Review

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Rethinking the use of direct oral anticoagulants for secondary thromboprophylaxis in patients with thrombotic antiphospholipid syndrome

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SUMMARY Patients with thrombotic antiphospholipid syndrome (APS) are at high risk for recurrent thrombosis, and indefinite anticoagulation is recommended. Patients with APS merit indefinite anticoagulation, and vitamin K antagonists (VKAs) have historically been the standard treatment. Direct oral anticoagulants (DOACs) present an appealing alternative to VKAs. Due to their pharmacokinetic and pharmacodynamic characteristics, DOACs offer advantages over VKAs, namely the lack of need for laboratory monitoring, the usage of a fixed dosage, and the absence of significant interaction with dietary components and drugs. The efficacy and safety of DOACs in patients with APS have been studied in four phase II/III clinical trials (three with rivaroxaban and one with apixaban). These studies showed DOACs' inferiority compared to VKAs in preventing recurrent thrombosis. Recurrence was significantly greater in patients with arterial thrombotic events and a triple positivity for antiphospholipid antibodies. No differences were observed in the incidence of venous thromboembolism between both groups. Major bleeding was similar in patients treated with DOACs or VKAs. Several observational studies have reported similar results. This review aims to analyse the existing evidence on the efficacy and safety of DOACs for secondary prevention in patients with APS.

Keywords Antiphospholipid syndrome, arterial and venous thrombosis, bleeding, direct-acting oral anticoagulants, secondary prevention, vitamin K antagonists

1. Introduction

Antiphospholipid syndrome (APS) is a complex autoimmune disease characterised by arterial, venous, or small vessel thrombosis in any tissue or organ that can present as obstetric morbidity. Meeting the clinical criteria previously mentioned and determining the presence of antiphospholipid antibodies (APLAs) as laboratory criteria is essential for diagnosis. APLAs include lupus anticoagulant (LA) measured by functional clotting assays, anticardiolipin antibody (aCL) and anti-β2 glycoprotein I (aβ2GPI) immunoglobulin (Ig) type G and/or type IgM assayed by solid phase enzyme-linked immunosorbent assay (ELISA) at medium (40-70 GPL units) or high (≥ 80 GPL units) titres. Laboratory testing must be positive on at least two separate occasions 12 weeks apart. New APS classification criteria have recently been published jointly by The American College of Rheumatology (ACR) and The European Alliance of Associations for Rheumatology (EULAR) (*1*). The 2023 criteria are intended to be more specific than the Sydney 2006 criteria (*2*) to better identify patients with APS (99% and 86%, respectively).

APS management is based on long-term anticoagulation due to the high risk of recurrent thrombosis among non-treated patients (*3,4*). Patients with APS should receive indefinite oral anticoagulation with vitamin K antagonists (VKAs). In patients with venous thrombosis the goal is to achieve and maintain an International Normalised Ratio (INR) between 2-3 and in patients with arterial thrombosis to maintain an INR of 2-3 or 3-4, depending on the thrombotic and bleeding risk. In case of recurrence despite an adequate INR in both, arterial and venous thrombosis, the recommendation is to maintain an INR of 3-4 or to add low doses of acetylsalicylic acid (*5*).

Direct oral anticoagulants (DOACs) have shown a similar, in some case even superior, efficacy and safety

profile compared to VKAs in the treatment and secondary prevention of venous thromboembolism (VTE) (*6-8*) and in the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (*6,8-10*). However, controversy has arisen around the use of these drugs in APS. This study aims to review the currently available literature to determine the efficacy and safety of these drugs in secondary thromboprophylaxis in APS to detect groups of patients who may benefit from this antithrombotic therapy.

2. Evidence from clinical trials

Four randomized controlled trials (RCT) have been conducted to evaluate the efficacy and safety of DOACs in secondary prevention of patients with APS (Table 1) (*11-14*). These RCTs include RAPS (rivaroxaban in antiphospholipid syndrome) (*11*), TRAPS (trial on rivaroxaban in antiphospholipid syndrome) (*12*), rivaroxaban versus VKA in APS: a randomized non-inferiority trial (*13*), and ASTRO-APS (apixaban for the secondary prevention of thrombosis among patients with antiphospholipid syndrome) (*14*). RCTs involved 474 patients, comprising 234 assigned to DOACs and 240 to VKAs. Studies were conducted in the United Kingdom (*11*), Italy (*12*), Spain (*13*), and the United States (*14*). Women accounted for 70.8%, and 56% of the participants had triple positive for APLAs. The mean follow-up time was 18.8 months.

