# Prevention of thrombosis in antiphospholipid syndrome

*Wendy Lim*

*Department of Medicine, McMaster University, Hamilton, ON, Canada*

**Antiphospholipid syndrome (APS) is an acquired autoimmune condition characterized by thrombotic events, pregnancy morbidity, and laboratory evidence of antiphospholipid antibodies (aPL). Management of these patients includes the prevention of a first thrombotic episode in at-risk patients (primary prevention) and preventing recurrent thrombotic complications in patients with a history of thrombosis (secondary prevention). Assessment of thrombotic risk in these patients, balanced against estimated bleeding risks associated with antithrombotic therapy could assist clinicians in determining whether antithrombotic therapy is warranted. Thrombotic risk can be assessed by evaluating a patient's aPL profile and additional thrombotic risk factors. Although antithrombotic options for secondary prevention of venous thromboembolism (VTE) have been evaluated in clinical trials, studies in primary prevention of asymptomatic aPL-positive patients are needed. Primary prevention with aspirin may be considered in asymptomatic patients who have a high-risk aPL profile, particularly if additional risk factors are present. Secondary prevention with long-term anticoagulation is recommended based on estimated risks of VTE recurrence, although routine evaluation of thrombotic risk can assist in determining whether ongoing anticoagulation is warranted. Studies that stratify thrombotic risk in aPL-positive patients, and patients with APS evaluating antithrombotic and non-antithrombotic therapies will be useful in optimizing the management of these patients.**

**Learning Objectives**

- To understand the factors that influence thrombotic risk in patients with aPL
- To have a rational approach to primary and secondary prevention of thrombosis in patients with aPL or APS

Antiphospholipid syndrome (APS) is characterized by venous or arterial thrombosis or pregnancy morbidity in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPL). Prevention of a first thrombotic episode in at-risk patients (primary prevention) and preventing recurrent thrombotic complications in patients with a history of thrombosis (secondary prevention) are key goals in managing patients with aPL. Evaluation of the thrombotic risk in patients with aPL and knowledge of the bleeding risk associated with antithrombotic agents is required to properly weigh the risks and benefits of administering antithrombotic therapy in the primary and secondary prevention settings. Scoring systems to assess thrombotic risk have been developed for patients with aPL incorporating factors that appear to influence thrombotic risk, including the aPL profile and cardiovascular risk factors. Antithrombotic options for the prevention and treatment of thrombotic disease in patients with aPL have been evaluated in clinical studies with recent interest in the direct oral anticoagulants (DOACs), given their increasing use and convenience in the general population. Therapies that do not influence bleeding risk are another attractive option in the management of patients with aPL and APS.

This review will discuss the diagnosis of APS and focus on the assessment of thrombotic risk in patients with aPL and APS, review bleeding risks associated with anticoagulant use, and summarize the available data on antithrombotic agents for primary and secondary prevention. Emerging non-anticoagulant treatments that have been evaluated in human subjects will be briefly reviewed. Prevention of pregnancy loss associated with APS is beyond the scope of this review and will not be discussed.

## APS diagnosis

aPL are autoantibodies directed primarily against phospholipid-bound proteins, with the most common target being $\beta_2$-glycoprotein I ($\beta_2$-GPI). Expert-based consensus on the clinical and laboratory criteria for definite APS are used to diagnose and classify the syndrome, known as the updated Sapporo criteria (Table 1).[1] The clinical criteria include objectively confirmed venous, arterial or small vessel thrombosis, or pregnancy morbidity. The laboratory criteria require the detection of aPL on 2 or more occasions at least 12 weeks apart, measured using recommended procedures.[2] The aPL recognized in the criteria include lupus anticoagulant (LA), anticardiolipin (aCL) antibodies, or anti–$\beta_2$-GPI antibodies. Assays for these antibodies are widely available, but there is considerable inter- and intra-laboratory variation in the laboratory testing for aPL, particularly for aCL and anti–$\beta_2$-GPI antibodies.

Although the aPL used in the classification criteria are limited to LA (nonspecific inhibitor), aCL, and anti–$\beta_2$-GPI antibodies, other aPL have been identified that may have an association with APS including antibodies to prothrombin (PT) and phosphatidylserine.[3] Patients with APS may also have clinical manifestations not recognized in the classification criteria including thrombocytopenia, livedo reticularis, valvular heart disease, nephropathy, and cognitive deficits.[4] Patients with aPL and clinical manifestations not recognized in the consensus criteria are considered to have "noncriteria aPL" or "noncriteria

Conflict-of-interest disclosure: The author declares no competing financial interests.

Off-label drug use: None disclosed.

