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Comment on:

FAILURE OF RIVAROXABAN TO PREVENT THROMBOSIS IN FOUR PATIENTS WITH ANTI-PHOSPHOLIPID SYNDROME

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Article type: Letter to the Editor (matters arising)
Key message

Additional data suggesting that rivaroxaban does not seem to be efficient in all APS patients.

Letter to the Editor

Sir, we read with a great interest the letter published recently by Dufrost et al.[1] on failure of rivaroxaban to prevent thrombosis in patients with APS, as well as the interview between Dr. Hannah Cohen and Prof. Bernard Lauwerys [2]. We think that this subject is important because we have observed growing use of direct oral anticoagulants (DOAC) in APS patients. Rivaroxaban in Anti-Phospholipid Syndrome (RAPS) study is the only randomized controlled trial studying the use of rivaroxaban versus warfarin to prevent thrombosis recurrence [3]. The primary outcome was the percentage change in endogenous thrombin potential, selected because of the low frequency of clinical outcomes and the ability of this particular test to measure biological activity of both drugs according to Cohen’s interview. The authors conclude that rivaroxaban could be an effective alternative to vitamin K antagonist (VKA) therapy in APS patients since no thrombotic event was observed. Although we appreciate the randomized controlled nature of the study, we think that author’s conclusion is an overstatement because of the short duration of the study follow-up (210 days), and the nature of the study which was not designed to demonstrate clinical non-inferiority. We also think that predicting a drug’s efficacy in APS only on the basis of anticoagulation does not reflect the complexity of APS pathophysiology, which involves platelets, endothelial cells, monocytes, and immune and inflammatory mechanisms as well [4].

To illustrate, we report two new cases of APS patients; they both relapsed under DOAC, after having been stable under VKA therapy.

The first patient is a 66 year-old SLE female diagnosed in 1967 (oral ulcers, polyarthritis, ANA, immune thrombocytopenic purpura). SLE associated-APS was diagnosed in 2007 after
a deep vein thrombosis of the right arm in the context of LA and anti-beta2gp1 positivity. She remained relapse-free under VKA therapy during 8 years and then switched to rivaroxaban (20mg) in 2015. Because of refractory ITP (corticosteroids, rituximab and splenectomy) eltrombopag was started. Six months later (one year after rivaroxaban switching), she experienced chest pain associated with elevated troponin, leading to the diagnosis of myocardial micro-thrombosis on MRI of the heart. Concomitantly, multiple cerebral ischemia and cutaneous arterial micro-thrombosis (confirmed by biopsy) occurred within a week, which led to the diagnosis of catastrophic APS. She improved after corticosteroids, intravenous immunoglobulin, curative heparin therapies, plasmapheresis and rivaroxaban/eltrombopag withdrawal.

The second patient is a 44 year-old female diagnosed with primary triple-positive APS in 2007 (stroke with Libman-Sacks endocarditis and obstetrical morbidity) and treated by warfarin. Despite subtherapeutic INR, no relapse was observed on yearly-repeated echocardiography and cerebral MRI during the 7 years follow-up. Rivaroxaban (20mg) was initiated in 2014. The compliance was suboptimal. In May 2017 Libman-Sacks endocarditis relapsed with new ischemic strokes. Remission improved after switching by heparin, then warfarin. An aortic valve replacement by mechanical prosthesis was required.

We notice that DOACs are increasingly prescribed to treat APS patients, whatever the expression of their disease. Among the DOACs, rivaroxaban is primarily prescribed for the treatment of APS according to initial RAPS results [3].

However evidence-based medicine inspires caution. The Task Force on APS Treatment Trends of the 15th International Congress on Antiphospholipid Antibodies stated that there was insufficient evidence to make recommendations at this time regarding the use of these DOACs in the APS, which can only be considered when there is known VKA
allergy/intolerance, in patients with only venous APS. Thus VKA remains the mainstay of anticoagulation in thrombotic APS and the non-adherence is not a reason to switch [5].

In APS-ACTION registry, an international multicenter prospective database, of 428 thrombosis APS patients, 19 were under DOAC, of whom 6 had relapse during the 2-years follow-up (15.8% annual thrombosis risk), compared to 1.5% risk in VKA-receiving patients [6], suggesting that DOAC and VKA do not have similar efficacy.

Furthermore Cohen’s study included only patients at low risk (neither prior arterial thrombotic event nor previous relapse with INR between 2.0 and 3.0). Because it is difficult to evaluate if “standard intensity” [2] anticoagulation by VKA will be safe before starting, DOAC should be considered only as a second line treatment. Moreover an inaugural venous event does not exclude later arterial thromboses. Our first patient had no prior arterial history before the catastrophic APS. Thus we endorse the conclusion of Dufrost et al.[1] and do not agree that rivaroxaban offers an effective, safe and convenient alternative to warfarin in APS patients, as Cohen suggested [2].

The manifestations of APS span a heterogeneous clinical spectrum. Awaiting randomized controlled trials with clinical outcome [7,8] and prolonged follow-up to clarify whether DOACs are efficient alternatives to VKAs, cautions and stringent clinical review are especially necessary in known high risk patients (table 1).
Table 1: Clinical phenotypes of APS require caution with the use of direct oral anticoagulants.

<table>
<thead>
<tr>
<th>Lack of evidence-based medicine</th>
<th>No evidence-based medicine</th>
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<tr>
<td>Venous thrombotic APS without previous relapse with INR between 2.0 and 3.0</td>
<td>Arterial and small vessel thrombotic APS</td>
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<td>Libman-Sacks endocarditis</td>
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<td>Association with pro-thrombotic treatment</td>
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<td>Triple-positive aPL profile</td>
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<td>Poor compliance (no biological monitoring and short half time)</td>
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<td>Relapsing patient despite anticoagulant.</td>
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Conflicts of interest:

Prof. LAMBERT receives fees from BAYER, BMS-PFIZER and DAICHY-SANKIO.

QS, SMD, CMY, JB and SG declare no conflicts of interest.

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References


3. Cohen H, Hunt BJ, Efthymiou M et al. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus


