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Review

# Risk of venous and arterial thrombosis according to type of antiphospholipid antibodies in adults without systemic lupus erythematosus: A systematic review and meta-analysis

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ABSTRACT

*Aim:* To evaluate the magnitude of venous and arterial thrombosis risk associated with antiphospholipid antibodies (APLs) in adults without systemic lupus erythematosus (SLE).
*Methods:* Case-control and cohort studies were selected from the MEDLINE and Cochrane Library databases. Two investigators independently extracted data on study design, patient characteristics, venous and arterial events and exposure to APLs, including lupus anticoagulant (LA), anticardiolipin (aCL), anti-β2 Glycoprotein I (β2GpI), anti-prothrombin (aPT), anti-phosphatidyl serine (aPS), and anti-phosphatidyl ethanolamine (aPE).
*Results:* 30 studies were included (16,441 patients). The odds ratio (OR) for venous thrombosis was 6.14 (95% confidence interval [CI] 2.74–13.8) in LA-positive patients (5 studies, 1650 patients) and 1.46 (CI 1.06–2.03) in aCL-positive patients (12 studies, 5375 patients). None of the associations with more recently identified APLs was significant, but fewer studies were available. For arterial thrombosis, the OR for LA and aCL was 3.58 (CI 1.29–9.92) and 2.65 (CI 1.75–4.00) respectively. The associations between β2GpI, aPT and aPS and the risk of arterial thrombosis were also significant, the OR being 3.12 (CI 1.51–6.44), 2.95 (CI 1.31–6.66) and 6.00 (CI 3.07–11.7), respectively. Owing to the heterogeneity of cut-off values for each APL assay, we were unable to perform any sensitivity analysis to determine the optimal value. The presence of low-quality studies may have led to overestimation of the magnitude of the associations.
*Conclusions:* LA and aCL were significantly associated with an increased risk of thrombosis, especially arterial, in patients without SLE. Systematic thromboprophylaxis in high-risk patients with APL should be evaluated.



**Contents**



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## 1. Introduction

Antiphospholipid antibodies (APLs) have been described as risk factors for venous or arterial thrombosis [1]. In systemic lupus erythematosus (SLE) patients, the prevalence of lupus anticoagulant (LA) and anticardiolipin (aCL) antibodies varies from 11 to 30% and from 17 to 39%, respectively [2]. At 20 years of follow-up, LA-positive SLE patients have a 50% higher risk of venous or arterial thrombosis [3]. Concerning this autoimmune disease, the impact of APL detection on therapy has not been clearly established, but many authors advise prophylactic aspirin [4,5]. In patients without SLE, the estimated prevalence of APL ranges from 1 to 5.6% according to one review, [3] suggesting that even in this population, the risk of a first thrombosis could be sufficiently high to warrant specific therapeutic management for APL-positive patients. Quantification of the risk of venous and arterial thrombosis associated with APL is therefore particularly important. Several studies have tried to evaluate the association of APL with venous thrombotic events, especially that of LA and aCL, in patients without SLE. A meta-analysis published in 1998 concluded that the risk of venous thrombosis was increased 10-fold in LA-positive patients and by 50% in aCL-positive patients [6]. However, this meta-analysis deserves updating to include all the studies performed since 1998 and more recently identified APLs. During the last 20 years, better understanding of the pathogenic mechanisms of antiphospholipid antibody syndrome (APS) has led to the identification of several new APLs and the development of specific tests for their detection. These new APLs are directed against plasma proteins bound to particular anionic surfaces and do not recognize anionic phospholipids in the same way as aCL [7,8]. They include anti-β2 Glycoprotein I (β2GpI), identified in 1990, anti-prothrombin (aPT), anti-phosphatidyl serine (aPS) and anti-phosphatidyl ethanolamine (aPE) [9–14]. Patients with thrombosis may be positive for these antibodies, mainly in the absence of LA and aCL [15,16]. The clinical significance of their presence is still debated, as the clinical relevance of immunoglobulin (Ig) APL isotypes (IgG, IgM and IgA) [17].

Previous studies have evaluated the association between APL and risk of arterial thrombosis, but no meta-analysis has estimated this risk.

We therefore conducted a meta-analysis to estimate the risk of both venous and arterial thrombosis associated with APLs, including new APLs, in adults without SLE.

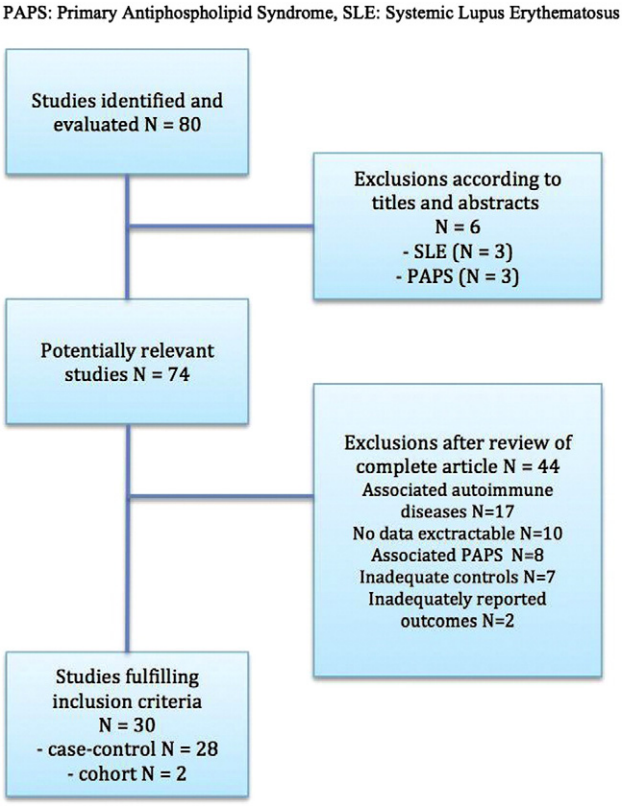


**Fig. 1.** Study flow diagram. PAPS: Primary Antiphospholipid Syndrome, SLE: Systematic Lupus Erythematosus.

## 2. Material and methods

We followed the Meta-Analysis of Observational Studies in Epidemiology guidelines during all stages of design, implementation, and reporting of this meta-analysis [18]. We identified all relevant published and unpublished observational studies that specifically examined the association between APL (exposure) and venous or arterial thrombosis (outcome) in patients without SLE (study population). Selection criteria were determined before data collection.

### *2.1. Data sources and searches*

An exhaustive literature search, both computer-assisted and manual, was performed with no restriction on language or dates. The computer-assisted search was conducted on the MEDLINE and Cochrane Library electronic databases (see search strategy in Appendix A, Fig. A1). To find additional references, we manually checked the reference lists of all articles identified, and also consulted Google scholar and conference proceedings in the fields of haemostasis, thrombosis, and internal medicine.

### *2.2. Study selection*

We selected case-control and cohort studies that included non-SLE patients and described exposure to APL and outcome (thrombosis). For case-control studies, cases were patients with thrombosis compared to a control group without thrombosis, information on APL testing being required for both groups. Cohort studies had to comprise both APL-positive and APL-negative patients experiencing thrombosis during follow-up. Studies were categorized according to antiphospholipid immunoglobulin G (IgG) antibody type (namely aCL, β2GpI, aPT, aPS, and aPE), and type of thrombotic event (venous or arterial).

The studies included patients experiencing either a first event or a recurrence of venous or arterial thrombosis, and in both cases the