Management of Antiphospholipid Antibody Syndrome
A Systematic Review

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ANTIPHOSPHOLIPID ANTIBODIES were first described in 1906 in a study by Wassermann et al1 among patients with positive serologic test results for syphilis. Antiphospholipid antibodies are a heterogeneous group of autoantibodies directed against phospholipid-binding proteins. Antiphospholipid antibodies can be broadly categorized into those antibodies that prolong phospholipid-dependent coagulation assays, known as lupus anticoagulants (LA), or anticardiolipin antibodies (aCL), which target a molecular congener of cardiolipin (a bovine cardiac protein). The presence of these antibodies in patients with arterial or venous thrombosis or pregnancy morbidity comprises the antiphospholipid antibody syndrome (APS). This syndrome is referred to as primary APS when it occurs alone and secondary APS when it occurs in association with other conditions, such as systemic lupus erythematosus (SLE). Antiphospholipid antibodies are also found in patients with infections such as human immunodeficiency virus2 and may develop during therapy with medications such as chlorpromazine.3,4 Their clinical importance in these settings is unknown. The

Context Antiphospholipid antibodies are autoantibodies directed against proteins that bind to phospholipid. Antiphospholipid antibody syndrome (APS) refers to the association between antiphospholipid antibodies and thrombosis risk or pregnancy morbidity. Patients with APS may be at increased risk of recurrent arterial or venous thrombosis or pregnancy loss.

Objective To systematically review the evidence for treatment of thrombosis risk in patients with antiphospholipid antibodies or APS.

Evidence Acquisition Search of MEDLINE (1966 to November 2005) and Cochrane Library electronic databases (2005) and reference lists for randomized trials, meta-analyses of randomized trials, and prospective cohort studies of the treatment of thrombosis risk in patients with antiphospholipid antibodies or APS. Studies were selected on the basis of clinical relevance.

Evidence Synthesis Among patients with antiphospholipid antibodies, the absolute risk of developing new thrombosis is low (<1% per year) in otherwise healthy patients without prior thrombotic events, may be moderately increased (up to 10% per year) in women with recurrent fetal loss without prior thrombosis, and is highest (>10% in the first year) in patients with a history of venous thrombosis who have discontinued anticoagulant drugs within 6 months. Compared with placebo or untreated control, anticoagulation with moderate-intensity warfarin (adjusted to a target international normalized ratio [INR] of 2.0-3.0) reduces the risk of recurrent venous thrombosis by 80% to 90% irrespective of the presence of antiphospholipid antibodies and may be effective for preventing recurrent arterial thrombosis. No evidence exists that high-intensity warfarin (target INR, >3.0) is more effective than moderate-intensity warfarin. For patients with a single positive antiphospholipid antibody test result and prior stroke, aspirin and moderate-intensity warfarin appear equally effective for preventing recurrent stroke. Treatment issues that have not been addressed in clinical trials, or for which the evidence is conflicting, include the role of antithrombotic prophylaxis in patients with antiphospholipid antibodies without prior thrombosis, the optimal treatment of noncerebrovascular arterial thrombosis, recurrent thrombosis despite warfarin therapy, and treatment of women with antiphospholipid antibodies and recurrent fetal loss.

Conclusions In patients with APS, moderate-intensity warfarin is effective for preventing recurrent venous thrombosis and perhaps also arterial thrombosis. Aspirin appears to be as effective as moderate-intensity warfarin for preventing recurrent stroke in patients with prior stroke and a single positive test result for antiphospholipid antibody. The optimal treatment of other thrombotic aspects of APS needs to be addressed in well-designed prospective studies.

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Sapporo criteria are a widely used consensus definition of APS.3

Treatment of antiphospholipid antibodies is problematic because of a lack of laboratory standardization, limited data on their natural history, and a lack of randomized treatment trials. Depending on the assay, antiphospholipid antibodies are reported in up to 10% of healthy individuals and in 30% to 50% of patients with SLE.4 Antiphospholipid antibodies are more common in patients with thrombosis but a causal association is unproven and the clinical relevance of transient or low titer antiphospholipid antibodies remains uncertain. Furthermore, a recent systematic review has questioned the association between isolated aCL and thrombosis.5

We systematically reviewed laboratory testing, diagnostic criteria, and treatment of thrombosis in patients with antiphospholipid antibodies. We reviewed the management of antiphospholipid antibody–associated recurrent fetal loss but did not address preconception anticoagulation. The treatment of patients who are pregnant and develop thrombotic complications is the same irrespective of the presence of antiphospholipid antibodies and is addressed in comprehensive reviews and guidelines.5,9 We did not consider the treatment of antiphospholipid antibody–associated thrombocytopenia or catastrophic APS.