RAPS study, the first in this field, was a prospective, open-label, non-inferiority clinical trial in patients with APS and a history of VTE, whose main objective was to demonstrate the non-inferiority intensity anticoagulation achieved with rivaroxaban when compared to warfarin, using endogenous thrombin measurement (*11*). One hundred and sixteen patients treated with warfarin for at least three months after the VTE event were included. Although rivaroxaban did not meet the primary endpoint of the study versus warfarin, no recurrent thrombotic events were observed and both drugs were equally safe in terms of major bleeding.

TRAPS (*Trial on Rivaroxaban in AntiPhospholipid Syndrome at high-risk for thromboembolic recurrence*) study was a prospective, randomized, non-inferiority trial comparing the efficacy and safety of rivaroxaban versus warfarin for the prevention of recurrent thrombotic events, major bleeding and death from vascular cause in patients with triple-positive APLAs (LA, aCL and aβ2GPI) (*12*). Patients were randomized to receive rivaroxaban 20 mg/day or warfarin (target INR 2.5). The trial was prematurely stopped by the adjudication and safety committee for an excess of events in the rivaroxaban group. At the time of trial termination, 120 patients had been randomized: 59 in the rivaroxaban group and 61 in the warfarin group. Seven patients experienced arterial events in the rivaroxaban arm, whereas there were no cases of arterial thrombosis in the warfarin group. In the rivaroxaban arm, ischemic stroke occurred in 4 (7%) patients, and myocardial infarction occurred in 3 (5%) patients. No episode of VTE was recorded in either arm. There were 4 and 2 cases of major bleeding in the rivaroxaban and warfarin groups, respectively (hazard ratio [HR], 2.5; 95% confidence interval [CI], 0.5-13.6; $p = 0.3$). The use of rivaroxaban in patients with APS and triple-positive APLAs were associated with an increased rate of arterial thrombotic events compared with warfarin.

A Spanish study evaluated the efficacy and safety of rivaroxaban administered at doses of 20 mg or 15 mg daily depending on renal function, compared with VKAs in patients with thrombotic APS (*13*). After three years of follow-up, recurrent thrombosis occurred in 11 of 95 patients (11.6%) treated with rivaroxaban and in 6 of 95 (6.3%) treated with VKAs (relative risk [RR], 1.83; 95% CI, 0.71-4.76; $p = 0.21$). Notably, 9 of the 11 recurrences in the DOAC arm were strokes (81.8% *vs.* 0%; $p < 0.001$). Rivaroxaban did not meet the specified criterion for non-inferiority to VKAs. The incidence of major bleeding was 6.3% (6/95) in the rivaroxaban group and 7.4% (7/95) in the VKA group (RR 0.86; 95% CI, 0.30-2.46; $p = 0.77$). In this study, rivaroxaban showed a near doubling of the risk for recurrent thrombosis compared to VKAs for thrombotic APS.

More recently, in the ASTRO-APS study, 48 patients with APS were randomised to receive apixaban 2.5 mg/12 h, apixaban 5 mg/12 h or warfarin (*14*). The primary efficacy objective was the combined endpoint of thrombosis (arterial and venous) and death from vascular cause, and the primary safety objective was major bleeding and clinically relevant minor bleeding. The primary efficacy endpoint occurred in 6 of 23 patients (26%) treated with apixaban (3 in the 2.5 mg group and 3 at the 5 mg dose). All were strokes. None of the patients randomised to warfarin had thrombotic recurrence. The incidence of major bleeding was 4% (1/25) in the warfarin group with no events in apixaban-treated patients. Apixaban showed inferiority compared to warfarin in preventing recurrent thrombosis, especially strokes, among patients with APS.

