PharmaNote®
Vol. 37, Issue 7 April 2022 Established 1985

The Clot Thickens: Is There Enough Evidence to Use Direct Oral Anticoagulants in Antiphospholipid Syndrome?

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Antiphospholipid syndrome (APS) is an autoimmune disease characterized by a hypercoagulable state that leads to arterial and venous thrombosis, as well as obstetrical events, in patients with antiphospholipid antibodies.[1] Prevalence of APS is estimated to be 50 cases per 100,000 and affects women five times more commonly than it does men.[1,2] The mean age for diagnosis is typically between the ages of 30 and 40 years.[1]

Patients who are positive for antiphospholipid antibodies (aPL) are usually identified during evaluation for systemic autoimmune diseases, early miscarriages, elevated activated partial-thromboplastin time (aPTT), or thrombolytic event.[1] Other major clinical manifestations of APS include valvular heart disease, nephropathy, thrombocytopenia, hemolytic anemia, and cognitive dysfunction.[1] APS is diagnosed using the revised Sapporo Criteria, which requires the presence of either vascular thrombosis or pregnancy complications, in patients with presence of antiphospholipid antibodies, as described in Table 1.[1] Patients can be further classified as having a high risk or low risk aPL profile, defined in Table 2, which may further impact treatment decisions.[3]

The pathophysiology of APS begins with B1 lymphocytes producing aPL of which there are three types.[1] These include lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein antibodies.[1] Patients with all three types of antibodies present are considered to have triple positive APS, which is a high risk phenotype for thrombosis, however patients can be symptomatic even with only one form of antibody present, which is generally considered a lower risk phenotype.[1] The major target of these antibodies is the β2-glycoprotein I (β2GPI), a plasma protein that binds to phospholipid surfaces on endothelial cells, monocytes, and platelets, and even more readily when dimerized by binding to an anti-β2GPI antibody.[1,4] This binding results in an increased expression of prothrombotic cellular adhesion molecules, reduced activity of tissue factor pathway inhibitor, reduced activated protein C activity, and increased complement.[1] These effects result in increased inflammation, thrombosis, and pregnancy complications.[1]

A prospective cohort study conducted in Finland in 2014 evaluated the incidence of first thrombotic event in 119 asymptomatic carriers of aPL.[5] Participants were further evaluated by the number of antibodies positive, with 30% being either double- or triple-positive, 56% single lupus anticoagulant positive, 8% single anticardiolipin antibody positive, and 5% single anti-β2-glycoprotein antibody positive.[5] The annual rate of first thrombotic event in single-positive carriers was 0.65%, which is similar to the known risk of thrombosis in healthy Caucasian adults.[5] However, the rate of first thrombotic event was two times higher in patients with double- and triple-positive APS at 1.27%.[5] This study showed that double- and triple-positivity carries an increased risk of thrombosis among patients with APS.[5]

Current Methods of Treatment

Current treatment options include recommendations from several governing bodies. The European League Against Rheumatism (EULAR) has a published guideline for the treatment of

Table 1 | Revised Sapporo Criteria for APS Diagnosis[6]

Criteria	Diagnosis	Clinical Pearl
Vascular	1+ clinical episode of thrombus in tissue or organ	Must be confirmed by imaging
Pregnancy	1+ unexplained death of fetus ≥10th week of gestation	Fetus must be morphologically normal
	1+ premature births (<34 weeks gestation)	Resulting from eclampsia, severe preeclampsia, or placental insufficiency
	3+ unexplained consecutive spontaneous abortions prior to 10th week of gestation	Excludes maternal anatomic or hormonal abnormalities and chromosomal causes
Laboratory	Lupus anticoagulant (LA) detected	True positive if detected on two or more occasions at least 12 weeks apart
	Anticardiolipin (aCL) titers in serum or plasma measured at >40 GPL or >99th percentile by standardized ELISA	
	Anti-β^2-glycoprotein antibody titer >99th percentile by standardized ELISA	

GPL: IgG antiphospholipid units/mL; ELISA: enzyme-linked immunosorbent assay

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Table 2 | Definitions of Antiphospholipid (aPL) Profiles[3]

High Risk	Low Risk
LA positive	Isolated aCL or anti-β^2-glycoprotein antibodies
Double positive*	
Triple aPL positive	
Persistently high aPL titers	

*Includes combination of any LA, aCL antibodies, or anti-β^2-glycoprotein antibodies

APS, and has divided the disease into four different prophylaxis and treatment categories: primary prophylaxis, secondary prevention, obstetrical APS, and catastrophic APS. Although a formal American guideline for the treatment of APS does not exist, the Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report includes a section on the use of warfarin and direct oral anticoagulants (DOACs) in APS. Additionally, the International Society of Thrombosis and Hemostasis (ISTH) and the International Congress on Antiphospholipid Antibodies Task Force have published guidance on treatment options in APS, all of which contain similar recommendations, as seen in **Table 3**.

Patients that fall into the primary thromboprophylaxis include asymptomatic aPL carriers, meaning patients who are positive for aPL, but have not yet experienced a thrombotic event.[3] The EULAR guidelines recommend low dose aspirin in the range of 75 to 100 mg daily for primary prophylaxis in patients with a high-risk aPL profile, but without vascular or obstetric criteria for APS diagnosis.[3] This recommendation is supported by a meta-analysis of seven observational studies of asymptomatic aPL carriers that found the risk of first thrombosis was reduced by half in patients receiving low dose aspirin.[3] Primary thromboprophylaxis may be considered for patients with a low-risk aPL profile.[3]

Secondary thromboprophylaxis is defined by the EULAR guidelines as prevention of a recurrent thrombotic event in patients with definite APS and at least one previous thrombotic event.[3] Warfarin is considered by many organizations, including CHEST, EULAR, and ISTH, as the gold standard for secondary thromboprophylaxis in APS patients. Warfarin is a vitamin K antagonist that inhibits the production of clotting factors II, VII, IX, and X, as well as Proteins C and S. Patients with APS experience both suppressed activated Protein C activity, as well as decreased tissue factor pathway inhibitor, leading to a hypercoagulable state.[1] The recommended INR range for APS patients on warfarin is 2-3, however the EULAR guidelines also state that this goal may be increased to 3-4 in patients who continue to have recurrent thromboses while in a therapeutic range.[3]

The category of obstetric APS includes options for both primary prevention for pregnant women with a high-risk aPL profile but no history of thrombosis or pregnancy complications, as well as secondary prevention for patients with a history of obstetric APS only and patients with a history of thrombotic APS who become pregnant.[3] Warfarin is contraindicated in pregnancy and therefore not a listed treatment option for these patients. Catastrophic APS is characterized by recurrent thromboses while on therapeutic anticoagulation, with multiple organ involvement, developing over a short period of time. Treatment for these patients typically includes combination therapy with glucocorticoids, heparin, and plasma exchange or IVIG.[3]

DOACs play a limited role in the treatment of APS due to the lack of evidence for their use in this disease state. The 2021 update to the Antithrombotic Therapy for VTE Disease by the CHEST guidelines recommends warfarin with a target INR of 2.5 over DOACs, especially in patients with triple-positive APS.[7] The EULAR guidelines recommend against the use of rivaroxaban in patients with triple-positive APS due to the high risk of recurrent thrombotic events. The EULAR guidelines do state that DOACs may be considered in patients who are unable to achieve target INRs on warfarin despite adequate adherence or for those with contraindications to warfarin.[3] The goal of this paper is to detail the safety and efficacy of DOAC use in patients with diagnosed APS through the evaluation of multiple clinical trials.