**EVIDENCE ACQUISITION**

We searched MEDLINE (1966 to November 2005), The Cochrane Library (2005, Issue 4), and The Cochrane Pregnancy and Childbirth Group (The Cochrane Library 2005, Issue 2) databases using the following terms singly and in combination: antiphospholipid (antibody) syndrome, antiphospholipid antibody, lupus anticoagulant, anticardiolipin antibody, thrombosis, (deep) venous thrombosis, pulmonary embolism, arterial thrombosis, arterial occlusive disease, cerebrovascular disorders, stroke, myocardial infarction, anticoagulants, platelet aggregation inhibitors, warfarin, antplatelet, aspirin, incidence, prevalence, pregnancy, and pregnancy loss. We further reviewed reference lists and articles from the authors’ libraries. We based our recommendations concerning laboratory testing and diagnosis of APS on published international consensus guidelines. In evaluating thrombosis treatment, we focused on randomized controlled trials or meta-analyses of randomized controlled trials. If these trials were not available, prospective studies were examined before retrospective studies.

**EVIDENCE SYNTHESIS**

**Laboratory Detection of Antiphospholipid Antibodies**

Laboratory testing for antiphospholipid antibodies is complicated because there is uncertainty about their antigenic target. Both LA and aCL may demonstrate specificity for β2-glycoprotein I,10,11 but many other antigenic targets have been described including prothrombin15 and annexin V.13 In some cases, antibodies directed against β2-glycoprotein I rather than anionic phospholipids are believed causal in this syndrome.14 Consensus guidelines describing laboratory techniques for measuring aCL and LA have been published.15,16

**Lupus Anticoagulants**

Lupus anticoagulants, also referred to as nonspecific inhibitors, are antibodies that block phospholipid surfaces important for coagulation. They reduce the coagulant potential of the plasma and prolong the clotting time in coagulation tests based on the activated partial thromboplastin time.17 Failure of the prolonged clotting time to correct after a 1:1 mix with normal platelet-free plasma and correction of the clotting time after addition of excess phospholipids confirms the presence of LA.18 Consensus guidelines recommend screening for LA with 2 or more phospholipid-dependent coagulation tests, including the activated partial thromboplastin time, dilute Russell viper venom time, kaolin clotting time, dilute prothrombin time, textarin time, or taipan time.19 Anticoagulant therapy may interfere with the detection of LA.19

**Anticardiolipin Antibodies**

Anticardiolipin antibodies share a common in vitro binding affinity for cardiolipin and can be detected using enzyme-linked immunosorbent assays. The immunoglobulin isotype may be IgG, IgM, or IgA. It is widely believed that the IgG isotype is most strongly associated with thrombosis, although this has not been tested in large prospective studies.20 Enzyme-linked immunosorbent assay tests for aCL are poorly standardized and aCL testing has shown poor concordance between laboratories.17 Anticardiolipin antibodies are reported as a titer specific to the isotype (IgG, IgM, or IgA phospholipid antibody titer), but because the accuracy and reliability of assays are limited, consensus guidelines recommend semi-quantitative reporting of results (low, medium, or high titer).21

**Anti–β2–Glycoprotein I Antibodies**

Anti–β2–glycoprotein I antibodies22,23 are currently not included in the Sapporo criteria but may be incorporated in future updates. The laboratory assay for these antibodies is not standardized, making comparison between studies difficult.11 The clinical relevance of anti–β2–glycoprotein I antibodies also is uncertain, although there is some evidence that these antibodies are more specific for APS.24

**Diagnostic Criteria for APS**

According to the Sapporo criteria, APS is present in patients with 1 clinical and 1 laboratory criterion. Clinical criteria include objectively confirmed arterial, venous, or small-vessel thrombosis, or pregnancy morbidity consisting of recurrent fetal loss before the 10th week of gestation, 1 or more unexplained fetal deaths at or beyond the 10th week of gestation, or premature birth due to placental insufficiency, eclampsia, or preeclampsia. Laboratory criteria include medium or high titer IgG or IgM aCL or the presence of LA on 2 or more occasions at least 6 weeks apart.15,16

