Received: 19 October 2019 | Revised: 25 October 2019 | Accepted: 29 October 2019

DOI: 10.1002/rth2.12287

COMMENTARY

rpth research & practice in thrombosis & haemostasis

# Direct oral anticoagulants in antiphospholipid syndrome with venous thromboembolism: Impact of the European Medicines Agency guidance

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Handling Editor: Mary Cushman

Antiphospholipid syndrome (APS) is an autoimmune condition characterized by thrombosis and pregnancy morbidity.[1] Thrombotic APS variably involves arterial, venous, and microvascular circulations. The pathophysiology of thrombotic APS is thought to involve the generation of autoantibodies that bind to the major B-cell epitope on domain I of the $\beta_2$-glycoprotein. This binding and subsequent thrombus formation occurs through intermediary processes that likely include oxidative stress,[2] complement activation,[3] and neutrophils[4] invoking a "2-hit" process of initial endothelial disruption followed by thrombus formation.[5] Laboratory diagnostic criteria for APS include the presence of any one of the qualifying antibody isotypes (anticardiolipin IgG or IgM, anti–$\beta_2$-glycoprotein-1 IgG or IgM) and titers, or the presence of a lupus anticoagulant (LA) initially and again at least 12 weeks later.

Anticoagulant therapy is the mainstay of treatment for thrombotic APS, and due to the high risk for thrombosis progression and recurrence, indefinite anticoagulation is often considered.[6] Even with use of vitamin K antagonists (VKA) the annual rate of recurrent thrombosis is at least 1.5%[7] and potentially as high as 30% over 5 years.[8,9]

Direct oral anticoagulants (DOACs) offer a simpler therapeutic regimen with greater convenience than VKA therapy, and are approved for the treatment and secondary prevention of venous thromboembolism (VTE).[10,11]

There remains great interest to offer APS patients an alternative to VKA therapy, provided that this is safe and effective. The limited available evidence from prospective and retrospective studies was presented in a systematic review[12] and a patient-level meta-analysis.[13] Concerningly, these analyses reported recurrent thrombosis rates around 15% among APS patients treated with DOACs with as high as a 4-fold increased risk for recurrence among those patients that have all 3 APS lab tests positive—"triple positivity."[13] These publications have significant limitations (eg, meta-analyses include multiple case reports with an n = 1 that potentially amplify selection and publication biases, patients that experienced thrombosis on other anticoagulants prior to receiving a DOAC were included, and studies were retrospective).

There are 5 small randomized controlled trials involving DOAC treatment of patients with APS and a history of thrombosis. The first (RAPS) randomized 116 patients with APS and a history of VTE to either rivaroxaban 20 mg daily or dose-adjusted warfarin (target International Normalized Ratio [INR], 2.5).[14] The investigators reported that the percentage change in endogenous thrombin potential at 42 days for rivaroxaban was inferior to that of warfarin; but no thromboembolic events occurred over the 210-day follow-up in either group. The authors concluded that rivaroxaban might be an effective and safe alternative in patients with APS and previous VTE. The TRAPS (Rivaroxaban in Thrombotic Antiphospholipid Syndrome) study compared rivaroxaban 20 mg daily to warfarin (target INR, 2.5) among patients with triple-positive APS and prior VTE or arterial thrombosis.[15] TRAPS was terminated prematurely by the data safety monitoring board because the rate of thromboembolic events was 12% among those randomized to rivaroxaban (4 ischemic strokes and 3 myocardial infarctions) compared to 0% among those

randomized to warfarin after 569 days' follow-up. No VTEs were observed. Most recently in a randomized controlled trial, Ordi-Ros and colleagues[16] failed to demonstrate that rivaroxaban 20 mg daily was noninferior to VKA (target INR, 2.5; or target INR, 3.5 in patients with a history of recurrent thrombosis) among 190 adults with VTE or arterial thrombotic APS with a comparative risk for recurrent thrombosis of 1.83 (exceeding the predetermined noninferiority margin of 1.4) and a relative risk for stroke of 19 (95% confidence interval [CI], 1.12-321.9). A Canadian study followed 81 patients with APS receiving rivaroxaban for about a year, but the results are not yet known (ClinicalTrials.gov Identifier: NCT02116036); another study with a different DOAC (apixaban) is ongoing.[17,18]

For several reasons, more evidence is needed regarding the efficacy and safety of DOACs in patients with APS. Randomized trials of DOACs in patients with VTE did not test patients for antiphospholipid antibodies and excluded patients with known APS. The syndrome is heterogenous; it is believed that recurrent thrombosis risk can be stratified (high, moderate, low) based on antibody titer, the presence of LA positivity, triple positivity, and perhaps arterial thrombosis vs. VTE as the presenting clinical thrombotic event.[6,13] While TRAPS and now Ordi-Ros suggest a concerning lack of efficacy of rivaroxaban compared with VKA therapy, it is possible that this observation does not extend to all subgroups of APS patients or to other DOACs.

In May 2019, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee issued a guidance statement surrounding the use of DOACs among patients with APS.[19] The statement reads in part:

> *Direct acting Oral Anticoagulants (DOACs) including rivaroxaban/apixaban/edoxaban/dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.*

This statement introduces a potential Pandora's box of uncertainty regarding the implications of an APS diagnosis among patients with a first unprovoked VTE. Current guidelines recommend DOACs over VKA for the treatment of VTE.[20,21] Yet a subset of these patients will harbor antiphospholipid antibodies (and a smaller subset will have APS). It is not possible at the time of diagnosis of unprovoked VTE to know whether APS is present, as the diagnosis requires repeat testing at over 12 weeks. Clinicians are left with uncertainty if initial acute testing is abnormal.[6] The clinician treating unprovoked VTE may have several questions in light of the EMA recommendations (Table 1).

Unprovoked VTE is common. The 2014 US estimates suggested that 1 016 000 total VTE events (676 000 deep vein thrombosis events and 340 000 pulmonary embolism events) occur annually, and it is estimated that 30% of all VTEs are unprovoked[22]. This suggests an annual US incidence of 304 800 unprovoked VTE. At present, few such patients are tested for APS.

**TABLE 1** Questions that the clinician treating unprovoked VTE may ask in light of the EMA Recommendations

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| Is there adequate evidence to adhere to the EMA recommendation and refrain from selecting a DOAC among all patients with a diagnosis of APS? |
| Does the EMA recommendation imply that all patients with acute unprovoked VTE be tested for APS prior to prescribing a DOAC for initial anticoagulation? |
| Are there medico-legal ramifications for the clinician if a DOAC is selected for treatment of acute VTE, yet the patient experiences recurrent VTE and is subsequently diagnosed with APS? |
| Is there a subset of patients with unprovoked VTE that is more likely to have APS and should be evaluated for APS prior to prescription of acute anticoagulant therapy?<br>• What are the characteristics of patients with unprovoked VTE that are likely to have APS?<br>• Is there evidence justifying a workup for APS among patients with unprovoked VTE?<br>• What is the false-positive rate of APS evaluation among patients with unprovoked VTE?<br>• What harm (eg, psychological disutility) would be associated with a false-positive diagnosis? |
| Is it feasible to evaluate all or select patients with unprovoked VTE for APS? |
| Would evaluation of all or select patients with unprovoked VTE for APS be cost effective? |
| What is the number needed to test to inform choice of anticoagulant that would prevent 1 VTE recurrence? |

Abbreviations: APS, antiphospholipid syndrome; DOAC, direct oral anticoagulant; VTE, venous thromboembolism.

Universal testing for APS among patients with unprovoked VTE would be costly. Using costs from our health care institution, the mean cost for LA testing, cardiolipin, and $\beta_2$-glycoprotein-1 antibodies is US$394. Repeat testing would add further expense to confirm a diagnosis of APS. We estimate that the annual expense for routine APS testing among individuals with unprovoked VTE in the United States would be $138 104 880.

About 10% of patients with unprovoked VTE will be diagnosed with APS if all patients are tested.[23] Therefore, 10 patients would need to be evaluated to potentially change the management of 1 patient. Further, it is uncertain whether patients with APS discovered in this manner are similar to patients with clinically detected APS who were enrolled in prior clinical trials comparing DOACs with VKA.

If testing to determine APS status prior to choosing treatment among patients with unprovoked VTE is elected, then perhaps the epidemiology of APS can inform who should be tested. Clinical manifestations of APS generally affect young and middle-aged adults, with 85% of patients between 15 and 50 years of age.[24] Also, APS is more common in women than men, with a male-to-female ratio that varies and ranging from 1:3.5 for primary APS to 1:7 for secondary APS associated with systemic lupus erythematosus.[23] These

epidemiology data may inform future research on identification of patients with unprovoked VTE and adequately high pretest probability for APS to warrant testing.

The US Food and Drug Administration recently updated their guidance regarding APS for rivaroxaban(CITE),[28] and the US package insert for both rivaroxaban and apixaban include the EMA language noted above.[10,11] In the absence of definitive published level I evidence, the EMA guidance statement may be perceived as premature and may discourage ongoing research (ClinicalTrials.gov Identifier: NCT03684564) in this arena. We therefore suggest that societies that provide leadership on this topic, including the International Society of Thrombosis and Haemostasis,[25] APS Action,[26] and Anticoagulation Forum,[27] consider guidance statements for clinicians on whether to evaluate patients with unprovoked VTE for antiphospholipid antibodies. We call for further studies to create a sufficient body of evidence to inform the pragmatic anticoagulant treatment of patients with APS.

## RELATIONSHIP DISCLOSURE

SCW and SMS report grant support from Bristol-Myers Squibb and Pfizer Pharmaceuticals with all support paid to Intermountain Healthcare. SCW and SMS serve as Co-Chairs for the American College of Chest Physicians Living Guideline Writing Panel: Antithrombotic and Thrombolytic Therapy.

## AUTHOR CONTRIBUTIONS

MF, SMS, and SCW were involved in all aspects of the inception, creation, modification, data acquisition, and analysis of this invited commentary.

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