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RECOMMENDATIONS AND GUIDELINES

Use of direct oral anticoagulants in patients with thrombotic antiphospholipid syndrome: Guidance from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis

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Abstract

Clarity and guidance is required with regard to the use of direct oral anticoagulants in antiphospholipid syndrome (APS) patients, within the confines of the recent European Medicines Agency recommendations, discrepant recommendations in other international guidelines and the limited evidence base. To address this, the Lupus Anticoagulant/Antiphospholipid Antibodies Scientific and Standardization Committee (SSC) chair and co-chairs together with SSC Control of Anticoagulation members propose guidance for healthcare professionals to help them manage APS patients. Uncertainty in this field will be addressed. This guidance will also serve as a call and focus for research.

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antiphospholipid antibodies, antiphospholipid syndrome, arterial thrombosis, direct oral anticoagulants, triple positivity, venous thromboembolism, vitamin K antagonists

1 | SCOPE AND METHODOLOGY

Vitamin K antagonists (VKAs), notably warfarin, are the standard treatment for thrombotic antiphospholipid syndrome (APS).[1–4] This acquired autoimmune disorder is manifested by thrombosis (in the arterial, venous, or microvascular circulation) and obstetrical events, in association with persistent antiphospholipid antibodies (aPL; one or more of lupus anticoagulant [LA], IgG and/or IgM anti-beta 2 glycoprotein 1 [aß2GP1], and anticardiolipin antibodies [aCL]).[5]

The use of VKAs for the anticoagulation of APS patients has been challenged by the introduction in case reports, small series (Table 1), cohort studies, and randomized controlled trials (RCTs) of direct oral anticoagulants (DOACs). When compared with VKA, DOAC advantages include fixed-dose prescribing, no need for monitoring of anticoagulant effect, simplified perioperative management, reduced major and intracranial bleeding, fewer drug-food interactions, and significantly fewer drug-drug interactions. These attributes are especially advantageous among patients with APS, who often require indefinite anticoagulation.[6] Furthermore, APS patients may experience difficult INR (international normalized ratio) control due to an interaction between their antibody and reagents used in the INR determination.[7] Recent professional guidance statements have been issued regarding the use of DOACs in APS patients. Based on the results of one RCT,[8] the European League Against Rheumatism (EULAR) guidelines recommend that rivaroxaban be avoided in triple-positive APS patients (ie, presence of LA, aß2GP1, and aCL).[4] The European Medicines Agency (EMA) recommends against the use of DOACs in APS patients, especially in those who are triple-positive;[9] and the European Society of Cardiology recommends against DOAC use in all APS patients.[10] The British Society for Haematology (BSH) addendum to the existing guidelines recommends against the use of DOACs for arterial thrombosis in APS patients; and in APS patients with venous thrombosis, a switch from DOAC to VKA in those who are triple positive, with consideration of continuation of the DOAC if non-triple positive.[11] These discrepant recommendations have resulted in uncertainty regarding the use of DOACs in APS patients.[12]

The Lupus Anticoagulant/Antiphospholipid Antibodies Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH), in collaboration with the SSC on Control of Anticoagulation, has produced guidance herein to help healthcare professionals manage thrombotic APS patients. Definitive studies have not been done to establish with certainty the place of DOACs in the treatment of APS in all clinical situations. The purpose of this guidance is to provide advice to clinicians while there is limited evidence. This guidance also serves as a call and focus for research. The guidance statements included in this document are, as with other guidance documents, endorsed by the ISTH Guidance and Guidelines Committee panel[13,14] and based on the following premises: (1) our statements may provide guidance but do not replace clinical judgement for the management of individual patients; (2) the wording "we recommend" reflects a strong guidance statement, whereby the clinician should consider adopting the practice in a majority of cases; and (3) the wording "we suggest" reflects a weak guidance statement, whereby the clinician may adopt the guidance statement or use an alternative approach to manage patients.

2 | BACKGROUND AND AVAILABLE EVIDENCE

2.1 | What are the results from clinical studies of DOACs for thrombotic APS?

Results from case series and clinical studies (RCTs, cohort, or case control studies)[8,15–21] are summarized in Tables 1 and 2, respectively. These include rates of major and clinically relevant non-major bleeding that are reported in Table 2.

2.2 | What are the results of systematic reviews of thrombotic APS patients on DOACs?

Three systematic reviews[22–24] were performed using different designs and analysis. These yielded inconsistent results and some had important shortcomings, which limit their applicability to clinical practice.

An individual patient data (IPD) meta-analysis of 447 APS patients treated with DOACs[22] reported an overall annual thrombosis recurrence rate of 11.7%. Markers for recurrent thrombosis in patients treated with oral Xa inhibitors (n = 303) were male sex; triple-positivity; a history of arterial or small vessel thrombosis; a higher number of clinical criteria for APS classification; a history of thrombosis during VKA treatment; and prior prolonged treatment with low-molecular-weight-heparin, which is generally limited to oral anticoagulant-refractory patients. Among patients treated with the direct thrombin inhibitor dabigatran (n = 144), markers of recurrent thrombosis included a higher number of clinical criteria for APS classification and a history of thrombosis during VKA treatment. Of the 73 patients who had recurrent thrombosis while on a DOAC, 31 had arterial events. Of these, three had prior arterial thrombosis alone, 10 had prior arterial plus venous thrombosis, and 18 had prior venous thromboembolism (VTE) alone.

A systematic review involving 728 patients[23] reported an annualized frequency of thrombotic recurrence during DOAC treatment

TABLE 1 Characteristics and results from case series of direct oral anticoagulants for thrombotic antiphospholipid syndrome

First Author	Year	PMID	Patients, n	History of thrombosis, n				Triple positivity[a], n	Drug (regimen)	Design	Recurrence rate, %
				V	A	SV	O				
Schaefer et al	2014	25118790	3	2	2	0	1	2	Rivaroxaban (20mg OD) n = 1 Rivaroxaban (NR) n = 1 Dabigatran (150mg OD) n = 1	R	100
Win et al	2014	25043836	3	3	2	0	0	NR	Rivaroxaban (20mg OD) n = 2 Dabigatran (150mg BID) n = 1	R	100
Noël et al	2015	25864630	26	17	12	5	6	7	Rivaroxaban (20mg OD) n = 13 Rivaroxaban (15mg OD) n = 2 Dabigatran (150mg BID) n = 11	R	3.8
Sciascia et al	2015	25923780	35	35	0	NR	NR	NR	Rivaroxaban (20mg OD)	P	0
Signorelli et al	2016	26219490	6 (2 excl.)	6	1	0	0	2	Rivaroxaban (20mg OD) n = 2 Rivaroxaban (NR) n = 4	R	100
Betancur et al	2016	26743321	8	8	3	0	2	1	Rivaroxaban (20mg OD) n = 6 Rivaroxaban (NR) n = 1 Apixaban (5mg BID) n = 1	R	0
Hładyj et al	2016	27504026	23	14	12	NR	1	4	Rivaroxaban (NR)	R	4.3
Dufrost et al	2017	28431092	4	4	1	1	0	4	Rivaroxaban (20mg OD) n = 4	R	100
Kunk et al	2017	27632140	11	11	NR	NR	NR	3	Rivaroxaban (NR) n = 5 Apixaban (NR) n = 6	R	0
Mateos Rodriguez et al	2017	28546102	2	2	2	0	0	0	Rivaroxaban (20mg OD) n = 2	R	0
Resseguier et al	2017	28355988	21 (2 excl.)	18	2	1	4	2	Rivaroxaban (20mg OD) n = 17 Rivaroxaban (15mg BID) n = 4	P	4.8
Scanvion et al	2018	29373704	2	1	1	0	1	1	Rivaroxaban (20mg OD) n = 2	R	100
Martinelli et al	2018	29519861	13	1	NR	NR	NR	6	Rivaroxaban (20mg OD) n = 13	P	31
Johnsen et al	2018	29297243	3	2	1	0	NR	1	Dabigatran (NR) n = 3	R	100
Christen et al	2019	31724442	2	1	0	0	NR	0	Rivaroxaban (20mg OD)	P	50
Abu-Zeinah et al	2019	30835035	10	NR	NR	NR	NR	5	NR	R	10

Abbreviations: A, arterial thrombosis; BID, twice a day; Excl, excluded patients; NR, No reported; O, obstetrical morbidity; OD, once a day; P, prospective study; R, retrospective study; SD, standard deviation; SV, small vessel thrombosis; V, venous thrombosis.

[a]Triple aPL-positivity, ie, presence of lupus anticoagulant, anticardiolipin, and anti-ß$_2$-glycoprotein 1 antibodies (same isotype).

TABLE 2 Characteristics and results from clinical studies of direct oral anticoagulants for thrombotic antiphospholipid syndrome

Title	RAPS RCT	RE-COVER ®, RE-COVER II™, and RE-MEDY™ (*Post hoc*)	ASTRO-APS	TRAPS	RAPS pilot study	EUDRA 2010-019764-36	-	-
First author	Cohen et al[15]	Goldhaber et al[16]	Woller et al[17]	Pengo et al[8]	Legault et al[18]	Ordi-Ros et al[19]	Sato et al[20]	Malec et al [21]
Publication year	2016	2016	2018 (interim results)	2018	2018 (poster)	2019	2019	2019
Country	UK	International	USA	Italy	Canada	Spain	Japan	Poland
Reference/PMID	27570089	27807306	2889387	30002145	NA	31610549	31635559	31757182
Type	Open label, non-inferiority RCT	Double-dummy, non-inferiority RCT	Open label, non-inferiority RCT	Open label, non-inferiority RCT	Single-arm pilot feasibility study	Open label, non-inferiority RCT	Case-control	Cohort
Design	Prospective	Prospective	Prospective	Prospective	Prospective	Prospective	Retrospective	Prospective
APS population	APS according to Sydney criteria with previous VTE, exclusion of patients with previous arterial thrombosis due to APS	Known APS patients	APS according to Sydney criteria	APS according to Sydney criteria with triple positivity[a]	APS according to Sydney criteria with previous VTE with and without arterial thrombosis	APS according to Sydney criteria with previous thrombosis	APS according to Sydney criteria with previous thrombosis	APS according to Sydney criteria with previous thrombosis
Total population	n = 116	n = 151	n = 30	n = 120	n = 82	n = 190	n = 54	n = 176
DOAC	Rivaroxaban = 54	Dabigatran = 71	Apixaban	Rivaroxaban = 59	Rivaroxaban = 82	Rivaroxaban = 95	Rivaroxaban = 5 Apixaban = 1 Edoxaban = 12	Rivaroxaban = 36 Apixaban = 42 Dabigatran = 4
Dose	20mg OD 15mg OD for CrCl 30-49 N = 2	150mg BID	2.5mg BID (2015) 5mg BID (since 2016)	20mg OD 15mg OD for CrCl 30-50 N = 2	20mg OD	20mg OD 15mg OD according to renal function N = 5	NA	Rivaroxaban 20mg OD Apixaban 5mg BID dabigatran 150mg BID
Control	Warfarin, Target INR 2.5 (range 2-3)	Warfarin, Target INR 2.5	Warfarin Target INR 2.5	Warfarin Target INR 2.5	None	VKA Target INR 2.5 or 3.1-4.0	Warfarin Target INR 2.5 (range 2-3)	VKA Target INR 2.5 (range 2-3)
Primary endpoint	Less than 20% difference from warfarin in mean % change in ETP (D1-D42)	VTE/VTE-related deaths	Thrombosis (arterial and/or venous)	Thrombosis, major bleeding, and vascular deaths	Feasibility (identification for enrolment and consent), and compliance	Thrombosis	Thrombosis or bleeding	Thrombosis (arterial and/or venous)
Primary result	Difference in mean ETP change of 98%	3 (dabigatran) vs 4 (warfarin) HR = 0.43 (95% CI 0.08-2.38)	No details available. *"Higher than expected rate of stroke"*	11 (rivaroxaban) vs 2 (warfarin) Risk of events: HR = 6.7 (95% CI 1.5-30.5)	Enrolment: 82/135 (60.7%)	11 (rivaroxaban) vs. 3 (VKA) HR = 1.94 (95% CI 0.72-5.24)	6 (DOACs) vs. 8 (warfarin) Risk of events: HR = 12.1 (95% CI 1.73-248)	10 (DOACs) vs. 12 (VKA) Risk of events: HR = 3.98 (95% CI 1.54-10.28)

(Continues)

TABLE 2 (Continued)

Title	RAPS RCT	RE-COVER ®, RE-COVER II™, and RE-MEDY™ (*Post hoc*)	ASTRO-APS	TRAPS	RAPS pilot study	EUDRA 2010-019764-36	-	-
Follow-up	210 days	Up to 36 months	13 months	569 days (mean)	18.8 months	36 months	60 months	51 months
Thrombosis (DOAC vs VKA)	0% vs 0%	4.2% vs 5.0%	NA	12% vs 0%[d]	3.7% vs NA	11.6% vs 6.3%	33% vs 22%[d]	12% vs 10.6%
Annualized thrombosis rate in DOAC group	0%	NA	NA	7.69%	2.3%	4.2%	6.7%	3.5%
Bleeding (DOAC vs VKA)	5% vs 4%[b]	7.1% vs 15.6%	NA	7% vs 3%[c]	0% vs NA	9.5% vs 5.3%[b]	5.6% vs 5.6%[b]	5% vs 2.4%[b]
Important additional data	28% of patients (24.6% [14/57] in the rivaroxaban arm and 32.2% [19/59] in the warfarin arm) were triple aPL-positive; Improved quality of life in rivaroxaban arm	NA	The protocol was modified twice: (a) 5mg BID instead of 2.5 mg BID and (b) exclusion from enrolment of patients with prior arterial thrombosis; brain MRI, then enrolment of those without evidence of prior stroke or white matter changes disproportionate for patient age	Prior arterial thrombosis in 19% (11/59) patients in rivaroxaban arm 57% (4/7) of patients with arterial recurrent thrombosis had history of arterial thrombosis	NA	Patients with prior recurrent thrombosis on high-intensity VKA randomized to rivaroxaban 20mg OD vs high-intensity VKA Prior arterial thrombosis in 38% (37/95) and arterial and venous thrombosis in 11.6% (11/95) 9.5% (9/95) had strokes in rivaroxaban arm vs 0 on warfarin Risk of VTE (HR = 0.7), arterial thrombosis (HR = 3.84[d]) especially stroke (HR = 20[d]). Post-hoc analysis suggested that in patients treated with rivaroxaban, the presence of livedo, small vessel or cardiac valvular disease was associated with an increased risk of recurrent thrombosis	Comparison of 14 patients before and after switching for factor Xa inhibitors: 14-fold increased risk[d] of recurrent thrombosis with DOAC vs warfarin	Risk of VTE alone (HR = 3.98[d]), no difference between rivaroxaban or apixaban, no difference between single or double positive patients. Triple positivity did not reach statistical significance even If the rate was higher in the recurrence group (40% vs. 21%).

(Continues)

TABLE 2 (Continued)

Title	RAPS RCT	RE-COVER ®, RE-COVER II™, and RE-MEDY™ (*Post hoc*)	ASTRO-APS	TRAPS	RAPS pilot study	EUDRA 2010-019764-36	-	-
Conclusions of the authors	*"Peak thrombin was significantly lower on rivaroxaban vs warfarin; ETP on rivaroxaban explained by altered reaction kinetics, overall TG curve not indicative of increased thrombotic risk"* *"Rivaroxaban could be an effective and safe alternative in patients with APS and previous VTE requiring standard-intensity anticoagulation"*	*"The efficacy and safety of dabigatran etexilate were not significantly affected by the presence of thrombophilia or APS"*	NA	*"The use of rivaroxaban in high-risk patients with APS was associated with an increased rate of events compared with warfarin»*	*"No safety signals were reported, and the rate of thromboembolism is similar to previous studies of warfarin in APS, implying that rivaroxaban is relatively safe and efficacious in APS patients with VTE"*	*"Rivaroxaban did not show non inferiority to dose adjusted VKAs for thrombotic APS, although it showed a non–statistically significant near doubling of the risk for recurrent thrombosis"*	*"Factor Xa inhibitors may not be recommended for APS"*	*"During long-term follow-up of real-life APS patients, DOACs are less effective and less safe as VKAs in the prevention of thromboembolism"*
Comments	This trial was not designed or powered to compare clinical outcomes	*Post-hoc* analysis of trials not designed or powered to assess the clinical relevance of dabigatran vs warfarin in APS patients. No details regarding aPL testing (Sydney criteria?)	Trial still active (follow-up) but not recruiting. Results are not available so far (expected publication in 2020) however information regarding protocol modifications are described	Conclusions are limited to triple aPL-positive APS patients[a]	Single arm feasibility study which did not compare outcomes in patients treated with rivaroxaban vs warfarin	Organ involvement (heart and skin) may be associated with thrombotic recurrence	Retrospective design without randomization	No randomization. No difference of recurrent thrombosis or bleeding between rivaroxaban and apixaban. Of note, results are reported based on the drug being used at the end of follow-up as 23 of the 82 patients on DOAC switched therapy.

Abbreviations: APS, antiphospholipid syndrome; BID, twice daily; CrCl, creatinine clearance (Cockcroft & Gault); CI, confidence interval; D, day; DOAC, direct oral anticoagulant; ETP, endogenous thrombin potential; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; MRI: magnetic resonance imaging; NA, not available; OD, once daily; RAPS, rivaroxaban in antiphospholipid syndrome; RCT, randomized controlled trial; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a] Triple aPL-positivity, ie, presence of lupus anticoagulant, anticardiolipin, and anti-ß$_2$-glycoprotein 1 antibodies (same isotype mentioned in the study by Pengo et al and Sato et al[8,20]).

[b] Rates of clinically relevant non-major bleeding.

[c] Rates of major bleeding.

[d] Statistically significant ($P < .05$).

of 11%. Risk factors for recurrent thrombosis included: a higher number of prior thrombotic events, a history of combined arterial and venous thrombosis, previous treatment with LMWH, use of immunosuppressant treatment, and patient preference as the sole reason for switching to a DOAC. A meta-analysis of two published RCTs (the RAPS [Rivaroxaban in Antiphospholipid Syndrome][15] and TRAPS [Rivaroxaban for Thrombotic Antiphospholipid Syndrome][8] trials) with 6 months follow-up did not identify an increased risk of pooled arterial or venous thrombosis in patients treated with rivaroxaban versus VKA.[23] This result can be explained by exclusion of events beyond 6 months of follow-up (which excluded 8 of the 13 events in the TRAPS trial) and pooling of venous and arterial thrombosis (which may have obscured an increased risk of arterial thrombosis, as was seen in the TRAPS trial). Results of this analysis differ from that of Dufrost et al,[22] probably due to differences in data analysis (eg, individual patient data versus published data, pooling arterial and venous thrombosis versus analyzing them separately), and number of patients.

A third meta-analysis studied the use of DOACs in patients with VTE and thrombophilia.[24] In the APS subgroup, a meta-analysis of six studies found no statistically significant difference between DOACs and warfarin for prevention of recurrent VTE. The authors concluded that DOACs could be as effective and safe as VKAs to prevent VTE. However, the aim of anticoagulation in APS is to prevent *both* VTE and arterial events. In this regard, a key limitation of this study is that it did not examine arterial thrombotic events, an important source of morbidity and mortality in patients with APS. Furthermore, aPL were not routinely screened for and no analysis was performed according to the aPL profile.

2.3 | What are the positions of regulatory authorities and scientific societies?

The EMA recommendation against the use of DOACs for APS, especially in triple-positive patients, was based on an analysis by the Pharmacovigilance Risk Assessment Committee (PRAC),[9] triggered by the TRAPS RCT.[8] It is important to emphasize that the EMA recommendation does not constitute a contraindication to the use of DOACs in APS; the modification to the summary of product characteristics of DOACs corresponds to section 4.4 "Special warnings and precautions for use" and not section 4.3 "Contraindications." The patient information leaflet has also been modified to: "if you know that you have a disease called APS […], tell your doctor who will decide if the treatment may need to be changed." This advice has been adopted by the Spanish,[25] United Kingdom (UK),[26] and French Regulatory Agencies,[27] as well as the United States Food and Drug Administration (US FDA).[28] Guidance from scientific societies is variable. The European Society of Cardiology and a consortium of French scientific societies (pulmonology, vascular medicine, cardiology, hematology, etc) recommend against the use of any DOAC in any APS patient.[10,29] In contrast, German societies recommend avoidance of DOACs in triple-positive patients only.[30] EULAR recommendations advise avoidance of rivaroxaban only in patients with triple-positivity or arterial events and state that DOACs "could be considered in other patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (eg allergy or intolerance to VKA)."[4]

3 | WHAT DO WE KNOW?

