

# New insights into the management of antiphospholipid syndrome-related thrombosis

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Antiphospholipid syndrome (APS) is a clinical autoimmune disorder characterized by thrombosis, venous or arterial, and recurrent pregnancy morbidity in association with the persistence of antiphospholipid antibodies (aPLs). The clinical variety of aPLs ranges from asymptomatic individuals to those with multiple organ thromboses and failure developing over a short period, also known as catastrophic APS. Warfarin is the best available, most effective treatment for the secondary prevention of recurrent thrombosis. However, there are still controversies in the duration of treatment and the intensity of anticoagulation. Recommendations for primary thrombosis prevention in asymptomatic aPL individuals vary from no treatment to low-dose aspirin. In some groups of patients with special clinical characteristics other therapies are used, such as immunosuppression. Recent publications based on *in vivo* animal models have shown that new therapeutic approaches can be effective in reversing pathogenic effects of autoimmune aPL. Nevertheless, whether they could be used therapeutically for preventing APS-related clinical events remains to be elucidated. This article will briefly review this evidence.

## Definitions & current criteria for the antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a clinical autoimmune disorder characterized by thrombosis, venous or arterial, and recurrent pregnancy morbidity in association with the persistence of antiphospholipid antibodies (aPLs) [1,2]. Since its recognition as a separate entity in the early 1980s, the APS has increasingly gained the interest of hematologists, obstetricians and rheumatologists. At first, APS was thought to be closely associated with systemic lupus erythematosus (SLE), but it was soon observed that APS is also found in patients without evidence of an underlying autoimmune disorder. The newly revised 2006 criteria advises against using the term secondary APS when APS is in the context of autoimmune diseases [3]. Rather than distinguishing between primary and secondary APS, documenting the coexistence of SLE (or other diseases) with APS is recommended. The detection of lupus anticoagulant (LA), and/or high levels of anticardiolipin (aCL) and anti- $\beta_2$  glycoprotein I (anti- $\beta_2$ GPI) antibodies is a mandatory laboratory feature for the diagnosis to be made [3]. Titers greater than 40 units or more than the 99th percentile are required for IgG/IgM aCL and anti- $\beta_2$ GPI. Persistent positivity of laboratory tests is important; the recent criteria suggest an interval of at least 12 weeks between the two positive tests instead of 6 weeks as in the 1999 Sapporo criteria [1]. It

is important to emphasize that the proposed time interval is based on expert opinion, but it is vital that studies validating it are carried out. A recent work has shown that the risk of thrombosis is not increased in SLE patients with negative LA and transiently positive aCL, even when fulfilling the 1999 Sapporo laboratory criteria [4]. The authors defined aCL as transiently positive when less than two-thirds of the aCL determinations (IgG/IgM >20 units) were positive during follow-up. It is expected that the use of a higher titer (>40 units) and a longer time interval (>12 weeks), would provide greater reassurance that the aPLs detected are relevant to a predisposition to APS. It is well known that aPLs consist of a heterogeneous family of immunoglobulins. Antibodies directed against anionic phospholipids themselves are mainly found in infections and do not tend to be associated with the clinical features of APS. On the other hand, APS-related aPLs target phospholipid-binding proteins, such as  $\beta_2$ GPI and prothrombin [5,6]. In a systematic review, IgG anti- $\beta_2$ GPI seemed to be more consistently associated with venous thrombosis than IgM antibodies [7]. However, a number of methodological and standardization limitations were recognized. In a meta-analysis regarding aPL and miscarriage, LA consistently showed the highest strength of association with late pregnancy morbidity. However, the importance of testing anti- $\beta_2$ GPI was uncertain, as only five studies met the

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criteria for inclusion in the meta-analysis. In four studies an assay with cardiolipin and  $\beta_2$ GPI was used, and only one used an assay for the measurement of true anti- $\beta_2$ GPI [8]. More recently, accumulating evidence has demonstrated that the presence of IgG anti- $\beta_2$ GPI and antiprothrombin antibodies predicts a higher risk of first or recurrent thromboembolic events. This information was not only found by retrospective studies [9,10], but also by recent prospective studies [11,12]. However, the inclusion of antiprothrombin antibodies in the classification criteria for APS is still considered premature. The common denominator for all of the published data is that the risk of thrombosis progressively increases with the number of positive aPL tests. In line with this evidence, the new criteria strongly advise classifying APS patients in clinical studies into four categories according to the type and/or number of laboratory criteria present [3].

