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Non-vitamin K antagonist oral anticoagulants and antiphospholipid syndrome

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Abstract. The current treatment of thrombotic APS patients includes long-term anticoagulation with oral vitamin K antagonists (VKAs), with warfarin being the one most commonly used. However, the use of VKAs can be challenging, especially in patients with APS. VKAs monitoring in patients with aPL is complicated by the heterogeneous responsiveness to LAs of reagents used in the International Normalized Ratio test, potentially resulting in instability of anticoagulation. For decades, VKAs were the only available oral anticoagulants. However, non-VKA oral anticoagulants, including a direct thrombin inhibitor (dabigatran etexilate) and direct anti-Xa inhibitors (rivaroxaban, apixaban and edoxaban), are currently available. The use of these agents may represent a major step forward since, unlike VKAs, they have few reported drug interactions and they do not interact with food or alcohol intake, thereby resulting in more stable anticoagulant intensity. Most importantly, monitoring their anticoagulant intensity is not routinely required due to their predictable anticoagulant effects. In this review, we discuss the clinical and laboratory aspects of non-VKA oral anticoagulants, focusing on the available evidence regarding their use in patients with APS.

Introduction. APS is characterized by thrombosis (venous and/or arterial) and/or pregnancy morbidity in association with persistently positive aPL, namely LA, aCL and/or anti-β2-glycoprotein I antibodies. Persistent aPL positivity is defined when LA, aCL and/or anti-β2-glycoprotein I antibodies are detected on a minimum of two consecutive occasions at least 12 weeks apart in accordance with the international (Sydney) consensus statement criteria [1, 2]. Thrombosis in APS can potentially occur in any vessel of the body, in arteries, veins and the microcirculation [1]. The long-term management of thrombosis in APS patients is based on vitamin K antagonists (VKAs), with warfarin being the one most frequently prescribed. The anticoagulant effect of VKAs is monitored using the International Normalized Ratio (INR) based on the PT of the patient. Current recommendations in APS are to use VKAs with a target INR of 2.5 (range 2.0–3.0) for an indefinite period following a first episode of venous thromboembolism (VTE), or a recurrent VTE event that occurs while off anticoagulation [3, 4]. In patients with recurrent thrombosis despite therapy with VKAs with a target INR of 2.5 (range 2.0–3.0), a target INR of >3.0 may be taken into consideration [4]. The optimal management of patients with aPL with arterial thrombosis is still controversial, and includes either VKAs therapy with a target INR of >3.0 or the association of antiplatelet agents and VKAs with a target INR of 2.5 (range 2.0–3.0) [2, 4]. For decades, VKAs were the only available oral anticoagulants. However, problems with VKAs, including the narrow therapeutic window and numerous interactions (both drug and dietary), are well known. Routinely monitoring the INR is essential to maintaining the target therapeutic range, however this is costly and inconvenient. Moreover, INR monitoring in patients with aPL is further complicated by the heterogeneous responsiveness to LAs of reagents used in the INR test, potentially resulting in instability of anticoagulation, with frequent INR tests not necessarily reflecting the true level of anticoagulation. LA testing in patients on VKAs may be challenging due to the prolonged basal clotting time, which limits the test's diagnostic accuracy. Options for anticoagulation have increased steadily over the past few decades, with a greater number of agents for the prevention and management of thromboembolic disease. In addition to heparin and VKAs, anticoagulants that directly target the enzymatic activity of thrombin and factor Xa have been developed.Non-VKA oral anticoagulants (NOACs) are currently available, including a direct thrombin inhibitor (dabigatran etexilate) and direct anti-Xa inhibitors (rivaroxaban, apixaban and edoxaban). The use of these agents may represent a major step forward since, unlike VKAs, they have few reported drug interactions and they do not interact with food or alcohol intake, thus resulting in more stable anticoagulant intensity [5, 6]. Furthermore, laboratory monitoring of the anticoagulant intensity of NOACs is not routinely required due to their more predictable anticoagulant effects. Their efficacy has been demonstrated in large phase III clinical trials, and both rivaroxaban and

dabigatran have been approved for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF) [5, 6]. Rivaroxaban and apixaban were licensed for the treatment of deep vein thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism (PE) following acute DVT in adults based on the results of the EINSTEIN-DVT, EINSTEIN-PE study and AMPLIFY international multicentre randomized trials [7–10]. Similarly, the RE-COVER trial showed that for the treatment of acute VTE, a fixed dose of dabigatran was as effective as warfarin, had a safety profile that was similar to that of warfarin, and did not require laboratory monitoring [11]. Table 1 summarizes the main features of NOACs [12–14].

