



ASH evidence-based guidelines: should asymptomatic patients with antiphospholipid antibodies receive primary prophylaxis to prevent thrombosis?

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A 35-year-old female presents with a prolonged activated partial thromboplastin time (aPTT) on routine testing, which is found to be due to a lupus anticoagulant. She has no medical issues, no personal or family history of thrombosis, no history of pregnancy loss, and no symptoms suggestive of an underlying rheumatologic disorder. She is a non-smoker and does not take oral contraceptives. You are asked to provide recommendations regarding the need for primary thromboprophylaxis. As you begin your literature search, you formulate the following clinical question: "In asymptomatic patients with antiphospholipid antibodies, does primary prophylaxis prevent thrombotic complications?"

Antiphospholipid antibodies (aPL) are autoantibodies directed against phospholipid binding proteins, most commonly β_2 -glycoprotein I. The presence of aPL in the normal healthy population has been estimated to range from 1.0% to 5.6%; in patients with systemic lupus erythematosus (SLE) the prevalence ranges from 11% to 86%.¹ Repeated measurements of aPL documented at least 12 weeks apart, including lupus anticoagulant, anticardiolipin antibodies or anti- β_2 -glycoprotein I antibodies, in conjunction with clinical events of arterial or venous thrombosis or pregnancy morbidity defines the antiphospholipid antibody syndrome (APS).²

A PubMed search was performed using the MeSH terms "Antiphospholipid Antibodies" or "Antiphospholipid Syndrome" and "Thrombosis" and "Primary Prevention" (search completed May 26, 2009). A total of 104 citations were retrieved and reviewed for inclusion. We excluded studies enrolling patients who had a history of thrombosis or pregnancy morbidity, children, pregnant women or evaluated pregnancy morbidity as the outcome. A total of 5 studies were identified³⁻⁷ (1 duplicate study⁸), and 2 further studies^{9,10} were identified by manual review of the reference list of relevant review articles. A total of 7 studies were therefore included in this review (**Table 1**).

Based on the literature review, only one published prospective clinical trial addresses our clinical question of interest. The Antiphospholipid Antibody Acetylsalicylic Acid

(APLASA) study was a randomized, double-blind, placebo-controlled clinical trial in asymptomatic patients with persistently positive aPL comparing the efficacy of aspirin 81 mg daily versus placebo for the prevention of thrombotic complications.³ A total of 98 study participants with aPL measured on 2 occasions 6 weeks apart (study designed based on the initial consensus criteria for APS) were randomized. Participants in this study were predominantly female, and notably over 60% of patients had SLE. The study was terminated early because of an unexpectedly low rate of thrombotic events, and analyzed after all patients had completed 1 year of follow-up. A total of 3 thrombotic events (arterial or venous) occurred in the aspirin group, and no thrombotic events occurred in the placebo group. Although limited by the small number of patients enrolled and infrequent outcome events, this study demonstrated that in patients with persistently positive aPL, aspirin was no more effective than placebo for the primary prevention of thrombotic events.³

The other studies addressing our clinical question include cohort studies examining asymptomatic aPL-positive patients and cohort studies of aPL-positive patients with SLE. In asymptomatic aPL-positive patients, thromboprophylaxis with aspirin or low molecular weight heparin during high-risk periods (ie, surgery or prolonged immobilization) appears to be effective in reducing thrombotic complications.¹⁰ In the APLASA as well as other studies, most of the aPL-positive patients who developed thrombo-

Table 1. Studies addressing primary prophylaxis in asymptomatic patients with antiphospholipid antibodies.