**Table 1. Revised classification criteria for definite APS**

| **Definite APS is present if at least 1 clinical criterion and 1 laboratory criterion are met:** |
|---|
| **Clinical criteria** |
| Vascular thrombosis |
| One or more objectively confirmed episodes of arterial, venous, or small vessel thrombosis occurring in any tissue or organ. Thrombosis must be confirmed by objectively validated criteria. For histopathologic confirmation, thrombosis must be present without significant inflammation of the vessel wall |
| Pregnancy morbidity |
| One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation with normal fetal morphology documented by ultrasonography or 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, pre-eclampsia, or placental insufficiency; or |
| Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomical or hormonal causes excluded, and paternal and maternal chromosomal causes excluded |
| **Laboratory criteria** |
| All laboratory criteria should be present on 2 or more occasions, at least 12 weeks apart using recommended procedures. |
| LA, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (scientific subcommittee on LAs/phospholipid-dependent antibodies), or |
| aCL antibody of IgG and/or IgM isotype, present in medium or high titer (>40 GPL or MPL, or greater than the 99th percentile), measured by standardized ELISA, or |
| anti–β2-GPI antibody of IgG and/or IgM isotype, present in titer greater than the 99th percentile, measured by a standardized ELISA according to recommended procedures |

Adapted from Miyakis et al.[1]

GPL, immunoglobulin G (IgG) phospholipid units; MPL, IgM phospholipid units. (1 phospholipid unit = 1 microgram of antibody.)

manifestations." It is notable that patients enrolled in studies from the mid-2000s examining aPL and APS generally meet the updated Sapporo criteria, which have assisted in standardizing the patients enrolled in studies evaluating aPL and APS. This is important for clinicians to recognize when determining the generalizability of study findings to individual patients with aPL and APS.

## Thrombotic risk in patients with aPL and APS

### *aPL profile*

Patients with this syndrome may have varied clinical presentations and aPL profiles. The different types of aPL (LA, aCL, and anti–$\beta_2$-GPI) and combination of positive tests (single, double, or triple positivity constituting the aPL profile), antibody isotypes (IgG or IgM), antibody titers (low vs moderate to high), and persistence of aPL, all influence thrombotic risk to varying degrees. Of the aPL recognized by the classification criteria, LA is associated with the highest risk of thrombosis with an odds ratio (OR) reported in the range of 4.09 to 16.[5] Thrombotic risk with aCL, and to a lesser extent anti–$\beta_2$-GPI, is inconsistent with some studies suggesting no association with thrombosis[5-8] and other studies suggesting increased risk only with specific antibody isotypes and/or high titer antibodies. The consensus criteria only recognize IgG and IgM isotypes of aCL and anti–$\beta_2$-GPI, and these antibodies must be present at moderate or high titer (>40 GPL or MPL for aCL or exceeding the 99th percentile for aCL and anti–$\beta_2$-GPI).[1]

The aPL profile, or the number of positive aPL tests, has been shown to correlate with thrombotic risk. Patients with triple-positive aPL tests (positive testing for LA, high-titer aCL, and anti–$\beta_2$-GPI) have been shown in retrospective and prospective studies to be at increased risk of a first thrombotic event, recurrent thrombotic events, and pregnancy morbidity, with ORs for thrombosis ranging from 5 to 33.[7,9-11] In a retrospective analysis of 160 patients with triple-positive aPL testing, a cumulative incidence of thrombosis of 12.2%, 26.1%, and 44.2% was observed after 1, 5, and 10 years of follow up.[10] In a prospective study of 194 patients with persistent LA and/or aCL, the highest incidence of thrombosis was found in patients with persistent LA who were also positive for anti–$\beta_2$-GPI and anti-PT antibodies. The reported rate of thrombosis was 8.4% per patient-year.[11]

Given this, an individual patient's aPL profile can be classified as high or low risk, based on the number of positive tests and the specific aPL tests that are positive. A high-risk aPL profile consists of positivity for LA, triple-positive aPL testing (LA + aCL + anti–$\beta_2$-GPI), or isolated persistently positive aCL at medium to high titers (the latter only studied in patients with systemic lupus erythematosus [SLE]). A low-risk aPL profile includes isolated intermittently positive aCL or anti–$\beta_2$-GPI at low to medium titers.[12]

### *Presence of concomitant thrombotic risk factors*

Thrombotic risk in patients with aPL and APS is also influenced by the presence of other recognized risk factors for venous and arterial thrombosis, supporting the hypothesis that the development of thrombosis is multifactorial and accumulation of multiple risk factors results in clinical disease. The Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study randomized 98 asymptomatic patients with aPL to receive aspirin or placebo, alongside an observational study where 74 nonrandomized patients (61 received aspirin and 13 received no aspirin) were followed prospectively. A combined total of 10 patients developed thrombotic events, 6 from the randomized study. Among the patients who developed thrombosis, 7 had risk factors for venous thrombosis (immobilization, obesity) or one or more traditional cardiovascular risk factors (hypertension, smoking).[13]