As stated above, thrombosis management in patients with APS centres on VKAs at a target INR of 2.5 (range 2.0–3.0) for an unspecified period of time after a first episode of VTE, or a recurrent VTE event occurring while off anticoagulation [2, 3]. However, in APS patients with recurrent thrombosis and those with arterial thrombosis, the optimal intensity of anticoagulation is still debated, as a limited number of such patients were included in the clinical trials. Although most opinion leaders in APS consider maintaining a target INR of >3.0 a valid therapeutic option, there is still no consensus on the issue [2]. This aspect plays a pivotal role when considering the use of NOACs in APS. In fact, it is worth mentioning that in randomized control trials (RCTs) assessing the therapeutic dose of NOACs*vs* VKAs, warfarin at a target INR of 2.5 (i.e. range 2.0–3.0) has been used as the comparator [7, 8, 11, 15]. Table 2 summarizes the available reports regarding the use of NOACs in APS [16–24]. In the largest series reported to date [17], a preliminary experience using rivaroxaban in patients with APS with previous VTE and poor anticoagulation control with VKAs showed a good safety and efficacy profile in a study population of 35 patients with APS. Twenty-four had previous DVT and 11 had both DVT and PE. They were all receiving a VKAs and had a target INR of 2–3; those requiring a higher target INR were excluded. The included patients' time in therapeutic range was 65% or lower. Indications for switching from a VKA to rivaroxaban 20 mg OD for the secondary prevention of VTE included erratic INR control [median 13 (9–23) INR tests within the last 6 months] in 29 patients and INR consistently in the sub-therapeutic range in six patients. One could speculate that some patients with APS were included in the study populations in the phase III clinical trials of rivaroxaban or dabigatran vs VKA administration in patients with VTE. However, the aPL profile was not reported in these trials [8, 11, 15], and thus prospective studies on the use of NOACs in APS are currently on-going. Rivaroxaban in APS (IRSCTN 68222801) is a prospective, randomized controlled trial of warfarin vs rivaroxaban in patients with thrombotic APS (with or without SLE) being maintained at a target INR of 2.5 (i.e. range 2.0–3.0) [25, 26]. Rivaroxaban in APS has recently stopped recruiting participants and the results are anxiously awaited. Another trial, Rivaroxaban in Thrombotic APS (NCT02157272) is currently recruiting patients with aPL and a history of thrombosis (objectively proven arterial, venous and/or biopsy proven microthrombosis). Taken together, the available reports seem to support the use of NOAC therapy for secondary thromboprophylaxis for APS patients with previous VTE who require a target INR of 2–3. The use of NOACs in patients with previous arterial thrombosis or in patients requiring a target INR >3 is still a matter of discussion.

Laboratory monitoring of new oral anticoagulants

As compared with VKAs, NOACs have shown more stable pharmacokinetics and pharmacodynamics, relatively few food and drug interactions, and a broader therapeutic window, thus ensuring a much more predictable anticoagulant effect. The use of fixed doses of NOACs seems to eliminate the need for routine laboratory monitoring. However, selected scenarios should be considered including the following: acute thrombotic events under NOAC treatment, so as to distinguish between inadequate anticoagulation due to non-compliance and treatment failure; overdosing (accidental or deliberate), which may potentially increase the bleeding risk; acute ischaemic strokes, since the presence of NOACs could impact on the decision regarding the use of a tissue-type plasminogen activator; extremes of body weight; and renal or hepatic impairment (as discussed below). Furthermore, laboratory testing could also play a crucial role in patients receiving NOACs who require semi-urgent surgery since knowing the drug concentration or anticoagulant activity would help the physician to balance the risk of bleeding against the consequences of delaying the procedure [27, 28]. A number of routine coagulation assays have been tested to assess coagulation status in patients receiving NOACs. Generally speaking, tests such as PT and aPTT cannot provide an accurate quantitative measurement of the anticoagulant effect and/or plasma drug concentration. In detail, dabigatran is a direct thrombin inhibitor, making PT insufficiently sensitive in detecting therapeutic levels of the agent or for measuring the anticoagulant activity [29, 30]. Although higher doses of dabigatran have been associated with a prolongation of the aPTT [31], the concentration–response relationship appears linear only for concentrations higher than 200 ng/ml [32], thus not making aPTT the ideal tool for estimating dabigatran levels. However, it is worth noting that a normal aPTT may rule out significant

anticoagulation in patients treated with dabigatran. This makes aPTT suitable as a potential qualitative marker of activity, but inappropriate for quantitative assessment. Conversely, ecarin clotting time provides a quantitative assessment of dabigatran activity; however, this test is not routinely available [27, 33–35].Direct anti-Xa inhibitors prolong the PT in a concentration-dependent manner, with rivaroxaban appearing to have a greater effect [36]. However, in patients receiving direct anti-Xa inhibitors, the degree of PT prolongation depends on thromboplastin reagents, thus limiting the use of this test to the quantitative assessment of the anticoagulant effect of rivaroxaban or apixaban [34]. On the other hand, the PT may prove to be useful if qualitative assessment of the presence or absence of rivaroxaban is desired. INR monitoring is not appropriate for rivaroxaban [6, 27, 28]. Anti-factor Xa assays can provide a quantitative measure of rivaroxaban activity, but their availability is generally limited to specialized coagulation laboratories.

Lupus anticoagulant testing and NOACs

Detection of LA according to the guidelines of the Scientific and Standardization Committee on lupus anticoagulant/phospholipid-dependent antibodies includes screening, mixing and confirmation tests performed on at least two different principles [37]. Performing LA testing in patients on anticoagulation is generally not recommended as they have prolonged basal clotting times and LA reagents can have heterogeneous sensitivity to anticoagulants [38]. Similarly to VKAs, detecting and monitoring LA may be affected by NOACs. Table 3 summarizes the available evidence reporting the effect of NOACs on LA testing [17, 39–43]. To date, LA testing in patients receiving NOACs would appear to be unreliable [17]. False positive dRVVT may occur with rivaroxaban, mainly at peak therapeutic plasma levels (165–270 ng/ml). The observation that dRVVT is the test most often affected by rivaroxaban is not surprising, as Russell's viper venom and rivaroxaban share the same target (factor Xa). Some studies suggested that ratios using taipan/ecarin snake venoms, which directly activate prothrombin, can be used to detect LA as they do not seem to be affected by the presence of direct factor X inhibitors [39, 40]. However, in our experience, false-positive results were seen with all types of LA testing, suggesting that they cannot be used diagnostically for patients receiving NOACs [17]. Nonetheless, this needs to be confirmed in studies designed specifically to address this issue.

Renal and hepatic impairment

Either adjusting the dose or avoiding NOACs altogether should be considered in case of renal impairment. Since all NOACs are at least in part eliminated by the kidneys, impairment of renal function may significantly affect the blood levels of these drugs. Special attention is required when considering dabigatran for patients with renal impairment since about 80% of the dose is eliminated through the urine [44]. In a subgroup analysis of the RE-LY trial (the Randomized Evaluation of Long-Term Anticoagulation Therapy With Dabigatran Etexilate), patients with moderate renal impairment (creatinine clearance 30–50 ml/min) showed a 3-fold increase in dabigatran plasma concentrations as compared with patients with normal renal function, resulting in a higher rate of haemorrhagic complications [45]. The Summary of Product Characteristics recommends reducing the dabigatran dose to 150 mg OD in case of moderate renal impairment and avoiding its use in patients with severe renal impairment (creatinine clearance of <30 ml/min) [5]. Dose adjustment of rivaroxaban is usually not required in patients with mild renal impairment (creatinine clearance 50–80 ml/min). In patients with VTE who have moderate renal impairment (creatinine clearance 30–49 ml/min), a reduction of the rivaroxaban dose (from 20 to 15 mg OD) has to be taken into consideration when the risk of bleeding outweighs the risk of recurrent thrombotic episodes. Special care should be taken in patients with a creatinine clearance of 15–29 ml/min receiving direct fX inhibitors. Finally, the use of rivaroxaban is not recommended in patients with severe renal impairment (creatinine clearance <15 ml/min) [6]. A recent open-label study evaluating apixaban pharmacokinetics, pharmacodynamics and safety in subjects with mild, moderate or severe renal impairment and in healthy subjects following a single 10-mg oral dose concluded that dose adjustment of apixaban does not seem to be required on the basis of renal function alone [46]. However, to date, as with rivaroxaban, apixaban is not recommended in patients with severe renal impairment [47], and further studies are warranted to investigate this aspect. Phase III trials for NOACs predominately excluded patients with active liver disease. Hepatic impairment can affect the disposition of NOACs considerably, not only because of the hepatic metabolism of the direct FXa inhibitors but also because moderate to severely impaired hepatic function will affect coagulation.