3. Direct oral anticoagulants in secondary prevention in arterial thrombosis in patients with antiphospholipid syndrome

RCTs have consistently demonstrated a significantly increased risk of subsequent arterial thrombosis in patients treated with DOACs. The overall incidence of new arterial thrombosis in the group treated with DOACs was 10.3% versus 1.3% in those receiving VKAs (odds ratio [OR], 5.43; 95% CI, 1.87-15.75; $p < 0.001$) (*15*). Compared with VKAs, rivaroxaban and apixaban showed a higher rate of stroke (8.6% versus 0%; OR, 10.74; 95% CI, 2.29-50.38; $p < 0.001$). No differences were observed for myocardial infarction (1.3% versus 0%; OR, 2.15;

Table 1. Results of clinical trials investigating the efficacy and safety of direct oral anticoagulants for secondary prevention of thrombosis in patients with thrombotic antiphospholipid syndrome

	RAPS (*11*)	TRAPS (*12*)	Ordi-Ros *et al*. (*13*)	ASTRO-APS (*14*)
Year	2016	2018	2019	2022
Country	United Kingdom	Italy	Spain	United States
Initial thrombosis event	VTE	Arterial and venous	Arterial and venous	Arterial and venous
Median follow-up in months	7	20.4	36	12
DOACs/comparison	Rivaroxaban 20 mg day / Warfarin (INR 2.5)	Rivaroxaban 20 or 15 mg day / Warfarin (INR 2.5)	Rivaroxaban 20 or 15 mg day / VKA (INR 2-3)	Apixaban 5 or 2,5 mg/12 h / Warfarin (INR 2-3)
Sample size	57 / 59	59 / 61	95 / 95	23 / 25
Mean age	47 / 50	46.5 /46.1	47* / 51*	46 / 48.5
Female gender, %	74 / 71	66 /62	64 / 63	83 / 84
APLAs profile, %				
Simple	60 / 48	0 / 0	34 / 32	22 / 28
Double	28 / 32	0 / 0	5 / 8	17 / 8
Triple	12 / 20	100 / 100	61 / 60	30 / 28
Efficacy primary endpoint	Intensity of anticoagulation achieved by thrombin measurement	Recurrent thrombosis	Recurrent thrombosis	Combined endpoint for arterial and venous thrombosis and death from vascular cause
Recurrent thrombosis	None for both groups	12% versus 0%	11.6% versus 6.3%, (p = 0.21)	26% versus 0%
Major bleeding	None for both groups	7% versus 3%, (p = 0.30)	6.3% versus 7.4%, (p = 0.77)	0% versus 4%
Study findings	Rivaroxaban did not meet the primary efficacy endpoint versus warfarin (endogenous thrombin 1086 nmol/L per minute versus 548 nmol/L per minute, respectively; $p < 0.0001$); however, no recurrent thrombotic events were observed.	Rivaroxaban was inferior to warfarin for prevention of recurrent thrombosis.	Rivaroxaban did not demonstrate non-inferiority to VKAs. The recurrent thrombosis rate was twice as high as with VKAs.	Apixaban was inferior to warfarin for prevention of recurrent thrombosis.

*Ordi-Ros *et al*. used median and interquartile range. Abbreviations: APLAs, antiphospholipid antibodies; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

95% IC, 0.35-13.11; $p = 0.41$) or peripheral embolism (0.4% versus 1.3%; OR, 0.58; 95% CI, 0.12-2.92; $p = 0.51$).

Observational cohorts comparing DOACs to VKAs also show an increased incidence of arterial events in patients treated with DOACs. In the study by Williams *et al*., a nearly 3-fold increased risk of arterial recurrence was observed with rivaroxaban, apixaban and edoxaban compared to warfarin (*16*). This ratio was previously detected with rivaroxaban in a prospective series (*17*).

Meta-analyses have reported a significantly increased risk of new arterial thrombosis with DOACs compared to VKAs. Except for the meta-analysis by Sánchez-Redondo *et al*. (*18*), a higher incidence of new arterial events have been demonstrated in patients treated with DOACs with varying follow-up periods (6 to 72 months). Reviews by Wu *et al*. (OR, 2.27; 95% CI, 1.28-4.00; $p < 0.005$) (*19*), Gullapalli *et al*. (OR, 2.61; 95% CI, 1.44-4.71; $p < 0.001$) (*20*) and Attachaipanich *et al*. (OR, 4.06; 95% CI, 1.33-12.40) (*21*) consistently show a significant increase in arterial recurrence in patients treated with DOACs. Gullapalli *et al*. also analysed the risk of recurrent arterial thrombosis in the patient subgroup additionally receiving antiplatelet therapy. A higher risk was reported in the DOACs arm, although statistical significance was not reached (6.7% in the DOACs arm versus 2.3% in the VKAs arm) (*20*).

4. Direct oral anticoagulants in secondary prevention of venous thromboembolism in patients with antiphospholipid syndrome

Clinical trials found that the incidence of VTE was low in individuals with APS treated with either DOACs or VKAs (1 pulmonary embolism [PE] and 3 cases of deep vein thrombosis [DVT] with DOACs, and 3 events of DVT with VKAs). No differences were observed in the incidence of VTE between both groups (1.7% versus 1.3%; OR, 1.20; 95% CI, 0.31-4.55; $p = 0.79$) (*15*). The risk of PE (0.4% versus 0%; OR, 1.49; 95% IC, 0.23-9.53; $p = 0.68$) and DVT (1.3% versus 1.3%; OR, 1.03; 95% CI, 0.23-4.57; $p = 0.97$) was similar.

In observational studies that have compared DOACs to VKAs, the results regarding the incidence of VTE are heterogeneous. Three cohorts' studies (*16,17,22*) report a similar incidence of VTE, a statement not corroborated by Sato *et al*. (*23*). Notably, in this series two of the three events were cerebral venous sinus thrombosis (CVST).

Several meta-analyses have demonstrated that the incidence of VTE among both treatments is similar. A recent meta-analysis analysing 1,145 patients from 9 studies conclude that the incidence of VTE is similar in individuals with APS treated with either DOACs or warfarin (OR, 1.22; 95% CI, 0.68-2.17; $p = 0.51$) (*19*). Another analysis pooling 12 studies with a total of 1,437 patients showed an incidence of venous thrombosis (DVT/PE/CVST) of 3.8% in patients treated with DOACs and 2.6% in those treated with VKAs (OR, 1.17; 95% CI, 0.66-2.07; $p = 0.60$) (*20*).

5. Influence of immune phenotype on recurrent thrombosis

APLAs profile has prognostic implications. Triple positivity (AL, aCL and aβ2GPI) increases the risk of recurrent thrombosis. In a Chinese study of patients with APS, the recurrence was significatively higher in triple positive patients treated with DOACs versus VKAs (RR, 3.65; 95% CI, 1.49-8.93) (*19*). In the series by Dufrost *et al*. involving 122 patients with APS, there was a clear trend towards new thrombosis in triple-positive patients treated with DOACs versus warfarin (OR, 3.69; 95% CI, 1.12-12.14; $p = 0.05$) (*24*). In the meta-analysis by Gullapalli *et al*. involving a total of 1,437 patients with APS, the recurrence was significantly higher in the triple positive DOACs arm (RR, 4.50; 95% CI, 1.91-10.63; $p = 0.0006$) (*20*). In another recent meta-analysis triple positivity was associated with a 4-fold increased risk for thrombotic recurrence (*25*). A study comparing the occurrence of new thrombosis with rivaroxaban, apixaban and dabigatran versus VKAs showed a significantly higher incidence of recurrence in triple positive patients (56% versus 23%, respectively; OR, 4.3; 95% CI, 2.3-7.7; $p < 0.0001$) (*26*).

The results the regarding the recurrence of thrombosis in patients with single/double positive APLAs are controversial. In the previously mentioned RAPS study, 85% of patients were single/double positive (*11*). The authors found no difference in the development of new thrombotic events between rivaroxaban and warfarin in this subgroup of patients. The study by Legault *et al*. analysed the safety of rivaroxaban (single arm) in 82 patients with APS, none of whom were triple positive. After a median follow-up of 19 months, four recurrences were observed (two strokes and two VTE events) (*27*). The authors conclude that the incidence of recurrent thrombosis is comparable to VKA treatment. In a retrospective cohort of patients with APS treated with DOACs, the incidence of a new thrombosis was 1.7 events/year in triple positive patients compared to 0.7 for single/double-positive patients (RR 2.72; 95% CI, 0.41-18.0) (*28*). More recently, a retrospective study including 50 patients with non-triple positive APS and VTE treated with DOACs observed a low incidence of new thrombosis (0.64 events per 100 patients/year) (*29*). In contrast, in other series no differences were observed between single/double and triple positive groups, although without reaching statistical significance (*16,30*).