DOACs vs. Warfarin

As previously mentioned, warfarin is a vitamin K antagonist that inhibits the production of clotting factors II, VII, IX, and X, as well as anticoagulant proteins C and S.[8] Since warfarin does not affect the activity of already synthesized coagulation factors, the therapeutic effects of warfarin are not seen until these mature factors are depleted through normal catabolism.[8] This process depends on the half-life of the clotting factors, and as a result, it typically takes three to five days before the effects of warfarin are seen on a patient's INR.[8] Additionally, since warfarin also inhibits the anticoagulant proteins C and S, a temporary hypercoagulable state is induced when warfarin is first initiated.[8] The efficacy of warfarin is measured by the International Normalized Ratio (INR). The goal INR range will differ for each patient depending on their indication for anticoagulation, with the most common INR range being 2-3. This INR must be monitored regularly, anywhere from once weekly to every six weeks, depending on the patient's time in therapeutic range. This may pose a challenge for patients. Warfarin monitoring can typically be done as a point of care test using a finger prick, however, this reading is not reliable in patients with APS and these patients require a venous blood draw to measure INR.[8] Additionally, many factors may affect a patient's INR including diet, acute illness, and concomitant medications.[8]

DOACs are an appealing option for anticoagulation in many patients as they require significantly less monitoring than warfarin. There are two classes of medications that fall within the category of DOACs: factor Xa inhibitors and direct thrombin inhibitors.[9] The factor Xa inhibitors include apixaban, rivaroxaban, and edoxaban. The direct thrombin inhibitor is dabigatran. These agents have great safety and efficacy data in many common disease states requiring anticoagulation, such as atrial fibrillation.[9] However,

Table 3 | EULAR Treatment Options for APS by Classification[3]

Primary Thromboprophylaxis	Secondary Thromboprophylaxis	Obstetric	Catastrophic
Low dose aspirin (LDA)	Warfarin +/- LDA	LDA	Glucocorticoids + heparin + plasma exchange or IVIG
	DOAC +/- LDA*	Prophylactically dosed heparin +/- LDA	
		Therapeutic dose heparin +/- LDA	
	Low molecular weight heparin (LMWH)	Addition of hydroxychloroquine or low dose prednisolone during 1st trimester	Refractory cases: B cell depletion (rituximab) or complement inhibition (eculizumab)
		Intravenous immune globulin (IVIG)	

*Limited data, not for patients with triple-positive APS

there is limited data on the use of DOACs in the setting of APS. Table 4 outlines the key differences between warfarin and the available DOACs for use.

Clinical Trials

Rivaroxaban vs. Warfarin for APS (RAPS Trial)[15]

The RAPS trial was a randomized, controlled, open-label, non-inferiority trial conducted at two hospitals in the United Kingdom.[15] This study randomized patients with APS on warfarin (target INR 2.5) for prevention of venous thromboembolism (VTE) 1:1 to either continue receiving warfarin or to receive rivaroxaban 20 mg daily (dose adjusted based on renal function).[15] The primary outcome was the percentage change in endogenous thrombin potential (ETP) from randomization to day 42. Endogenous thrombin potential is a measure of thrombin formation capacity, and can reflect a patient's coagulability with higher values indicating a hypercoagulable state.[15] Levels of ETP were obtained at baseline and at day 42. Non-inferiority was set at less than 20% difference from warfarin in mean percentage change.[15] Patients were included if they had thrombotic APS and at least one VTE when taking no or subtherapeutic anticoagulation.[15] Eligible patients also had to be on warfarin with target INR 2.5 for at least three months since their last VTE event.[15] Patients were excluded if they had previous arterial thrombotic events due to APS or recurrent VTE while on therapeutic warfarin (INR 2-3).[15] Of those included, 28% of patients in the RAPS trial had triple-positive APS, with 14 in the rivaroxaban group and 19 in the warfarin group.[15]

A total of 116 patients were included with 57 patients randomized to receive rivaroxaban and 59 to receive warfarin. At day 42, ETP was significantly higher in the rivaroxaban group compared to the warfarin group (1086 vs. 548 nmol/L/min; [95% CI, 1.7-2.5]; p <0.0001).[15] The mean percentage change did not meet the established non-inferiority threshold of less than 20%.[15] However, peak thrombin generation was lower in the rivaroxaban group compared to the warfarin group (55.6 vs. 85.7 nmol/L; [95% CI 0.5-0.8]; p = 0.00061), which would favor rivaroxaban in terms of thrombotic risk.[15] During the six months of trial follow up, there were no thrombotic events or major bleeding events in either group.[15]

The authors of the RAPS trial concluded that rivaroxaban may be a safe and efficacious alternative to warfarin in patients with APS who require standard intensity anticoagulation, despite rivaroxaban not meeting non-inferiority of the primary outcome and many limitations.[15] With the trial using a laboratory surrogate marker to assess thrombotic risk it was unable to confirm any definitive clinical efficacy or difference between the two treatment options.[15] Additionally, this study excluded patients with recurrent VTE while on standard dose anticoagulation and those with previous arterial thromboembolism, therefore the results cannot be extrapolated to this population.[15]

Rivaroxaban in APS (TRAPS Trial)[16]

The TRAPS trial was a prospective, randomized, phase 3, open-label noninferiority study conducted at 14 centers in Italy.[16] The trial evaluated the efficacy and safety of rivaroxaban 20 mg daily compared with warfarin (target INR 2.5) in patients with triple-positive APS.[16] The primary composite outcome was the prevention of thromboembolic events, major bleeding, and death. Secondary outcomes evaluated the individual components of the primary outcome. The study included adult patients aged 18 to 75 years with laboratory confirmed triple-positive APS and history of thrombosis.[16] Patients were excluded if they had a known hypersensitivity to rivaroxaban, a creatinine clearance less than 30, if they were currently pregnant or breastfeeding, if they were being treated with concomitant anticoagulants including low molecular weight heparins (LMWH), if they were taking strong p-glycoprotein and/or CYP3A4 inhibitors, if they had known liver cirrhosis, or if they met any of the pre-specified hemorrhagic risk-related criteria, which included uncontrolled hypertension, defined as a sustained systolic blood pressure greater than or equal to 180 mmHg.[16]

Enrolled patients had routine hospital visits at one and three months after enrollment, then every six months thereafter.[16] Additionally, INR was maintained between 2 and 3 and checked at least every 4 weeks.[16] Compliance and vital signs were checked via phone interview every three months.[16] The follow up period was initially planned to be 4 years however, the trial was stopped prematurely due to an excess of primary outcome events in the rivaroxaban group.[16] At the time of study termination, there were a total of 120 patients randomized, 59 patients were in the riva-

Table 4 | Comparison Between Warfarin and Direct Acting Anticoagulants (DOACs)[9,10,11,12,13,14]

Drug	Warfarin	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
Mechanism	Vitamin K antagonist	Factor Xa inhibitor			Direct thrombin inhibitor
Onset	Initial effect: 24 to 72 hours Full effect: 5 to 7 days	3 to 4 hours	1 to 2 hours	2.5 to 4 hours	1 hour
Half life	36 to 42 hours	8 to 15	10 to 14 hours	7 to 13 hours	12 to 17 hours
Monitoring	Frequent INR	CBC, aPTT, PT, SCr, and LFTs prior to initiation, then at least annually			
Usual Dose	Varies	5 mg twice daily	60 mg once daily	20 mg once daily with evening meal	150 mg twice daily
Renal Dose Adjustment	None	For afib only: Reduce dose to 2.5 mg twice daily if at least two of the following criteria are met: Age ≥80 years Body weight ≤60 kg Serum creatinine ≥1.5 mg/dL	CrCl 15-50 mL/min: 30 mg once daily CrCl <15 mL/min: avoid use CrCl ≥95 mL/min: avoid use (AFib only)	CrCl 15-50 mL/min: 15 mg once daily with evening meal CrCl <15 mL/min: avoid use	CrCl 15-30 mL/min: 75 mg twice daily CrCl <15 mL/min: avoid use
Metabolism	Hepatic Major – CYP2C9 Minor— CYP2C8, 2C18, 2C19, 1A2, and 3A4	Hepatic Major – CYP3A4/5 Minor— CYP1A2, 2C8, 2C9, and 2C19	Minimal via hydrolysis, conjugation and oxidation by CYP3A4	Hepatic – CYP3A4/5	Hepatic – glucuronidation

roxaban group and 61 patients were in the warfarin group.[16]