Tailored labelling restrictions stated in Summary of Product Characteristics for rivaroxaban, apixaban and dabigatran regarding impaired hepatic function are based on both the Child–Pugh classification and on liver-related exclusion criteria applied in pivotal clinical trials [5, 6, 47, 48]. Rivaroxaban is not recommended in patients with coagulopathy caused by hepatic disease and clinically relevant bleeding risk, including cirrhotic patients classified as Child–Pugh B and C. Administering apixaban can be considered with caution in cases of mildly (Child–Pugh A) or moderately (Child–Pugh B) impaired liver function or in patients with alanine aminotransferase and aspartate aminotransferase levels >2 times upper limit of normal. Apixaban is contraindicated in patients with severe hepatic impairment and in those with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Dabigatran is not recommended in subjects with elevated liver enzymes (>2 times upper limit of normal). Dabigatran is not indicated in patients with hepatic impairment or severe liver disease that is expected to have any impact on survival [48].

Pregnancy and breastfeeding

APS can affect young women of childbearing age. To date, all NOACs should be avoided in pregnancy and during breastfeeding, and thus special care is needed when prescribing anticoagulation to women of fertile age [5, 6, 47]. Haemorrhagic complications associated with embryo-fetal toxicity have been observed in animal models receiving rivaroxaban at clinically relevant plasma concentrations [49]. Similarly, since there are no data on the use of NOACs in pregnancy, as with rivaroxaban, dabigatran and apixaban, NOACs should be avoided in this setting.

Potential interactions with food and concomitant drugs

Unlike VKAs, NOACs have few reported drug interactions and they minimally interact with food and alcohol intake. However, close monitoring for potential interactions when initiating treatment with NOACs or when any change in concomitant treatment occurs is still desirable. Rivaroxaban should be taken with food, as a decrease of about 40% in absorption when administered without food has been reported [50]. Concomitant administration of dabigatran and proton pump inhibitors have been shown to decrease the absorption of dabigatran by 30%. However, no change in dose is currently recommended [51]. NOACs have drug–drug interactions mediated by the permeability glycoprotein (P-gp) efflux transporter protein alone (dabigatran etexilate, edoxaban) or in combination with cytochrome P450 3A4 (CYP3A4) enzymes (rivaroxaban, apixaban). Simultaneous use of potent P-gp inhibitors (e.g. systemic ketoconazole, ciclosporin and dronedarone) and NOACs is not recommended for dabigatran etexilate. Similarly, the concomitant use of inhibitors of both P-gp and CYP3A4 (e.g. azole antimycotics, HIV protease inhibitors) is generally contraindicated for direct FX inhibitors due to decreased exposure and effect. Finally, NOACs have interactions with antiplatelet agents and NSAIDs, with a consequent increase in bleeding risk. Combining NOACs with antiplatelet therapy is generally discouraged outside selected scenarios (e.g. acute coronary syndromes or stenting) and close monitoring is needed when patients are treated concomitantly with NOACs and antiplatelet agents or NSAIDs. A complete list of interactions can be consulted in the approved product labelling [5, 6, 47]. Some agents, including carbamazepine, rifampicin, phenobarbital and phenytoin, are known to reduce the plasma concentration of both rivaroxaban and dabigatran, and therefore simultaneous use should be avoided [5, 6]. Conversely, clarithromycin, amiodarone and quinidine may increase dabigatran levels, therefore close clinical monitoring for bleeding, especially in high risk patients (e.g. aged over 75 years, low body weight or patients with creatinine clearance 30–50 ml/min) is highly recommended [5].