6. Major bleeding as an adverse effect of anticoagulant therapy

Anticoagulant therapy carries an increased risk of bleeding complications. In this regard, DOACs

Table 2. Clinical guideline recommendations for anticoagulation therapy in patients with thrombotic antiphospholipid syndrome

Clinical Guidelines	Recommendation
European Alliance of Associations for Rheumatology (EULEAR), 2019 (*5*)	For patients with venous thrombosis, indefinite anticoagulation is recommended. DOACs may be an alternative in patients unable to achieve target INR with VKAs, or intolerant to VKAs. Rivaroxaban should not be used in triple positive patients due to the increased risk of recurrent thrombosis. For arterial events, indefinite anticoagulation is also recommended, avoiding the use of DOACs.
European Society of Cardiology (ESC), 2019 (*35*)	Indefinite treatment with VKAs is recommended. DOACs are not recommended.
American Society of Hematology (ASH), 2020 (*36*)	Indefinite anticoagulation with VKAs is recommended. The use of DOACs is discouraged.
British Society for Haematology (BSH), 2020 (*37*)	For patients with venous thrombosis, indefinite anticoagulation is recommended. DOACs should not be used in triple-positive patients. Evidence is insufficient to establish recommendations in single or double positive patients. In general, it is suggested to avoid them; however, if patients are already being treated with DOACs, they may be continued depending on the clinical profile and patient preferences. In patients with arterial thrombosis, indefinite treatment with VKAs is recommended. DOACs are not recommended.
National Institute for Health and Care Excellence (NICE), 2020 (*38*)	VKAs are recommended in triple positive patients.
International Society on Thrombosis and Haemostasis (ISTH), 2020 (*39*)	In patients with high-risk thrombotic APS*, VKAs are recommended. In patients with APS without high-risk criteria who are already on DOACs therapy, it may be maintained depending on the clinical profile and patient preference.
American College of Cardiology (ACC), 2024 (*40*)	DOACs are not considered standard treatment in patients with APS.

*High-risk thrombotic APS is defined as meeting at least one of the following criteria according to the Sydney Convention (2006): a) triple positivity, b) arterial thrombosis, c) small vessel thrombosis with organ involvement, d) cardiac valvular heart disease. *Abbreviations*: APS, antiphospholipid syndrome; APLAs, antiphospholipid antibodies; DOACs, direct oral anticoagulants; INR, international normalised ratio; VKAs, vitamin K antagonists.

have proven superior to VKAs in patients with atrial fibrillation, particularly in reducing the incidence of intracranial haemorrhage by up to 50% (*31-33*).

In the four RCTs with DOACs, 20 major bleeding events were reported, 10 in each treatment arm. Pooled data showed no difference between therapy with DOACs or VKAs (4.3% versus 4.2%; OR, 1.02; 95% CI, 0.4-2.47; $p = 0.97$) (*15*). There was also no difference for clinically relevant non-major bleeding (6.0% *vs.* 2.9%; OR, 1.90; 95% CI, 0.78-4.66; $p = 0.16$).

All meta-analyses show that the risk of bleeding is similar in patients with APS treated with DOACs or VKAs. The rates of major bleeding were 4.4% and 4.2%, and the rates of clinically relevant non-major bleeding were 5.6% and 5.5%, respectively, during a mean follow-up period of 12-36 months *(19,20,24-26,*34). The incidence of intracranial haemorrhage was also equivalent for both groups (0.37% for DOACs and 0.42% for VKAs).

7. Conclusion

In conclusion, patients with APS are at high risk of recurrent thrombosis; therefore, they require indefinite anticoagulant therapy. Based on the outcomes of RCTs with rivaroxaban and apixaban, DOACs are generally not recommended (Table 2). Nevertheless, the outcomes were poor in high-risk APS patients, including those with previous arterial thrombosis and triple positivity. Furthermore, these studies were small and lacked sufficient power to evaluate thrombotic outcomes robustly. Currently, the clinical guidelines of EULAR (*5*), the British Society for Haematology (*37*) and the International Society on Thrombosis and Haemostasis (*39*) suggest that DOACs could be an alternative in patients unable to achieve the INR target with VKA drugs or who are intolerant to them, as well as in non-high-risk APS patients, including single- or double-positive serology and prior venous thrombosis. In these patients, the use of DOACs appears reasonably safe. We emphasize the need for ongoing research further to optimize anticoagulant therapy for this challenging patient population.

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