As with the original classification criteria [1], APS requires the combination of at least one clinical and one laboratory criterion. The new consensus statement suggests avoiding classification of APS if a positive aPL test and the clinical manifestation are separated by less than 12 weeks or more than 5 years [3]. The revised

APS classification criteria strongly recommend searching coexisting inherited and acquired thrombosis risk factors in patients with APS. Thus, patients who fulfill criteria should be stratified according to the presence or absence of contributing causes of thrombosis. The clinical criterion remains mostly unchanged, except for the inclusion of transient cerebral ischemia and stroke as forms of vascular thrombosis. Superficial venous thrombosis is not included in the clinical criteria. The revised clinical criteria for APS are shown in Box 1 [3]. Other important information provided in the consensus statement is the inclusion of specific definitions for commonly associated manifestations of APS, such as livedo reticularis, cardiac valve disease, thrombocytopenia and nephropathy [3]. Recently, Kaul and colleagues published a descriptive study with the primary objective of analyzing aPL-positive registry patients using the 2006 revised APS classification criteria [13]. Only 59% of the patients meeting the 1999 APS Sapporo classification criteria met the 2006 APS classification criteria. The revised criteria will have positive implications in APS in research, but also in clinical practice by limiting the inclusion of a heterogeneous group of patients and providing a risk-stratified approach.

Box 1. Revised clinical criteria for the antiphospholipid syndrome.

**Vascular thrombosis**

- One or more clinical episodes of arterial, venous or small vessel thrombosis in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e., unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without evidence of inflammation in the vessel wall.

**Pregnancy morbidity**

- One or more unexplained deaths of a morphologically normal fetus at or beyond the tenth week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
- One or more premature births of a morphologically normal neonate before the 34th week of gestation because of:
  - Eclampsia or severe preeclampsia defined according to standard definitions
  - Recognized features of placenta insufficiency
    - Abnormal or nonreassuring fetal surveillance test(s), for example, a nonreactive nonstress test, suggestive of fetal hypoxemia
    - Abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, for example, absent end-diastolic flow in the umbilical artery
    - Oligohydramnios, for example, an amniotic fluid index of 5 cm or less
    - A postnatal birth weight less than the tenth percentile for the gestational age
- Three or more unexplained consecutive spontaneous abortions before the tenth week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Data taken from [3].

Catastrophic APS is a recognized presentation of the disorder, with multi-organ failure secondary to widespread thrombotic microangiopathy. The organs most commonly affected are the kidneys, lungs, brain, skin, heart and gastrointestinal tract. It is a life-threatening complication with a high mortality rate. Criteria currently exist for patients with catastrophic APS [14].

