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ANTIPHOSPHOLIPID SYNDROME (RAS ROUBEY, SECTION EDITOR)

Use of New Oral Anticoagulants in Antiphospholipid Syndrome

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Abstract The current mainstay of treatment of thrombotic APS is long-term anticoagulation with oral vitamin K antagonists (VKA) such as warfarin. However, the use of warfarin is problematic, particularly in patients with antiphospholipid syndrome (APS). The new oral anticoagulants (NOAC) include dabigatran etexilate (Pradaxa®), a direct thrombin inhibitor, and rivaroxaban (Xarelto®), Apixaban (Eliquis) and Edoxaban (Lixiana®), which are direct anti-Xa inhibitors. Unlike warfarin, these agents do not interact with dietary constituents and alcohol, have few reported drug interactions, and monitoring of their anticoagulant intensity is not routinely required due to their predictable anticoagulant effects. In this chapter, we discuss clinical and laboratory aspects of NOAC. 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. However these trials may not be directly applicable to patients with antiphospholipid syndrome (APS) where prospective clinical studies of NOAC are the way forward.

Keywords New oral anticoagulants · Warfarin · Antiphospholipid syndrome · Drug interactions · Pregnancy · Breastfeeding · Bleeding · Perioperative management

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Introduction

Antiphospholipid syndrome (APS) is characterised by thrombosis, venous and/or arterial, and/or pregnancy morbidity (recurrent miscarriages, one or more unexplained deaths ≥10 weeks of a morphologically normal fetus or one or more premature births of a morphologically normal neonate <34 weeks associated with severe pre-eclampsia/eclampsia or recognized features of placental insufficiency) in association with persistently positive antiphospholipid antibodies i.e. lupus anticoagulant (LA), IgG and/or IgM anticardiolipin and/or anti-beta 2 glycoprotein I antibodies. Persistent aPL positivity is defined as aPL present on at least two consecutive occasions at least 12 weeks apart in accordance with the International (Sydney) consensus statement criteria [1, 2]. Thrombotic APS is a potentially life-threatening condition, in which thrombosis has been described in almost every vessel of the body, in arteries, veins and in the microcirculation [1].

Vitamin K antagonists (VKA), with warfarin the most commonly used VKA, are currently the mainstay of long-term treatment of thrombotic APS. The anticoagulant effect of warfarin is monitored using the International Normalised ratio (INR) based on the prothrombin time of the patient (PT). Current recommendations are to maintain 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 which occurs whilst off anticoagulation [3, 4]. However, 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 INR of >3.0 [5]. Problems with warfarin include a narrow therapeutic window and numerous drug and dietary interactions that necessitate regular monitoring of the INR, which is inconvenient and costly, but essential to maintain the INR within the target therapeutic range. Warfarin monitoring in patients with aPL

can be further complicated by the variable responsiveness of reagents used in the INR test to LAs, leading to instability of anticoagulation. This instability necessitates frequent monitoring of the INR and means the result may not accurately reflect the true level of anticoagulation. Furthermore, LA detection in patients on warfarin may be problematic because of a prolonged basal clotting time, which limits the test's diagnostic utility and ability to monitor LA status in patients with established APS. The limitations of warfarin and other VKA have driven a search for new agents. The new oral anticoagulants (NOAC) include dabigatran etexilate (Pradaxa®), a direct thrombin inhibitor (DTI), and rivaroxaban (Xarelto®), apixaban (Eliquis) and edoxaban (Lixiana®), which are direct anti-Xa inhibitors. These agents represent a major advance as, unlike warfarin, they do not interact with dietary constituents and alcohol intake, and have few reported drug interactions which affect anticoagulant intensity [6, 7]. Furthermore, monitoring of anticoagulant intensity of NOAC is not routinely required due to their predictable anticoagulant effects. Their efficacy has been demonstrated in large phase III clinical trials [8, 9], and both rivaroxaban and dabigatran have been licensed by the European Medicines Agency (EMA) [10, 11] and endorsed by the National Institute for Health and Care Excellence (NICE) [12, 13] for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF).

New Oral Anticoagulants: Evidence for Use in Clinical Practice and Current Licensed Indications

Table 1 summarises the main characteristics of NOAC. All are fixed-dose orally administered agents which exert their anticoagulant effects within hours rather than days and, due to their predictable pharmacokinetics, do not require routine laboratory monitoring with coagulation tests. Following phase III international multicentre trials in a total of about 21,500 patients, dabigatran and rivaroxaban were licensed in the UK and Europe for the prevention of VTE in adults undergoing elective total hip replacement or knee replacement in 2009 [14–19]. Table 1 details a comparison of the pharmacological characteristics of NOAC.

