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# Increased risk of thrombosis in antiphospholipid syndrome patients treated with direct oral anticoagulants. Results from an international patient-level data meta-analysis

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ABSTRACT

*Background:* Direct oral anticoagulants (DOACs) are widely used for secondary prevention of venous thromboembolism (VTE) but their clinical efficacy and safety are not established in Antiphospholipid Syndrome (APS) patients. There is only one randomized controlled trial published while others are still ongoing. Many non-randomized studies have been published in this field with conflicting opinions.

*Purpose of review:* We conducted a systematic review using MEDLINE, EMBASE and Cochrane databases from 2000 until March 2018 regarding APS patients treated with DOACs. We performed a patient-level data meta-analysis to a) estimate the prevalence of recurrent thrombosis in APS patients treated with DOACs in the literature, and b) identify variables associated with recurrent thrombosis.

*Results:* We identified 47 studies corresponding to 447 APS patients treated with DOACs. Three commercially available DOACs were analyzed: rivaroxaban ($n$ = 290), dabigatran etexilate ($n$ = 144) and apixaban ($n$ = 13). A total of 73 out of 447 patients (16%) experienced a recurrent thrombosis while on DOACs with a mean duration until thrombosis of 12.5 months. Rates of recurrent thromboses were 16.9% and 15% in APS patients receiving either anti-Xa inhibitors or dabigatran respectively. Triple positivity (positivity for all three antiphospholipid antibodies) was associated with a four-fold increased risk of recurrent thrombosis (56% vs 23%; OR = 4.3 [95%CI; 2.3–7.7], p < 0.0001) as well as a higher number of clinical criteria for APS classification. In patients treated with anti-Xa inhibitors, history of arterial thrombosis was associated with a higher risk of recurrent thrombosis (32% vs 14%; OR = 2.8 [95%CI; 1.4–5.7], p = 0.006).

In conclusion, DOACs are not effective in all APS patients and should not be used routinely in these patients. Randomized controlled trials assessing clinical efficacy and safety as primary endpoints are underway. In the meantime, a registry of APS patients on DOACs could be proposed to establish in which APS subgroups DOACs would be a safe alternative to warfarin.

*Abbreviations:* APS, antiphospholipid syndrome; aPL, antiphospholipid antibodies; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; SLE, systemic lupus erythematosus; INR, international normalized ratio; LA, Lupus anticoagulant; aCL, anticardiolipin antibody; a$\beta_2$-GPI, anti-$\beta_2$-glycoprotein-I; VTE, venous thromboembolism; TG, thrombin generation; RCTs, randomized controlled trials

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## 1. Introduction

Definite antiphospholipid syndrome (APS) includes, according the Sapporo-Sydney criteria, at least one clinical criterion (arterial, venous or small vessel thrombosis or obstetrical morbidity) with positivity of at least one antiphospholipid antibody (aPL): lupus anticoagulant (LA), IgG or IgM anticardiolipin antibodies (aCL) and IgG or IgM anti-$\beta_2$-glycoprotein-I (a$\beta_2$-GPI), detected on a minimum of two consecutive occasions at least 12 weeks apart [1]. APS can be primary or associated with an autoimmune disease, mainly systemic lupus erythematosus (SLE) [2]. All APS patients do not carry the same risk of thrombosis: those who are triple positive, i.e. for all three aPL tests have a higher risk for thrombosis, > 5 events per 100 patient per year [3].

The cornerstone of APS patient management is secondary thromboprophylaxis with long-term warfarin treatment [4]. Four direct oral active anticoagulants (DOACs), rivaroxaban, apixaban, edoxaban, and dabigatran etexilate, are approved in the general population for secondary thromboprophylaxis after an episode of venous thromboembolism (VTE) [5–8].

The use of DOACs in APS patients is controversial because of conflicting data from several case reports, case series, cross-sectional studies and one randomized controlled trial [9, 10].

### 1.1. Aims

We conducted a systematic review and patient-level data meta-analysis to estimate the rate of recurrent thrombosis in APS patients treated with DOACs and to identify risk factors predisposing to thrombotic events.

## 2. Materials and methods

### 2.1. Meta-analysis protocol

Our study protocol was registered on PROSPERO (CRD42018084898). All stages of the conception of this meta-analysis were conducted according to PRISMA guidelines [11].

