Role of Novel Oral Anticoagulants in the Treatment of Antiphospholipid Syndrome

C. Whitney White, PharmD, BCPS^{*,†}; Angela R. Thomason, PharmD, BCPS^{*};
and Katie Boyd, PharmD, BCPS^{‡,§}

ABSTRACT

Background: Antiphospholipid syndrome (APS) is an autoimmune disease characterized by thrombosis or pregnancy loss with persistent positive antibodies. Standard treatment for APS with history of thromboembolism is heparin or low-molecular-weight heparin followed by a vitamin K antagonist (VKA). Novel oral anticoagulants (NOACs) could be effective in patients with APS, but none carry indications for treatment related to APS.

Clinical Evidence: Five case reports or series with rivaroxaban and dabigatran suggest thrombotic events occur most often in the higher risk population (arterial thrombosis and/or triple positive antibodies) or in patients who had recurrent VTEs on warfarin therapy. An observational cohort in 26 APS patients using dabigatran or rivaroxaban described a recurrent thrombotic event in only 1 patient after 8 months of treatment. The event-free survival rate was 87.9% at 12 months. Three controlled clinical trials are underway to evaluate the thrombotic risk of NOACs (RAPS, TRAPS, and ASTRO-APS).

Discussion: There are no completed studies that evaluate the use of NOACs in APS compared to VKAs. One major disadvantage of the NOACs is the limited availability of reversal agents for patients with a major bleeding episode. An increased risk of thrombotic events is associated with arterial occlusions and triple antibody positivity APS with both warfarin and NOACs; this is currently being researched in the TRAPS study.

Conclusion: Based on current available evidence, VKAs remain the standard of care in the treatment of APS. Results of ongoing trials may offer more guidance on how to appropriately use NOACs for patients with APS.

Key Words—antiphospholipid syndrome, novel oral anticoagulants, warfarin

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Antiphospholipid syndrome (APS) is an autoimmune disease characterized by thrombosis or pregnancy loss with persistent positive antibodies. Thrombosis is one of the hallmarks of the syndrome, with venous thromboembolism (VTE) as the most common manifestation.^{1,2} Among patients with acute VTE, approximately 10% are positive for APS.³ Other common manifestations of APS are renal thrombotic microangiopathy, transient ischemic attack, stroke, myocardial infarction, cardiac valvular disease, cognitive impairment, thrombocytopenia,

and hemolytic anemia.^{1,2,4} Of the autoantibodies associated with APS, lupus anticoagulant is the strongest predictor of thrombotic complications related to the disorder.^{2,4,5}

Diagnosis of APS is confirmed by having a documented clinical episode (vascular thrombosis or pregnancy morbidity) and at least one positive antibody laboratory test. The antibody laboratory test must be positive on 2 or more occasions, at least 12 weeks apart.^{4,6} Plasma antibodies associated with APS are lupus anticoagulant, anticardiolipin, and anti-beta

^{*}Associate Professor of Pharmacy Practice, McWhorter School of Pharmacy, Samford University, Birmingham, Alabama; [†]Clinical Pharmacy Specialist, Adult Medicine, St. Vincent's Birmingham, Birmingham, Alabama; [‡]Assistant Professor of Pharmacy Practice, McWhorter School of Pharmacy, Samford University, Birmingham, Alabama; [§]Clinical Pharmacy Specialist, Baptist Health Center Primary Care, Birmingham, Alabama. Corresponding author: Angela R. Thomason, PharmD, BCPS, Department of Pharmacy Practice, 800 Lakeshore Drive, Birmingham, AL 35229-7027; phone: 205-726-4476; fax: 205-726-2669; e-mail: adrobert@samford.edu

2-glycoprotein I. Coagulation assays are used to identify lupus anticoagulant antibodies, because they are associated with a prolonged clotting time. In contrast, immunoassays are used to measure immunologic reactivity to phospholipids to determine the presence of anticardiolipin and anti-beta2-glycoprotein I antibodies.^{7,8} Guidelines for detection of lupus anticoagulant stress the importance of proper patient selection for testing in order to avoid false-positive results.⁹ Testing for lupus anticoagulant in asymptomatic patients is highly discouraged.¹⁰