Studies specifically evaluating risk factors for thrombosis in patients with aPL and APS have identified hypertension and hypercholesterolemia as risk factors,[14,15] and smoking was identified as a risk factor for stroke in women with aPL.[6] Nine of the 10 individuals who developed thrombosis in the APLASA study also had an underlying autoimmune disease, most commonly SLE. SLE itself increases thrombotic risk, with risk of venous thromboembolism (VTE) up to 20-fold higher compared

with patients without SLE.[16] The presence of aPL appears to modulate the risk of thrombosis in patients with SLE, conferring a further two to threefold increase in risk. In a cohort of 144 patients with SLE and no history of thrombosis, the presence of aPL was associated with a thrombosis rate of 29 per 144 aPL-positive patients (20.1%) compared with 11 per 144 aPL-negative patients (7.6%; $P = .003$).[17]

### *Scoring systems*

Scoring systems have been developed in an attempt to summarize the risk factors that contribute to thrombotic risk, focusing on aPL profile,[18,19] but in some cases also incorporating cardiovascular risk factors.[20] The Global APS Score (GAPSS) is the best-studied among the different scoring systems and assesses thrombotic risk in patients with SLE.[20,21] The score incorporates aPL profile (including antiphosphatidylserine/PT [aPS-PT] antibodies) and cardiovascular risk factors (hyperlipidemia and hypertension) resulting in a score from 0 to 20. The GAPSS was evaluated prospectively in a cohort of 137 patients with APS (n = 67) and asymptomatic patients with aPL.[20] Thirty-one percent of the cohort had SLE and 21% had triple positivity for aPL. The mean GAPSS was higher in patients who developed thrombosis compared with those without, with a GAPSS of 16 or greater being predictive of thrombosis. Although of interest, it is notable that the GAPSS utilizes a nonstandard aPL test (aPS-PT enzyme-linked immunosorbent assay [ELISA]), which is not widely available, and was studied using a low-positive cutoff value that would not be considered to be a part of the diagnostic criteria for APS. The GAPSS has not been evaluated in the absence of the aPS-PT assay. Consequently, scoring systems may be a potential tool for risk assessment but are currently premature in their development and warrant further validation using widely available assays.

## Bleeding risk in patients with aPL

Patients with APS may have abnormalities that predispose to bleeding but these are generally rare. Moderate thrombocytopenia is a frequent finding in patients with APS, with a platelet count $<100 \times 10^9$/L observed in up to 30% of patients with APS.[4] Severe thrombocytopenia associated with bleeding in patients with APS is usually associated with catastrophic APS (CAPS) or immune thrombocytopenia. Bleeding can also occur in APS patients who develop autoantibodies to PT or other coagulation factors.[22] However, given the rarity of these conditions, the majority of bleeding complications that occur in patients with APS are usually attributable to antithrombotic therapy.

### *Bleeding risk with oral anticoagulants*

Bleeding associated with anticoagulant use is based on numerous factors, including patient-specific factors (eg, age, presence of liver or renal disease), concomitant antiplatelet medications, and the intensity and control of anticoagulation with vitamin K antagonists.[23] Clinical risk prediction tools have been developed to assist in predicting bleeding risk, but are best used in patients who have a low thrombotic risk where bleeding risk will more strongly influence decisions regarding anticoagulation. Furthermore, these scores have almost exclusively been derived in patients with atrial fibrillation, with little data on their predictive value outside of that setting being available. In unselected patients receiving vitamin K antagonists for VTE, the risk of major bleeding is estimated at 7.2 events per 100 patient-years and the risk of fatal bleeding is 1.31 per 100 person-years. The case fatality rate of bleeding is reported at 13.4%.[24]

DOACs, including direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban) have been approved for use in the treatment of VTE, based on trials demonstrating the efficacy and safety compared with warfarin or low molecular weight heparin. It is notable that these agents have not been specifically studied in patients with APS, although such studies are ongoing. When compared with warfarin in randomized trials, bleeding with DOACs is decreased; major bleeding is reduced by 28% (relative risk [RR], 0.72) and intracranial bleeding by 57% (RR, 0.43).[25] In patients receiving DOACs for VTE, the rate of major bleeding is 1.8 per 100 patient-years[26] and the risk of fatal bleeding is 0.16 per 100 patient-years with a case fatality rate of 7.6%.[27]

### *Bleeding risk with aspirin*

In studies evaluating aspirin for primary prevention of cardiovascular disease, low-dose aspirin (100 mg or less daily) compared with placebo or no treatment is associated with an increased risk of gastrointestinal (GI) bleeding, intracranial hemorrhage, and hemorrhagic stroke.[28] Major GI bleeding is increased by 58% in patients taking aspirin (OR, 1.58; 95% confidence interval [CI], 1.29-1.95). Depending on a patient's baseline bleeding risk, the risk of major GI bleeding varies from 0.23 to 1.04 per 1000 person-years. Intracranial hemorrhage (including hemorrhagic stroke) is increased by 30% (OR, 1.30; 95% CI, 1.00-1.68) or 0.20 to 1.25 per 1000 person-years. Hemorrhagic stroke is increased by 27% (OR, 1.27; 95% CI, 0.96-1.68), occurring from 0 to 1.26 per 1000 person-years. Compared with the general (non-aspirin treated) population, the risk of major bleeding with low-dose aspirin is 3.6 per 1000 person-years.[28]

## Risk of first episode VTE in asymptomatic patients with aPL and the role of primary prevention

Asymptomatic patients who have only the laboratory criteria for definite APS (ie, have no history of thrombosis or pregnancy morbidity but have persistent aPL) have a lower thrombotic risk compared with patients with APS. In unselected asymptomatic aPL patients, the annual risk of thrombosis ranges from 0% to 2.8%.[29] A prospective cohort study of asymptomatic, persistently positive aPL patients without underlying autoimmune disease had no thrombotic episodes over 36 months of follow up.[30] Similar findings were seen in the APLASA study, where the patients with aPL randomized to placebo and followed for a mean $2.30 \pm 0.95$ years had an incidence rate of thrombosis of 0 per 100 patient-years; many of the patients in this study also had SLE.[13] In other cohorts that included a proportion of patients with SLE (between 24% to 37% of the cohort), the incidence of thrombosis is reported between 2.5% to 2.8%.[11,31] These estimates may overestimate thrombotic risk given a high likelihood of selection bias in the inception cohorts, and the presence of patients with SLE in these cohorts. To place these risks in context, the incidence of thrombosis in the general population is estimated at 100 per 100 000 per years (0.1 per 100 patient-years).[32]

### *Aspirin*

Acknowledging the difficulties in determining thrombotic risk in asymptomatic, non-SLE individuals with aPL, thrombotic risk is still felt to be increased compared with patients without aPL. Evaluation of primary prevention has focused on aspirin, because the bleeding risks associated with therapeutic range warfarin have not been low enough to justify its use. The APLASA trial randomized asymptomatic, persistently aPL-positive patients to receive daily aspirin 81 mg or placebo, and included a parallel prospective cohort of patients taking aspirin.[13] There was no benefit to aspirin for primary prophylaxis (thrombosis rate 2.70 per 100 patient-years in the aspirin arm and 0 per 100 patient-years in the placebo arm;

hazard ratio [HR] 1.04; 95% CI, 0.69-1.56). Most (65%) of the patients randomized had SLE. It is notable that the study was closed early due to a lower than expected event rate, had a short follow-up period, and was underpowered to detect differences in the study arms. A significant number of the patients were also found to have a low-risk aPL profile.[12] Observational studies have suggested that low-dose aspirin is effective in reducing thrombotic complications in patients with SLE and aPL.[17,33,34] Aspirin has been studied in a patient level meta-analysis, which included 5 studies of 497 patients.[35] A total of 49% of the patients in the aspirin group and 30% of the no-aspirin group had SLE. The HR for the risk of a first thrombosis of any type in asymptomatic aPL patients treated with aspirin compared with those not treated with aspirin was 0.43; 95% CI, 0.25-0.75. Aspirin reduced the rate of arterial thrombosis (HR, 0.43; 95% CI, 0.20-0.93) but not venous thrombosis (HR, 0.49; 95% CI, 0.22-1.11). It is notable that no significant risk reduction was observed when only prospective studies or studies at highest methodologic quality were included. Consequently, the data supporting aspirin use, particularly for patients without SLE, still remains unclear. A randomized trial that stratifies asymptomatic aPL patients by thrombotic risk is needed to determine the benefit of aspirin in this setting.

