Thrombosis and the Antiphospholipid Syndrome

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The antiphospholipid syndrome is an antibody-mediated hypercoagulable state characterized by recurrent venous and arterial thromboembolic events. Several studies have determined that the frequency of antiphospholipid syndrome in patients presenting with a venous thromboembolic event is between 4% and 14%. Because of the high risk for recurrent thromboembolism in these patients, current recommendations suggest a longer, potentially lifelong, course of antithrombotic therapy following an initial event. Although most authorities agree on an extended course of therapy, considerable controversy surrounds the optimal target therapeutic INR for patients with antiphospholipid syndrome. For an initial venous thromboembolic event, a target INR of 2.0 to 3.0 is supported by two prospective, randomized clinical trials. In contrast, relatively limited data exist for an initial arterial thromboembolic event in patients who have the antiphospholipid syndrome, and therapeutic recommendations range from aspirin to warfarin with a high target INR. Recurrent thromboembolic events can be extremely difficult to treat, and some patients may benefit from the addition of immunosuppressive therapies. Importantly, as many as 50% of the initial thromboembolic events sustained by patients with antiphospholipid antibodies occur in the setting of additional, coincident prothrombotic risk factors, indicating the importance of addressing any additional risk factors, such as hypercholesterolemia, in these patients. Prospective studies are needed to address the role of thromboprophylactic strategies in asymptomatic individuals with antiphospholipid antibodies in the absence of additional risk factors.

The antiphospholipid syndrome is an antibody-mediated prothrombotic disorder, similar to heparin-induced thrombocytopenia. Consequently, the diagnosis of a patient with the antiphospholipid syndrome requires the presence of specific clinical manifestations as well as the identification of an antiphospholipid antibody (**Table 1**).[1] Clinical manifestations of the syndrome include venous and/or arterial thromboembolism or adverse outcomes during pregnancy. For patients with thrombotic complications, venous thrombosis is encountered most commonly, occurring in the lower extremities in up to 50% of patients with the syndrome.[2] Other prominent clinical manifestations that are frequently seen in these patients, but which are considered non-diagnostic for the antiphospholipid syndrome, include cardiac valvular abnormalities, livedo reticularis, and a variety of non-thrombotic neurologic manifestations.[2,3]

Laboratory criteria for the syndrome consist of elevated anticardiolipin antibody levels and/or a lupus anticoagulant detected in the blood on two or more occasions, at least 6 weeks apart. Although anti-β_2-glycoprotein I antibodies are currently not included in the diagnostic laboratory criteria for antiphospholipid syndrome, many investigators consider the presence of these autoantibodies to be more specific for the syndrome.[4] Testing for lupus anticoagulants should follow the criteria recommended by the Scientific Subcommittee on Lupus Anticoagulants and Antiphospholipid Antibodies of the International Society on Thrombosis and Haemostasis,[5] as summarized in **Table 1**. Interpretation of laboratory tests for lupus anticoagulants can be difficult in the presence of anticoagulant therapy, particularly heparin.[6]

Primary antiphospholipid syndrome refers to patients with the syndrome who do not have any other rheumatologic or autoimmune conditions, whereas secondary antiphospholipid syndrome refers to patients who also have systemic lupus erythematosus (SLE) or other conditions. In general, the clinical manifestations of the antiphospholipid syndrome are similar for primary and secondary forms of the disease.

Pathogenesis

Antiphospholipid antibodies from patients with the syndrome have been shown to play a direct role in the development of thrombotic manifestations in experimental animal models.[3] Several hypotheses have been proposed to explain the molecular basis of the prothrombotic state associated with these antibodies.[2,3] Antiphospholipid antibodies have been reported to bind to and activate endothelial cells, interfere with natural anticoagulant pathways,

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Table 1. Clinical and diagnostic laboratory criteria for the diagnosis of antiphospholipid antibody syndrome (the "Sapporo criteria").[1,2]

Clinical criteria (one or more of the following clinical events must be present)

- Vascular thrombosis.
  - One or more episodes of arterial, venous, or small vessel thrombosis, affecting any tissue or organ.
- Pregnancy morbidity
  - Unexplained death of a morphologically normal fetus at or after the 10th week of gestation.
  - Premature birth of morphologically normal neonates at or before the 34th week of gestation, because of severe preeclampsia or eclampsia, or severe placental insufficiency.
  - Three of more unexplained consecutive spontaneous abortions before the 10th week of gestation.