### Current treatment of venous &/or arterial thrombosis in APS

The most frequent initial manifestation among patients with APS is venous thromboembolism [15]. The predisposing factors that influence recurrence were analyzed in a retrospective cohort study of 61 patients with APS [16]. The main findings were that there are no differences between patients with primary and SLE-associated APS with respect to recurrence, and that pregnancy and the use of oral contraceptives influence recurrence. Treatment with warfarin was most effective in preventing recurrent arterial and venous thrombosis. Treatment includes unfractionated (UFH) or low-molecular-weight heparin (LMWH) for at least 5 days according to accepted regimens overlapped with oral anticoagulant therapy until the patient has achieved a therapeutic International Normalized Ratio (INR) [17]. It is still unclear whether a high- or moderate-intensity regimen is better. In 1995, in a retrospective analysis, Khamashta and colleagues showed that high-intensity anticoagulation (INR target: 3.0–3.5) was significantly more effective [18]. Some 10 years later, the Warfarin in the Antiphospholipid Syndrome (WAPS) trial, a randomized prospective study with a follow-up of 3.6 years, found no significant difference in the effectiveness of preventing thrombosis recurrence and total and major bleeding rates between both oral anticoagulation schedules [19]. In another randomized clinical trial, Crowther and colleagues [20] found that high intensity warfarin is not better than moderate intensity warfarin (INR: 2.0–3.0) in preventing recurrent thrombosis. In this study, 114 patients with APS were enrolled at 13 clinical centers and followed for a mean of 2.7 years. The incidence of recurrence was 10.7% among patients who received high- and 3.4% among those who received moderate-intensity warfarin.

APS is a high risk factor for thrombosis recurrence; 70% of patients with this thrombophilic disorder experience recurrent events

5–6 years after the initial thrombosis [21]. Prospective studies such as the Italian Registry and our recent report, or even the WAPS, have reported an incidence of recurrent thrombosis of 3–24% per year [11,19,22]. Schulman and colleagues found that 29% of patients with APS suffered a recurrence within 4 years after discontinuing anticoagulation in a prospective study published in 1998 [23]. Based on these findings, experts recommend long-term secondary prophylaxis, but the optimal duration of this therapeutic approach is still unknown.

Lifelong anticoagulation therapy is supported by a trial that included 211 patients with a single aCL-positive test and a first thrombosis episode who were randomized to 6 months or indefinite treatment. A total of 23 out of 105 patients from the first group had a new thrombotic event compared with three out of 106 patients in the second group. All of the patients with long-term anticoagulation who experienced recurrence discontinued warfarin before developing the new event [23]. A decision regarding extended anticoagulation may be influenced by the type of aPL involved. LA seems to be a higher risk for thrombosis, and some experts suggest that its presence should prompt long-term treatment. It remains controversial whether stopping warfarin is the best measure for patients whose laboratory tests become negative or whose thromboses were triggered by surgery or oral contraceptives.

An inevitable risk of hemorrhage is always present in patients undergoing anticoagulant therapy. APS patients showed the same frequency of severe and fatal bleeding as observed in other pathologic conditions that require warfarin [24,25]. Fondaparinux, a selective factor Xa inhibitor, is an option for the prevention and treatment of venous thromboembolism; its use in deep vein thrombosis or pulmonary embolism has been approved in patients receiving concomitant oral anticoagulants. It has been compared with UFH in pulmonary embolism showing no difference in effectiveness, with the advantage of being administered on an out-patient basis [26]. Further studies are needed to determine if this drug is a better alternative for APS patients.

Patients with recurrent thrombotic events despite anticoagulation represent a difficult situation. If the recurrence occurs with an INR below the target range (inadequate anticoagulation), the patient should be treated as a new episode in an individual without warfarin. If at the time of

rethrombosis, the INR was adequate, it should be considered a warfarin failure. Treatment includes increasing the intensity of anticoagulation (target INR: 2.5–3.5 or 4.0), switching to LMWH or adding antiplatelet drugs to the therapy schedule.

The most common arterial manifestation occurring in APS patients involves cerebral circulation; the frequency of stroke reaches 13%, transient ischemic attack to 7% and amaurosis fugax to nearly 3% [15]. aPLs have been clearly established as a risk factor in the first cerebrovascular ischemia and in young people, but the role of aPLs in recurrent events remains uncertain. The association to other arterial territories is less important [27]. The value of thrombolytics for aPL-related stroke is currently being investigated. Different studies evaluated the role of this therapy in acute cerebrovascular ischemia in the general population, and it has been clearly established that outcome is only better if thrombolytics are administered within 3 h from the onset of symptoms [28]. It is unknown if the subset of APS patients may benefit from a delayed initiation of tissue plasminogen activator. Patients with APS, stroke and heparin-induced thrombocytopenia (HIT) may be treated with argatroban, a synthetic molecule derived from L-arginine. A 50% reduction in new stroke occurrence in HIT patients treated with argatroban compared with warfarin was reported and no difference was found in intracranial or major bleeding between treatment and control groups [29,30].

The aPL in Stroke Study (APASS) compared warfarin versus aspirin in patients with and without aPL. Among the 1770 patients evaluated in the study, no significant difference was reported in the effectiveness and risk of bleeding between warfarin or aspirin treatment [31]. The presence of aPL did not influence the occurrence of a recurrent event in a 2-year follow-up, with an incidence of approximately 24% of new events in both groups (with a positive or negative test for LA and/or aCLs). According to this study, patients with a first episode of ischemic stroke and a positive test for aPL with no other indication for warfarin therapy may be treated either with aspirin 325 mg/day or moderate intensity anticoagulation (target INR: 1.4–2.8) [32]. This randomized controlled study (APASS) has the important limitations of including patients with one single determination of aPL, patients with low titer aCL and/or IgA aCL, and not randomizing to high-intensity oral anticoagulants.

Current research is directed at the development of safe and effective oral antithrombotic agents as an alternative for warfarin therapy. An oral form of heparin has been developed. Recent studies have shown that the addition of some carrier molecules can facilitate the enteric absorption of both UFH and LMWH and reach levels that are adequate for both prevention and treatment of venous thromboembolism. Pre-clinical and clinical studies suggest that oral heparins can confer a clinically efficacious effect, but further confirmation is sought in planned clinical trials [33].

The treatment of patients who are pregnant and undergo thrombosis is the same regardless of the presence of aPL and is addressed in consensus guidelines [34]. This review does not cover the therapeutic approaches of aPL-associated thrombosis during pregnancy and aPL-related pregnancy morbidity [35].

### Current treatment recommendations in catastrophic APS

The catastrophic variant of APS represents less than 1% of all patients with APS and is usually a life-threatening condition with an approximately 50% mortality rate. The major causes of death are cardiac and respiratory failure. The clinical manifestations depend on the organs affected by the thrombotic events, the extent of the thrombosis and also manifestations of the systemic inflammatory response syndrome (SIRS), which are presumed to be due to excessive cytokine release from affected and necrotic tissues. The SIRS is responsible for some of the nonthrombotic features, such as adult respiratory distress syndrome, frequently seen in catastrophic APS [36]. Trigger factors include infections, trauma and warfarin withdrawal, but in almost 45% of cases, they remain unidentified. Pathogenesis of the catastrophic APS seems dependent on a two- or three-hit hypothesis [37]. Bucciarelli and colleagues reported a retrospective series of 250 patients, analyzing prognostic factors, clinical features and treatment outcomes [38]. The most frequent initial therapeutic approach (85.1%) was anticoagulant therapy, mainly UFH in 60.7% cases, with 63% of episodes with recovery. Corticosteroids were administered in intravenous doses of 500–1000 mg/day for 1–3 days or 1–2 mg/kg/day (either oral or intravenous doses) with a recovery rate of 55.8%. Other individual strategies included cyclophosphamide, plasma exchange, intravenous

immunoglobulins and antiaggregants. The best outcome was obtained when combination therapy was implemented. Anticoagulation plus corticosteroids plus plasma exchange achieved a recovery rate of 77.8% followed by this combination plus intravenous immunoglobulins (69%). The international consensus guidelines for the management of catastrophic APS [14] urge immediate aggressive treatment if catastrophic APS is suspected. Eliminating precipitating factors should be applied in addition to first-line therapies (UFH plus high-dose corticosteroids). If clinical response is poor, plasma exchange and/or intravenous immunoglobulins should be added. Plasma exchange with fresh frozen plasma should be especially indicated if features of microangiopathic hemolytic anemia appear [14].

