

# Should aspirin be used as a preventive therapy for thrombosis in patients with antiphospholipid antibodies?

**Original article** Erkan D *et al.* (2007) Aspirin for primary thrombosis prevention in the antiphospholipid syndrome. A randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. *Arthritis Rheum* 56: 2382–2391

## SYNOPSIS

**KEYWORDS** antibodies, antiphospholipid syndrome, aspirin, prevention, thrombosis

### BACKGROUND

Antiphospholipid syndrome is characterized by the presence of antiphospholipid antibodies and the occurrence of vascular thrombotic events and pregnancy morbidity; many patients, however, persistently test positive for antiphospholipid antibody but remain asymptomatic.

### OBJECTIVE

The objective of this study was to investigate whether aspirin prevents primary thrombosis in patients who test positive for antiphospholipid antibody but who have not yet shown other symptoms of antiphospholipid syndrome.

### DESIGN AND INTERVENTION

Two studies were presented by the authors: a multicenter, double-blind, placebo-controlled, randomized trial and a secondary observational analysis. Patients included in the randomized trial were aged  $\geq 18$  years, and had either a positive lupus coagulant test or positive anti-cardiolipin antibody IgG/IgM/IgA isotype on two occasions, at least 6 weeks apart. Patients with a diagnosis of antiphospholipid syndrome, a history of thrombosis, pulmonary embolism or transient ischemic attack, or those who had previously used warfarin or aspirin, were excluded from this study. Participants were randomly allocated to receive either preventive treatment with aspirin or placebo. All patients were assessed for demographic characteristics and underwent serological tests at study entry; follow-up interviews were conducted 3 months

after baseline, and at 6-month intervals thereafter. Patients who were not included in the randomized trial because of previous aspirin use were included in the observational study.

### OUTCOME MEASURES

The primary outcome measure of these studies was the occurrence of acute thrombosis, and the secondary outcome measure was the occurrence of transient ischemic attack.

### RESULTS

A total of 98 patients were included in the randomized trial, and were randomly allocated to receive treatment with 81 mg aspirin ( $n = 48$ ) or placebo ( $n = 50$ ). A total of 74 patients who were initially excluded from the randomized trial were then included in the observational study; these participants were similarly randomized to receive aspirin ( $n = 61$ ) or non-aspirin ( $n = 13$ ). In the randomized trial, three patients developed acute thrombosis, compared with none in the placebo group (hazard ratio 1.04, 95% CI 0.69–1.56,  $P = 0.83$ ). Two patients from the aspirin group and one from the placebo group developed transient ischemic attack (hazard ratio 1.08, 95% CI 0.72–1.62,  $P = 0.68$ ). In the observational study, the incidence of acute thrombosis was 2.70 per 100 patient-years in patients receiving aspirin, compared with 0 per 100 patient-years in patients not receiving aspirin.

### CONCLUSION

The authors conclude that patients with positive antiphospholipid antibody results who are persistently asymptomatic for antiphospholipid syndrome do not benefit from preventive therapy with low-dose aspirin. The incidence of acute thrombosis in these patients is low, and cardiovascular events are increased in the presence of additional risk factors.

## COMMENTARY

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This study by Erkan *et al.* provides important information for the care of asymptomatic people with antiphospholipid antibodies, concluding that 81 mg/day prophylactic aspirin does not decrease the risk of thromboembolic disease. The rate of thrombotic events in patients treated with placebo was lower than anticipated; in fact, because of the low rate and lack of a large aspirin effect, it would require over 30,000 subjects in each treatment arm to test whether aspirin offers a significant benefit.

The investigators enrolled 98 adults with persistent antiphospholipid antibody in a randomized, double-blind trial of low-dose aspirin or placebo for primary prevention of thrombosis. 'Asymptomatic' was strictly defined: subjects were excluded if they fulfilled the original Sapporo criteria for antiphospholipid syndrome,<sup>1</sup> had prior thrombosis, pulmonary embolism or transient ischemic attack, used warfarin or antiplatelet therapy, were allergic to aspirin, had severe thrombocytopenia, active peptic ulcer disease, malignancy, HIV or hepatitis C infection, or if they had a history of serious bleeding. The majority of participants without rheumatic disease were identified by abnormal thrombosis tests at preoperative screening. Stratification ensured subjects with low-risk (cardiolipin antibody titers of 20–39 units per liter) and high-risk (positive lupus anticoagulant or cardiolipin antibody level  $\geq 40$  units per liter) antiphospholipid antibody profiles were evenly distributed in each arm. Those already taking aspirin and patients who declined randomization were invited to participate in an observational study. Most subjects had lupus or another autoimmune disease, although 12% in the randomized trial and 31% in the observational study did not.

The interim analysis showed a very low thrombosis rate in all subjects; therefore, study enrollment was terminated, and participants were followed for at least 1 year (mean follow-up  $> 2$  years). There were five thrombotic events in the aspirin group; no confirmed acute thromboses occurred in the placebo group (only one transient ischemic attack). Four subjects experienced thrombotic events in the observational study, all of whom were receiving aspirin. Nine out of 10 subjects with thrombosis or transient ischemic attack had high-risk antiphospholipid profiles, and 9 out of 10 had underlying autoimmune disease.

This important trial shows that low-dose aspirin does not prevent thrombotic events in a rigorously defined asymptomatic population with persistent antiphospholipid antibody. Moreover, even asymptomatic patients with underlying autoimmune disease have a low risk of thrombosis, toward the lower end of the range reported in other studies.<sup>2–4</sup> In those with high anticardiolipin antibody titers or a persistent lupus anticoagulant (i.e. a high-risk antiphospholipid antibody profile), thrombosis risk is increased (6 [11%] of 57 subjects), but low-dose aspirin does not decrease the risk. The study sample size was small and follow up was brief. Further observation and stratified analysis might reveal differential effects of aspirin on arterial versus venous thrombosis risk.

This study confirms that the persistence of high-titer anticardiolipin antibody ( $\geq 40$  units per liter) and lupus anticoagulant are associated with a higher frequency of thrombosis than low levels of anticardiolipin antibody alone. It also affirms that these markers are not sufficiently specific to guide prophylactic therapy. Improved tests to assess thrombosis risk in patients with autoimmune disease are needed, as are better approaches to the prevention of antiphospholipid complications. Primary prophylaxis studies using non-aspirin antithrombotic agents in asymptomatic patients with high-risk antiphospholipid antibody profiles are also needed. Until then, management regimens for patients with high-risk antiphospholipid antibody profiles and those with other vascular risk factors<sup>5</sup> will still need to be individualized. Aspirin prophylaxis in the asymptomatic patient with persistent antiphospholipid antibodies, however, is not warranted.

## References

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## Competing interests

The author declared no competing interests.

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## PRACTICE POINT

In asymptomatic patients with persistently positive antiphospholipid antibody, aspirin is not effective for the primary prevention of thrombosis