In patients with recurrence of VTE on anticoagulation therapy with either a novel oral anticoagulant (NOAC) or vitamin K antagonist (VKA), the 2016 guidelines from the American College of Chest Physicians recommend 1 month of low-molecular-weight heparin along with an evaluation for adherence and malignancy. However, the guidelines note that this recommendation is based on low-quality evidence and assessment of probable cause of reoccurrence. After a 1-month period, patients should restart their oral anticoagulation therapy unless cancer was identified. In addition, the guidelines recommend choosing anticoagulation therapy based on patient-specific factors such as renal or liver disease, coronary artery disease, adherence, and patient preference. The 2016 guidelines mention APS as a risk factor associated with recurrent VTE, although specific treatment is not outlined.¹¹ Prior to the new guidelines, the standard treatment for APS with history of thromboembolism was long-term therapy with a VKA such as warfarin to target an international normalized ratio (INR) of 2.5 (range, 2.0-3.0).¹² In APS patients who have had recurrent thromboembolic events and arterial thrombosis, a target INR of 3.0 (2.5-3.5) was suggested.⁵ However, this is controversial. Two studies have shown high-intensity warfarin therapy (INR 3.1-4.0) was not superior to moderate-intensity warfarin therapy (INR 2-3) in the prevention of thrombosis in patients with APS.^{13,14} Therefore, moderate-intensity warfarin (INR 2-3) therapy is preferred for patients with APS compared to high-intensity warfarin in the prevention of recurrent thrombosis.¹²

Treatment of APS with a VKA presents a challenge in monitoring and adjustment, and it can be complicated by lupus anticoagulant interference on INR results. Lupus anticoagulant interference can lead to variability and misinterpretation of the INR, which can result in under-dosing of the VKA and VTE recurrence.^{15,11} VKAs also have several drug-drug and drug-food interactions that require dietary restrictions and frequent laboratory monitoring to

achieve a therapeutic INR.⁵ Despite treatment with VKAs, thrombosis still occurs in 5% to 20% of APS patients; therefore, complete protection against all future thrombotic events is highly improbable in some APS patients.^{13,16}

Several new APS treatment approaches are emerging, including combination antiplatelet therapies (low-dose aspirin plus clopidogrel or dipyridamole), oral anti-factor Xa medications (rivaroxaban, apixaban), direct thrombin inhibitors (dabigatran), statins (fluvastatin, rosuvastatin), hydroxychloroquine, and B-cell depletion therapy (rituximab).¹⁶ In theory, the NOACs should be effective in patients with APS. Several NOACs (rivaroxaban, dabigatran, edoxaban, and apixaban) are on the market, but none carry indications for treatment related to APS or other hypercoagulable disorders. The NOACs are more attractive because of the need for less routine laboratory monitoring, fewer diet restrictions, decreased drug interactions, and a once- to twice-daily dosing strategy. In addition, they have predictable anticoagulant effects, yet these agents are at a disadvantage because of limited reversal possibilities and the possibility of patient-specific dosage adjustments.^{5,15} An overview of the NOACs is outlined in **Table 1**.¹⁷⁻²² Currently, dabigatran, rivaroxaban, and apixaban have published literature related to treatment in APS and are the focus of this article.

CLINICAL EVIDENCE

Case Studies

Several case reports have been published regarding the use of NOACs in APS (**Table 2**). Five of the case reports reference rivaroxaban, whereas 2 include patients on dabigatran. Signorelli et al reported 8 patients (mean age of 36 years and 62.5% female) who suffered a thrombotic event while on NOAC therapy. Of those 8 patients, 3 had a thrombotic event on warfarin therapy prior to switching to rivaroxaban, and 5 had a reported target INR range of 3 to 4. In addition, one patient was identified as nonadherent to medication regimens including warfarin and rivaroxaban.²³ Win and Rodgers reported 3 patients with a thrombotic event on NOAC therapy within 6 to 12 months after switching from warfarin therapy. All these patients had either failed warfarin therapy or had difficulty maintaining a therapeutic INR due to nonadherence or genetic predisposition related to cytochrome P450 (CYP) 2C9. Two patients were switched to rivaroxaban, and one patient received a reduced dose of dabigatran (150 mg daily). All 3 patients reported a thrombotic event while receiving