When the clinical situation deteriorates, third-line treatments may be considered, although experience is limited. These measures include the use of cyclophosphamide, fibrinolytics, defibrotide, prostacyclin and anti-cytokine therapies. It has been recently reported that cyclophosphamide was associated with an improved survival in patients with SLE-associated catastrophic APS, especially in the presence of active lupus manifestations [39]. This study found a worsening outcome when using this drug in primary catastrophic APS. Recently, the use of rituximab has been reported for patients refractory to standard treatment in both APS and catastrophic APS. Anti-CD20 monoclonal antibody has proven useful in patients with thrombocytopenia, with reversal of the low platelet counts and no further episodes of thromboses or bleeding [40,41]. In summary, this variant of APS is a poor prognosis entity. An early aggressive multimodal approach may improve outcomes. Further prospective studies are needed.

#### Primary prevention in patients with aPLs

No evidence-based recommendations exist for primary venous or arterial thrombosis prevention in aPL-positive individuals. Recommendations vary from no treatment to antiaggregants (low-dose aspirin, clopidogrel) or anticoagulant agents [42,43]. The Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study was the first controlled clinical trial of primary thrombosis prevention in 98 asymptomatic persistently aPL-positive individuals. Their results showed no benefits from low-dose aspirin compared with placebo. One of the drawbacks of

this study was the inclusion of individuals with IgA aCL, which is a laboratory criterion not included in the updated APS criteria [3]. In addition, almost half of the individuals have a low-risk aPL profile defined as negative LA and positive IgG, IgM or IgA aCL (20–39 units). The investigators concluded that the ideal primary prevention strategy should be risk-stratified according to guidelines based on the Framingham Heart study. If patients with hypertension, diabetes, hyperlipidemia or smoking habits are also found to have aPL-positive tests, prophylactic use of low-dose aspirin seems to be reasonable. They should also receive counseling regarding the importance of modifying these risk factors [44].

#### New therapeutic approaches

Recent publications based on *in vivo* animal models have shown that new therapeutic approaches can be effective in reversing pathogenic effects of autoimmune aPL [45,46]. For example, hydroxychloroquine significantly diminished thrombus size and time of thrombus persistence in mice injected with purified human aPL [47]. This drug is currently used in patients with SLE and was associated with a decreased risk of thrombosis in patients with SLE and aPL [48,49]. According to a recent study [48], hydroxychloroquine may also be protective against thrombosis in asymptomatic aPL-positive individuals. Patients who suffer thrombosis recurrence despite oral anticoagulation may benefit from this antimalarial drug, but the use of hydroxychloroquine in long-term thromboprophylaxis has not yet been evaluated. In other studies the thrombogenic and pro-inflammatory effects of aPL *in vivo* could be attenuated in mice fed with statins for 15 days [50]. Hydroxychloroquine and statins are likely to become important in the near future. New data have demonstrated that activation of p38 mitogen-activated-protein kinase (MAPK) and NF- $\kappa$ B occurs in monocytes, endothelial cells and platelets pretreated with aPL. The induction of an endothelial procoagulant and proinflammatory phenotype is now widely accepted as a major pathogenic mechanism underlying the thrombophilic diathesis. In a recent study, the SB 203580 (a p38 MAPK inhibitor) significantly reduced the increased adhesion of monocytes to endothelial cells *in vitro*, the number of leukocytes adhering to endothelial cells, the thrombus size, the tissue factor activity



in carotid arteries and in peritoneal mononuclear cells, and the expression of adhesion molecules in the aorta of mice, and completely abrogated platelet aggregation induced by IgG purified from a patient with APS [51]. Therefore, the p38 MAPK inhibitors were demonstrated to be effective in reversing the pathogenic effects of aPL in animal models and could be good candidates to be used into the management of APS-related thrombosis. These inhibitors are now under clinical trials as a novel therapeutic strategy for inflammatory diseases. Similar results were found when a NF- $\kappa$ B inhibitor (MG132) was used *in vivo* in mice [52]. Prothrombotic and proinflammatory properties of IgG and IgM aPLs from APS patients were downregulated by MG132. Nevertheless, whether they could be used therapeutically for preventing APS-related clinical events remain to be elucidated in clinical trials.

