

## Oral Direct Anticoagulants in Thrombosis Management in Anti-Phospholipid Syndrome: Unanswered Questions

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### Abstract

Anti-phospholipid syndrome comprises a broad spectrum of manifestations with thrombotic events as a serious issue. The current mainstay of treatment for thrombotic anti-phospholipid syndrome is heparin followed by long-term anticoagulation with vitamin K antagonists. Vitamin K antagonists' management in this group of patients is frequently cumbersome, requires close monitoring and may affect patient's quality of life. There is also a high recurrence rate in high risk patients. The introduction of the oral direct inhibitors of coagulation for the management for thromboembolism is currently established for several indications.

These agents are fixed dose with predictable anticoagulant effect and do not interact with dietary constituents and have few drug interactions. They have a rapid onset of action and don't routinely require monitoring. The shortcomings of vitamin K antagonists and the advantages of the oral direct inhibitors encouraged their trial in anti-phospholipid syndrome. Case series of their use paved the road for designing clinical trials aiming to study their potential role in this important group of patients.

In this article, we reviewed the literature regarding the current state of oral direct anticoagulants in thrombosis management in general, cited the case series results and presented the ongoing clinical trials that are currently underway. We also raise some practical points relevant to their application in specific situations. It is premature to pass comments on their applicability, but the seriousness of the issue

**Keywords:** Antiphospholipid syndrome; Antiphospholipid antibodies; Warfarin; Oral direct anticoagulants

syndrome (CAPS) (multiple organ thromboses commonly associated with microangiopathy [1].

### Introduction

The Anti-phospholipid syndrome (APS) whether primary or associated with auto-immune disorders can be accompanied by many thrombotic events. Possible mechanisms include the effects of inflammatory activity and antiphospholipid antibodies (aPLs). The only available oral anticoagulant drugs have been vitamin K antagonists (VKA). New oral anti-coagulants have proved their effectiveness in other situations.

It is the aim of this review to explore a possible role for the new Oral Direct Inhibitors (ODI) in the management of (APS)-associated thrombosis highlighting the possible obstacles of their use in that context.

Primary Anti-phospholipid syndrome is characterized by thrombosis and/or pregnancy morbidity occurring in patients with persistent aPLs [1]. It comprises a broad spectrum: a) asymptomatic aPL positivity (no history of thrombosis or pregnancy morbidity); b), livedo reticularis, thrombocytopenia, hemolytic anemia, cardiac valve disease, aPL-associated nephropathy, skin ulcers, or cognitive dysfunction; c) pregnancy morbidity (recurrent embryonic or fetal loss, preeclampsia, and growth restriction); d) venous, arterial, or small vessel thrombosis; and e) catastrophic Anti-phospholipid

### Anti-Phospholipid Antibodies and Thrombosis in Immune Disorders

Among 98,308 adults with auto-immune hemolytic anemia, immune thrombocytopenia, rheumatoid arthritis, or systemic lupus erythematosus (SLE), or in patients having more than one of these diseases, the risk of at least one venous thrombo-embolism (VTE) event was 19.74, 7.72, 4.90, 9.89, and 13.35 per 1,000 person-years, respectively; versus a risk of 1.91 per 1,000 person-years in 198,044 enrollees. compared retrospectively was reported [2].

Possible mechanisms include the effects of inflammatory activity and aPLs [3]. aPLs might increase the risk of VTE through various mechanisms, including affecting reactants involved in coagulation [4]. In addition glucocorticoid therapy might be associated with an increased risk of VTE [5].

Among 1000 patients from 13 European countries with APS who were followed up for 10 years, 53.1% of the patients had primary APS, 36.2% had APS associated with SLE and 10.7% APS associated with other diseases [6].

Thrombotic events appeared in 166 (16.6%) patients during the first 5-year period and in 115 (14.4%) during the second 5-year period. The most common events were strokes, transient ischaemic attacks, deep

vein thromboses and pulmonary embolism. 127 (15.5%) women became pregnant (188 pregnancies) and 72.9% of pregnancies succeeded in having one or more live births.

The most common obstetric complication was early pregnancy loss (16.5% of the pregnancies). Intrauterine growth restriction (26.3% of the total live births) and prematurity (48.2%) were the most frequent fetal morbidities. 93 (9.3%) patients died and the most frequent causes of death were severe thrombosis (36.5%) and infections (26.9%). Nine (0.9%) cases of CAPS occurred and 5 (55.6%) of them died [6].

### Is Long-Term Anti-Coagulation an Integral part of Treatment of APS?

For many decades, the only available oral anticoagulant drugs have been VKAs, which are still the cornerstone of long-term treatment of thromboembolism. This holds true for treatment of thrombotic APS, where the current mainstay is heparin followed by VKA such as warfarin [6]. Limitations of VKA uses include a narrow therapeutic window, need for repeated monitoring, many food and drug interactions and high variability of response with the need for repeated dose titration. Because of its indirect mechanism of action, the onset and offset of action with warfarin take several days.

### The Special Case of Anti-coagulation in APS

#### Optimal intensity of anticoagulation is not established

In APS patients with recurrent thrombosis and those with arterial thrombosis, the optimal intensity of anticoagulation is not established, as an insufficient number of such patients were included in the clinical trials. A number of experts state that they should be maintained at a target International Normalized Ratio (INR) of >3.0 [7] Warfarin with an INR range of 2.0 to 3.0 for patients is advised with a first venous thromboembolic event [8]. Higher anticoagulation intensity is recommended for patients presenting with arterial events. Combined therapy with warfarin and aspirin is another possibility.

#### Optimal duration of anti-coagulation

On the basis of an increased risk of recurrence during the first 6 months following warfarin withdrawal, long-term anticoagulation is considered the standard treatment [9]. Due to long term and variability of action, this may pose a problem in APS accompanied by thrombocytopenia.

#### Suboptimal anti-coagulation monitoring

Inaccuracy of INR due to antiphospholipid antibodies with variable responsiveness of thromboplastin reagents to aPL, which may potentially influence the validity of the prothrombin time (PT)/(INR) [10] may occur.

#### High recurrence rate is observed also on warfarin treatment in high risk APS patients [11]

Therefore, VKA management in APS patients is frequently cumbersome, requires close INR monitoring and may affect patient's quality of life [12].

### New Oral Anticoagulants: The Direct Oral Inhibitors

The introduction of the ODI of coagulation, also known as new generation oral anticoagulants (NOAC) for the management of thromboembolism is currently established in many indications. These include the direct thrombin inhibitor (DTI) dabigatran etexilate (Pradaxa®) [13], and the direct anti-factor Xa inhibitors rivaroxaban (Xarelto®) [14], apixaban (Eliquis®) [15], and edoxaban (Lixiana®) [16] (Table 1).

These agents, unlike warfarin, have the advantage of a fixed dose with predictable anticoagulant effect, do not interact with dietary constituents or alcohol, and have few reported drug interactions that affect anticoagulant intensity.

ODIs inhibit only a single target-either factor Xa or thrombin- and have a rapid onset of action such that peak plasma levels are achieved 1 to 4 hours after oral administration. With half-lives of about 12 hours, the ODIs also have a rapid offset of action [17]. All-oral regimens of rivaroxaban and apixaban are available out-of-hospital treatment [17]. Furthermore, monitoring of anticoagulant intensity of ODIs is not routinely required due to their predictable anticoagulant effects.

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Factor targeted	Xa	Xa	Xa	Thrombin
Bioavailability	>80%	>50%	>50%	6%
Plasma protein binding	92-95%	87%	40-59%	34-35%
Peak level in hours	3	3	2-Jan	2
Half lifetime	9	14-Sep	11-Sep	14-17
Dose/day	1	1	1	2
Renal Elimination	66%	25%	35%	Renal (80% unchanged) dialyzable

Table 1: Direct oral anti-coagulants [13-16].

#### ODI drug interactions

Plasma levels may be affected by P-glycoprotein inducers or inhibitors [18]. Cytochrome P450 CYP3A4 involved in hepatic clearance of rivaroxaban and apixaban – plasma levels may be affected by CYP3A4 inducers or inhibitors [19].

#### The Established Success of ODI and Future Expectations

These agents have been approved for several therapeutic indications based on phase III prospective randomised controlled clinical trials using warfarin at a target INR of 2.5 (i.e. range 2.0-3.0) as the comparator.

Rivaroxaban, Apixaban and Dabigatran are currently licensed by the European Medical Agency and approved by the Food and Drug Administration for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery

and the prevention of stroke and systemic embolism in eligible adult patients with nonvalvular atrial fibrillation.

The treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent DVT and PE following an acute DVT in adults was also licensed for Rivaroxaban and Phase III trials on treatment of DVT and PE with Apixaban, Dabigatran and Edoxaban have been completed [20-24].

Strong recommendation for ODI use in European Society of Cardiology guidelines 2012 for patients with atrial fibrillation; and also recommendation for VTE treatment in American College of Chest Physicians guidelines, 2012 have been reported [8,25].

### Is there a need to monitor ODI effect?

Routine monitoring is not required. Prothrombin time reagents show very poor sensitivity to ODI action, and the activated partial thromboplastin time (aPTT) may also be prolonged because of lupus anticoagulant [26-31]. A chromogenic

antifactor Xa and chromogenic anti-IIa assays in combination with appropriate specific calibrators provide a quantitative measure of rivaroxaban or apixaban and dabigatran activity, respectively, but these assays are not widely available [28,32].

Measurement of the anticoagulant effect of ODI, which is challenging, may be needed in clinical circumstances such as bleeding, potential drug interactions, extreme body weight, deteriorating renal function, perioperative management, reversal of anticoagulation, suspicion of overdose, and assessment of adherence [28]. Assessment of ODI concentrations must be interpreted in relation to the timing of drug administration in accordance with the pharmacokinetic profile of drugs [33].

### Lessons from Clinical Experience with ODI Use in APS

Although phase 3 trials including a significant number of patients have given credibility to ODI use in thromboembolism, no APS subgroup studies were highlighted in these trials [20-24].

Three APS patients who had had no thromboembolism recurrence on warfarin but were switched to ODIs were reported at Mayo Clinic Center [34]. They included a woman with primary APS that developed thrombotic endocarditis with symptomatic cerebral emboli after transition to dabigatran, another woman with primary APS experienced ischemic arterial strokes and right transverse-sigmoid sinus thrombosis after conversion to rivaroxaban and a man with secondary APS who suffered porto-mesenteric venous thrombosis after switching to rivaroxaban.

None of these patients had failed warfarin prior to the transition to ODI. A case series of 12 patients and previous single VTE episode and/or ischemic stroke (7 women and 5 men; mean age  $42 \pm 10$  years) who were switched from VKAs (warfarin or acenocoumarol) to rivaroxaban for at least 2 months were reported [33]. Prior to the switch, the target INR range was between 2.0 and 3.0, with the value on the day of the first dose of rivaroxaban between 1.9 and 2.5. Patients with a history of stroke and/or multiple risk factors for thrombotic events additionally received low-dose acetylsalicylic acid.

The duration of treatment with rivaroxaban (20 mg daily) in secondary prevention of VTE ranged from 2 to 16 months. In all cases the change of anticoagulation therapy was due to logistic problems with INR monitoring that interfered with the professional activities of

the patients and/or unstable INR values resulting in time in the therapeutic range below 50%.

Two cases showed thrombotic recurrence [33] as follows:

**Case 1:** A 36-year-old female with APS and coexisting systemic lupus erythematosus (SLE) was treated with warfarin for 19 months following idiopathic DVT. She was managed with rivaroxaban for 5 months before developing a second DVT during the exacerbation of SLE. Her antiphospholipid antibodies involved positivity for lupus anticoagulant (LA), elevated immunoglobulin G (IgG) anti-beta-2 glycoprotein I antibodies ( $\alpha\beta 2\text{GPI}$ ; 99.2 SGU) and IgG anti-cardiolipin antibodies (aCL; 36.7 GPL) above the 99th percentile.

**Case 2:** A 56-year old female with APS and coexisting SLE was initially treated with acenocoumarol and low-dose ASA for 44 months before switching to rivaroxaban. Her history was significant for ischemic stroke, idiopathic DVT and hypertension. While on remission of SLE, she developed a second DVT following a minor lower limb injury with a 7-day enoxaparin use instead of rivaroxaban. After 2 weeks while back on rivaroxaban the symptoms of DVT occurred. The patient was managed with rivaroxaban for 2 months prior to the accident and DVT. The patient was positive for LA, high IgM  $\alpha\beta 2\text{GPI}$  (203.1 SMU), as well as IgG aCL (72.3 GPL) and IgM aCL (190.1 MPL) above the 99th percentile each [33].

### In The Pipeline; Ongoing Phase 3 and 4 Clinical Trials of ODI in APS

#### Rivaroxaban studies

1) Prospective randomised controlled phase II/III clinical trial of rivaroxaban versus warfarin in patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS) trial ( sponsored by Arthritis Research UK and Bayer PLC) [35].

This is an open label prospective non-inferiority randomized controlled phase II/III trial (RCT) in patients with thrombotic APS, with or without (SLE), who have had either a single episode of VTE while not on anticoagulation or recurrent episode(s) which occurred while off anticoagulation or on sub-therapeutic anticoagulant therapy.

Following at least three months of warfarin, 156 patients are randomized to remain on warfarin (target INR 2.5) or to switch to rivaroxaban 20 mg once daily (with consideration of dose reduction to 15 mg once daily for renal insufficiency [creatinine clearance 30-49 ml/min]).

Thrombin generation is compared 42 days after randomisation in the two groups, assessed by the thrombin generation test, with the endogenous thrombin potential a key parameter.

The trial started: 30/11/2012, overall trial end date 31/01/2015 and recruitment is closed. 2) Rivaroxaban in Antiphospholipid Syndrome Pilot Study: A Multicenter Feasibility Study of Rivaroxaban for Patients with Antiphospholipid Syndrome and Prior Arterial or Venous Thrombosis [36].

A multicenter Phase IV trial led by the team of St. Joseph's Healthcare, Hamilton, Canada : It studies the ability to identify and recruit 150 eligible patients at 6 clinical centres over 18 months with compliance success as a patient missing fewer than 5% of days with pill administrations, as measured by pill counts. It started in June, 2014 and the estimated completion date is December 2016.

3) A third prospective, randomized clinical trial Comparing Rivaroxaban vs Warfarin in High Risk Patients With Antiphospholipid Syndrome (TRAPS) [37]: A multicentre, interventional, prospective, parallel, randomized, controlled, open-label, phase III Rivaroxaban 20 mg qd (or 15 mg qd in patients with moderate renal insufficiency) vs warfarin (INR target 2.5), non-inferiority study, in 536 triple aPL-positive APS patients in approximately 40 Internal Medicine and Thrombosis centres. The leading centre is University of Padova, Italy.

The cumulative end point of incident acute thrombosis (arterial or venous) confirmed by appropriate imaging studies, major bleedings, and death in triple aPL-positive APS patients will be compared. The study started December 2014 and ends in December 2018.

### Apixaban studies

4) Apixaban for the Secondary Prevention of Thromboembolism Among Patients With the Antiphospholipid Syndrome (ASTRO-APS), sponsored by the Intermountain Health Care, Inc., Bristol-Myers Squibb [38].

It is a prospective, randomized, open-label blinded endpoint pilot phase II/III study among 200 patients with a clinical diagnosis of APS and are already taking an anticoagulant for the secondary prevention of thrombosis .

Subjects will be randomized to receive either warfarin (target INR range 2-3) or apixaban 2.5 mg twice daily. The study started February 2015 with estimated completion in December 2017.

## Questions that Need to be Addressed with ODI Use

### ODI Dose modification, when are they needed?

Neither rivaroxaban nor apixaban are recommended in patients with severe renal impairment (creatinine <15 ml/min), or in patients with hepatic disease associated with coagulopathy, clinically relevant bleeding risk, or severe hepatic impairment [14,15]. Rivaroxaban dose reduction is allowed with creatinine clearance of 30-49 ml/min) [14].

Dabigatran is predominantly excreted by the kidneys (80% unchanged). It is contraindicated in patients with severe renal impairment (CrCL <30 mL/min). No treatment experience is available for patients with elevated liver enzymes [13].

### Is peri-operative bridging needed in cases receiving ODI?

ODIs have predictable pharmacokinetics, a relatively short half-life and a rapid onset of action after oral administration, and, therefore, unlike with warfarin, bridging with a parenteral anticoagulant, generally LMWH, is not required when they are discontinued before or initiated after surgery [39,40].

### How can we switch from one anti-coagulant to the other?

The necessity to convert patients from one anticoagulant to another needs careful assessment of coagulation profile in case of VKA and good history taking to define exact timing of switching to avoid over or under coagulation as follows [25,41].

### VKA to ODI

If INR is less than 2.0, then immediate switch is recommended. If INR 2.0–2.5. Then the choice is between immediate and next day switch is allowed. However, if INR is more than is 2.5: use of INR and VKA half-life to estimate time to fall of INR to less than 2.5 before switch is mandatory.

### ODI to LMWH s.c. and vice versa

Alternative anticoagulant is started when next dose would have been given.

### ODI to VKA

Both anticoagulants are administered concomitantly until INR reaches an appropriate range. INR is measured just before next intake of ODI and is retested 24 hours after last dose of ODI and is monitored in first month until stable values (2.0–3.0) achieved.

### ODI to ODI

Alternative anticoagulant is initiated when next dose is due except where higher plasma concentrations are expected (e.g. renal impairment).

## How Can we Manage Bleeding with ODI?

ODI have no current antidotes but are luckily short acting. Dose delay is necessary in minor bleeds. Local compression is necessary with supportive measures as activated charcoal for recent ingestion of dabigatran or rivaroxaban in major bleeds. Gastrointestinal bleeding is more common with dabigatran use. Hydration is important to enhance renal clearance of both rivaroxaban and dabigatran.

Temporary hemostatic support with Plasma Complex concentrate PCC, activated PCC, e.g. factor VIII inhibitor bypass activity (FEIBA), or recombinant factor VIIa (rVIIa) as well as antifibrinolytic therapy (tranexamic acid) can be used . Renal replacement therapy should be considered for dabigatran which is dialyzable [42-46].

The utility of ODIs for VTE treatment in vulnerable patients, such as those who are morbidly obese, those of very low body weight, pregnant women, nursing mothers, those with serious thrombophilic defects or those requiring concomitant antiplatelet therapy , remain to be established [17].

## Conclusion

Up till now, there is no consensus regarding ODI use in APS. Oral direct inhibitors can be considered in APS patients with a first or recurrent VTE occurring off or on sub-therapeutic anticoagulation, only when there is known VKA allergy/intolerance or poor anticoagulant control [42]. At this point, ODI are not of first choice, although there have been several case series reports of their use in this context with conflicting results.

The management of APS, either primary or secondary, entangles dealing with other autoimmune diseases. Autoimmune diseases, with SLE on top of the list, together with APS, naturally, are characterized by being multisystem diseases. Patients are managed using polypharmacies. They are also chronic disorders that require treatment for long periods of time. This creates a need for utmost attention to all the clinical pharmacological aspects of a newly

introduced group of drugs. This is exceptionally important when it entangles a serious issue like thrombosis management.

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