Advances in Rheumatology

POSITION ARTICLE AND GUIDELINES Open Access

Antiphospholipid Syndrome Committee of the Brazilian Society of Rheumatology position statement on the use of direct oral anticoagulants (DOACs) in antiphospholipid syndrome (APS)

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Abstract

Background: The term Direct Oral Anticoagulants (DOACs) refers to a group of drugs that inhibit factor Xa or thrombin. Even though their use for treating different thrombotic or prothrombotic conditions is increasing recently, there is no compelling evidence indicating that those medications are safe in all antiphospholipid syndrome (APS) patients.

Methodology: To address this issue, specialists from the Antiphospholipid Syndrome Committee of the Brazilian Society of Rheumatology performed a comprehensive review of the literature regarding DOACs use in APS to answer the three following questions: (1) potential mechanisms of action of these drugs that could be relevant to APS pathogenesis, (2) DOACs interference on lupus anticoagulant testing, and (3) the efficacy of DOACs in APS.

Position statement: After critically reviewing the relevant evidence, the authors formulated 8 Position Statements about DOACs use in APS.

Conclusion: DOACs should not be routinely used in APS patients, especially in those with a high-risk profile (triple positivity to aPL, arterial thrombosis, and recurrent thrombotic events). In addition, DOACs interferes with LA testing, leading to false-positive results in patients investigating APS.

Keywords: Antiphospholipid syndrome, Factor Xa inhibitors, Rivaroxaban, Apixaban, Edoxaban, Antithrombins, Dabigatran

Background

Direct oral anticoagulants (DOACs) are medications used for treating different thrombotic or prothrombotic conditions, such as non-valvular atrial fibrillation (AFib) [1–5], deep vein thrombosis (DVT) [6–9], and pulmonary embolism (PE) [10], as well as for thromboprophylaxis after elective lower limb orthopedic surgery [11] and for acutely ill medical patients [12–14]. Until now, this class of medication comprises five different drugs, dabigatran, rivaroxaban, apixaban, endoxaban and betrixaban (not discussed in this review, since it is not available in Brazil at this time), each of them with different half-life, pharmacokinetics, pharmacodynamics, and even clinical indications. Table 1 provides summarized information regarding those drugs [15–19].

In the pivotal trials, DOACs were non-inferior to the standard-of-care warfarin, with a good safety profile.

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Table 1 Characteristics of DOACs. Adapted from references [15–19]

Drugs	Mechanism of action	Brand name	Clinical indications	Half-life	Elimination	Drug interactions (see Table 2)
Dabigatran	Direct thrombin inhibitor	Pradaxa	- Non-valvular AFib; - Treatment of DVT and PE; - Reduction in the risk of recurrence of DVT and PE.	12–14 h	Renal (80%)	- P-gp inducers - P-gp inhibitors
Rivaroxaban	Factor Xa inhibitor	Xarelto	- Non-valvular AFib; - Treatment of DVT and PE; - Reduction in the risk of recurrence of DVT and PE; - Prophylaxis of DVT following hip or knee replacement surgery; - Prophylaxis of DVT and PE in acutely ill medical patients; - Risk reduction of major cardiovascular events in stable atherosclerotic vascular disease (in combination with ASA).	5–13 h	Renal (67%)	- Combined P-gp and strong CYP3A4 inhibitors and inducers
Apixaban	Factor Xa inhibitor	Eliquis	- Non-valvular AFib; - Treatment of DVT and PE; - Prophylaxis of DVT following hip or knee replacement surgery.	12 h	Faecal (56%)	- Strong dual inhibitors of P-gp and CYP3A4
Edoxaban	Factor Xa inhibitor	Savaysa (USA) / Lixiana (Brazil)	- Non-valvular AFib; - Treatment of DVT and PE following 5–10 days of initial parenteral anticoagulation.	10–14 h	Renal (50%)	- P-gp inducers and inhibitors.

AFib atrial fibrillation, *ASA* acetylsalicylic acid, *BID* twice daily, *CrCl* creatinine clearance, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *P-gp* P-glycoprotein, *QD* once daily

More recently, after the results of the COMPASS trial [24], the U.S. Food and Drug Administration (FDA) approved rivaroxaban (2.5 mg twice daily in association with acetylsalicylic acid [ASA]) to reduce the risk of major cardiovascular events (myocardial infarction, stroke and/or cardiovascular death) in patients with stable atherosclerotic vascular disease (i.e. chronic coronary artery disease and peripheral artery disease).

In addition to the increasing number of indications, DOACs present some appealing advantages over vitamin K antagonists (VKA), such as: (1) rapid onset of the anticoagulant effect after drug initiation, shortening hospitalization time and often obviating the need of in-hospital treatment; (2) no need of laboratory monitoring of the anticoagulant effect, being therefore more convenient for the patients, (3) fixed therapeutic dosage, and (4) fewer interactions with dietary components and other drugs, which translates into a more stable anticoagulant effect, irrespective to the patient's diet and commonly prescribed medications [25–28].

Nevertheless, some potentially serious drug interaction between different DOACs and other frequently used medications, such as cyclosporine, tacrolimus, imidazole and triazole derivatives, antiretroviral therapies (especially ritonavir and telaprevir), amiodarone, anticonvulsants (carbamazepine, phenobarbital, phenytoin), selective serotonin reuptake inhibitors and rifampicin, have been recently described and may increase the risk of bleeding or decrease the efficacy of DOACs [20–23] (Table 2). In addition, DOACs should not be prescribed to pregnant woman and to patients with severely impaired renal function (estimated GFR < 30 mL/min/1.73 m2 of body surface area), since these groups of patients were excluded from pivotal trials.

