrombotic recurrences. Second, the possibility that a clinical subset of APS vascular exists, i.e., those who have recurrences despite correct OAT, must be seriously considered. This fact represents a treatment failure, and some studies have shown that this is not at all a rare event [9], [12] and [37]. In particular, this happens in higher risk patients for aPL profile (triple positivity, Miyakis types 1 and 2a) [38].

Thrombotic recurrence rates in all of the studies are always higher than bleeding rates with the exception of[24], and high intensity INR range is less effective in preventing thrombosis and gives a higher bleeding risk. Generic cardiovascular risk factors and inherited thrombophilia can also further increase thrombotic risk [12] and [20].

In conclusion, OAT with the standard 2–3 INR range can still be considered a good therapeutic strategy for non-high risk APS patients [39], [40], [41] and [42] suffering from their first venous thrombotic event. However, poor or no evidence is available for the optimal treatment of APS vascular patients with arterial

thrombosis [43], of high risk patients (due to aPL profile or to other associated acquired or inherited risk factors) or of patients who have vascular recurrences despite appropriate therapy. Large prospective, randomized clinical trials are needed in these clinical settings.

Take-home messages

·APS vascular patients have thrombotic recurrences more frequently than non-APS thrombotic patients. This often occurs also if APS patients are under oral anticoagulant treatment.

·To better define the subset of APS patients a higher risk for thrombotic recurrence is mandatory, but this is rarely performed, either in clinical trials, or in the "real world" clinical practice

·Emerging risk factors for thrombotic recurrences are: the aPL "profile", withdrawal of OAT, associated general risk factors and inherited thrombophilia

·This subset of patients, at very high risk for clinical characteristics and laboratory diagnosis, would be to consider for a randomized, prospective trial, using a new therapeutic strategy.

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Appendix.

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Table 1.

Clinical Characteristics of APS Piedmont Cohort patients	
Number of patients	177
Age years at diagnosis (mean ± sd)	44 ± 16
Female (%)	69
PAPS (%)	56
"Generic" risk of arterial thrombosis (%)[a]	52
Triggering events of venous thrombosis (%)[b]	28
Thrombophilia (%)[c]	13
Death (%)	1.7

a Risk factors for arterial thrombosis that were taken into consideration: diabetes mellitus, hypertension, hypercholesterolemia, obesity, smoking habit and family history.

b Risk factors for venous thrombosis: recent surgical intervention, peri-operative immobilization, oral estroprogestinic treatment, pregnancy, malignancy.

c Thrombophilia: antithrombin deficiency, prot C and prot S deficiencies, factor V Leiden and G 20210 prothrombin mutations, hyperhomocysteinemia > 40 μM/l, and factor VIII > 200%.

Table 2.

Observational cohort studies: recurrent thrombosis and bleeding rates in APS patients.

Author, year (ref.)	Vascular patients	Followup	Classification criteria	Thrombosis rates	Bleeding rates major bleeding
Ruiz-Irastorza, 2002 [18]	66	1 year	Sapporo	9.1% pt-yr warfarin (INR 3–4)	6.0% pt-yr
Turiel, 2005 [19]	56	5 years	Sapporo	5.4% pt-yr	n.e.
Forastiero, 2005 [20]	97	3.7 years	Before Sapporo	7.8% pt-yr	n.e.
Wittkowski, 2006 [21]	36	1.7 years	Sapporo	9.6% pt-yr warfarin (INR 2–3)	3.2% pt-yr
Tarr, 2007 [22]	84	5 years	Sapporo/Sydney	1.7% pt-yr	n.e.
Cervera, 2009 [23]	502	5 years	Sapporo	3.3% pt-yr	1.5% pt-yr
Pengo, 2010 [9]	160	> 5 years	Triple positivity	5.2% pt-yr	0.8% pt-yr
APS Piedmont, 2011 [12]	177	5 years	Sydney	6% pt-yr 2.5% pt-yr (warfarin) 5% pt-yr (ASA)	1.6% pt-yr

n.e. = not evaluated.

Table 3.

Intervention studies: recurrent thrombosis and bleeding rates in APS patients.

Author year (ref.)	Vascular patients	Followup	Classification criteria	Thrombosis rates	Bleeding rates Major bleeding
Crowther 2003 [24]	114	2.7 years	Sapporo	1.3% pt-yr warfarin (INR 2–3) 3.2% pt-yr warfarin (INR 3–4)	2.2% pt-yr 3.6% pt-yr
Giron-Gonzales 2004 [25]	176	3 years	Sapporo	2.5% pt-yr (recurrences + death) warfarin (INR 2.5–3.5) 0.5% pt-yr (recurrences) warfarin (INR 2.5–3.5)	0.6% pt-yr
Levine 2004 [26]	720	2 years	Sapporo (stroke patients)	13% pt-yr warfarin (INR 1.4–2.8) 11% pt-yr aspirin	n.e.
Ames 2005 [29]	67	3.3 years	Sapporo	4.0% pt-yr warfarin (INR 2–3) 10.5% pt-yr warfarin (INR 3–4)	0.6% pt-yr 10.5% pt-yr
Finazzi 2005 [30]	109	3.6 years	Sapporo	1.6% pt-yr warfarin (INR 2–3) 3.1% pt-yr warfarin (INR 3–4.5)	1.6% pt-yr 1.0% pt-yr
Okuma 2010 [31]	20	3.9 ± 2 years	Sydney (stroke patients)	16.2% pt-yr low-dose aspirin 2.5% pt-yr warfarin + low-dose aspirin	2.5% pt-yr

n.e. = not evaluated.