3.1 | DOAC use for APS-related arterial thrombosis

DOACs are standard treatment for prevention of stroke or systemic embolism due to atrial fibrillation (AF).[31] However, this does not apply to APS-related stroke or arterial thrombosis in other sites. While limited data exist to guide the optimal anticoagulant intensity in APS-related arterial thrombosis,[32] current APS guideline recommend standard-intensity VKA (target INR 2.5, range 2.0-3.0), with or without low dose aspirin, or high-intensity VKA (target INR 3.5, range 3.0-4.0),[1–4] taking into consideration the individual's risk of bleeding and recurrent thrombosis. DOACs were established to be non-inferior to standard-intensity VKA in phase 3 trials of AF and VTE.[31,33] However, these doses were not validated specifically in patients with APS and recent RCTs,[8,19] and meta-analyses[22,23] in APS patients demonstrated increased thrombotic event rates for rivaroxaban compared to warfarin. It is important to note that the most recent trial[19] failed to demonstrate non-inferiority of rivaroxaban compared with VKA and has not yet been included in available meta-analyses; a study comparing apixaban to warfarin is ongoing with publication of results expected in 2020.[54]

3.2 | DOAC use for APS-related small vessel thrombosis or organ involvement

Small vessel involvement in APS is less common than large vessel thrombosis.[35] Accumulated data suggest that patients with small vessel disease (eg, livedo, aPL-related nephropathy, myocardial infarction with non-obstructive coronary arteries [MINOCA]) have a different presentation with aPL-mediated hypercoagulability as well as vasculopathy (vessel wall involvement).[36,37] Small vessel thrombotic manifestations can be resistant to conventional anticoagulation with VKA.[36] Case reports suggest that a history of small vessel disease is associated with a higher risk of thrombosis recurrence when factor Xa inhibitors are prescribed (12% versus 3%) than in patients with no history of small vessel disease.[22] Furthermore, Ordi-Ros et al suggested that in patients treated with rivaroxaban, the presence of livedo, small vessel, or cardiac valvular disease was associated with an increased risk of recurrent thrombosis.[19] In SLE patients, aPL-positivity is associated with a three-fold increased risk of both heart valve disease (including Libman-Sacks endocarditis) and pulmonary hypertension (including pulmonary arterial hypertension).[38,39]

3.3 | DOAC use for APS-related single venous thromboembolism

No thrombotic events were reported in the RAPS RCT during 7 months follow-up in the groups randomized to rivaroxaban or warfarin.

However, this study was not designed or powered for comparison of clinical events.[15] Of note, 28% of patients overall (24.6% [14/57] in the rivaroxaban arm and 32.2% [19/59] in the warfarin arm) were triple-positive. A single-arm pilot study also called RAPS (Rivaroxaban for Antiphospholipid Syndrome)[18] reported no safety signals, and the rate of VTE was similar to previous studies of warfarin in APS,[3] implying that rivaroxaban could be relatively safe and efficacious in APS patients with VTE. However, this was a single-arm study with no VKA control group. Moreover, the antibody profile of the patients in this study was not reported. In the intention to treat analysis of the RCT by Ordi-Ros et al, no increased risk of venous events was found in patients treated with rivaroxaban versus VKA (hazard ratio [HR], 0.70 [confidence interval (CI), 0.12-4.18]).[19] Similarly a meta-analysis of pivotal RCTs concluded that prevention of recurrent VTE with DOACs was as effective and safe as with VKAs.[24] However, the objective in APS is to prevent both recurrent VTE and arterial events, regardless of the site of previous thrombosis. Even with a history of a single episode of VTE, APS patients may be at risk of arterial thrombosis. This was observed in the Dufrost et al meta-analysis, in which 58% (18/31) of APS patients with an arterial thrombosis while on a DOAC had had a prior single episode of VTE.[22] Characteristics of these patients were: female (50%), mean age 43.7 years, 13 patients treated with rivaroxaban and five with dabigatran. Half of these patients (56% [10/18]) were triple-positive. A key challenge is to identify those thrombotic APS patients who may be best served by treatment with a DOAC rather than VKA.