Of note, despite being increasingly employed in the management of other prothrombotic states, the use of DOACs in patients with antiphospholipid syndrome (APS) was not extensively evaluated in the pivotal trials (namely, RE-COVER, RE-SONATE, RE-MEDY, EINSTEIN, EINSTEIN-PE, AMPLIFY, and HOKUSAI-VTE trials) [6–10]. In fact, it is expected that around 10% of patients with venous thrombosis will test positive for antiphospholipid antibodies (aPL) [29]. Even though, in post-hoc studies of phase 3 DOACs trials, only a fraction of the expected patients were reported. Goldhaber et al. described the post-hoc analysis of dabigatran trials. They identified 43 APS patients (1.7%) treated with dabigatran in RE-COVER/RE-COVER II trials (vs. 43 warfarin patients) and 38 (2.7%) in RE-MEDY trial (vs. 54 warfarin patients) [30]. The authors stated that the incidence of VTE/VTE-related deaths in aPL positive patients did not differ between groups [30], but this study was underpowered to draw definite conclusions on the use of

Table 2 Drug-drug and food-drug interactions of DOACs. Adapted from references [20–23]

Pharmacokinetic interaction		Pharmacodynamic interaction
Can decrease DOAC concentration	Can increase DOAC concentration	Can increase risk of bleeding
Carbamazepine	Amiodarone	Aspirin
Phenobarbital	Clarithromycin	ADP receptor ($P2Y_{12}$) inhibitors (clopidogrel, prasugrel, ticarelor)
Phenytoin	Cyclosporin A	Fibrinolytics (alteplase, tenecteplase)
Rifampin	Diltiazem	Heparins
St John's Wort	Dronedarone	NSAIDs
	Grapefruit components (p.e. furanocoumarins)	SNRIs/SSRIs
	Itraconazole	Warfarin
	Ketoconazole	
	Nelfinavir	
	Quinidine	
	Ritonavir	
	Tacrolimus	
	Verapamil	

DOAC Direct oral anticoagulants, *NSAIDs* non-steroidal anti-inflammatory drugs, *SNRIs* serotonin norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors

dabigatran in this subgroup of patients [31]. In AMPLIFY study [7], 74 patients (2.85%) in the apixaban arm were diagnosed with thrombophilia (vs. 59 in enoxaparin + warfarin arm), but no specific analysis of APS patients was provided [7, 31]. In the EINSTEIN and EINSTEIN-PE trials, 6.2% patients in the rivaroxaban group (vs. 6.8% in warfarin group) and 5.7% (vs. 5.0% in warfarin group), respectively, had a known thrombophilia. Efficacy and safety endpoints were consistent with the overall observed effect; however, again, there was no specific analysis of APS patients [6, 10, 31]. Moreover, published trials on the use of rivaroxaban in APS failed to demonstrate non-inferiority of rivaroxaban when compared to warfarin (one using intermediate/laboratory and 2 using clinical outcomes – please see Randomized clinical trials (RCT) section below) [32–34].

This position statement will cover the published data regarding the use of DOACs in APS patients and will discuss the potential uses and contraindications of this class of drugs in this very specific group.

Questions to explore

The authors will explore the published data about DOACs use in APS, especially regarding their potential mechanisms of action that may influence APS treatment, their impact on lupus anticoagulant (LA) testing, and their efficacy in this subset of patients.

Methodology

Specialists from the Antiphospholipid Syndrome Committee of the Brazilian Society of Rheumatology performed a comprehensive review of the literature regarding DOACs use in APS to address the three following questions: (1) potential mechanisms of action of these drugs that could be relevant to APS pathogenesis, (2) DOACs interference on LA testing, and (3) the efficacy of DOACs in APS.

MEDLINE, EMBASE, Cochrane, and BIREME databases were searched up until March 20th, 2020. No language restriction was applied. We divided MeSH terms in two groups and combined each term of group 1 with each term of group 2, as following: (1) "antiphospholipid syndrome", "antiphospholipid antibodies", "lupus anticoagulant", "anticardiolipin antibodies", "beta 2 glycoprotein I"; and (2) "dabigatran", "rivaroxaban", "apixaban", "edoxaban". All retrieved articles were screened according to its title, abstract and full-text (if title and abstract were appropriate) and our group selected the most relevant ones to answer the proposed questions.

After critically reviewing the relevant evidence, the authors formulated a Position Statement on the use of DOACs in APS. All participants had the opportunity to express their opinion and contributed to the final document.

Literature review and analysis

Mechanism of action

DOACs exert their anticoagulant effects by directly inhibiting either factor Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran). This inhibition occurs in a reversible, competitive, highly selective and dose-dependent way [25, 35, 36].

Factor Xa and thrombin play very important roles in normal hemostasis. The primary physiologic trigger of clotting event (initiation) is the interaction between tissue factor and activated factor VII (VIIa). Factor VIIa

then activates factor X in factor Xa, which in turn generates thrombin from prothrombin. The initial small amount of thrombin activates factor V, factor VIII, factor XI, and platelets, resulting in an explosive thrombin generation (amplification). Then, the high thrombin levels convert fibrinogen into fibrin, forming and stabilizing the clot (propagation) [37, 38].

Artang et al. studied the effects of rivaroxaban, apixaban, and dabigatran on thrombin generation measurements using the Calibrated Automated Thrombogram (CAT) in 10 healthy male volunteers. Lag time was the thrombin generation assay (TGA) parameter most strongly associated with DOACS levels in all drugs. Endogenous thrombin potential (ETP) and thrombin peak height were significantly reduced for both rivaroxaban and apixaban, but not for dabigatran, with moderate and strong correlation, respectively, with factor Xa inhibitors levels. The authors demonstrated that thrombin peak height was superior to ETP in predicting factor Xa inhibitors concentrations. It also showed nonlinear exponential decay pattern, what may suggest it may be a useful parameter to monitor factor Xa inhibitors effect at lower concentrations [39].