Adverse effects of new oral anticoagulants – bleeding complications.

Bleeding risk is the major fear with any anticoagulant. Based on phase III clinical trials involving >50 000 patients and the available clinical experience reported so far, the overall risk of bleeding complications with NOACs at therapeutic doses is comparable to that of VKAs, with lower rates of intracranial haemorrhage in the AF studies [52, 53]. A recent meta-analysis attempted to quantify the relative odds of fatal bleeding in patients on NOAC vs VKA therapy [54]. Twenty trials were included in the meta-analysis reporting 4056 first-time, major bleeding events. The computed odds ratio for fatal bleeding given that a major bleeding event occurred was 0.65 (95% CI: 0.52, 0.81) favouring the NOAC agents (P = 0.0001). However, it is worth noting that the reduced odds of fatal bleeding with NOACs was not demonstrated after controlling for bleeding location. One could speculate that the fatal bleeding risk reduction was due to a disproportionate amount of intracranial bleeding in the VKA arms.

Some further considerations are warranted. The incidence of major bleeding with rivaroxaban and VKAs was similar (3.6 vs 3.45%) in the ROCKET-AF study [55] and lower (0.8% vs 1.2%) in the Einstein-Extension Study [56]. However, mucosal bleeding (mainly genitourinary, gingival, epistaxis and gastrointestinal) and anaemia were seen more frequently during long-term rivaroxaban compared with VKAs [54]. Similarly, in our preliminary experience [17], we observed no major bleeding events or severe side-effects except for two women in whom worsening of menorrhagia was seen. Dabigatran was shown to be as effective as warfarin for the acute treatment of VTE. When pooling data from the RE-COVER and RE-COVER II trials comparing the incidence of bleeding with dabigatran vs VKAs [57], Majeed and co-workers reported that the incidence of any bleeding event was significantly lower with dabigatran [hazard ratio (HR) 0.70; 95% CI: 0.61, 0.79], as was the incidence of the composite of major bleeding events and clinically relevant non-major bleeding events (HR 0.62; 95% CI: 0.50, 0.76). The incidence of major bleeding events was also significantly lower with dabigatran in the double-dummy phase (HR 0.60; 95% CI: 0.36, 0.99) but not statistically different in the two treatment arms when the entire treatment period was considered. In this analysis, increasing age, reduced renal function, Asian ethnicity and concomitant antiplatelet therapy were associated with higher bleeding rates in both treatment groups.