Table 1. Summary of the characteristics of the novel oral anticoagulants¹⁷⁻²²

Drug	Rivaroxaban	Apixaban	Edoxaban	Betrixaban	Dabigatran
Target	Factor Xa	Factor Xa	Factor Xa	Factor Xa	Thrombin
Bioavailability	>80%	50%	62%	34%	3-7%
Protein binding	92%-95%	87%	55%	60%	35%
Half-life ^a	9 hours	12 hours	10-14 hours	20 hours	12-17 hours
Deep vein thrombosis dose and frequency	20 mg once daily	5 mg twice daily (may reduce to 2.5 mg after 6 months of therapy)	60 mg once daily	80 mg once daily ^b	150 mg twice daily
Dose to be taken with food	Yes	May be taken without regard for food.	May be taken without regard for food.	No (fatty food reduces bioavailability by 50%)	No (food delays time to peak by 2 hours)
Drug interactions	CYP3A4 inhibitors, P-gp inhibitors	CYP3A4 inhibitors, P-gp inhibitors	CYP3A4 inhibitors, and P-gp inhibitors	NR	Proton pump inhibitors, antacids, dronedarone, P-gp inhibitors
Renal elimination	66% renal	27%	50%	5%-7%	80%
Renal dosing adjustments ^c	CrCL < 30 mL/min: avoid use	Patients with serum creatinine >2.5 mg/dL or CrCL <25 mL/min were excluded in trials.	CrCL <15 to 50 mL/min: 30 mg once daily CrCL <15 mL/min: not recommended	NR	Contraindicated in CrCL ≤30 mL/min
Hepatic dosing adjustments	Contraindicated in Child-Pugh class B and C	Child-Pugh class C: Not recommended	Child-Pugh class B and C: Not recommended	NR	Child-Pugh Class C/severe impairment: Not recommended
Additional comments	Note: CrCl 15 to 50 mL/min: 15 mg once daily with the evening meal in nonvalvular atrial fibrillation. Dose reduction in patients with moderate to severe chronic kidney disease may be considered, although safety and efficacy of this approach has not been established.	Note: if a patient is ≥80 years of age and either weighs ≤60 kg or has a serum creatinine ≥1.5 mg/dL, then reduce dose to 2.5 mg twice daily.	Reduced efficacy in nonvalvular atrial fibrillation patients with CrCl >95 mL/min. Should not be used in patients with CrCl >95 mL/min.	Currently in phase 3 studies. Potential reversal agent: andexanet alfa by the same company.	Do not break, chew, or open capsules (increased absorption by 75%).

Note: CrCl = creatinine clearance; CYP = cytochrome P450; NR = not reported; P-gp = P-glycoprotein.

^a Under normal renal clearance.

^b Dose based on the phase 3 clinical trial currently in progress. Currently being studied as a twice-daily dose in venous thromboembolism (VTE) prevention in total knee replacement.

^c Based on Cockcroft-Gault formula for renal clearance.

Table 2. Published case reports and observational data related to thrombotic events with new oral anticoagulants²³⁻²⁸

Primary author, year of publication	NOAC	No. of patients reported prior to start of NOACs			After switch to NOACs			Manifestations while on NOAC (<i>n</i> >1)
		No. of patients included	Triple antibodies positive	History of arterial thrombosis	No. of patients with a thrombotic event on NOAC	Mean NOAC therapy until event, months	Median NOAC therapy until event, months	
<i>Case reports</i>								
Signorelli et al, 2015	Rivaroxaban	8	3	2	8	3.4	3	DVT (2) Arterial thrombosis of arm (1) Cognitive alterations (2) Acute myocardial infarction (1) Stroke (2)
Win and Rodgers, 2014	Rivaroxaban (2), dabigatran (1)	3	NR	2	3	9	6,12	Venous thrombosis (2) Transient ischemic attack (1)
Schaefer et al, 2014	Dabigatran (1), rivaroxaban (2)	3	NR	1	3	5.6	6	Cerebral infarct and nonbacterial thrombotic endocarditis (1) Left parietal and right frontal stroke (1) Intrahepatic and extrahepatic portal vein thrombus, splenic thrombus, and mesenteric thrombus (1)
Son et al, 2014	Rivaroxaban	12	5	2	2	3.5	2,5	DVT (2)
Savino et al, 2015	Rivaroxaban	35	NR	0	0 ^a	0	0	None
<i>Observational study</i>								
Noel et al, 2015	Rivaroxaban (15), dabigatran (11)	26	7	12	1 ^b	8	8	Microthrombotic recurrence (1)