Tripodi et al. performed a similar analysis using apixaban and the results were consistent with those previously reported. Apixaban altered all paramenters of CAT, increasing lag time and decreasing ETP, thrombin peak height, and velocity index. They also found that those effects were more prominent in the presence of thrombomodulin, an endothelial protein C activator [40].

Even though, when those parameters were tested in APS patients randomized to receive rivaroxaban or warfarin, rivaroxaban did not reach the noninferiority threshold for the percentage change in ETP at day 42. Nonetheless, peak thrombin generation was significantly lower in rivaroxaban group, when compared to warfarin, and no episode of recurrent thrombosis was observed during the short follow-up period. The details of Cohen et al. publication will be presented in the section "Randomized Clinical Trials" below in this paper [32].

Some authors have proposed that DOACs may also modulate inflammatory response. Both factor Xa and thrombin cleave PARs (protease-activated receptor), which are protein G-associated thrombin receptors activated by proteolysis, resulting in signal transduction, inflammation and thrombosis [41]. By inhibiting factor Xa and thrombin, DOACs may block those pathologic processes universally present in APS patients and therefore exert anti-inflammatory, anti-fibrotic and anti-angiogenic effects [42].

In addition, Arachchillage et al. found that patients taking rivaroxaban presented lower levels of C3a, C5a and SC5b-9 than those taking warfarin. There was no difference between Bb fragment levels between groups. These findings suggest that rivaroxaban may reduce complement activation, especially in the classic pathway. As complement activation plays a significant pathogenic role in APS, the authors hypothesized that APS patients may benefit from rivaroxaban beyond its anticoagulating effect [43], which needs confirmation in prospective clinical trials.

Investigating the presence of lupus anticoagulant in patients using DOACs

It is widely known that different anticoagulants, such as warfarin and other VKA, unfractionated heparin (UFH), argatroban, lepirudin, and even some low-molecular-weight heparins (LMWH) may interfere with the detection of LA, as they interfere with clot formation [44–46].

Merriman et al. identified that many subjects taking rivaroxaban presented a positive LA test. Of the 32 patients randomized to rivaroxaban in their center, twenty-one were tested for LA and 19 presented a positive screening test. Dilute Russel's viper venom time (dRVVT) ratio was the test most affected by rivaroxaban. In contrast, only two out of twenty-one had an abnormal Kaolin clotting test, and only five out of fifteen had an abnormal aPTT (activated partial thromboplastin time) (Triniclot). An aPTT phospholipid correction test (STA-Clot method), which would be expected to be positive in the presence of true LA, was performed in twelve of the 19 positive LA subjects, with negative results in all of them; anti-beta-2-glycoprotein I (aßGPI) and anticardiolipin (aCL) antibodies were within the normal range in 10 of the 12 patients. Finally, thirteen of the 19 subjects were retested for the presence of LA after discontinuation of rivaroxaban and only one tested positive. The authors concluded that rivaroxaban might lead to false positive LA tests, especially for dRVVT ratio, as Russel's viper venom is a protease that cleaves factor X into Xa and rivaroxaban targets the factor Xa [45, 47].

The study by van Os et al. tested LA in the presence and in the absence of an in vitro preparation of rivaroxaban using three different assays: aPTT (screen PTT-LA and confirm Actin FS), dRVVT (screen LA-1 and confirm LA-2), and snake venom assay (screen Taipan snake venom time and confirm Ecarin venom time). The addition of rivaroxaban prolonged all conventional assays (PTT-LA, Actin FS, LA-1 and LA-2) in all groups, including normal pooled plasma of healthy subjects, leading to false-positive results. While dRVVT ratio was the most affected, aPTT ratio was only minimally influenced, as both PTT-LA and Actin FS had comparable prolongations. Rivaroxaban did not influence either Taipan venom time or Ecarin time [48].

Since then, different reports evaluated the impact of DOACs in the interpretation of LA assays. In summary,

because of the higher prolongation of the screen dRVVT when compared with the confirm dRVVT, dRVVT ratio was the most affected assay, with high rates of false-positive results, both in in vitro and in ex vivo studies. It is noteworthy that, among factor Xa inhibitors, false-positive LA rates were less frequent with apixaban than with rivaroxaban (highest rates) and edoxaban. Additionally, screen Taipan snake venom time (TSVP) and confirm Ecarin clotting time (ECT) do not seem to be affected by the use of rivaroxaban, representing a possible alternative to dRVVT in this setting. Dabigatran induced high rates of false-positive LA, similar to those observed with rivaroxaban. Table 3 summarizes data regarding effect of different DOACs on different LA testing [45, 46, 48–65].

In order to provide a more accurate LA analysis in patients on DOACs, Exner et al. tested an activated charcoal product (DOAC Stop™) intended to extract DOACs from test plasmas. They found that DOAC Stop™ was capable of removing all types of DOACs (rivaroxaban, apixaban, edoxaban, and dabigatran) and it corrected false-positive dRVVT (screen, confirm and ratio) caused by the presence of those medications [66, 67]. Other authors performed similar studies with comparable results [56, 68]. The use of the antidotes idarucizumab (monoclonal antibodies against dabigatran) and adexanet alfa (recombinant human coagulation factor Xa for rivaroxaban and apixaban) may be considered for testing LA in patients using those medications, but difficulty of access and high costs could limit this approach [47]. Góralczyk et al. suggested another option based on their findings: as LA was corrected after > 24 h of discontinuation of rivaroxaban, they recommended that blood should be drawn at least 24 h after the last dose of the drug [62]. In this matter, Douxfils et al. suggested that LA testing should be performed preferably at trough level (C_{TROUGH}) (i.e. 12 or 24 h after last drug intake for bid [dabigatran, apixaban] or qd [rivaroxaban, edoxaban] drugs, respectively). Since invalid results may still happen, the authors state the real need for LA testing should be carefully evaluated in these scenarios and results should be interpreted with caution [65]. Favaloro et al. reported false positive (especially with rivaroxaban) and false negative (especially with apixaban) LA results in patients using DOACs [69], leading to a mistaken diagnosis of APS.

Current evidence on the efficacy of DOACs in APS patients

Randomized clinical trials (RCT)

To date, six trials on the use of DOACs in APS were registered in ClinicalTrials.gov and only three of them have been fully published.

The first published trial was the RAPS trial (Rivaroxaban in AntiPhospholipid Syndrome – NCT02116036), a prospective, randomized, controlled, non-inferiority, phase 2/3 study of rivaroxaban 20 mg once daily vs. warfarin (INR target 2.0–3.0) in thrombotic primary or secondary APS patients. Patients with arterial events and recurrent venous thrombosis were excluded. The authors decided to use percentage change in the ETP as the primary efficacy outcome, rather than clinical evidence of thrombosis. Nonetheless, after 6 weeks, rivaroxaban did not reach the non-inferiority laboratory threshold, when compared to warfarin [32]. No thrombotic episodes were registered during the follow-up period of 6 months, even though triple positivity (defined as positive aCL and β2GPI antibodies greater than the 99th percentile and a positive LA) was present in 20% vs. 12% of the warfarin and rivaroxaban groups, respectively. Rivaroxaban did not reach non-inferiority threshold for ETP [32, 70].

Pengo et al. recently published the results of TRAPS trial (Rivaroxaban in Thrombotic AntiphosPholipid Syndrome – NCT02157272). It was a randomized, open-label, multicenter, non-inferiority trial designed to evaluate the efficacy of rivaroxaban 20 mg once daily (or 15 mg once daily in case of moderate renal insufficiency) vs. warfarin INR target 2.0–3.0 in preventing thromboembolic events, risk of major bleeding and vascular death in high-risk APS patients, that is the presence of triple positivity for LA, aCL and aß2GPI (aCL and aß2GPI ELISA tests had to be positive for the same isotype). Past history of arterial events was not an exclusion criterium. After a mean follow up of 569 days, the study was prematurely terminated due to an excess of arterial thrombotic events in the rivaroxaban arm (4 ischemic strokes and 3 myocardial infarctions vs. none in the warfarin arm). Additionally, the number of major bleeding events was numerically higher in the rivaroxaban group (4 vs. 2). The authors concluded that the use of rivaroxaban in high-risk APS patients showed no benefits, as it leads to an excessive risk of events [33].

ASTRO-APS (Apixaban for the Secondary Prevention of Thrombosis Among Patients With APS – NCT02295475) is a prospective, randomized, open-label, blinded event, phase 4 pilot trial, comparing the efficacy of apixaban (vs. warfarin – target INR 2.0–3.0) in the secondary prevention of thrombosis in APS patients. Exclusion criteria included previous history of arterial events, recurrent thrombosis while receiving warfarin at a target INR of 2–3 or history of catastrophic APS (CAPS) [71]. After the study design was published, its protocol was modified due to an unanticipated excessive risk of arterial events during the first months of the trial in the apixaban group. To address this issue, apixaban dose was increased from 2.5 mg twice a day to 5 mg

Table 3 Effect of different DOACs in commonly used LA assays. Adapted from references [45, 46, 48–64]

Reference	DOAC	Tests analyzed	Results
Merriman (2010)	Rivaroxaban	aPTT (Triniclot), aPTT (STAClot), dRVVT (screen, confirm and ratio), Kaolin, DTT	False positive dRVVT ratio (88.9%) - all other tests negative / normalization of LA after discontinuation in all but one patient
van Os (2011)	Rivaroxaban	aPTT (screen PTT-LA and confirm Actin FS), dRVVT (screen LA-1 and confirm LA-2), and snake venom assays (screen TSVT and confirm ECT)	False positive dRVVT ratio (40% of SLE w/o aPL became LA positive after rivaroxaban mixing)
Halbmayer (2012)	Dabigatran	dRVVT (screen, confirm, standard ratio, and normalized ratio)	Higher frequency of false positive dRVVT ratio with increasing dabigatran concentrations
Martinuzzo (2014)	Rivaroxaban, dabigatran	aPTT, dRVVT (screen, confirm, ratio), SCT (screen, confirm, ratio)	False positive dRVVT ratio (76.5–100%)
Hillarp (2014)	Apixaban	aPTT, dRVVT (screen, confirm and ratio)	Apixaban did not cause false-positive results
Kim (2014)	Dabigatran	aPTT (PTT-LA, STAClot-LA)	False positive aPTT ratio (50% borderline and 40% positive)
Arachchillage (2015)	Rivaroxaban	Textarin time, dPT, dRVVT (3 methods: Siemens LA-1/LA-2, HemosIL dRVVT screen and confirm, and in-house dRVVT), TSVT/ECT	In vitro: false positive dRVVT ratio by conventional assays, but not in-house assay (90% normal controls and 92% LA-negative APS patients) Ex vivo: false-positive dRVVT ratio (100%) - remained false-positive at 18 h after the last dose of rivaroxaban
Bonar (2015)	Dabigatran	dRVVT (screen, STAClot confirm and ratio)	False positive dRVVT ratio (in vivo and ex vivo)
Góralczyk (2015)	Rivaroxaban	aPTT (PTT-LA screen and STAClot confirm), dRVVT (2 methods: HemosIL screen and confirm, and LA-1/LA-2)	False positive dRVVT ratio (patients were retested and became LA negative after 24 h of rivaroxaban discontinuation)
Bonar (2016)	Rivaroxaban, apixaban	dRVVT (screen, STAClot confirm and ratio)	False positive dRVVT ratio (rivaroxaban, but not apixaban, caused increased dRVVT ratio ≥ 1.2)
Gosselin (2016)	Rivaroxaban, apixaban, and edoxaban	dRVVT (3 methods: Siemens LA-1/LA-2, CRYOCheck LA-1/LA-2, dRV-LS/dRV-LR), hexagonal phase (STAClot-LA)	False positive dRVVT ratio (for all DOACs)
Pouplard (2016)	Rivaroxaban	dRVVT (STAClot DRVVT), TSVT/ECT	False positive dRVVT ratio; TSVT/ECT was not influenced by rivaroxaban
Ratzinger (2016)	Rivaroxaban, apixaban, and dabigatran	aPTT, dRVVT	False positive dRVVT ratio: - Dabigatran: 43.3%; - Rivaroxaban: 30%; - Apixaban: 20.7% (w/o dose dependent increase).
Antovic (2017)	Rivaroxaban, apixaban, and dabigatran	aPTT, dRVVT	False positive dRVVT ratio (≥1.2): - Dabigatran: 73%; - Rivaroxaban: 75%; - Apixaban: 76%.
Seheult (2017)	Rivaroxaban, apixaban, and dabigatran	aPTT, dRVVT, TII + PT	False positive dRVVT ratio and TTI + PT (aPTT was less affected); Apixaban was less affected than rivaroxaban; After rivaroxaban discontinuation, LA positivity dropped from 83 to 26%.
Flieder (2018)	Rivaroxaban, apixaban, and	aPTT, dRVVT (HemosIL and STAClot)	False positive dRVVT ratio: - Dabigatran: 20% (HemosIL) and 71% (STAClot);