3.4 | DOAC use for high-risk triple-positive APS patients

APLs predict an increased risk of recurrent VTE after a first VTE.[40] Having the same type of aPL on two occasions or having two or three different aPL types (ie, double- or triple-positivity) on either the same or different occasions is associated with recurrent thrombosis in patients with a first unprovoked VTE who stop anticoagulant therapy.[41] This supports active identification of APS patients for consideration of extended duration anticoagulation to minimize thrombosis recurrence.[42] LA is the APS laboratory marker thought to carry the highest risk for thrombosis,[43] and the occurrence of a thrombotic event may be associated with higher mortality in patients with LA.[44] LA detection is also essential to identify triple-positivity, the highest risk aPL phenotype for recurrent thrombosis[45] (triple-positive is defined as positivity for all three criteria aPL: LA, aCL, and aß$_2$GP1; some authors consider triple-positivity only if aCL and aß$_2$GP1 share the same isotype[8,20]). To date LA alone or in combination with another aPL (double-positivity), does not appear to be a marker for an increased risk of thrombosis in patients treated with DOACs.[22,23] Regarding triple-positive APS patients, the TRAPS trial[8] demonstrated that patients treated with DOACs versus VKA had a higher risk of thrombosis. In the same way, the Ordi-Ros study[19] and an IPD meta-analysis[22] indicated that triple-positive patients are at higher risk of recurrent thrombosis when treated with DOACs (triple-positivity in APS patients treated with DOACs with recurrent thrombosis versus no recurrence: 63.6% versus 32.1% [no odds ratio (OR) available] and 56% versus 23% [OR = 4.3; 95%CI: 2.3-7.7, $P < .0001$], respectively). Consequently, EMA, EULAR, BSH, and German recommendations advise against DOAC use in APS patients with triple-positivity.[4,9,11,30] Whether this recommendation should be extended to patients with single- or double-positivity (defined as positive for one or two out of the three aPL tests among LA, aCL, or aß$_2$GP1) regardless of LA positivity is unknown.

4 | AREAS OF UNCERTAINTY

4.1 | What percentage of patients with thrombosis have APS and are receiving treatment with DOACs?

A systematic review reported that aPL are present in 10% of patients with deep venous thrombosis,[46] which concurs with a recent real world study that reported a 9% prevalence of APS in 491 patients with a first unprovoked VTE,[41,47] suggesting possible underdiagnosis of APS. If the true prevalence of APS is 1/2000 as has been estimated, then many patients with VTE have aPLs that have not been detected.[48] Should aPL testing be undertaken in all patients with unprovoked VTE, then it is estimated that 10 patients would need to be tested to identify 1 patient with aPLs. A recent commentary[12] estimated that in the United States alone, annual testing of individuals with otherwise unprovoked VTE would cost more than US$138 000 000. Further research is necessary to inform the implications of aPL testing and how these results may optimize patient care. Furthermore, the exact number of APS patients on DOACs has not been estimated and is currently unknown. Patient selection for aPL testing, including for younger patients with newly diagnosed unprovoked VTE, should be as is advised in current guidelines, ie, according to their likelihood of having APS determined by the clinician and based on Sydney clinical classification criteria.[5,49] Results of testing for aPL in the acute phase of thrombosis should be interpreted with caution, as false positive and negative LA may occur due to acute changes and the effects of anticoagulants on LA testing. Choice of anticoagulant is currently not an indication for testing for aPL. The identification of APS patients treated with a DOAC and their enrolment in an international registry (for example, that of the registry on behalf of the LA/aPL ISTH SSC) may inform future care.[50]

4.2 | Why might DOACs be insufficient for the prevention of thrombosis in APS?

Many hypotheses for why DOACs may be insufficient of thrombosis in APS have been proposed, including: (1) low patient adherence to DOACs (however, in two RCTs[8,19] adherence was high); (2) inadequate dosing regimens (once versus twice daily)[34]; (3) inhibition of only one coagulation factor instead of several with VKA, leading to higher thrombin generation;[51] (4) the need for higher anti-Xa activity and plasma rivaroxaban levels for the prevention of arterial versus venous events as has been proven in animal models, but has not been established in APS patients[52]; (5) DOACs have relatively short half-lives with low drug concentrations at trough whereas

VKAs are considerably longer-acting and provide a more stable level of anticoagulation (whether or the extent to which this could be overcome with higher DOAC doses is untested); (6) suboptimal circulating DOAC concentrations due to renal hyperfunction in young patients.[53] A formal assessment of DOAC concentrations and clinical outcomes in thrombotic APS patients could be informative.

4.3 | Can we extrapolate results from rivaroxaban trials to all DOACs?