Although consensus-derived diagnostic criteria such as those formu-
lated by the Sapporo international workshop require repeated measurement to establish a diagnosis of APS, there is no evidence that transient antiphospholipid antibodies are less important than persistent antibodies. Two of the largest studies to examine the prognostic importance of antiphospholipid antibodies tested patients on only one occasion: at the time of presentation with stroke and 6 months following the diagnosis of venous thromboembolism.

**Association of Antiphospholipid Antibodies and Thrombosis**

Cross-sectional studies among healthy blood donors report LA in 8% of patients, IgG aCL in 6.5% of patients, and IgM aCL in 9.4% of patients. Persistently positive antiphospholipid antibodies are unusual in healthy individuals (<2% of healthy blood donors initially found to have aCL still had increased levels 9 months later). In a general obstetric population, the prevalence of LA was 0.3% and the prevalence of aCL was 2.2% to 9.1%, which was similar to that observed among patients who are not pregnant (5.6%). In comparison, the prevalence of antiphospholipid antibodies of 20% among women with recurrent fetal loss compared with 5% in healthy women. The association between antiphospholipid antibodies and fetal loss is strongest for loss occurring after 10 weeks. The association between antiphospholipid antibodies and the risk of premature birth due to eclampsia or preeclampsia and intrauterine growth restriction remains controversial; studies contributing data to this area tend to be small, retrospective, and have conflicting results.

**Determining Thrombosis Risk in APS**

The optimal treatment of thrombosis risk in patients with APS requires assessment of thrombosis risk associated with antiphospholipid antibodies so that the potential benefits of antithrombotic therapies for preventing thrombosis can be balanced against the risk of bleeding.

**Patients Without Prior Thrombosis.**

In patients with SLE, the incidence of thrombosis was 2 per 100 person-years in a prospective cohort of 551 patients of whom 49% had either LA or aCL. The OR of thrombosis was 3.20 (95% confidence interval [CI], 1.43-7.14) for LA and 6.80 (95% CI, 1.53-30.20) for high-titer aCL. However, patients with SLE have a high prevalence of thrombosis even in the absence of antiphospholipid antibodies and there are only limited data describing the risk of thrombosis in patients with an isolated antiphospholipid antibody who do not have SLE. Among 552 randomly selected blood donors, no thrombotic events were observed after 12 months of follow-up among patients found to have aCL. Consequently, the risk of thrombosis among healthy women who are incidentally found to have an antiphospholipid antibody is likely to be low (<1% per year).
Patients With Prior Thrombosis. The risk of recurrent thrombosis among patients with antiphospholipid antibodies is based on limited retrospective studies of untreated patients or studies of patients followed up prospectively after their anticoagulant drugs have been discontinued.7 Three prospective studies suggest that there is an increased risk of recurrence, ranging from 10% to 67% per year.26,48,49 In a large prospective study,26 412 patients with a first episode of venous thromboembolism who completed 6 months of anticoagulation were tested for aCL and followed up prospectively after anticoagulant drugs were discontinued. After 4 years, 20 (29%) of 68 patients with increased aCL had recurrent thrombosis compared with 47 (14%) of 334 patients without aCL (risk ratio, 2.1; 95% CI, 1.3-3.3).26 Most patients included in these studies did not conform to the consensus definition for APS because antiphospholipid antibody testing was performed only once and testing was often performed after recurrence. In patients who received no antithrombotic treatment, retrospective studies report recurrence rates of 0.19 events50 or 0.29 events per year of follow-up.51 These studies report recurrent thrombosis in 52% to 69% of patients during 5 to 6 years of follow-up, regardless of the type of antithrombotic therapy.50,51 The incidence of thrombosis was highest during the first 6 months following discontinuation of warfarin therapy, with an event rate of 1.30 events per year of follow-up.51 Recurrent thrombosis in APS tends to occur in the same vascular distribution as the original event. Patients with venous thrombosis generally have recurrent venous events and patients with arterial thrombosis have recurrent arterial events.50,52

Risk of Bleeding. Estimates of bleeding risk are derived from studies evaluating anticoagulant therapy in patients with APS. Major bleeding occurs at a frequency of 2% to 3% per year, which is comparable with the bleeding rates observed in patients without APS but who receive anticoagulant therapy.53,54 Patients with antiphospholipid antibodies directed against prothrombin may rarely present with a bleeding diathesis.55

Antithrombotic Treatment of APS

A proposed treatment algorithm of antithrombotic treatment recommendations and corresponding levels of evidence on which the recommendations are based is shown in the Figure.