### *Aspirin and low-dose warfarin*

The ALIWAPAS trial compared low-dose aspirin vs low-dose aspirin and low-intensity warfarin (international normalized ratio [INR], 1.5) in 166 aPL-positive patients with SLE and/or obstetric morbidity.[36] A further 66 patients were followed in a parallel prospective cohort, where 65 of these patients received low-dose aspirin alone. Because this study included patients with pregnancy morbidity, these patients would be classified as definite APS as per the updated Sapporo criteria, frequently termed "obstetric APS." A total 35% of the patients in the aspirin group and 36% of the aspirin + warfarin group had obstetric APS, and the remainder had SLE. There was no difference in the number of thrombotic events between the treatment arms (HR, 1.07; 95% CI, 0.27-4.3). However, there were 11 bleeding events in the aspirin + warfarin arm with no bleeding reported in the aspirin arm. This study was closed early because of poor recruitment and was subsequently underpowered to detect differences in efficacy between the treatment arms. The 95% CI around the HR for the primary outcome could include benefit or harm due to treatment with warfarin + aspirin rather than aspirin. However, any benefit with combination therapy is almost certainly outweighed by the increase in bleeding events observed in the aspirin + warfarin arm.

### *Primary prevention in asymptomatic aPL-positive patients*

Recommendations for primary prevention of thrombosis in asymptomatic individuals with aPL remain controversial. In the absence of randomized trials evaluating prophylactic strategies, recommendations are based on analysis of lower quality studies and expert opinion.[12] The bleeding risk associated with aspirin may be justified if thrombotic risks are sufficiently high. The risk of thrombosis in asymptomatic aPL-positive patients appears to be increased, but many estimates have included patients with SLE, which is associated with an increase in baseline thrombotic risk. Considering the aPL profile of an individual patient and the presence of additional risk factors can provide additional information when weighing risks.

In non-SLE individuals with aPL and no previous thrombosis, low-dose aspirin was given a 2C recommendation (based on low or very low quality evidence) for use in those with a high-risk aPL profile, especially in the presence of additional thrombotic risk factors.[12] In patients with SLE and aPL (positive LA, isolated persistent aCL at medium-high titers), primary thromboprophylaxis with hydroxychloroquine (see later discussion) and low-dose aspirin is recommended.[12]

## Risk of recurrence in patients with APS and secondary prevention of thrombosis

Deep vein thrombosis of the lower extremities is the most common initial manifestation among patients with APS, occurring in ~30% of patients.[5] Patients who have APS with a first episode VTE appear to be at increased risk of recurrent thrombosis if anticoagulants are discontinued. However, recurrence rates are difficult to estimate, because many studies addressing this question included patients who would not meet the updated Sapporo criteria. A systematic review of 8 studies evaluating patients with a first episode VTE and aPL found that the risk of recurrence after discontinuing anticoagulants in patients with aPL was 40% higher compared with patients without aPL, with an unadjusted RR of thrombosis of 1.41 (95% CI, 0.99-2.36; $P = .09$).[37] However, it was acknowledged that the included studies were of low quality, included patients with only one measurement of aPL (not meeting current diagnostic criteria for APS), and the CIs were wide, resulting in uncertainty. To frame these estimates in the appropriate context, the rate of recurrent VTE in patients with unprovoked VTE who do not have APS is ~10% to 12% after 1 year, 20% to 25% after 3 years, 30% after 5 years, and 40% after 10 years.[32,38] If the risk of recurrence is 40% higher in patients with aPL/APS, the rate of recurrent VTE in patients with unprovoked VTE who have APS if anticoagulants were discontinued would be ~14% to 17% after 1 year, 40% after 5 years, and over 50% after 10 years. These estimates likely overestimate risk, but provide a framework to consider treatment decisions related to anticoagulant discontinuation.

### *Antithrombotic treatment of APS*

Patients with APS who have a first episode VTE should be treated with warfarin or vitamin K antagonist administered at standard intensity (INR, 2.0-3.0), based on the results of 2 randomized trials.[39,40] The treatment of patients with APS and arterial thrombosis remains controversial.[12] A systematic review of observational studies of patients meeting the updated Sapporo criteria who have arterial events concluded that such patients are at high risk of recurrence when treated with vitamin K antagonists at standard intensity, with decreased recurrence at higher intensity anticoagulation (INR, >3.0).[41] Based on expert opinion, the option of using standard intensity warfarin with antiplatelet agents has also been recommended for patients with APS and arterial thrombosis.

The convenience and safety of DOACs for VTE treatment, and secondary stroke prevention in atrial fibrillation has generated interest in using these agents in patients with APS. The Rivaroxaban in Antiphospholipid Syndrome (RAPS) trial has closed to recruitment but final results have not yet been published.[42] There are 3 additional trials evaluating DOACs (2 trials evaluating rivaroxaban and 1 trial assessing apixaban; see www.clinicaltrials.gov [#NCT02157272, #NCT02116036, and #NCT02295475]). Until the results of these studies are published, use of DOACs in patients with APS is not routinely recommended, and should only be undertaken after appropriate discussion with patients and within the context of a follow-up plan that will allow rapid review of patients, should additional evidence with respect to safety or efficacy become available. Warfarin or vitamin K antagonists would be the preferred treatment outside the context of a clinical trial.