Management of bleeding associated with new oral anticoagulants

The general principles of bleeding management are similar whether patients are on VKAs or NOACs [58–60]. Importantly, special attention should be paid to time since the last dose of NOACs and the concomitant use of other medications that can potentially increase the bleeding risk (antiplatelet agents and NSAIDs) or interfere with NOAC metabolism. Currently, supportive strategies are the mainstay for the treatment of bleeding with NOACs, and include discontinuation of the drug, mechanical compression, surgical haemostasis measures and administration of transfusion support; and because the half-life of these agents is short, they will, unlike VKAs, quickly disappear from the circulation [58–60]. Conversely, management of major or life-threatening bleeding or emergency surgery is challenging. Haemodialysis plays a role in reversing the anticoagulant effect of dabigatran overdose or severe bleeding because of low protein binding of this agent, thus resulting in the potential removal of about 60% of the drug over 4 h [5, 44]. Conversely, dialysis is not effective for patients treated with apixaban or rivaroxaban because of the high protein binding (over 85% for both). An in vitro study showed that oral activated charcoal can reduce the absorption of dabigatran (in < 3 h) [58]. Due to the current absence of specific antidotes, general haemostatic agents have been used to reverse the anticoagulant effect of NOACs. These agents include prothrombin complex concentrate (PCC), an activated PCC (aPCC) and recombinant factor VII activated (rFVIIa) (Table 4). Preclinical and phase-I studies have shown that in healthy individuals [58, 61–63], PCCs have the ability to reverse the effect of apixaban and rivaroxaban, but not dabigatran. It should be emphasized that all studies in humans have been conducted on healthy individuals. Moreover, there are insufficient data to recommend a 4-factor PCC over a 3-factor PCC or vice versa in this scenario, even though data supporting the use of 4-factor PCC seem to be more consistent [64–66]. The use of activated PCC (e.g. factor VIII inhibitor bypass activity) appears promising for NOAC reversal, particularly for patients treated with dabigatran. However, one should bear in mind that aPCC could potentially increase the thromboembolic risk. The current use of rFVIIa is not supported by solid data, and available evidence seems to indicate that rFVIIa is less consistently effective when compared with PCC or aPCC. Target antidotes are currently at various stages of clinical development. A humanized monoclonal antibody fragment (aDabiI-Fab, idarucizumab) is being tested to establish whether it can reverse the effect of dabigatran. An interim analysis from the RE-VERSE AD trial showed that idarucizumab completely reverses the anticoagulant effect of dabigatran within minutes (ClinicalTrials.gov, no. NCT02104947) [67]. Preliminary results of a phase II trial in healthy individuals showed that andexanet reverses the effect of apixaban and rivaroxaban. Andexanet is a human recombinant FXa variant with modifications that make it catalytically inactive, maintaining a high affinity binding directed at FXa inhibitors [68]. PER977 is a synthetic small molecule that binds oral thrombin and FXa inhibitors in a non-covalent way, thereby preventing them from exerting an anticoagulant effect. Studies in humans to investigate its ability to reverse the effect of NOACs are currently under way (ClinicalTrials.gov, no. NCT02207257/NCT01826266) [68].

Conclusion

In summary, existing evidence suggests that the use of NOACs for secondary thromboprophylaxis for APS patients with previous VTE is promising. Until new data from on-going clinical trials are available, there is not enough evidence to consider using NOACs in patients with APS and previous arterial events. LA testing in patients receiving NOACs may be unreliable.

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TABLE 1
Pharmacological characteristics of NOACs

		Factor Xa inhibitor	
Characteristics	**Direct thrombin inhibitor**		
Agent	**Dabigatran**	**Rivaroxaban**	**Apixaban**
Molecular mass, Da	628	436	460
Target	Thrombin	FXa	FXa
Prodrug	Yes (as etexilate)	No	No
Bioavailability, %	3–7	80	50
Time to peak concentration (h)	1–3	2–4	1–3
Protein binding (%)	35	92–95	87
Half-life (h)	12–17	7–13	18–15
Metabolism	Glucuronidation (<10%)	CYP3A4 > CYP2J2	CYP3A4/5 > CYP21A2, SC8, 2C9/19, 2J2
Excretion	80% renal	33% renal	25% renal
	20% liver	67% liver	75% fecal

FXa, activated factor X; NOAC: non-vitamin K antagonist oral anticoagulants; h: hours.