Venous Thromboembolism. Venous thromboembolism is the most common initial clinical manifestation among patients with APS, occurring in 32% of patients who meet consensus conference criteria for the diagnosis.56 Initial treatment of venous thromboembolism in patients with APS consists of initial unfractionated or low-molecular-weight heparin for at least 5 days, overlapped with warfarin therapy.57 Compared with placebo or untreated control, moderate-intensity warfarin (adjusted to a target international normalized ratio [INR] of 2.0-3.0) reduces the risk of recurrent venous thrombosis by 80% to 90% irrespective of the presence of antiphospholipid antibodies.58

For long-term treatment of venous thromboembolism, retrospective case series suggested that high-intensity warfarin (INR, >3.0) was more effective than either aspirin or warfarin administered with a target INR of less than 3.0.50,51 However, 2 randomized trials53,54 have shown that high-intensity warfarin is not better than moderate-intensity warfarin (INR, 2.0-3.0) in preventing recurrent thrombosis. In the first trial,53 among 114 patients with APS who were randomized (74% with previous venous thrombosis) and followed up for a mean duration of 2.7 years, the incidence of recurrent thrombosis was 10.7% among patients who received high-intensity warfarin and 3.4% among those who received moderate-intensity warfarin (HR, 3.1; 95% CI, 0.6-15.0). Major bleeding rates were comparable in the 2 groups, occurring in 5.4% of patients treated with high-intensity warfarin and 6.9% of patients receiving moderate-intensity warfarin (HR, 1.0; 95% CI, 0.2-4.8). Overall bleeding rates were also comparable in the 2 groups, occurring in 25% and 19% of patients, respectively (HR, 1.9; 95% CI, 0.8-4.2).53 In the second trial,54 among 109 patients with APS who were randomized (89% had previous venous thrombosis) and followed up for a median duration of 3.6 years, the incidence of recurrent thrombosis was 11.1% among patients who received high-intensity warfarin and 5.5% among those who received moderate-intensity warfarin (HR, 1.97; 95% CI, 0.49-7.89). Bleeding rates were not significantly different in the 2 groups (27.8% vs 14.6%; HR, 2.18; 95% CI, 0.92-5.15).54

Both of these studies were designed to demonstrate that high-intensity warfarin was better than moderate-intensity warfarin for prevention of recurrent thrombosis. Neither study was powered to demonstrate equivalence of the 2 interventions. When the results of the 2 studies were combined in a meta-analysis using Peto method,59 a significant excess of minor bleeding was evident in patients allocated to high-intensity warfarin (OR, 2.30; 95% CI, 1.16-4.58; P = .02). The pooled data did not demonstrate a significant difference in recurrent thrombosis (high-intensity warfarin vs moderate-intensity: OR, 2.49; 95% CI, 0.93-6.67), total bleeding (OR, 1.73; 95% CI, 0.93-3.31), or major bleeding (OR, 0.73; 95% CI, 0.23-2.31).

The optimal duration of anticoagulation for prevention of recurrent thrombosis in patients with antiphospholipid antibodies is unknown. The risk of recurrence appears to be highest in the 6-month period immediately following discontinuation of anticoagulant drugs but it is unknown whether the absolute risk of recurrence decreases with increasing duration of anticoagulation. In 1 prospective study,50 105 patients with a single positive test result for aCL who were randomly assigned to stop warfarin after 6 months experienced 23 recurrent events compared with 3 recurrent events in 106 patients receiving indefinite anticoagulation (HR, 7.7; 95% CI, 2.4-25.0). All patients who experi-
enced recurrent events in the indefinite treatment group had discontinued warfarin before developing recurrent thrombosis. In a second prospective observational study, which measured both LA and aCL after presentation with a first episode of venous thromboembolism, the HR for recurrence at 3 months was 4.0 (95% CI, 1.2-13.0) for patients who were antiphospholipid antibody–positive compared with patients who were antiphospholipid antibody–negative. Although these patients received anticoagulant drugs, the incidence of recurrent thrombosis appears to be increased among those with antiphospholipid antibodies compared with those who do not have antiphospholipid antibodies. Prospective studies of patients with APS receiving antithrombotic therapy (mainly warfarin, but also including patients receiving aspirin or no treatment) report an incidence of recurrent thrombosis of 3% to 24% per year. Retrospective studies report higher recurrence rates, ranging from 53% to 69%. Consequently, the general consensus is to treat patients with APS and venous thrombosis with indefinite duration of anticoagulation.

Decisions regarding duration of anticoagulation may also be influenced by the type of antiphospholipid antibody (LA vs aCL or both) and whether the antibody response is persistent. Because there is a perception that LA compared with aCL is more strongly associated with thrombosis, the presence of LA may prompt extended anticoagulation, although this is based on expert opinion only. It is unknown whether

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**Figure. Algorithm for Antithrombotic Treatment of Patients With Antiphospholipid Antibodies**

- **Patients With Antiphospholipid Antibodies**
  - **Prior Thrombosis?**
    - Yes
      - **Venous Thrombosis**
        - First Episode or Recurrent Episode While Not Receiving Warfarin or While the INR Was Below the Target Range
        - Warfarin (INR, 2.0-3.0)
        - Low-Molecular-Weight Heparin or Unfractionated Heparin
      - Recurrent Episode While Receiving Warfarin
        - Options
          - Low-Molecular-Weight Heparin
          - Unfractionated Heparin
          - Warfarin With a Higher Target INR
          - Warfarin Plus Antiplatelet Agent
    - No
      - **Arterial Thrombosis**
        - First Episode or Recurrent Episode While Not Receiving Aspirin or Warfarin or While the INR Was Below the Target Range
        - Warfarin (INR, 1.4-2.8) or Aspirin
      - Recurrent Episode While Receiving Warfarin or Aspirin
    - **Pregnant?**
      - Yes
        - Consider Prophylactic Unfractionated Heparin or Low-Molecular-Weight Heparin Plus Aspirin, Particularly if Prior Pregnancy Loss
      - No
        - No Treatment or Low-Dose Aspirin

INR indicates international normalized ratio. Circled capital letters indicate strength of evidence supporting treatment recommendations.

*Importance of transient antiphospholipid antibodies is uncertain.*

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anticoagulation can be discontinued in patients whose LA testing becomes negative or if the only laboratory finding is a persistent low-titer aCL.

In conclusion, patients with antiphospholipid antibodies and a first episode of venous thrombosis should be treated with warfarin administered to achieve an INR of 2.0 to 3.0. The optimal duration of anticoagulation is uncertain but based on prospective data suggesting a high rate of recurrence after warfarin discontinuation; indefinite anticoagulation is recommended.

**Arterial Thromboembolism.** Arterial events in the APS most commonly involve the cerebral circulation, with stroke being the initial clinical manifestation in 13% and transient ischemic attack in 7% of patients with APS.60 The association between APS and other arterial thrombosis, including myocardial infarction, is less certain.60

Warfarin and aspirin appear to be equivalent for the prevention of thromboembolic complications in patients with a first ischemic stroke and antiphospholipid antibodies. In the Antiphospholipid Antibodies and Stroke Study (APASS),25 a prospective cohort study within the randomized double-blind Warfarin Aspirin Recurrent Stroke Study61 that compared warfarin (INR, 1.4-2.8) and aspirin (325 mg/d) for prevention of recurrent stroke or death, patients were classified into 2 groups based on the presence or absence of antiphospholipid antibodies. Among the 1770 patients included in APASS, there was no difference in the risk of thrombotic events in patients treated with warfarin (relative risk [RR], 0.99; 95% CI, 0.75-1.31) compared with aspirin (RR, 0.94; 95% CI, 0.70-1.28) and no difference in the risk of bleeding. The presence of either LA or aCL was not associated with increased risk for recurrent stroke or death. The combination therapy with unfractionated heparin (5000 units subcutaneously twice daily) and aspirin (75-581 mg/d) significantly reduced pregnancy loss compared with aspirin alone (RR, 0.46; 95% CI, 0.29-0.71). However, this particular comparison was examined only in 2 trials involving 140 patients.63,65 The combination of low-molecular-weight heparin (5000 units subcutaneously daily) and aspirin (75 mg/d) compared with aspirin alone did not significantly reduce pregnancy loss (RR, 0.78; 95% CI, 0.39-1.57), based on 1 trial of 98 patients.66 Aspirin (50-81 mg/d) compared with placebo or usual care did not reduce the rate of pregnancy loss in 3 trials (RR, 1.05; 95% CI, 0.66-1.68).67-69 Low doses of subcutaneous unfractionated heparin (5000 units twice daily) appear to be as effective as high-dose heparin (10 000 units twice daily) (RR, 0.83; 95% CI, 0.29-2.38).69