Table 3 Effect of different DOACs in commonly used LA assays. Adapted from references [45, 46, 48–64] *(Continued)*

Reference	DOAC	Tests analyzed	Results
	dabigatran		- Rivaroxaban: 70% (IL) and 100% (STAClot): - Apixaban: no influence. Less important change in aPTT in all DOACs.
Hillarp (2018)	Edoxaban	dRVVT (Technoclot and STAClot)	False positive dRVVT ratio on Technoclot, but not with STAClot
Martinuzzo (2018)	Rivaroxaban	dRVVT (HemosIL and STAClot)	False positive dRVVT ratio (89.2% with HemosIL and 86.2% with STAClot)
Platton (2018)	Rivaroxaban and apixaban	dRVVT (Siemens LA1 and LA2)	dRVVT screen and confirm were falsely increased for both rivaroxaban and apixaban groups. After treatment with DOAC Stop, both dRVVT screen and confirm decreased to normal values.

aPTT activated partial thromboplastin time, *DOAC* direct oral anticoagulant, *dRVVT* dilute Russell's viper venom time, *LA* lupus anticoagulant, *TII + PT* thromboplastin inhibition index with prothrombin time, *TSVT* Taipan snake venom time, *ECT* Ecarin clotting time

twice a day and the Data Safety Monitoring Board recommended researchers to obtain a brain magnetic resonance imaging (MRI) for all patients, excluding from randomization those with prior silent stroke or white matter changes disproportionate to the patient's age [72].

The Canadian RAPS trial (NCT02116036) is a pilot phase 4 single-arm feasibility study evaluating, as a secondary outcome, the rates of bleeding and thrombosis in APS patients receiving rivaroxaban 20 mg once daily for the secondary prevention of thrombosis. Patients with arterial thrombosis and recurrent events while taking adjusted warfarin, rivaroxaban or dabigatran were excluded. This protocol was last update in ClinicalTrials.gov in 2017 and its complete results were not published to date [73]. However, in a written communication quoted elsewhere [74], the authors state that there were 2 arterial (cerebrovascular) and 2 venous events in 129.8 patients-year of follow-up after rivaroxaban initiation ($N = 82$ patients, no triple positivity included, 5 had previous history of venous thromboembolism [VTE]). While the authors claimed that these event rates were similar to previous warfarin studies, the absence of a control arm and the lack of population comparability data prevent a definitive conclusion to be obtained [74].

NCT02926170 was a randomized, prospective, open-label phase 3 trial, designed to investigate the efficacy and safety of rivaroxaban 20 mg once daily (or 15 mg once daily, if estimated GFR 30–49 mL/min) vs. acenocumarol (INR target 2.0–3.0 or 2.5–3.5 in those with recurrent thrombotic episodes) for secondary thrombosis prophylaxis in APS patients. Patients with previous arterial events and recurrent thrombosis were allowed to participate [75]. Ninety-five patients were assigned to receive rivaroxaban and 95 to receive warfarin. Around 6% of patients in each group dropped out early. The mean follow-up time for rivaroxaban group was 33.1 months vs. 34.1 for warfarin group. Global AntiPhospholipid Syndrome Score (GAPSS) was similar between groups, but migraine and livedo racemosa were more frequent in patients treated with rivaroxaban; 13.7% of rivaroxaban patients were taking concomitant ASA (vs. 11.7% in warfarin). Mild to moderate mitral thickening was slightly more frequent in the rivaroxaban group (22.1 vs. 14.7%). In the per protocol analysis, overall recurrent thrombosis rates were 11.6% in rivaroxaban arm vs. 6.3% in warfarin arm (risk ratio [RR] 1.83 [95%CI 0.71–4.76]; p for noninferiority = 0.29; p for VKA superiority = 0.20). Stroke occurred in 9 (9.5%) patients taking rivaroxaban vs. 0 taking VKA (RR 19; 95%CI 1.12–321.9; p = < 0.001). In the intention to treat analysis, overall recurrent thrombosis rates were 12.6% in rivaroxaban group vs. 6.3% in warfarin group (RR 2 [95%CI 0.78–5.11]; p for noninferiority = 0.57; p for VKA superiority = 0.13). Both overall arterial events (RR 3.67 [95%CI 1.06–12.73]; $p = 0.040$) and stroke (RR 21 [95%CI 1.25–353.3]; $p = 0.001$) were more frequent in rivaroxaban group. Regarding safety outcomes, any bleeding, major bleeding, nonmajor clinically relevant bleeding, and minor bleeding did not differ between groups, in the as-treated analysis. In rivaroxaban-treated patients with previous arterial events, livedo racemosa or APS-related valvopathy, post hoc analysis suggested an increased risk of new thrombotic event during follow-up. In conclusion, rivaroxaban could not demonstrate its non-inferiority to VKAs in the secondary thrombosis prevention [34].

RISAPS (RIvaroxaban for Stroke patients with Anti-Phospholipid Syndrome – NCT03684564) is a recently registered randomized, controlled, phase 2/3, non-inferiority trial on the use of rivaroxaban (vs. warfarin) for the secondary prevention of stroke in APS patients who have had previous stroke or other ischemic brain manifestations. Rivaroxaban dose will be 15 mg twice a day and warfarin will be administered to achieve a target INR of 3.5 (range 3.0 to 4.0). The primary efficacy outcome will be the rate of change in brain white matter hyperintensity (WMH) volume on MRI, assessed on the 3D FLAIR sequence, between baseline and 24 months. The estimated completion date is October 2022 [76].

A summary of the most relevant aspects of the clinical trials cited above can be found in Table 4.

Observational studies

Martinelli et al. enrolled consecutively 28 APS patients (13 treated with rivaroxaban and 15 with VKA) retrieved from 672 patients with venous thrombosis referred to their clinics. When patient switched between treatment groups, the authors recorded both treatments as periods (i.e., one patients accounted for 1 period of rivaroxaban and 1 period of warfarin), what led to 13 periods of rivaroxaban and 20 periods of VKA. During follow-up, one patient taking warfarin (incidence rate of 2.4 [95%CI 0.2–11.3] per 100 patient years) developed acute myocardial infarction and 4 taking rivaroxaban (incidence rate of 19.4 [95%CI 6.5–46.2] per 100 patient years) had recurrent thrombosis (1 stroke, 2 acute myocardial infarction, and 1 cerebral vein thrombosis). All of those were triple positive. The cumulative incidence at 24 months was 42% (95% 8.3–75.7) for rivaroxaban vs. 7.1% (95%CI 1–41) for warfarin, with a HR of 7.53 (95%CI 0.84–67.6). After 24 months, no episodes of recurrent thrombosis were observed. The authors concluded that there was an increased risk of recurrent thrombosis in triple positive patients using rivaroxaban and that the limited experience on the use of DOACs in treating APS cannot establish their safety in this subset of patients [77].

Table 4 Summary of completed and ongoing clinical trials of the use of DOACs in APS. Adapted from references [32, 70–76]

Trial	Design	Patient Population	Intervention	Comparison	Primary Outcome	Results/ ECD
RAPS (NCT02116036)	Prospective, controlled, phase 2/3, non-inferiority RCT	Primary or secondary thrombotic APS with previous isolated venous thromboembolism	Rivaroxaban 20 mg once daily	Warfarin (INR 2.0–3.0)	Endogenous thrombin potential (ETP)	Rivaroxaban did not reach the non-inferiority threshold
TRAPS (NCT02157272)	Phase 3, open-label, multicenter, non-inferiority RCT with blinded end-point	Triple positive thrombotic APS patients	Rivaroxaban 20 mg once daily (CrCl> 50) or 15 mg daily (if CrCl 30–50)	Warfarin (INR 2.0–3.0)	Cumulative incidence of thromboembolic events, major bleeding and vascular death	Terminated prematurely due to an excess of events in rivaroxaban arm
ASTRO-APS (NCT02295475)	Prospective, open-label, blinded event, phase 4 pilot RCT	Primary or secondary thrombotic APS. Exclusion: previous arterial events and recurrent venous thromboembolism when taking warfarin with INR of 2.0–3.0.	Apixaban 2.5 mg twice a day (increased to 5 mg twice a day + brain MRI after protocol modification)	Warfarin (INR 2.0–3.0)	Rates of thrombosis and deaths caused by thrombosis/ major bleeding plus clinically relevant non-major bleeding over 1 year	Protocol modification (2017): unanticipated excessive risk of arterial events during the first months in apixaban group. ECD: December 2019.
Canadian RAPS (NCT02116036)	Pilot phase 4, open-label RCT	Primary or secondary thrombotic APS (history of arterial thrombosis allowed). Exclusion: arterial thrombosis or recurrent venous events while on anticoagulation.	Rivaroxaban 20 mg daily	None (single-arm)	Rates of venous and arterial thrombosis and rates of minor, major and fatal bleeding	Single-arm feasibility study; Rates of thrombosis similar to warfarin studies
NCT02926170	Prospective, open-label, phase 3 RCT	APS patients with previous arterial events and recurrent thrombosis	Rivaroxaban 20 mg once daily (CrCl> 50) or 15 mg daily (if CrCl 30–50)	Acenocoumarol (INR 2.0 to 3.0 or 2.5 to 3.5 if recurrent thrombosis)	New thrombotic event or incidence of major bleeding (time frame: 36 months)	Rivaroxaban did not reach the non-inferiority threshold
RISAPS (NCT03684564)	Prospective, controlled, phase 2/3, non-inferiority RCT	Primary or secondary thrombotic APS with previous stroke or other ischemic brain manifestations	Rivaroxaban 15 mg twice a day	Warfarin (INR between 3.0–4.0)	Rate of chance in brain white matter hyperintensity volume on MRI (baseline and 24 months)	ECD: October 2022

APS antiphospholipid syndrome, *CrCl* creatinine clearance, *DOACs* Direct oral anticoagulants, *ECD* estimated completion date, *INR* international normalized ratio, *RCT* randomized clinical trial