Note: DVT = deep vein thrombosis; NOAC = novel oral anticoagulants; NR = not reported.

^a 2 women reported increased worsening of menorrhagia.

^b 3 patients discontinued therapy due to adverse events (migraine, hypermenorrhea, and rectal bleeding).

NOAC therapy. All patients improved after switching to either enoxaparin ($n = 2$) or fondaparinux ($n = 1$).²⁴ Schaefer et al described 3 patients who experienced a thrombotic event while on NOAC. Two patients reported bleeding complications with warfarin, one of whom had a target INR of 3 to 4 prior to switching to a NOAC. The third patient switched to rivaroxaban due to patient preference related to frequent INR monitoring with warfarin. One patient was switched to lower dabigatran dose (150 mg once daily) based on moderate renal impairment, and others were dosed with rivaroxaban 20 mg daily due to patient preference. All patients experienced another thrombotic event on an NOAC. Two patients were transitioned to warfarin and one to enoxaparin.²⁵

Son et al followed 12 patients at one institution who were switched from a VKA to rivaroxaban due to logistical issues with the patients' professional activities in conjunction with frequent laboratory monitoring or unstable INR values. Patients ranged from 22 to 52 years of age, and 58% were female. Patients with a history of stroke and/or multiple risk factors for thrombotic events also received low-dose aspirin. Of the 12 patients, only 2 experienced a thrombotic event on rivaroxaban over a treatment range of 10 to 16 months. One patient had a deep vein thrombosis (DVT) during an exacerbation of systemic lupus erythematosus (SLE), and the other developed a DVT after a minor lower limb injury. Both of these patients had a coexisting SLE and triple positivity profile.²⁶

Savino et al tracked 35 patients who were either started on rivaroxaban prior to the clinical trial of rivaroxaban in APS (RAPS) or failed to qualify for the enrollment in the trial. Patients were excluded if they had arterial thrombosis. The patients ranged from 17 to 75 years of age, and the majority were female (24 women; 11 men). The patients either had a previous DVT, pulmonary embolism (PE), or both. All were previously treated with warfarin with a target INR of 2 to 3. Patients were followed for a median of 10 months (6-24 months) and were treated with rivaroxaban of 20 mg once daily. During that time frame, no patient suffered a recurrent thrombotic event. Two patients reported increased menorrhagia.²⁷

Observational Cohort Study

Noel et al conducted a multicenter observational study that followed 26 APS patients treated with either dabigatran ($n = 11$; 150 mg twice daily) or rivaroxaban ($n = 13$; 20 mg once daily). Two patients received a different dose of rivaroxaban ($n = 1$, 15 mg twice daily; $n = 1$, 15 mg daily). Twelve patients had

primary APS, 9 had APS associated with SLE, and 5 had APS associated with various other syndromes. Twenty-two patients had normal renal function, and 4 patients had moderate kidney impairment (glomerular filtration rate 40-60 mL/min/1.73 m²). Twenty patients had previous anticoagulation therapy (warfarin, $n = 19$; fondaparinux, $n = 1$). Two patients were switched from warfarin therapy: one patient had a recurrent venous thrombosis and the other had a bleeding event. Sixteen patients were switched to the NOAC due to labile INRs. One patient experienced a recurrent thrombotic event after 8 months of rivaroxaban. The event-free survival rate was 87.9% at 12 months and 82.4% at 24 months. Three patients withdrew from the rivaroxaban group due to adverse events ($n = 2$, bleeding events; $n = 1$, recurrent migraines).²⁸

Controlled, Clinical Trials

Three controlled, clinical trials are currently underway that evaluate NOACs compared to warfarin with an adjusted INR of 2 to 3 (target 2.5) in APS. An overview of the studies is outlined in **Table 3**.