Laboratory criteria (one or more of the following laboratory findings must be present)*

- Anticardiolipin IgG or IgM antibodies present at moderate to high levels on 2 or more occasions separated by at least 6 weeks (minimally greater than 20 IgG or IgM units).[6]
- Lupus anticoagulant, diagnosed by the ISTH criteria,† detected in the blood on 2 or more occasions separated by at least 6 weeks.

* Anti-β_2-glycoprotein I antibodies (IgG and IgM) are currently not included in the laboratory criteria for diagnosis of antiphospholipid syndrome, although a recent consensus meeting at the 11th International Conference on Antiphospholipid Antibodies, held in Sydney, Australia, in 1994, has proposed that these antibodies be included in the list of diagnostic laboratory studies.

† ISTH criteria for lupus anticoagulants includes: [1] prolongation of a phospholipid-dependent screening assay; [2] evidence of inhibitory activity with mixing studies; [3] evidence that the inhibitory activity is phospholipid-dependent; and [4] distinction of other coagulopathies.[5]

disrupt annexin V binding to anionic phospholipids, and interfere with fibrinolysis.[2,3] However, the clinical significance of any one (or more) of these pathways remains unclear.

Thrombosis in Patients with Antiphospholipid Antibodies

Elevated antiphospholipid antibody levels are associated with an increased risk for venous thromboembolic complications in patients with SLE (odds ratio of 6.32, confidence interval [CI] 3.71–10.78, compared to patients who do not have antiphospholipid antibodies)[7] as well as in patients who do not have SLE (odds ratio of 11.1, 95% CI of 3.81–32.3).[8] Antiphospholipid antibodies have also been associated with an increased risk for incident stroke, particularly in younger individuals.[9] Asymptomatic individuals with transiently elevated antiphospholipid antibodies (for example, post-infectious) have a low risk for thrombosis.[2] In general, the presence of a lupus anticoagulant is felt to be a stronger indicator of potential thrombotic risk than an elevated anticardiolipin antibody level.[10]

Elevated Antiphospholipid Antibody Levels in Patients with Thrombosis

Several studies have investigated the frequency of elevated antiphospholipid antibody levels in patients presenting with venous thromboembolism, with results ranging from 4% to 14%.[11-13] Given the clinical significance of these antibodies, most authorities include testing for antiphospholipid antibodies when evaluating a patient for a hypercoagulable state.[14] Importantly, patients who test positive for an antiphospholipid antibody on one occasion need to have a positive test on at least one more occasion, 6 weeks or more apart, before being diagnosed as having antiphospholipid syndrome (**Table 1**). Antibody levels have been reported to change over time, and it is unclear if a patient who has a transient antiphospholipid antibody after an initial thrombotic event has the same risk for recurrence as a patient with a persistent antibody.

Recurrent Thrombosis in Patients with Antiphospholipid Syndrome

Three retrospective studies reported that recurrent thrombosis occurred in 52%, 69%, and 51.8% of patients with antiphospholipid syndrome during the follow-up period (5, 6, and 6.4 years, respectively), regardless of antithrombotic strategy.[15-17] Prospectively, Schulman and colleagues[18] demonstrated that, for patients with an initial venous thromboembolic event who completed 6 months of oral anticoagulant therapy, the risk for recurrent thrombosis was 29% in patients with anticardiolipin antibodies compared to 14% in those without these antibodies (P = 0.0013). The risk for recurrent thrombosis appears to be highest in the first few months after discontinuing anticoagulant therapy.[18] In contrast, the role of antiphospholipid antibodies in recurrent stroke is less clear than for venous disease.[9]

Antithrombotic Therapy for Patients with Antiphospholipid Syndrome and Venous Thromboembolism

The current recommendation from the American College of Chest Physicians for anticoagulant therapy for patients with antiphospholipid syndrome who sustain a venous thromboembolic event is warfarin with a target INR of 2.5 (Grade 1A) for 12 months (Grade 1C+), with the suggestion to consider indefinite anticoagulant therapy (Grade 2C).[19] For the individual patient, it is instructive to review the primary data leading to the different opinions and the consensus recommendation concerning therapeutic management of these patients.

Retrospective studies

A higher therapeutic INR was initially recommended for these patients based on two retrospective studies.[15,16] Rosove and Brewer[15] described 70 patients with thrombosis and antiphospholipid antibodies (39 with an initial venous thromboembolic event; total follow-up after first event of

361 patient-years). Of 55 patients treated with warfarin, 3 patients with a target INR range of 2.0 to 2.9 sustained recurrent thromboembolic events, in contrast to none of the patients maintained at a target INR ≥ 3.[15] Non-fatal bleeding events interrupted warfarin therapy in 5 patients. Khamashta and colleagues[16] described 147 patients with the antiphospholipid syndrome followed for a total of 946.9 patient-years after their first thrombotic event (80 with a first venous thromboembolic event). Of the recurrent thrombotic events occurring with warfarin, 39 of 42 occurred in patients with a target INR < 3 compared to 3 events in patients with a target INR ≥ 3.[16] Nonfatal bleeding events occurred in 29 patients during warfarin therapy. These two retrospective studies included a high percentage of patients with secondary antiphospholipid syndrome and high rates of recurrent thromboembolism, which distinguished them from the prospective randomized trials described below.

Prospective studies with a target INR of 2.0 to 3.0

Several prospective studies investigating oral anticoagulant therapy have included patients who were subsequently found to have antiphospholipid antibodies (reviewed in [20]). Although not designed to address the optimal target INR for patients with antiphospholipid syndrome, the data would suggest that these patients did not have higher thromboembolic recurrence rates than patients with venous thrombosis who did not have antiphospholipid antibodies using a target INR of 2.0 to 3.0.

Prospective randomized trials

Two trials have been published that randomized patients who met criteria for antiphospholipid syndrome with thrombosis as the presenting symptom to a target INR range of 2.0 to 3.0 or to a higher target INR range of 3.1 to 4.0.[21,22] Crowther and colleagues[21] enrolled 114 patients with arterial (n = 27) or venous (n = 87) thromboembolic events and laboratory criteria for the syndrome (**Table 2**). Patients with a prior recurrence while on warfarin with a targeted INR > 2.0 were excluded (representing 6 of 325 screened). They found that the higher target INR was not superior to the standard target INR range of 2.0 to 3.0 in preventing recurrent thromboembolism (**Table 2**); however, the overall recurrence rate was much less than the estimated risk used to calculate the sample size required for the study.[21]

Finazzi and colleagues[22] enrolled a similar number of patients in their study (**Table 2**), although their planned sample size was much larger and the study was closed early due to decreased recruiting and concerns about investigator adherence to the protocol. As with the first study, patients with a history of recurrent thrombosis during anticoagulant prophylaxis were excluded (57 of 316 patients with confirmed thrombosis). Similar rates of recurrent thromboembolism as well as major hemorrhage were seen in the two groups of patients (**Table 2**), again suggesting that a higher target INR was not necessary for patients with antiphospholipid syndrome and venous thromboembolism.

Duration of anticoagulant therapy

Several studies have demonstrated that patients with antiphospholipid syndrome who have sustained a venous thromboembolic event are at high risk for recurrent thrombosis if anticoagulation is stopped.[16,18] Guidelines from the British Society of Hematology recommend therapeutic anticoagulation for 6 months after an initial venous thromboembolic event, with indefinite anticoagulation for patients with recurrent events.[23] In contrast, as noted above, the American College of Chest Physicians recommends treatment for 12 months and consideration of indefinite therapy after an initial event.[19] Individual management decisions should be based on the severity of the thrombotic event, the role of additional prothrombotic risk factors, and the potential for hemorrhagic complications.

Anticoagulant Therapy for Patients with Antiphospholipid Syndrome and Arterial Thromboembolism

Based on the retrospective studies of Rosove and Brewer[15] and Khamashta and colleagues,[16] it appeared that antiplatelet therapy with aspirin was insufficient to prevent recurrent thromboembolic events in these patients. As noted above, these two studies also found that the lowest risk for recurrent events occurred with warfarin therapy maintained at a higher target INR. These results were challenged by the prospective studies from Crowther and colleagues[21] and Finazzi and colleagues,[22] which found that a target INR of 2.0 to 3.0 was as effective in preventing recurrent events as a higher target INR. However, both of these studies included relatively few patients with arterial thromboembolic events, leading some authorities to still recommend a higher target INR for patients with antiphospholipid syndrome and arterial thromboembolism.[24] Bringing the

Table 2. Prospective randomized trials investigating optimal target INR for patients with antiphospholipid antibodies and thromboembolism.

Study	Treatment Arm	Patients	Patient-Years of Follow-Up	Recurrent Thrombo-embolism	Major Hemorrhagic Complications
Crowther, et al., 2003 [21]	Target INR 2.0 to 3.0	58	158	2	4
	Target INR 3.1 to 4.0	56	148	6	3
Finazzi, et al., 2005 [22]	Target INR 2.0 to 3.0	55*	165	3	3
	Target INR 3.0 to 4.5	54	162	6	2

* Three of these patients were treated with aspirin alone as 'standard' antithrombotic therapy. They did not sustain any of the recurrent thromboembolic events or major hemorrhagic complications.

argument full-circle, Derksen and colleagues[25] recently reported on 8 patients with antiphospholipid syndrome and stroke treated with low-dose aspirin therapy (38-80 mg/day). In this small study, they found a recurrent stroke rate of 3.5 per 100 patient years (95% CI 0.4 to 12.5), which is comparable to the recurrence rates in young adults with ischemic stroke who do not have antiphospholipid antibodies.[25]

The Antiphospholipid Antibodies and Stroke Study (APASS) sought to clarify the significance of antiphospholipid antibodies detected at the time of an initial ischemic stroke in predicting subsequent thromboembolic events.[26] This large, randomized, double-blind trial was a nested cohort study within the larger Warfarin vs. Aspirin Recurrent Stroke Study (WARSS) and compared adjusted-dose warfarin (target INR of 1.4 to 2.8) with aspirin (325 mg/day) for prevention of recurrent stroke or death. Patients with antiphospholipid antibodies present at baseline did not have an increased risk for recurrent thromboembolic events compared to patients who did not have these antibodies. Furthermore, there was no difference in outcome for patients treated with warfarin compared to patients treated with aspirin, regardless of baseline antiphospholipid antibody status.[26]

Several concerns have been raised about the results from APASS. First, patients were stratified according to a single determination of antiphospholipid antibodies at presentation with an ischemic stroke, which does not fulfill the diagnostic criteria for antiphospholipid syndrome (**Table 1**). Second, the patient group studied in the trial was older (mean age, 63.1 years) compared to most patients with the antiphospholipid syndrome (mean age, 42 years at diagnosis).[27] Elevated anticardiolipin antibody levels are more frequently encountered in elderly individuals in general.[28] Third, the target INR used in the APASS study was lower than what many individuals would use for prevention of recurrent thromboembolic events.

The optimal treatment for patients with antiphospholipid syndrome and arterial thromboembolic events remains controversial.[9,20,24,29] Although the American College of Chest Physicians recommended antiplatelet agents over oral anticoagulation for most patients with noncardioembolic stroke or transient ischemic attack, oral anticoagulation was suggested for patients with noncardioembolic stroke and "well-documented prothrombotic disorders" which included the antiphospholipid syndrome.[30] A target INR was not recommended, however.

Unusual Thrombotic Manifestations

Thrombotic complications in patients with antiphospholipid syndrome have been described affecting essentially every organ system and vascular bed.[2] For example, thrombotic complications have been reported affecting the sagittal veins, intra-abdominal veins, and the retinal veins. In general, treatment strategies for thrombosis in these unusual locations are similar to treatment strategies for deep venous thrombosis affecting the limbs or pulmonary emboli. Several studies have also reported an increased incidence of elevated antiphospholipid antibody levels in patients with osteonecrosis. Although anticoagulant therapy has been used anecdotally in patients with osteonecrosis, it has not been systematically investigated.

Thromboembolic Events During Pregnancy

Women with antiphospholipid antibodies have an increased risk for venous thromboembolism during pregnancy, particularly in the post-partum setting.[31] Recommended therapeutic options for pregnant women with antiphospholipid antibodies but without prior thromboembolism or pregnancy loss include: surveillance, mini-dose heparin (5000 units subcutaneously every 12 hours), prophylactic low molecular weight heparin, and/or low-dose aspirin (75 to 162 mg/day).[32] For pregnant women who sustain a thromboembolic event, therapeutic, adjusted-dose low molecular weight heparin would be the optimal therapy during pregnancy, followed by a minimum of 6 weeks of oral anticoagulant therapy in the post-partum setting.[32] If the antiphospholipid antibody persists, an extended course of anticoagulant therapy should be considered.