A number of phase III clinical trials have been undertaken in conditions other than major lower limb orthopaedic surgery. Following two phase III clinical randomised controlled trials (RCT) of warfarin versus single dose rivaroxaban (ROCKET-AF) or two fixed doses of dabigatran (RE-LY) involving a total of 32,284 patients with non-valvular atrial fibrillation (AF) for the prevention of stroke or systemic embolization, rivaroxaban and dabigaran were licensed for stroke prevention in 2011 [8, 9]. They were approved by NICE and the US Food and Drug Administration (FDA) for the same indication in 2012 [12, 13, 26]. Rivaroxaban was licenced for the treatment of deep vein thrombosis (DVT), prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults following the results of the EINSTEIN-DVT international multicentre randomised trial [27••]. Currently, rivaroxaban is the only NOAC which is licensed for the treatment of DVT and for the reduction in the risk of recurrence of DVT and PE, which has been approved by the FDA [28] and NICE [29]. Dabigatran is currently under review by NICE for the treatment of acute venous thromboembolic events [30].

Recently, rivaroxaban was also licensed for the treatment of acute symptomatic PE with or without symptomatic DVT (31) following the results of the EINSTEIN-PE study [32••], and is currently under review by NICE for this indication with the decision expected in September 2013 [33].

Following results from several clinical trials involving 11,964 patients [34–36], apixaban was licensed as an option for the prevention of VTE in adults after elective hip or knee replacement surgery and recommended for this indication by NICE [37]. Apixaban 5 mg twice daily has also been licensed for the prevention of stroke and systemic embolism in patients with non-valvular AF [38] following a phase III clinical trial involving 18,201 patients [39]; it is approved by the FDA and under evaluation by NICE for this indication [26, 40].

To date, clinical trials with NOAC have been undertaken in excess of 150,000 patients. Table 2 summarises the clinical trial and licence status of the NOAC and the situation as regards endorsement by NICE and the FDA. The safety and efficacy of NOAC in children aged 0–18 years have not been established and no data are available. Therefore, any of the NOAC is not recommended for use in children below 18 years of age [6, 31, 38].

Role of New Oral Anticoagulants in Antiphospholipid Syndrome

Current recommendations for anticoagulation with VKA are to maintain a target INR of 2.5 (range 2.0–3.0) for an indefinite period following a first episode of VTE, or a recurrent VTE event which occurs whilst off anticoagulation [3, 4]. However, 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, although a number of experts state that they should be maintained at a target INR of >3.0 [5]. It should be appreciated that clinical trials of therapeutic dose NOAC versus warfarin have used warfarin at a target INR of 2.5 (i.e. range 2.0–3.0) as the comparator [27••, 32, 41, 42].

NOACs would be expected to result in improved quality of life in patients with APS who generally require an

Table 1 Comparison of the pharmacological characteristics of new oral anticoagulants

Drug	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)	Dabaigatran (Pradaxa®)
Target	FactorXa	FactorXa	Factor Xa	Thrombin
Pro drug	No	No	No	Yes-Dabigatran etexilate
Bioavailability	>80 %	>50 %	50 %	6 %
Plasma protein binding	92–95 %	87 %	40–59 %	34–35 %
Time to reach peak drug level	3 hours	3 hours	1–2 hours	2 hours
Half-life with normal creatinine clearance	9 hours	9–14 hours	9–11 hours	14–17 hours
Dosing	Fixed dose once daily	Fixed dose, once daily	Fixed, once daily	Fixed dose , twice daily
Drug monitoring	No	No	No	No
Drug interactions	CYP3A4 inhibitors, P-gp inhibitors, azole antifungals HIV protease inhibitors	CYP3A4 inhibitors, P-gp inhibitors	Potent inhibitors of both CYP3A4 and P-gp inhibitors	Proton pump inhibitors
Elimination	66 % renally 33 % faecally	25 % renally 55 % faecally	35 % Rrenally 62 % faecally	Renal (80 % unchanged)
Routine coagulation monitoring	No	No	No	No

(Data from [6, 7, 20–25]).

indefinite period of anticoagulation, as, unlike warfarin, they do not require routine anticoagulant monitoring, have no reported interactions with food or alcohol and few reported drug interactions. Patients with thrombotic APS differ from other patients with VTE due to the presence of aPL, which are known to interfere with a number of haemostatic mechanisms, and which may therefore modulate the actions of anticoagulants. It is likely that patients with APS were included in the study populations in the phase III clinical trials of rivaroxaban or dabigatran versus VKA in patients with VTE. However, aPL status was not documented in these trials [27••, 32, 41], and thus prospective studies of the use of NOAC in patients with APS are needed. We are currently undertaking the RAPS (Rivaroxaban in AntiPhospholipid Syndrome, IRSCTN 68222801) trial [44]. RAPS is a prospective randomised controlled trial of warfarin versus 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).