Consensus recommendations suggest that women with antiphospholipid antibodies and a history of 2 or more early pregnancy losses or 1 or more late pregnancy losses who have no prior history of thrombosis receive treatment with combination aspirin and heparin (unfractionated or low-molecular-weight) during pregnancy.8 Aspirin (81 mg/d) should be started with attempted conception and heparin (5000-10 000 units every 12 hours) or low-molecular-weight heparin in prophylactic doses (enoxaparin, 1 mg/kg or 40-80 mg; dalteparin, 5000 units; or nadroparin, 3800 units, all administered once daily) should be started when a viable intrauterine pregnancy is documented and continued until late in the third trimester.70

**CONTROVERSIES**

**Antithrombotic Prophylaxis in APS**

The treatment of patients who are incidentally found to have an antiphospholipid antibody and have no prior thrombosis has not been adequately studied, except in patients with SLE. Consensus opinion suggests low-dose aspirin (81 mg/d) may be considered for asymptomatic patients who are not pregnant.71

**Optimal Treatment of First Noncerebral Arterial Thrombosis**

The optimal treatment of patients who have antiphospholipid antibodies and non–central nervous system arterial thrombosis is uncertain. Many patients with myocardial infarction and antiphospholipid antibodies are treated empirically with long-term warfarin therapy administered to achieve an INR of 2.0 to 3.0.

**Optimal Therapy for Recurrent Thrombosis During Warfarin Treatment**

Treatment of patients with APS who have recurrent thrombotic events is uncertain.72 For patients not receiving anticoagulant drugs, immediate initiation of anticoagulation with heparin followed up by long-term warfarin is indicated. Patients with recurrent thrombotic events despite warfarin pose a challenge for clinicians. The INR at the time of recurrence is important; an INR below the target therapeutic range represents inadequate anticoagulation as opposed to warfarin failure. These patients may be treated in the same manner as a patient presenting with new thrombosis without warfarin. Possible treatment options for recurrent
thrombosis despite warfarin in the target INR range include increasing the intensity of warfarin anticoagulation to achieve a higher target INR (target INR, 2.5−3.5 or 3.0−4.0), switching from warfarin to therapeutic doses of unfractionated heparin or low-molecular-weight heparin, or adding an antiplatelet agent to warfarin. Plasma exchange or intravenous immune globulin, particularly in patients with catastrophic APS, have also been suggested.75

CONCLUSIONS

Since initial reports of an association between aCL and thrombosis and fetal death,74 much of the research has focused on the pathogenesis and clinical features of APS. Prospective studies on the optimal treatment of thrombosis in APS have focused primarily on venous thrombosis and ischemic stroke. The results of these studies indicate that patients with antiphospholipid antibodies and venous thrombosis should be treated with long-term (potentially indefinite) anticoagulation with warfarin administered to achieve an INR of 2.0 to 3.0. Either moderate-intensity warfarin or aspirin is acceptable for patients with antiphospholipid antibodies and a first episode of stroke. Prospective studies addressing the issue of primary antithrombotic prophylaxis in asymptomatic patients with antiphospholipid antibodies are in progress.75,76 These and other well-designed prospective studies are required to complete the understanding of the optimal treatment of patients with antiphospholipid antibodies and APS.

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Study concept and design: Elékembo.

Acquisition of data: Lim, Elékembo.

Analysis and interpretation of data: Lim, Crowther, Elékembo.

Drafting of the manuscript: Lim, Elékembo.

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