### *Duration of antithrombotic treatment*

In patients with APS, prevention of a recurrent thrombotic event (secondary prevention) is critical. The rates of VTE recurrence in patients with APS have generally exceeded bleeding risk associated with anticoagulant use, resulting in the recommendation from a number of guideline panels to consider long-term anticoagulation in patients with thrombosis and APS.[12] Although this recommendation is applicable for most patients with APS who present with unprovoked thrombotic events, an approach considering the aPL profile among other predictors of recurrence (eg, unprovoked event, male sex, elevated D-dimer at time of anticoagulant discontinuation) is advocated.[12,43] For example, a patient with a first episode VTE occurring in the context of a recognized transient risk factor with a low-risk aPL profile may be a candidate for limited duration anticoagulation, particularly if there are significant concerns for bleeding. Ultimately, decisions regarding long-term anticoagulation must be individually evaluated and the presence of aPL is one consideration in the decision-making.

## Emerging therapies for preventing thrombosis in patients with aPL and APS

As our understanding of the pathophysiology of APS has increased, non–anticoagulant-based treatments, which do not specifically target the coagulation cascade, have been identified. Readers are encouraged to read recent reviews and recommendations from the 14th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends.[44,45]

### *Hydroxychloroquine*

Antimalarial agents including chloroquine and hydroxychloroquine are used as immunomodulating drugs in patients with SLE. A systematic review demonstrated that these agents are well tolerated, particularly hydroxychloroquine, and in an analysis that included 8 studies of which 3 studies specifically evaluated the effect of antimalarial agents on thrombosis, hydroxychloroquine was associated with decreased thrombotic events.[46] There were limitations in the quality of the evidence in this review. Hydroxychloroquine appears to limit organ damage and increase survival in patients with SLE with limited toxicity and is currently recommended as baseline therapy in all SLE patients in the absence of contraindications.[46] Recognized side effects of hydroxychloroquine include retinal toxicity (thinning), which can be detected using spectral-domain optical coherence tomography.

The presence of aPL in patients with SLE may be another compelling reason for hydroxychloroquine, resulting in a recommendation that patients with SLE and positive-LA or isolated persistent aCL at medium-high titers receive primary prophylaxis with hydroxychloroquine.[12]

In a cross-sectional study of asymptomatic aPL-positive patients with no history of thrombosis, pregnancy morbidity, or underlying SLE, hydroxychloroquine was found to be independently associated with a lower risk of a thrombotic event.[47] Unfortunately, a multicenter randomized trial examining hydroxychloroquine for thrombosis prevention in these patients was terminated due to low recruitment.[48] Thus, the role of hydroxychloroquine for primary prevention in asymptomatic aPL-positive patients without underlying autoimmune disease remains unclear.

### *Statins*

Statins are effective for primary and secondary prevention of coronary heart disease, but have also been shown to reduce the occurrence of VTE in healthy individuals.[49] Statins are recommended in APS patients with hyperlipidemia who have no contraindications to statin use, but are not recommended in the absence of hyperlipidemia based on the available data.[12] aPL-positive patients with recurrent thrombosis despite adequate anticoagulation statins may benefit from statins but this has not been formally evaluated.

### *B-cell inhibition*

Rituximab, an anti-CD20 monoclonal antibody, has been studied in patients with APS, particularly in the setting of CAPS, severe thrombocytopenia, or autoimmune hemolytic anemia. Case reports suggest that rituximab is effective in patients with APS, resulting in a task force recommendation that B-cell inhibition may be considered in difficult to treat APS patients, possibly in those with hematologic and microthrombotic/microangiopathic manifestations.[45]

### *Complement inhibition*

Complement activation has been described in the pathogenesis of pregnancy morbidity in patients with APS and eculizumab (a monoclonal antibody targeting C5), and has been used in a patient with CAPS. Complement inhibition may have a role in patients refractory to anticoagulation but requires further study. No differences were observed in C3a levels in patients with aPL with or without a history of thrombosis.[50]

## Conclusion

Patients with aPL are at increased risk of thrombosis but the magnitude of risk is dependent on several factors, including aPL profile and the presence of additional risk factors. In patients with thrombosis who meet the criteria for APS, risk is also determined by other recognized predictors of recurrence. An understanding of the thrombotic risk in these patients, balanced against the expected bleeding risk associated with antithrombotic therapy can assist clinicians in determining the optimal strategy for primary and secondary prevention. Classifying the aPL profile as high- or low-risk, in conjunction with concomitant risk factors, can provide a general estimate of risk and whether antithrombotic therapy is justified. Aspirin is recommended for primary prevention in individuals who have SLE and aPL, and in those who do not have SLE but have a high-risk profile, especially if additional risk factors are present. In general, secondary prevention of thrombosis with long-term anticoagulation is recommended in patients with APS, but in those patients where bleeding complications are an issue, evaluation of thrombotic risk can assist in determining whether ongoing anticoagulation is warranted.

## Correspondence

Wendy Lim, St. Joseph's Healthcare Hamilton, 50 Charlton Ave East, Room L208, Hamilton, ON L8N 4A6, Canada; e-mail: limwp@mcmaster.ca.

## References

1. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4(2):295-306.
2. Pengo V, Tripodi A, Reber G, et al; Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. Update of the guidelines for lupus anticoagulant detection. *J Thromb Haemost*. 2009;7(10):1737-1740.
3. Hoxha A, Ruffatti A, Tonello M, et al. Antiphosphatidylserine/prothrombin antibodies in primary antiphospholipid syndrome. *Lupus*. 2012;21(7):787-789.

4. Cervera R, Piette JC, Font J, et al; Euro-Phospholipid Project Group. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum*. 2002;46(4):1019-1027.
5. Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. *Blood*. 2003;101(5):1827-1832.
6. Urbanus RT, Siegerink B, Roest M, Rosendaal FR, de Groot PG, Algra A. Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in young women in the RATIO study: a case-control study. *Lancet Neurol*. 2009;8(11):998-1005.
7. Pengo V, Biasiolo A, Pegoraro C, Cucchini U, Noventa F, Iliceto S. Antibody profiles for the diagnosis of antiphospholipid syndrome. *Thromb Haemost*. 2005;93(6):1147-1152.
8. Brey RL, Abbott RD, Curb JD, et al. beta(2)-Glycoprotein 1-dependent anticardiolipin antibodies and risk of ischemic stroke and myocardial infarction: the Honolulu heart program. *Stroke*. 2001;32(8):1701-1706.
9. Ruffatti A, Tonello M, Del Ross T, et al. Antibody profile and clinical course in primary antiphospholipid syndrome with pregnancy morbidity. *Thromb Haemost*. 2006;96(3):337-341.
10. Pengo V, Ruffatti A, Legnani C, et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. *J Thromb Haemost*. 2010; 8(2):237-242.
11. Forastiero R, Martinuzzo M, Pombo G, et al. A prospective study of antibodies to beta2-glycoprotein I and prothrombin, and risk of thrombosis. *J Thromb Haemost*. 2005;3(6):1231-1238.
12. Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on antiphospholipid antibodies. *Lupus*. 2011;20(2):206-218.
13. Erkan D, Harrison MJ, Levy R, et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. *Arthritis Rheum*. 2007;56(7):2382-2391.
14. Danowski A, de Azevedo MN, de Souza Papi JA, Petri M. Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus. *J Rheumatol*. 2009;36(6):1195-1199.
15. Matyja-Bednarczyk A, Swadźba J, Iwaniec T, et al. Risk factors for arterial thrombosis in antiphospholipid syndrome. *Thromb Res*. 2014; 133(2):173-176.
16. Chung WS, Lin CL, Chang SN, Lu CC, Kao CH. Systemic lupus erythematosus increases the risks of deep vein thrombosis and pulmonary embolism: a nationwide cohort study. *J Thromb Haemost*. 2014;12(4):452-458.
17. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. *Arthritis Rheum*. 2009;61(1):29-36.
18. Otomo K, Atsumi T, Amengual O, et al. Efficacy of the antiphospholipid score for the diagnosis of antiphospholipid syndrome and its predictive value for thrombotic events. *Arthritis Rheum*. 2012;64(2):504-512.
19. Chen J, Sun S, Yan Q, Bao C, Fu Q. Elevated partial antiphospholipid score is a strong risk factor for thrombosis in patients with systemic lupus erythematosus: a validation study. *Clin Rheumatol*. 2016;35(2):333-340.
20. Zuily S, de Laat B, Mohamed S, et al; TAC(I)T investigators. Validity of the global anti-phospholipid syndrome score to predict thrombosis: a prospective multicentre cohort study. *Rheumatology (Oxford)*. 2015; 54(11):2071-2075.
21. Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. GAPSS: the Global Anti-Phospholipid Syndrome Score. *Rheumatology (Oxford)*. 2013;52(8):1397-1403.
22. Vivaldi P, Rossetti G, Galli M, Finazzi G. Severe bleeding due to acquired hypoprothrombinemia-lupus anticoagulant syndrome. Case report and review of literature. *Haematologica*. 1997;82(3):345-347.
23. Shoeb M, Fang MC. Assessing bleeding risk in patients taking anticoagulants. *J Thromb Thrombolysis*. 2013;35(3):312-319.
24. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med*. 2003;139(11):893-900.
25. Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. *Blood*. 2014;124(15):2450-2458.