The primary outcome occurred in 11 rivaroxaban patients and 2 warfarin patients (HR 6.7; [95% CI, 1.5-30.5]; p = 0.01), in the "as treated" analysis, which included patients who completed the study on their assigned treatment.[16] In the rivaroxaban group, 4 patients suffered an ischemic stroke and 3 patients suffered a myocardial infarction.[16] Neither of these events occurred in the warfarin group. No episode of venous thromboembolism occurred in either arm.[16] There were 4 cases of major bleeding in the rivaroxaban group and 2 cases in the warfarin group (HR 2.5, [95% CI, 0.5-13.6]; p = 0.3), which was not statistically significant, however the rate of major bleeding was numerically higher in the rivaroxaban group which is not typical of what other studies have shown comparing bleeding risk of DOACs with warfarin.[16] The intention to treat analysis, which included all patients who were randomized, maintained statistical significance in the primary outcome, and had two additional primary outcome events in the rivaroxaban group compared to the as treated analysis, one being bilateral deep vein thrombosis of the lower limbs 21 days after stopping rivaroxaban and the other being a cardiovascular-related death that occurred 433 days after stopping rivaroxaban.[16] Both of these patients were transitioned to a different anticoagulant at the time of rivaroxaban discontinuation.[16]

The study was terminated early due to the excess of arterial thromboembolic events that occurred in the rivaroxaban arm.[16] The average follow up period was 569 days for the as-treated cohort, and 611 days for the intention to treat cohort.[16] The authors of this study concluded that rivaroxaban likely does not protect high risk APS patients from arterial events.[16] The authors believe that one potential explanation for rivaroxaban's failure is suboptimal concentrations to protect against arterial thromboembolic events, as higher anti-Xa activity and plasma rivaroxaban levels have been demonstrated in animal models to prevent arterial compared to venous events.[16] The TRAPS trial raised awareness around rivaroxaban lack of efficacy in patients with high-risk, triple-positive APS. The results of this study cannot be extrapolated to patients with single- or double-positive APS.[16] Based on the results of this study, rivaroxaban should be avoided in patients with triple-positive APS, but may potentially be considered on a case by case basis in patients with single- or double-positive APS with contraindications to warfarin.[16]

DOACs vs. Warfarin in Single or Double Antibody Positive APS[17]

Williams et al. conducted a single-center, retrospective cohort study at the University of Colorado Health System between 2015 and 2020.[17] The goal of the study was to compare the proportion of patients who developed a recurrent venous or first arterial thrombosis with a DOAC versus those on warfarin.[17] If a patient in the warfarin group developed thrombosis while their INR was subtherapeutic, it was not counted towards the primary outcome.[17] The secondary outcome was the proportion of patients with documented major bleeding while on anticoagulation.[17] A total of 96 patients with single or double positive APS and history of venous thromboembolism were included.[17] Patients were excluded if any of the following criteria were met: active cancer requiring chemotherapy, triple positive APS, warfarin INR goal range other than 2-3, or history of arterial thrombosis.[17] Of the 96 included patients, 57 were prescribed warfarin and 39 were prescribed a DOAC with 90% of the DOAC patients prescribed rivaroxaban.[17] The rivaroxaban dose was not provided in the study, but authors stated that patients received "therapeutic doses."[17]

Six patients in the DOAC group had a thromboembolic event compared to three patients in the warfarin group, but this difference was not statistically significant (15.4% vs. 5.3%, p= 0.15).[17] Of the six patients who experienced a thromboembolic event in the DOAC group, three were arterial events, compared to one of three in the warfarin group.[17] All six patients who experienced the primary outcome in the DOAC group were on rivaroxaban with 3 of the events in the DOAC group occurring within the first 90 days of therapy initiation.[17] The rates of major bleeding were similar between the two groups (7% in the warfarin group, 7.7% in the DOAC group, p=0.99).[17]

Authors concluded with the results of this study that patients on DOACs, specifically rivaroxaban, are at an increased risk for recurrent thromboembolic events, even in patients who are not triple-positive, when compared to warfarin therapy.[17] This study did have several limitations. Any thrombotic or bleeding events that occurred outside the study hospital were likely unable to be evaluated.[17] Although this study was small and retrospective in nature, it provides additional insight into the use of DOACs in patients with APS, regardless of aPL profile.[17] Based on these results, rivaroxaban should be used with caution, and preferably avoided, in patients with APS.