Molecular mimicry is thought to be one of the mechanisms for the induction of APS in association with infectious agents. Synthetic peptides that share structural similarity with some regions of the  $\beta_2$ GPI molecule, and share high homology with viral and bacterial antigens were able to induce aPL and anti- $\beta_2$ GPI in mice [53]. In recent experimental studies,

mice treated with purified aPL and infused later with viral/bacterial peptides produced significantly decreased thrombus size in the *in vivo* model of induced thrombosis [54,55]. A viral peptide that shares similarity with the Vth domain of  $\beta_2$ GPI and a synthetic peptide that shares similarity with bacterial antigens and with the I/II region of  $\beta_2$ GPI were tested. Thus, peptides that mimic regions of  $\beta_2$ GPI and crossreact with viral/bacterial antigens were able to abrogate thrombogenic properties of aPL in mice. It may have important implications in designing new approaches for the treatment of APS-related thrombosis.

### Conclusion

Anticoagulation is the mainstay of the clinical management of thrombosis in APS. However, the optimal duration and intensity of therapy is still controversial, as the risk of recurrent thrombosis is very high. Catastrophic APS is a life-threatening complication of this disorder with a high mortality rate. An early aggressive approach may improve outcomes mainly when a combination therapy is implemented. Primary prevention in asymptomatic individuals with aPL does not seem to be justified except when other classical thrombosis risk factors are concomitantly present.

## Executive summary

### Definitions & current criteria for the antiphospholipid syndrome

- Antiphospholipid syndrome (APS) is a clinical autoimmune disorder characterized by thrombosis, venous or arterial, and recurrent pregnancy morbidity in association with a persistence of antiphospholipid antibodies (aPLs).
- Catastrophic APS is a recognized presentation of the disorder, with multi-organ failure secondary to widespread thrombotic microangiopathy.

### Current treatment of venous &/or arterial thrombosis in APS

- A target International Normalized Ratio of 2.0–3.0 is adequate in the majority of patients with APS and venous thrombosis. Optimal duration is unknown, but extended or lifelong therapy is indicated in some cases and may be influenced by the type of aPL involved.
- Patients with a first episode of arterial thrombosis may be treated with aspirin but long-term oral anticoagulation is warranted in high-risk APS patients.

### Current treatment recommendations in catastrophic APS

- An aggressive therapeutic approach is warranted in patients with catastrophic APS. The combination of anticoagulation and corticosteroids, plus either plasma exchange or intravenous immunoglobulins, achieves a high recovery rate.

### Primary prevention in patients with antiphospholipid antibodies

- Asymptomatic aPL-positive individuals do not benefit from low-dose aspirin for primary thrombosis prophylaxis, but prophylactic use of antiaggregants seems to be reasonable in individuals with additional risk factors.

### New therapeutic approaches

- Some therapeutic agents have been successfully tested in *in vivo* APS animal models. Hence, a series of new drugs are considered good candidates to be used in the treatment and prevention of thrombosis in APS.

### Future perspective

- Considering the different thrombotic risk according to the aPL profile, further prospective studies are required to categorize the optimal clinical management in APS-related arterial and/or venous thrombosis.

### Future perspective

Further large-scale, randomized, clinical trials of primary or secondary prevention of thrombosis are required that take into account the risk stratified according to the different aPL profile (type and number of antibodies). The optimal management of patients with arterial thrombosis in the setting of persistently positive aPL remains unanswered and well-designed trials are needed. The effectiveness of new therapeutic approaches must be clearly demonstrated in clinical studies before using as potential antithrombotic therapies in addition to oral anticoagulation. They could then perhaps be used therapeutically in patients who

suffer recurrent thrombosis despite adequate oral anticoagulation and may be useful in preventing the first thrombotic event in asymptomatic aPL-positive patients.

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*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.*

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