26. Wu C, Alotaibi GS, Alsaleh K, Sean McMurtry M. Case fatality of bleeding and recurrent venous thromboembolism during, initial therapy with direct oral anticoagulants: a systematic review. *Thromb Res*. 2014; 134(3):627-632.
27. Chai-Adisaksopha C, Hillis C, Isayama T, Lim W, Iorio A, Crowther M. Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Haemost*. 2015;13(11):2012-2020.
28. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016;164(12):826-835.
29. Finazzi G. Primary antithrombotic prevention in carriers of antiphospholipid antibodies without systemic autoimmune disorders. *Lupus*. 2012;21(7):747-750.
30. Girón-González JA, García del Río E, Rodríguez C, Rodríguez-Martorell J, Serrano A. Antiphospholipid syndrome and asymptomatic carriers of antiphospholipid antibody: prospective analysis of 404 individuals. *J Rheumatol*. 2004;31(8):1560-1567.
31. Finazzi G, Brancaccio V, Moia M, et al. Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: a four-year prospective study from the Italian Registry. *Am J Med*. 1996;100(5):530-536.
32. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23 suppl 1):I4-I8.
33. Tarr T, Lakos G, Bhattoa HP, Shoenfeld Y, Szegedi G, Kiss E. Analysis of risk factors for the development of thrombotic complications in antiphospholipid antibody positive lupus patients. *Lupus*. 2007;16(1):39-45.
34. Hereng T, Lambert M, Hachulla E, et al. Influence of aspirin on the clinical outcomes of 103 anti-phospholipid antibodies-positive patients. *Lupus*. 2008;17(1):11-15.
35. Arnaud L, Mathian A, Devilliers H, et al. Patient-level analysis of five international cohorts further confirms the efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies. *Autoimmun Rev*. 2015;14(3):192-200.
36. Cuadrado MJ, Bertolaccini ML, Seed PT, et al. Low-dose aspirin vs low-dose aspirin plus low-intensity warfarin in thromboprophylaxis: a prospective, multicentre, randomized, open, controlled trial in patients positive for antiphospholipid antibodies (ALIWAPAS). *Rheumatology (Oxford)*. 2014;53(2):275-284.
37. Garcia D, Akl EA, Carr R, Kearon C. Antiphospholipid antibodies and the risk of recurrence after a first episode of venous thromboembolism: a systematic review. *Blood*. 2013;122(5):817-824.
38. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica*. 2007;92(2):199-205.
39. Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med*. 2003; 349(12):1133-1138.
40. Finazzi G, Marchioli R, Brancaccio V, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost*. 2005;3(5):848-853.
41. Ruiz-Irastorza G, Hunt BJ, Khamashta MA. A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies. *Arthritis Rheum*. 2007;57(8):1487-1495.
42. Cohen AT, Hamilton M, Mitchell SA, et al. Comparison of the novel oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in the initial and long-term treatment and prevention of venous thromboembolism: systematic review and network meta-analysis. *PLoS One*. 2015; 10(12):e0144856.

43. Garcia DA, Lim W. Should the presence of an antiphospholipid antibody affect the duration of anticoagulant treatment in patients with venous thromboembolism? *Hematology Am Soc Hematol Educ Program*. 2013; 2013(1):681-683.
44. Andrade D, Tektonidou M. Emerging therapies in antiphospholipid syndrome. *Curr Rheumatol Rep*. 2016;18(4):22.
45. Erkan D, Aguiar CL, Andrade D, et al. 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. *Autoimmun Rev*. 2014;13(6):685-696.
46. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis*. 2010;69(1): 20-28.
47. Erkan D, Yazici Y, Peterson MG, Sammaritano L, Lockshin MD. A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. *Rheumatology (Oxford)*. 2002; 41(8):924-929.
48. Erkan D, Lockshin MD; APS ACTION members. APS ACTION–AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking. *Lupus*. 2012;21(7):695-698.
49. Glynn RJ, Danielson E, Fonseca FA, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med*. 2009;360(18):1851-1861.
50. Devreese KM, Hoylaerts MF. Is there an association between complement activation and antiphospholipid antibody-related thrombosis? *Thromb Haemost*. 2010;104(6):1279-1281.