Author, year	Study design	N	Number of aPL measurements	Comparison/intervention	Results/conclusions
Asymptomatic aPL patients					
Hereng et al, 2008 ⁵	Retrospective	103	2; Unknown time interval between measurements	ASA (n = 75) vs Observation (n = 28)	-Lower frequency of thrombotic events in ASA group, especially in the subgroup of patients with SLE or AIT -36% of patients had SLE
Erkan et al, 2007 ³	RCT with parallel prospective cohort	RCT: 98 Cohort: 74	≥ 2; 6 weeks apart	RCT: ASA 81 mg daily (n = 48) vs Placebo (n = 50) Cohort: ASA (n = 61)	-HR: 1.04 (95% CI 0.69-1.56) -> 60% of patients in RCT had SLE -ASA not effective in preventing thrombosis compared to placebo
Giron-Gonzalez et al, 2004 ¹⁰	Prospective	178	≥ 2; 8-12 weeks apart	ASA 325 mg/d or LMWH daily during high risk situations*	-All patients received thromboprophylaxis during high risk situations, no thrombotic events occurred
Erkan et al, 2002 ⁹	Cross-sectional	56	Not specified	Logistic regression analysis (ASA and/or HCQ use)	-Probability of thrombotic event decreased in patients taking ASA +/- HCQ (HCQ only in patients with CTD) -78% of patients had CTD
SLE patients					
Tektonidou et al, 2009 ⁷	Retrospective	288; 144 aPL positive	≥ 2; ≥ 12 weeks apart	Adjusted survival analysis (ASA 80-100 mg/d, HCQ)	-HR per month: ASA 0.98 (95% CI 0.96-0.99) and HCQ 0.99 (95% CI 0.98-1.00) -Duration of use of ASA and HCQ associated with decreased thrombosis
Kaiser et al, 2009 ⁶	Retrospective	1930; 516 aPL positive	1	Logistic regression analysis (HCQ use)	-OR 0.63 (95% CI 0.48-0.83) -HCQ protective against thrombosis
Tarr et al, 2007 ^{4,8}	Prospective	272; 81 aPL positive	≥ 2; 6 weeks apart	Prophylaxis (n = 52) vs Observation (n = 29)**	-Lower incidence of thrombosis in prophylaxis group vs observation group (1/52 vs 2/29 had stroke or TIA)

AIT indicates autoimmune thrombocytopenia; aPL, antiphospholipid antibodies; ASA, aspirin; CI, confidence interval; CTD, connective tissue disease; HCQ, hydroxychloroquine; HR, hazard ratio; LMWH, low molecular weight heparin; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; SLE, systemic lupus erythematosus; TIA, transient ischemic attack.

*Enoxaparin 1 mg/kg once daily for surgery or immobilization; ASA 325 mg/d during pregnancy; both in combination with counseling and treatment to reduce vascular risk factors

**52/81 patients received primary prophylaxis (ASA = 50, oral anticoagulants = 1, clopidogrel = 1)

sis had additional thrombotic or cardiovascular risk factors.^{3,9} However, it is notable that most of these studies included patients with SLE, which is potentially problematic since SLE itself has been shown to be independently associated with thrombosis.¹¹⁻¹³ Therefore, the results of these studies may not be entirely applicable to non-SLE populations.

Among asymptomatic aPL-positive patients with SLE, primary prophylaxis with aspirin and hydroxychloroquine

appears to reduce the frequency of thrombotic events. In a Markov decision analysis, prophylactic aspirin, oral anticoagulant therapy and observation were compared in asymptomatic aPL-positive patients with SLE.¹⁴ Prophylactic aspirin was effective in reducing the number of thrombotic events compared to inducing bleeding episodes.

For the clinician who is faced with a patient who has persistently positive aPL testing but no history of thrombosis or pregnancy morbidity, we recommend an individual

assessment of the patient's thrombotic risk. There is currently no good quality evidence to support the routine use of aspirin for primary thromboprophylaxis in these patients, given that the benefit of aspirin is uncertain and because aspirin does carry a small, but not insignificant risk of bleeding (Grade 2B).¹⁵ In asymptomatic patients with SLE, aspirin and hydroxychloroquine may be beneficial based on observational data (Grade 2C). Reversible vascular risk factors should be addressed, and during periods of increased thrombotic risk aggressive thromboprophylaxis appears to be warranted (Grade 2C). The optimal type and duration of thromboprophylaxis remains unknown.

For the patient illustrated in the clinical vignette, given the absence of cardiovascular and thrombotic risk factors and the absence of signs and symptoms of SLE, we suggest that primary prophylaxis with aspirin is not warranted, either alone or in combination with hydroxychloroquine.

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