Dufrost et al. have recently performed a patient-level data meta-analysis and found 447 APS patients that were treated with DOACs (290 with rivaroxaban, 114 with dabigatran, and 13 with apixaban). Of those, 319 patients were derived from observational studies, including cases series ($N = 14$), case reports ($N = 21$) and abstracts ($N = 9$). Seventy-three (16%) patients experienced at least one episode of recurrent thrombotic event (28 VTE, 31 arterial thromboses, and 13 small vessels thromboses) during DOACs use, with a mean duration until thrombosis of 12.5 months. When triple positive patients were analyzed separately, recurrence rate was 56% (mean duration until thrombosis: 16.1 months); triple positivity (OR = 4.3; 95%CI 2.3–7.7; $p < 0.001$) was associated with a higher risk of recurrent thrombosis. A higher number of clinical APS classification criteria and the positivity for aCL or aβ2GPI were also associated with a significantly higher recurrence risk. In the anti-Xa subgroup analysis, male gender ($p = 0.026$), history of arterial (OR = 2.8; 95%CI 1.4–5.7; $p = 0.006$), small vessels thrombosis (OR = 5.3; 95%CI 1.2–23.2; $p = 0.028$), and triple positivity (OR = 6.9; 95%CI 3.4–13.9; $p < 0.001$) were associated with higher rates of recurrence. In the dabigatran subgroup analysis, no differences regarding previous events or antibodies profile were observed between groups [78].

One relevant finding that must be stressed is that patients with recurrence of thrombosis on DOACs were more likely to have a past history of recurrence during VKA treatment, maybe representing a subgroup of APS that has a higher probability of recurrence, irrespective of the anticoagulant therapy prescribed. Due to the aforementioned data, the authors concluded that DOACs are not effective in all APS patients and should not be routinely prescribed to this subset of patients [65].

Additional relevant studies have been published since this meta-analysis was performed. Sato et al. reported the results of a longitudinal cohort that included 206 APS patients, with 18 patients who were treated with anti-factor Xa therapy (5 rivaroxaban, 12 edoxaban, 1 apixaban). When compared to warfarin, event-free survival (thrombotic and hemorrhagic events) was significantly shorter in the anti-Xa therapy group (HR 12.1; 95%CI 1.73–248; $p = 0.01$). When compared to control group (warfarin patients selected from the same cohort, matched by age, gender, SLE coexistence, and concomitant antiplatelet therapy), event-free survival was also significantly shorter in anti-Xa patients (HR 4.62; 95%CI 1.54–13.6; $p = 0.0075$). In the multivariate analysis, results remained unchanged (HR 11.9; 95%CI 2.93–56; $p = 0.0005$) [79] Malec et al. investigated 82 APS patients (56 have previously been reported) who used DOACs (36 rivaroxaban, 42 apixaban, and 4 dabigatran), which were initiated after at least 3 months of anticoagulant therapy. Median follow-up was 45 [29–55] months (vs. 62 [50–63, 65–67] in warfarin group). DOACs group was compared with 94 patients using warfarin, regarding thrombotic and hemorrhagic events. Patients treated with DOACs had an increased risk of recurrent thromboembolic events and recurrent VTE alone. No differences were found when filtered by DOACs type (rivaroxaban and apixaban) or aPL status (single, double or triple positivity). Thrombotic events were associated with older age and higher GAPSS. The authors also reported an increased risk of bleeding in the DOACs group, but statistically significant difference was lost when excluded heavy menstrual bleeding or when analyzed only gastrointestinal bleeding [80]. Both studies aforementioned concluded that DOACs are, overall, less safe than warfarin in APS patients.

Regarding costs, Ciampa et al. performed a comparison between warfarin and a hypothetical use of rivaroxaban. Taking into account number of visits, number of laboratory tests for monitoring warfarin and the direct cost of both anticoagulants, the authors concluded that switching to rivaroxaban would increase the costs in 48%, for a 69% of time in therapeutic range. There are limitations related with indirect costs, time to target therapeutic range and differences in recurrent thrombosis or bleeding episodes on warfarin versus rivaroxaban during follow up [81].

Another APS subgroups that need consideration in this review are those with APS-related cardiac valvular disease and patients with microthrombotic disease. To date, we do not have studies in these specific subsets of disease. Extrapolating data on AFib, DOACs are not approved to treat valvular AFib [1–5]. Additionally, there is one letter that reported a 39 year-old female patient that developed CAPS after switching from warfarin to rivaroxaban [82].

All major DOAC trials excluded pregnant patients. There are evidences that these drugs can cross the placenta, raising concerns of embryopathy and adverse effects on fetal and neonatal coagulation [83]. There are no clinical trials of DOACs in APS pregnant patients.

Regarding the use of rivaroxaban during breastfeeding, three observational studies have been published to date, only one with an APS patient. In all of them, rivaroxaban concentrations in breast milk were quite low, but caution should be taken until clearer safety data are published [84–86]. Studies about dabigatran, apixaban or edoxaban concentrations in breast milk are still lacking.

APS treatment guidelines

European League Against Rheumatism (EULAR) recommendations for the treatment of APS were recently published and incorporated guidance on the use of DOACs

in APS patients. The authors stated that rivaroxaban should not be used in triple-positive patients (Level of evidence 1b/Grade of recommendation B). However, it may be considered in cases that INR target is not achieved despite good adherence to VKA or in the presence of contraindications (allergy or intolerance) (Level of evidence 5/Grade of recommendation D). This latter recommendation was based in two aforementioned studies [30, 32] in this review, that reported no excessive risk of recurrent thrombosis, but samples were small, high-risk patients were under-represented, and follow-up was short. Overall level of agreement for this recommendation was 9.1 (range 0–10) [87].