Rivaroxaban in antiphospholipid syndrome (RAPS) clinical trial is designed to evaluate the level of anticoagulation compared to warfarin in the APS population with or without SLE and a history of VTE. The secondary endpoints focus more on efficacy and safety. Patients with arterial thrombosis, severe renal impairment, history of nonadherence, or a thrombotic event while on warfarin with a therapeutic INR (2-3) were excluded from the trial.²⁹

The Trial on Rivaroxaban in Thrombotic Antiphospholipid Syndrome (TRAPS) is designed to determine noninferiority of rivaroxaban compared to warfarin in the prevention of acute thrombosis in patients with triple antiphospholipid antibody positive APS and bleeding risk. Currently in the recruitment phase, this multicenter trial will include patients with arterial thrombosis and moderate renal impairment (creatinine clearance [CrCL] 30-50 mL/min). The moderate renal impairment group will be dosed with rivaroxaban 15 mg once daily based on the recommendation by the American College of Cardiology/American Heart Association Task Force related to dosing in the trials associated with nonvalvular atrial fibrillation.^{22,30}

A feasibility pilot study is currently in progress with Apixaban for Secondary Prevention of Thrombosis among Patients with APS (ASTRO-APS). Patients will be enrolled from 2 health care systems comprising more than 160 outpatient clinics and

Table 3. Protocol summary of the clinical control trials for treatment of APS with new oral anticoagulants²⁹⁻³¹

Trial	Study design	Patient population	Intervention group	Primary endpoint	Secondary endpoints	Duration	Estimated enrollment	Estimated completion date
RAPS	Prospective, non-inferiority, open-label, phase 2/3	Thrombotic APS, with or without SLE	Rivaroxaban 20 mg once daily	Intensity of anticoagulation at day 42 by thrombin generation testing	Recurrent VTE; composite of recurrent VTE and other thrombotic events; serious adverse events	180 days	156	January 2015
TRAPS	Prospective, non-inferiority, open-label, phase 3	APS with triple positivity for aPL (high risk)	Rivaroxaban 20 mg once daily	Cumulative incidence of first thrombotic event, major bleed, or death	Single type of thromboembolic event, mortality, or bleeding (minor and major)	4 years or when 88 events have occurred	536	December 2018
ASTRO-APS	Prospective, randomized, open-label, blinded event pilot phase 2/3	APS without a thrombotic event within the last 6 months	Apixaban 2.5 mg twice daily	Capture the ability to identify, recruit, randomize, and retain patients	Report rates of thrombosis, death, and bleeding (major and minor)	13 months	200	December 2017

Note: aPL = antiphospholipid antibodies; APS = antiphospholipid syndrome; ASTRO-APS = Apixaban for Secondary Prevention of Thrombosis among Patients with APS; RAPS = rivaroxaban in antiphospholipid syndrome; SLE = systemic lupus erythematosus; TRAPS = Trial on Rivaroxaban in Thrombotic Antiphospholipid Syndrome; VTE = venous thromboembolism.

22 hospitals within the United States. The primary aim of the study is to determine recruitment, retention, and enrollment within the APS population. Secondary outcomes are related to the reporting of the efficacy (rates of thrombosis) and safety (bleeding) of apixaban. Exclusion criteria include severe renal impairment ($\text{CrCL} < 25 \text{ mL/min}$), concomitant dual antiplatelet therapy, thrombosis while receiving warfarin with a therapeutic INR (2-3), or the need for a higher target INR (3-4).³¹