### 2.2. Search strategy

We conducted a systematic literature search in MEDLINE, EMBASE and Cochrane databases including all articles published from 2000 until March 15, 2018 reporting treatment with DOACs in APS patients. Reference lists of eligible studies and congress abstracts books were reviewed. Search terms (including MeSH terms) were: *antiphospholipid antibodies*, *antiphospholipid syndrome*, *lupus coagulation inhibitor*, *antibodies anticardiolipin*, *familial antiphospholipid syndrome*, *anti-$\beta_2$-glycoprotein-I* and *lupus erythematosus systemic* and *direct oral anticoagulant*, *DOAC*, *novel oral anticoagulant*, *NOAC*, *rivaroxaban*, *apixaban*, *edoxaban*, *dabigatran*. No restrictions about language, study design and publication date were applied.

### 2.3. Eligibility

Eligible articles were randomized controlled trials, non-interventional cohorts, case-control or cross-sectional studies, case series, case reports, and abstracts. Studies inclusion criteria were: APS patients according to Sapporo-Sydney criteria treated with any DOACs (dabigatran etexilate, rivaroxaban, apixaban, edoxaban). The primary outcome was a documented recurrent thrombosis during follow-up. Non-inclusion criteria were a) poorly documented or undocumented recurrent thrombosis and b) absence of follow-up during DOACs treatment. During patient-level data extraction of case series, patients were excluded if a) recurrent thrombosis was undocumented, b) no DOACs were used, c) aPL tests were negative.

### 2.4. Search and extraction

According to PRISMA guidelines, after deleting duplicates, we excluded publications which were not eligible based on titles and abstracts. Then full text articles were reviewed and either excluded based on inclusion/exclusion criteria or included in the analysis. Data was extracted from eligible articles. In case of incomplete or unextractable data, we contacted authors. Individual patients' data were extracted in a standardized form and comprised demographics, past thrombotic

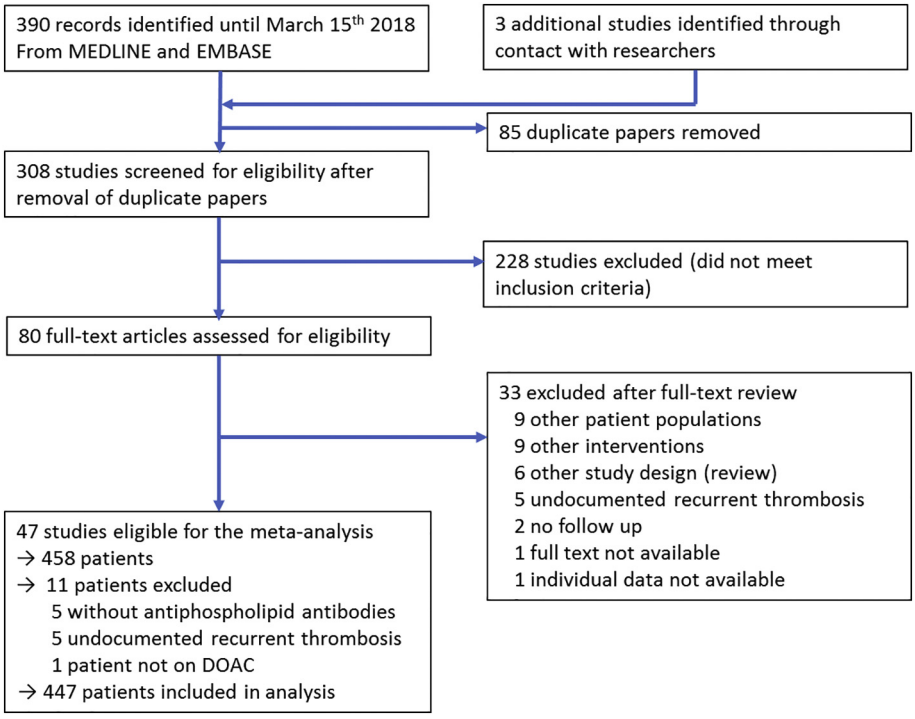


**Fig. 1.** Flow chart of study identification for meta-analysis.