American Society of Hematology (ASH) and American College of Chest Physicians (ACCP) recommendations for the treatment of venous thromboembolism made no specific recommendation regarding DOACs use in APS [88, 89].

Comments on switching DOACs to VKA

ASH guidelines provided some insights on how patients should be transitioned from DOACs to VKA. The recommendations were based on AFib, not DVT/PE, studies [88].

In patients with low-risk of recurrent VTE, VKA should be initiated on top of DOAC use. VKA dose should be titrated until target INR is achieved and, after that, DOAC should be withdrawn and VKA maintained in the same dose, until new INR evaluation. As DOACs may lead to spurious INR elevations, INR should be tested at DOAC-specific drug trough levels (i.e., 12 h after last dose of dabigatran or apixaban or 24 h after last dose of rivaroxaban or edoxaban). This can be easily accomplished by measuring INR right before next DOAC dose [88].

On the other hand, in patients with high-risk of recurrent VTE, DOAC should be replaced by LMWH or UFH bridging therapy. Then, VKA should be overlapped with LMWH or UFH until INR target is achieved. Patient's preference and ability to afford injections should be taken into account when opting for this strategy [88].

Position statement

- As both dRVVT and aPTT ratios may be influenced by the presence of DOACs, LA testing during DOACs use may lead to false-positive results, except if screen Taipan snake venom time and confirm Ecarin clotting time are available. The need for LA testing should be evaluated carefully in patients using DOACs. If LA is performed, blood collection should be performed at trough level (i.e., minimum concentration before next dose), which means 12 h after last dabigatran and apixaban dose and 24 h after last rivaroxaban or edoxaban dose. If a patient tests positive for LA during the use of DOACs, it may represent a false-positive result and the diagnosis of APS should rely on clinical features and aCL and aß2GPI immunoassays;
- aCL and aß2GPI immunoassays are not expected to be influenced by DOACs use and, therefore, are preferred for diagnosing APS in patients on DOACs;
- Based on the presented data, the gold standard treatment for APS patients is still VKA and these patients should not be routinely treated with rivaroxaban. Our opinion is that dabigatran, apixaban and edoxaban also should not be routinely used to treat APS patients, since no efficacy and safety data are available to date;
- APS patients with triple positivity and/or a history of arterial events should not be treated with rivaroxaban. These statements may also be applicable for dabigatran, apixaban or edoxaban, since no efficacy and safety data are available to date;
- In the setting of low recurrence risk (single venous event and absence of triple positivity/low risk antibody profile), DOACs may be considered for secondary prophylaxis in patients who refuse to take VKA, are allergic or intolerant to VKA compounds or have difficult or poor anticoagulant control despite good adherence.
- In patients with APS-related cardiac valvular disease or microthrombotic disease, we believe warfarin is the most appropriate treatment, and dabigatran, rivaroxaban, apixaban and edoxaban should not be used, since there is no efficacy data available and there is a report of possible harm;
- There are no published studies considering the efficacy of DOACs in primary thromboprophylaxis of APS (i.e., in patients with positive antiphospholipid antibody testing but without thrombotic manifestations of the syndrome) or in pregnant APS patients. We do not recommend the use of DOACs in these scenarios;
- Currently, we consider good practice switching APS patients taking DOACs to VKA compounds, provided no intolerance or contraindications exist for the later. In general, this can be achieved by overlapping warfarin with DOAC until the INR is in the therapeutic range. In patients receiving direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), it is important to test the INR right before the next dose (trough levels) to minimize the risk of spurious INR elevations. In high-risk patients, one can consider a transient switch from DOAC to LMWH or UFH as a "bridging therapy" while the initial VKA treatment is adjusted and until the target INR is achieved.

Conclusion

DOACs should not be routinely used in APS patients, especially in those with a high-risk profile (triple positivity to aPL, arterial thrombosis, and recurrent thrombotic events). In addition, DOACs interferes with LA testing, leading to false-positive results in patients investigating APS.

Abbreviations

aßGPI: anti-beta-2-glycoprotein I; aCL: anticardilipin; AFib: atrial fibrillation; aPL: antiphospholipid antibodies; APS: antiphospholipid syndrome; aPTT: activated partial thromboplastin time; ASTRO-APS: Apixaban for the Secondary Prevention of Thrombosis Among Patients With APS; BID: twice daily; CAPS: catastrophic antiphospholipid syndrome; DOACs: direct oral anticoagulants; dRVVT: dilute Russel's viper venom time; DVT: deep vein thrombosis; ECT: Ecarin clotting time; FDA: Food and Drug Administration; GFR: glomerular filtration rate; INR: international normalized ratio; LA: lupus anticoagulant; LMWH: low-molecular-weight heparin; MRI: magnetic resonance imaging; PAR: protease-activated receptor; PE: pulmonary embolism; QD: once daily; RAPS: Rivaroxaban in AntiPhospholipid Syndrome; RISAPS: Rivaroxaban for Stroke patients with AntiPhospholipid Syndrome; TRAPS: Rivaroxaban in Thrombotic Antiphospholipid Syndrome; TSVP: Taipan snake venom time; UFH: unfractionated heparin; VKA: vitamin K antagonists; VTE: venous thromboembolism; WMH: white matter hyperintensity

Acknowledgements

None.

Authors' contributions

All of the authors provided critical review, relevant edits, and feedback to direct content during multiple rounds of review. In addition, all authors have read and approved the final version of this manuscript.

Authors' information

All authors of this position statement are members of the Antiphospholipid Syndrome Committee of the Brazilian Society of Rheumatology. DA is also a member of the Antiphospholipid Syndrome Alliance for Clinical Trials & International Networking (APS ACTION).

Funding

None.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 28 October 2019 Accepted: 8 April 2020
Published online: 27 May 2020

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