TABLE 2
Clinical evidence for the use of NOAC in APS

Article	Year	Type of article	No. of patient (age, years)	Follow-up, months	NOA	Initial manifestation of APS	Indication for changing anticoagulation	Outcome
Bachmeyer*et al.* [19]	2014	CR	1 (28)	N/A	Rivaroxaban	Recurrent ST	Relapse on fondaparinux	No thrombotic relapse
Delgado *et al.* [20]	2015	CR	1 (77)	24	Rivaroxaban	AT	Recurrence on VKA (INR 2.3)	Arterial recurrence on rivaroxaban
Joalland *et al.* [21]	2014	CR	1 (17)	6	Rivaroxaban	Cutaneous lesions and DIC	N/A	New relapse on rivaroxaban, switched to VKA (INR 2.5–3.5)
Schaefer*et al.* [24]	2014	CS	3 [median age 43 (32–59)]	5–6	Dabigatran (n = 1), rivaroxaban (n = 2)	AT and VTE (n = 1), AT (n = 1), VTE (n = 1)	INR instability and bleeding on VKA (n = 1), logistic problems with INR monitoring (n = 1), VKA failure (n = 1)	CVE (n = 3)
Son *et al.*[22]	2014	CS	12 [mean age 42 (s.d. 10), years]	2–16 months	Rivaroxaban (ASA)	VTE/ischaemic stroke (n = 2)	INR instability and/or logistic problems with INR monitoring	DVT (n = 2)
Win *et al.*[18]	2014	CS	3 [median age 46 (19–53)]	6–12 (N/A in one case)	Dabigatran (n = 1), rivaroxaban (n = 2)	AT/VTE	Recurrence on VKA and enoxaparin (n = 2) and INR instability (n = 1)	Two extensive superficial venous thrombosis and one TIA
Sciascia *et al.* [17]	2015	CS	35 [median age 47 (17–75)]	Median 10 (6–24)	Rivaroxaban	VTE (DVT, n = 24; DVT + PE, n = 11)	INR instability (n = 29), INR constantly sub- therapeutic range (n = 6)	No thrombotic relapse, menorrhagia (n = 2)
Noel *et al.*[23]	2015	CS	26 [median age 43.5 (23–52)]	19 (range 8–29)	Dabigatran (n 11), rivaroxaban (n 15)	AT (n = 12), VTE (n = 17)	INR instability/therapeutic simplification (n = 17), recurrent thrombosis (n = 1), VKA-associated bleeding event (n = 1), atrial fibrillation (n = 1)	Arterial thrombosis (n = 1), bleeding event (n = 2), recurrent migraine (n = 1)
Signorelli F*et al.* [16]	2015	CS	8 [median age 36 (18–52)]	median 3 (0-12)	Rivaroxaban	VTE (n = 6) and VTE+AT (n = 2)	INR N/A	VTE (n = 4), AT (n = 2), cognitive alteration/refractory headaches (n = 2)

AT: arterial thrombosis; CR: case report; CS, case series; CVE: cerebrovascular event; DIC: disseminated intravascular; N/A: not available; NOAC: non-vitamin K antagonist oral anticoagulant; ST: superficial thrombophlebitis; VTE: venous thromboembolic event.

TABLE 3
Laboratory evidence for LA testing in patients on NOAC

Article	Year	LA testing	NOAC	Comments/suggestions
Merriman *et al.* [39]	2011	dRVVT, kaolin clotting time, DTT, aPTT based test with Staclot confirmation	Rivaroxaban	LA testing not recommended if patients are taking Rivaroxaban
van Os *et al.*[40]	2011	aPTT, dRVVT, taipan/ecarin time assays	Rivaroxaban	Taipan/ecarin ratio is a sensitive assay for LA testing not affected by the presence of rivaroxaban
Martinuzzo *et al.* [41]	2013	dRVVT and Siclica clotting time	Dabigatran	LA testing not recommended if patients are taking dabigatran
Arachchillage*et al.* [42]	2015	Three dRVVT assays, taipan venom time/ecarin clotting time and textarin time	Rivaroxaban	Taipan venom time/ecarin clotting time and textarin time are not affected even at peak rivaroxaban levels, enabling detection of LA *ex vivo*
Goralczyk *et al.* [43]	2015	Two dRVTT assays and an aPTT based test with Staclot confirmation	Rivaroxaban	Blood for LA testing should be drawn 24 h after the last dose of rivaroxaban
Sciascia *et al.* [17]	2015	aPTT, dRVVT, taipan/ecarin time assays	Rivaroxaban	Taipan/ecarin time is poorly affected by rivaroxaban but false-positive results were seen with all types of LA testing

DDT: dilute thromboplastin time.

TABLE 4
Pro-coagulant agents used for reversal

Reversal Agents
PCC: they contain various amounts of vitamin K-dependent coagulation factors (factors II, IX, X) and natural anticoagulants (proteins C and S) and they are classified as 4-PCC or 3-PCC, depending on whether or not they contain factor VII.
Activated PCC (factor VIII inhibitor bypassing activity): they contain factors II, VII, IX and X activated during the manufacturing process
Recombinant factor VII activated
Antidotes under development: aDabi-Fab (dabigatran), Andexanet alfa (apixaban, rivaroxaban) PER977 (rivaroxaban)

PCC: prothrombin complex concentrate.