DISCUSSION

The use of NOACs in the treatment of APS remains controversial, yet new data from emerging clinical trials may shed light on the utility of these new agents compared to the current standard of care with warfarin. There are no completed studies that evaluate the use of NOACs compared to VKAs in APS, yet approximately 10% of patients with acute VTE have APS. Some patients with APS were likely included in previous clinical trials with the NOACs.^{32,33} A small subset of patients with thrombophilic disorders (5%-7%) was included in the EINSTEIN and EINSTEIN-PE trials with rivaroxaban, but no specific information was recorded to identify the type of hypercoagulable disorder.^{34,35} In the case reports discussed above, thrombotic events seemed to occur most often in the higher risk population or in patients who had previously failed warfarin therapy. The studies by Son, Savino, and Noel, which demonstrated low event rates, included patients reflective of the general APS population.²⁶⁻²⁸ Methodology of the TRAPS clinical trial will target a higher risk population and should therefore provide more meaningful guidance on appropriate therapy across the APS spectrum.³⁰

The literature shows that there is an increased risk of thrombotic events associated with a history of arterial occlusions and/or triple antibody positivity APS regardless of treatment with warfarin or the NOACs. In previous trials related to DVT and atrial fibrillation, NOACs were compared to warfarin with a target INR 2 to 3. With arterial thrombosis, it is controversial whether a higher target INR range of 3 to 4 is beneficial in reducing the risk of thrombotic events in APS, yet the INR target is set at 2.5 in all 3 ongoing trials evaluating use of NOACs in APS. Therefore, equivalent dosing of NOACs for an adjusted INR of 3 to 4 is unknown. Patients with a history of arterial thrombosis and APS may be underdosed with current dosing guidelines. However, APS patients with previous DVT or PE event remained event-free for

a median of 10 months while being treated with an NOAC.²⁷ This is promising data, which hopefully will be confirmed with new controlled clinical trials.

When evaluating patients for APS, it is important to consider the impact of the anticoagulant on accuracy of diagnostic laboratory assays. Warfarin and heparin products have the potential to affect the results of many of the hypercoagulable panels. Thrombophilia testing is also vulnerable to interference by the NOACs. When the NOACs are given prior to testing, prolonged clotting times can cause false-positive results for protein C & S and for lupus anticoagulant in assays done with activated partial thromboplastin time (aPTT) and dilute Russell's viper venom time (dRVVT).³⁶ However, taipan/ecarin time is less affected by the presence of rivaroxaban and may provide the best specificity and positive predictive value in testing for APS while using rivaroxaban.^{23,27} NOACs can also affect whole blood clotting tests (eg, dabigatran prolongs activated clotting time).³⁷ Therefore, testing prior to the administration of anticoagulants or at least 4 to 6 weeks after discontinuation of therapy is recommended.³⁸

One major disadvantage of the NOACs is the limited availability of reversal agents for patients with a major bleeding event.^{4,5} In the case and observational studies, minor bleeding was reported with NOACs that required discontinuation of therapy.^{27,28} Currently, *Praxbind* (idaricizumab; Boehringer Ingelheim) is available for reversal of dabigatran, but no antidotes are available at this time for the oral Factor Xa inhibitors. Management of bleeding when using the NOACs includes supportive care with blood products and fluids as needed; use of gastric lavage, activated charcoal, or hemodialysis with dabigatran; or possibly use of activated prothrombin complex concentrate (FEIBA NF).³⁹

The 14th International Congress of Antiphospholipid Antibodies Task Force published a report on the current treatment trends related to APS in 2014, which recommended VKAs as the treatment option for APS patients with thrombotic events.¹⁶ However, NOACs may be considered in patients with thrombotic events on subtherapeutic anticoagulation or intolerance to VKAs.¹⁶ These recommendations were published prior to the availability of the clinical evidence presented in this article. Therefore, the clinical evidence sheds light on the possibility of NOACs for the general APS population. Emerging data from new clinical trials will need to be analyzed to formulate a more contemporary recommendation.

CONCLUSION

Based on current available evidence, VKAs remain the standard of care in the long-term treatment of APS. At this time, there is insufficient data to support the use of NOACs in APS patients with recurrent VTE on therapeutic anticoagulation or in APS patients with arterial thrombosis. Results of ongoing trials may offer more guidance on how to appropriately use NOACs for patients with APS.

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