Rivaroxaban vs. Vitamin K Antagonist in APS[18]

Ordi-Ros et al. conducted an open-label, randomized, noninferiority study across six university hospitals in Spain with a follow up period of three years.[18] The study included 190 patients with thrombotic APS who were randomized to receive either rivaroxaban 20 mg daily (dose adjusted based on renal function) or dose-adjusted warfarin (target INR 2-3 or 3.1-4 in patients with a history of recurrent thrombosis).[18] Patients were included if they had objectively confirmed arterial or venous thrombosis and a positive result on aPL testing on two separate occasions at least three months apart.[18] Exclusion criteria included: clinically significant bleeding diathesis, intracranial hemorrhage, stroke, or gastrointestinal bleeding within the previous three months, pregnancy or lactation, severe renal impairment defined as a CrCl less than 30 mL/min, alanine aminotransferase level greater than twice the upper limit of normal, Child-Pugh class B or C cirrhosis, nonadherence to warfarin regimen, or receiving CYP3A4 inducers.[19] The primary efficacy outcome was the proportion of patients with new thrombotic events and the primary safety outcome was major bleeding.[18] Secondary outcomes included time to thrombosis, type of thrombosis, changes in biomarker levels (D-dimer, von Willebrand factor, and platelet factor 4), cardiovascular death, and nonmajor bleeding.[18] There were a total of 190 patients included in this trial with 95 patients randomized to receive rivaroxaban and another 95 to receive warfarin (INR goal 2-3).[18] Rates of patients with triple-positivity and history of arterial thrombosis were similar between the two groups, however the rivaroxaban group had a larger proportion of patients with recurrent thrombosis (12.6% rivaroxaban vs. 16.8% warfarin, statistical difference not provided).[18]

The study was powered to determine whether rivaroxaban was noninferior to warfarin by 36 weeks for the primary efficacy outcome.[18] The noninferiority margin for risk ratio was 1.4.[18] In the per protocol analysis, 11 patients (11.6%) in the rivaroxaban group developed recurrent thrombosis, comparted to 6 patients (6.3%) in the warfarin group (RR, 1.83; [95% CI, 0.71-4.76], p for noninferiority = 0.29, p for warfarin superiority = 0.2).[18] In the intention to treat analysis, the primary outcome occurred in 12

Table 5 | Summary of Evaluated Trials[15,16,17,18]

Trial	aPL Profile	Treatment Arms	Primary Outcome	DOAC Efficacy	Bleeding Events
Cohen et al 2016[15]	Single, double, and triple positive	Rivaroxaban v. Warfarin	Percentage change in ETP from randomization to day 42	Non-inferior	No
Pengo et al 2018[16]	Triple positive	Rivaroxaban v. Warfarin	Composite outcome thrombo-embolic events, major bleeding, and death	No	Yes - rivaroxaban
Ordi-Ros et al 2019[18]	Single, double, and triple positive	Rivaroxaban v. Warfarin	Proportion of patients with new thrombotic events	No	Yes - rivaroxaban
Williams et al 2021[17]	Single and double positive	DOAC v. Warfarin	Recurrent venous or first arterial thrombosis	No	Yes - rivaroxaban