In addition to the increased thrombotic risk, women with antiphospholipid antibodies also have an increased risk for other adverse maternal and fetal outcomes during pregnancy (**Table 1**), presumably related to poor placental perfusion secondary to thrombosis. For women with a history of two or more early pregnancy losses, one or more late pregnancy losses, pre-eclampsia, fetal growth restriction, or abruption, the American College of Chest Physicians currently recommends mini-dose or moderate dose (adjusted dose subcutaneous heparin with a target anti-factor Xa level of 0.1 to 0.3 U/mL) unfractionated heparin or prophylactic low molecular weight heparin in addition to aspirin.[32] Intravenous immunoglobulin has also been used, but a randomized controlled study found no benefit of intravenous immunoglobulin compared with heparin and aspirin in reducing adverse obstetrical outcomes in women with antiphospholipid syndrome.[33]

Thrombosis of Vascular Access Grafts

Antiphospholipid antibodies have also been associated with an increased risk for thrombosis of arteriovenous grafts in patients with renal failure on chronic hemodialysis.[34] Low-intensity warfarin (target INR of 1.4 to 1.9) was not successful in improving survival of polytetrafluoroethylene grafts in one study, however, and was associated with an increased risk for major hemorrhagic complications compared to placebo.[35] Other antithrombotic strategies have been attempted in these patients, including low-molecular weight heparin, but none have been explored in a prospective trial. Antiphospholipid antibodies have also been reported to confer an increased risk for early renal allograft failure.[36]

Catastrophic Antiphospholipid Syndrome

The catastrophic antiphospholipid syndrome defines an accelerated form of the disorder characterized by multiorgan failure as a result of small vessel thrombosis.[37] Preliminary criteria for the catastrophic antiphospholipid syndrome have been proposed by an international group[38] and includes (1) evidence of involvement of three or more organs, systems, and/or tissues; (2) development of manifestations simultaneously or within a week; (3) confirmation by histopathology of small vessel occlusion in at least one organ or tissue; and (4) laboratory confirmation of the presence of antiphospholipid antibodies. Precipitating factors have been reported in up to a third of these patients, including recent infection, surgery, neoplasia, anticoagulation withdrawal, oral contraceptives, and obstetrical complications. However, it is unclear why these precipitating variables result in this aggressive clinical presentation in only a subset of patients with antiphospholipid syndrome.

Therapeutic interventions for patients with catastrophic antiphospholipid syndrome include antithrombotic therapy, steroids, cyclophosphamide, intravenous immunoglobulin, and plasmapheresis.[37] Almost half of the patients who present with this syndrome expire during the initial event, and about 25% of those who survive the initial event will eventually succumb to further events related to the antiphospholipid syndrome.[39]

Therapeutic Strategies for Recurrent Thromboembolism

Relatively few data are available for those patients who sustain a recurrent thromboembolic event in the setting of therapeutic oral anticoagulation. A variety of treatment strategies have been used, including addition of antiplatelet agents to higher-intensity oral anticoagulation, conversion from oral anticoagulants to therapeutic dose low-molecular weight heparin, and addition of immunomodulatory strategies. Immunomodulatory therapies that have been anecdotally used in patients with antiphospholipid syndrome include steroids, cyclophosphamide,[40] and rituximab,[41] but these are generally used in combination with an aggressive antithrombotic strategy. There are no data concerning how long these patients should be treated with immunosuppressive therapy.

Transplantation has also been explored as an alternative for patients with severe manifestations of the antiphospholipid syndrome. Recently, Statkute and colleagues[42] investigated the role of hematopoietic stem cell therapy in 28 patients with secondary antiphospholipid syndrome. Antiphospholipid antibody levels normalized in most of the patients after transplantation, and 18 of 22 patients on chronic oral anticoagulation discontinued therapy a median of 4 months post-transplant.[42] Four of these patients sustained recurrent thromboembolic events after discontinuing anticoagulants, however.