The majority of published DOAC studies describe the use of rivaroxaban for thrombotic APS.[8,15,18,19] Few cohort studies have looked at the use of dabigatran,[16] apixaban,[17,21,34] or edoxaban.[20] No dedicated study comparing dabigatran versus warfarin has been performed in APS patients. A meta-analysis of pivotal RCTs in the general population evaluated dabigatran in aPL-positive patients and did not identify a significant increased risk of recurrent venous thrombosis compared with warfarin; however, this analysis was restricted to recurrent venous events only and the impact of dabigatran on arterial thrombosis was not reported.[16] Among DOAC-treated patients included in an IPD meta-analysis, the proportion of patients treated with rivaroxaban, dabigatran, apixaban, and edoxaban was 65%, 32%, 3%, and 0%, respectively.[22] In another meta-analysis, the proportion was 77%, 21%, 3%, and 0%, respectively.[23] The main safety concerns in patients with a history of arterial thrombosis or triple-positivity were demonstrated with rivaroxaban. Whether these statements might be extrapolated to other DOACs is unknown. Of note, among 144 dabigatran-treated patients included in an IPD meta-analysis,[22] a history of arterial thrombosis (52% versus 32%) and triple-positivity (38% versus 41%) were not significantly associated with an increased risk of recurrent thrombosis. Too few data are available regarding apixaban and edoxaban and no conclusions can be drawn for these drugs at this time. Because of the paucity of data, the EMA applied their advice to all DOACs.[9] Results of ASTRO-APS (Apixaban for the Secondary Prevention of Thrombosis Among Patients With Antiphospholipid Syndrome), which randomized APS patients to apixaban or warfarin, are expected in 2020.[17,34]

5 | GUIDANCE STATEMENTS ON THE USE OF DOACs IN APS PATIENTS

The guidance below is based on expert consensus opinion following review of all available published evidence, to provide clinical guidance. All authors agreed on the following statements:

For patient management

1. We recommend that for the treatment of thrombotic APS among patients with any of the following (termed "high-risk" APS patients):

   a. triple positivity,
   b. arterial thrombosis,
   c. small vessel thrombosis or organ involvement
   d. heart valve disease according to Sydney criteria[5]

   VKA should be used instead of DOACs

2. We recommend that DOACs should not be used in APS patients with recurrent thrombosis while on therapeutic intensity VKA. In this circumstance, other therapeutic options may include an increased target INR range, treatment dose LMWH, or the addition of antiplatelet therapy.
3. We recommend that DOACs should not be used in APS patients who are non-adherent to VKA. In this circumstance, other options may include education on adherence to VKA treatment along with frequent INR testing.
4. In single or double positive non-"high risk" APS patients who have been on DOACs with good adherence for several months for a first episode of VTE, we recommend a discussion with the patient of options including perceived risks and uncertainties, in the spirit of shared decision-making and review of whether continued treatment with a DOAC is appropriate.
5. In single- or double-positive non-"high-risk" APS patients with a single prior VTE requiring standard-intensity VKA, with allergy or intolerance to VKA or erratic INRs despite patient adherence, we suggest that alternative VKAs, if available, should be considered prior to consideration of a DOAC.

For clinical research

6. We recommend that the potential use of DOACs in APS requires further, appropriately designed, clinical studies. For example, the RISAPS trial will investigate the use of high-intensity rivaroxaban 15mg twice daily versus high-intensity warfarin in APS patients with stroke or other ischemic brain manifestations: https://www.clinicaltrials.gov/ct2/show/NCT03684564.
7. We recommend that future studies should determine whether there is a lower-risk subset of APS patients (single- and/or double-positive aPL) in whom DOAC therapy is appropriate and whether findings with rivaroxaban represent a DOAC class effect or whether results may differ with DOACs other than rivaroxaban.
8. We recommend that all cases of DOAC use in APS should be reported to the international registry supported by the ISTH. This registry, currently being established (https://clinicaltrials.gov/ct2/show/NCT04262492), will ensure consistency of data collection and provide safety information in APS patients currently on DOACs.
9. We recommend that future research should include investigation of the implications of aPL testing among selected populations (such as those with unprovoked VTE, stroke, or demographics suggestive of possible APS), to optimize patient care, clinician decision-making, and resource utilization.

CONFLICTS OF INTEREST

S. Zuily reports, outside the submitted work, support to attend scientific meetings with honoraria for lectures from Alliance Bristol-Myers Squibb-Pfizer Pharmaceuticals, Aspen, Bayer Healthcare, and GlaxoSmithKline.

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AUTHOR CONTRIBUTIONS

S. Zuily and H. Cohen performed the original literature search and wrote the first draft. This manuscript has been read and approved for submission to the *Journal of Thrombosis and Haemostasis* by all authors and the ISTH Guidance and Guidelines Committee. All authors have fulfilled the conditions required for authorship. All authors designed, wrote, and provided critical review of the manuscript.

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