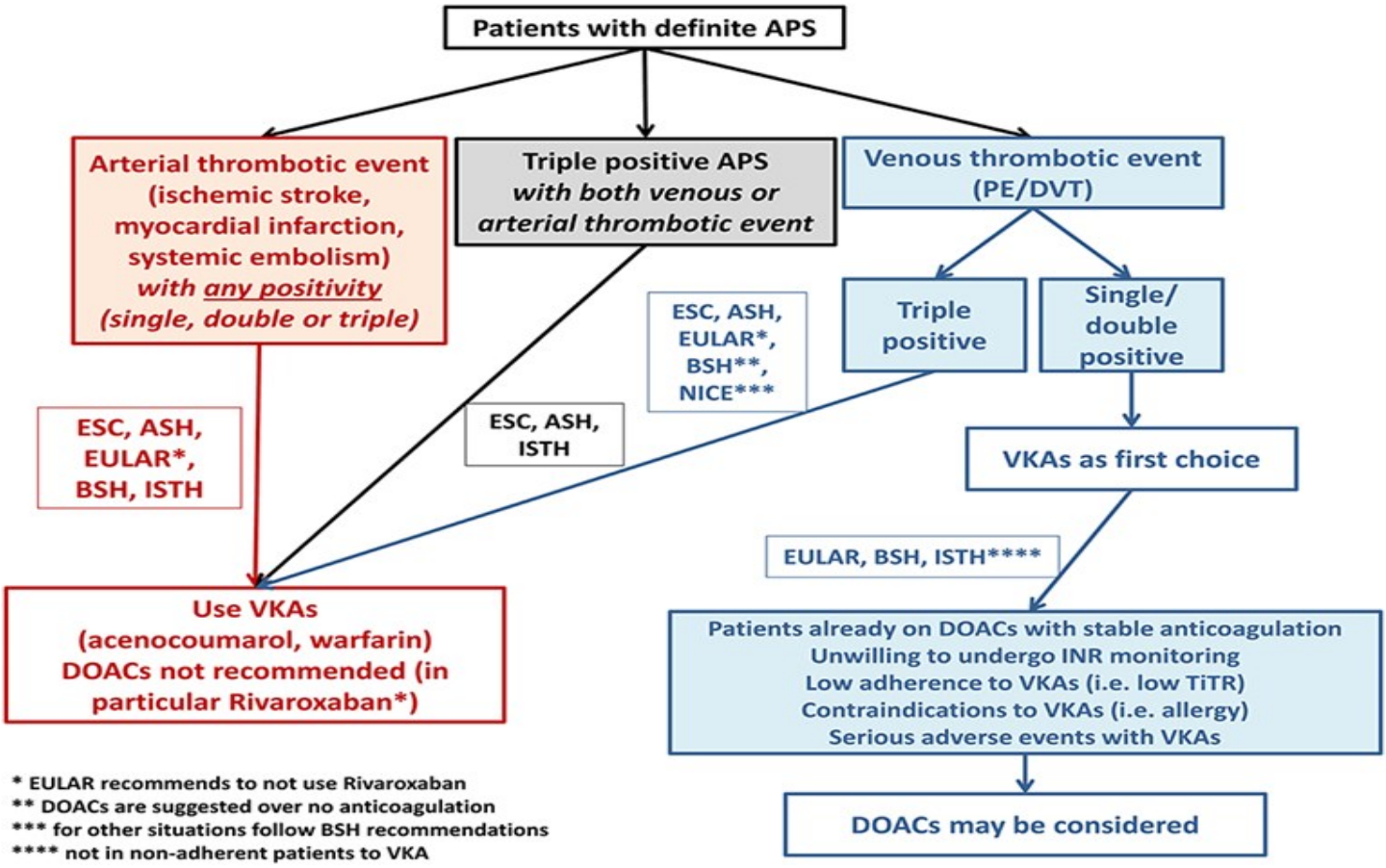
patients (12.6%) in the rivaroxaban group compared to 6 (6.3%) in the warfarin group (RR, 2.0; [95% CI, 0.78-5.11], p for noninferiority = 0.57, p for warfarin superiority = 0.13).[18] Rivaroxaban did not meet the threshold for noninferiority. The rates of thrombosis in patients with triple-positivity was evaluated in the subgroup analysis. In the rivaroxaban group, 58 patients had triple-positive APS.[18] Of those, 10 developed thrombosis (17.2%) compared to one patient out of 37 with single- or double-positive APS (2.7%).[18] In the warfarin group, 57 patients had triple-positive APS.[18] Of these 57 patients, five developed thrombosis (8.8%) compared to one patient out of 38 with single- or double-positive APS (2.6%).[18] Neither of these were statistically significant.[18] The rate of major bleeding was similar between the two groups.[18]

The secondary outcomes results found that the recurrent events in the rivaroxaban group were predominantly arterial, with a higher rate of stroke.[18] Nine stroke events occurred in the rivaroxaban group compared to none in the warfarin group (RR, 19.00, [95% CI, 1.12-321.9]).[18] Although this value was not statistically significant, it may hold a large clinical impact for patients and providers. This study showed that rivaroxaban failed to meet noninferiority to warfarin in patients with APS.[18] This makes it difficult to differentiate if rivaroxaban may still have efficacy in patients with a lower thrombotic risk, as some of the previously discussed trials have found. Although not statistically significant, the authors of the trial concluded that rivaroxaban did carry an increased risk of stroke in patient with APS.[18] Based on the results of this study, rivaroxaban should be avoided or used with extreme caution in patients with APS. A summary of all clinical trial outcomes can be seen in Table 5.

Conclusion

The medical organizations that have published statements and guidelines on anticoagulation in APS agree that DOACs should be avoided in patients with APS and history or arterial thromboembolism or triple-positivity, however their recommendations for specific populations of APS patients differ. Figure 1 provides a summary of the current guideline recommendations on anticoagulation in patients with APS. The 2020 American Society of Hematology (ASH) guidelines, the 2021 CHEST guideline update, and the 2019 European Society of Cardiology (ESC) guidelines recommend against the use of DOACs in all APS patients due to the lack of evidence.[7,19] The 2019 EULAR guidelines recommend against the use of DOACs in patients with triple positive

Figure 1 | Summary of Guideline Recommendations[19]



APS or history of arterial thrombosis, however they allow consideration for use in venous APS patients without triple positivity, and for patients who are intolerant to warfarin therapy or have low time in therapeutic range.[19] The 2020 British Society of Hematology (BSH) guidelines allow for consideration of DOAC therapy in venous APS patients, regardless of aPL profile, if they were already being treated with a DOAC and refused warfarin therapy.[19] The 16th International Congress on Antiphospholipid Antibodies Task Force Report published in 2020 recommended that DOACs should be avoided in the following APS patients: those with a history of arterial thrombosis, thrombotic APS with small vessel thrombosis or aPL related cardiac valvular disease, those with recurrent thrombosis while on standard intensity warfarin (INR goal 2-3), and those with triple-positive APS.

Although there is evidence to suggest against the use of rivaroxaban in patients with triple-positive APS, there is a strong lack of data regarding the use of DOACs in single- and double-positive APS. Prescribers should evaluate each patient on a case by case basis to determine the most appropriate anticoagulation strategy for each individual patient, taking into consideration the lack of data on DOACs in APS and weighing the risks and benefits of this treatment option to create a shared decision with the patient. More research is needed to evaluate the use of other DOACs, including apixaban and dabigatran, in patients with APS. At this time, research conducted only evaluates the use of rivaroxaban in APS patients.

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Drug Update:
New Indications and Dosage Forms
March 2022

Adlarity® (donepezil) Transdermal Patch
New Dosage Form: Acetylcholinesterase inhibitor indicated for the treatment of mild to severe Alzheimer's dementia. Patch is worn for 7 consecutive days to administer 5mg or 10mg dose per day.

Nasonex® (mometasone) Nasal Spray
New Regulation Status: Nasal corticosteroid used in the treatment of allergic rhinitis and rhinosinusitis was approved for Rx to OTC switch by the FDA pertaining to the 0.05mg/spray strength

Ztalmy® (ganaxolone) Oral Suspension
New Molecular Entity: $GABA_A$ receptor modulator indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder

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Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

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