Monitoring Anticoagulant Therapy in Antiphospholipid Syndrome

Many patients with antiphospholipid syndrome have a prolonged aPTT, which can complicate monitoring therapy with heparin. In these patients, an anti-factor Xa assay can be used, or a low-molecular weight heparin could be substituted for heparin. A small number of patients with antiphospholipid syndrome appear to have lupus anticoagulants that affect the prothrombin time, which can prolong the INR and potentially complicate using this test to monitor warfarin therapy.[43] This is not observed with all thromboplastin reagents, but appears to occur more frequently with recombinant thromboplastins with a low international sensitivity index.[44,45] For patients who appear to have a lupus anticoagulant that affects the prothrombin time, an alternative test, such as the chromogenic factor X assay, would be a more accurate way to monitor oral anticoagulant therapy.[43]

Table 3. "How I treat patients with antiphospholipid syndrome."

When do I order laboratory testing for antiphospholipid antibodies?

- Patients presenting with a new, spontaneous venous thromboembolic event.
- Younger patients presenting with a new, arterial thromboembolic event.
- Patients with atypical thromboembolic events and unusual presentations.

How do I treat patients with antiphospholipid syndrome and venous thromboembolic events?

- Confirm that baseline prothrombin time is normal (if not, evaluate further with mixing studies, factor II level).
- For initial thromboembolic event, treat with oral anticoagulation with a target INR of 2.5 (range, 2.0 to 3.0) for a minimum of 12 months.
- Treat any additional prothrombotic states, such as elevated homocysteine levels with folic acid.
- For recurrent thromboembolic events, use either a higher target INR (3.5, range 3.0 to 4.0), an alternative anticoagulant (e.g., low molecular weight heparin), or consider an immunomodulatory strategy, particularly if secondary antiphospholipid syndrome.

How do I treat patients with antiphospholipid syndrome and arterial thromboembolic events?

- Confirm that baseline prothrombin time is normal.
- For initial thromboembolic event, treat with oral anticoagulation with a target INR of 3.0 (2.5 to 3.5) for a minimum of 12 months.
- Treat any additional prothrombotic states, such as hypercholesterolemia and hypertension.
- For recurrent thromboembolic events, use either a higher target INR (above 3.0), an antiplatelet agent in addition to the anticoagulant, an alternative anticoagulant, or consider an immunomodulatory strategy.

Treatment of Additional Prothrombotic Risk Factors

Several studies have shown that additional prothrombotic risk factors may be associated with an increased risk for thrombosis in patients with antiphospholipid antibodies.[46,47] In fact, a recent prospective study found that 50% of patients with antiphospholipid syndrome had coincident risk factors for thrombosis at the time of a first thrombotic event.[47] These risk factors included surgery and prolonged immobilization in association with venous thromboembolism, and hypercholesterolemia and arterial hypertension with arterial thromboembolism. Elevated homocysteine levels have also been associated with an increased risk for arterial thrombosis in patients with lupus.[48] Appropriate treatment of additional prothrombotic risk factors that can be modified in patients with antiphospholipid antibodies is essential to minimize the associated thrombotic risk.

Thromboprophylaxis for the Asymptomatic Individual with Antiphospholipid Antibodies

A case-control study nested within the Physicians' Health Study found that aspirin (325 mg/day) did not protect against venous thromboembolism in males with anticardiolipin antibodies.[49] However, aspirin has been reported to potentially protect against thrombosis in women with antiphospholipid antibodies and prior pregnancy loss.[31] Furthermore, Erkan and colleagues[50] reported that aspirin, hydroxychloroquine, and steroids were used more frequently by asymptomatic individuals with elevated antiphospholipid antibody levels than patients with antiphospholipid syndrome and thrombosis. Although these reports are suggestive that thromboprophylaxis may be effective in some patients with antiphospholipid antibodies, these observations need to be confirmed in prospective, randomized clinical trials.

Summary

Even with the most complete datasets, it is still important for the physician to develop a therapeutic plan appropriate for the individual patient, based on clinical presentation, co-morbid conditions, and other variables. With uncommon disorders and limited datasets, such as with the antiphospholipid syndrome, decision-making becomes even more difficult. **Table 3** presents a strategy that the author uses when evaluating and developing a treatment plan for a patient with antiphospholipid syndrome and thrombosis, based on the available studies summarized in this article. Critical areas for future research include identifying which patients with antiphospholipid antibodies are at highest risk for thrombotic complications, developing new antithrombotic agents that are effective and safe, and investigating novel approaches to eliminate the autoantibody and, hopefully, the increased prothrombotic state.

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