Cautions and Contraindications

As with other anticoagulants, the use of NOAC should be implemented within a structured setting, with

Table 2 Development status of rivaroxaban, apixaban edoxaban and dabigatran

Indication	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Venous thromboembolism (VTE) prevention orthopaedic surgery	Phase III completed (Licensed for use) Approved by NICE and FDA	Phase III completed (Licensed for use) Approved by NICE	Phase III completed	Phase III completed (Licensed for use) Approved by NICE
Stroke prevention in nonvalvular atrial fibrillation (AF)	Phase III completed (Licensed for use) Approved by NICE and FDA	Phase III completed (Licensed for use) Awaiting NICE approval and approved by FDA	Phase III Aactive, not recruiting	Phase III completed (Licensed for use) Approved by NICE and FDA
Acute coronary syndrome (ACS)	Phase III completed	Phase II completed	No study in progress	Phase II completed
VTE prevention in medical inpatients	Phase III completed	Phase III completed	No study in progress	No study in progress
VTE treatment	Phase III completed (Licensed for use) Approved by NICE and FDA	Phase III completed	Phase III on-going	Phase III completed

(Data from [24–26, 27••, 28–31, 32••, 33–43]).

documented patient counselling and note taken of cautions and contraindications.

Renal and Hepatic Impairment

Renal impairment may necessitate dose reduction or avoidance of NOAC. Dose adjustment of rivaroxaban is not required in patients with mild renal impairment (creatinine clearance 50–80 mL/min). In patients with VTE with moderate renal impairment (30–49 mL/min) a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk of recurrent DVT and PE. Rivaroxaban should be used with caution in patients with a creatinine clearance of 15–29 mL/min, and is not recommended in patients with severe renal impairment (creatinine clearance <15 mL/min) [31]. The Summary of Product Characteristics (SPC) states that cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2-fold increase in rivaroxaban area under the plasma concentration curve (AUC) on average), nearly comparable to their matched healthy control group [31]. There are no data in patients with severe hepatic impairment. Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B [31]. As with rivaroxaban, apixaban is not recommended in patients with severe renal impairment, or in patients with hepatic disease associated with coagulopathy, clinically relevant bleeding risk, and severe hepatic impairment [38].

Dabigatran is predominantly excreted by the kidneys (80 % unchanged). Limited data are available on dabigatran pharmacokinetics in patients with renal impairment [6]. A small open-label study showed a higher plasma concentration of dabigatran in patients with increasing renal insufficiency compared with healthy patients [45]. The SPC recommends a reduced dabigatran dose (150 mg once daily) to prevent recurrent VTE in patients with moderate renal impairment. Dabigatran contraindicated in patients with severe renal impairment (CrCL <30 mL/min) (6). Patients with elevated liver enzymes, i.e. over twice the upper limit of normal (ULN), were excluded from the RE-LY trial [8] and therefore no treatment experience is available for this subpopulation of patients, hence dabigatran is not recommended [6].

Drug Interactions

Dabigatran and rivaroxaban are not metabolized by the cytochrome P450 system, limiting the potential for drug interactions [6, 31]. However, azole antifungals, such as ketoconazole and itraconazole (although fluconazole can be co-administered with caution) and HIV protease inhibitors (such as ritonavir), are all strong inhibitors of both CYP3A4 and P-glycoprotein, and concurrent use with rivaroxaban is not recommended due to an increased risk of bleeding. Rifampicin, phenytoin, carbamazepine, phenobarbitol or St John's wort may reduce the plasma concentration of both rivaroxaban and dabigatran, and therefore concomitant use should be avoided [6, 31]. Amiodarone, quinidine and clarithromycin may increase dabigatran levels and close clinical monitoring for bleeding, especially with high risk patients, such as those with CrCL 30–50 mL/min, aged over 75 years or of low body weight (45–50 kg) is indicated [6].

Pregnancy and Breast Feeding

Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications) with embryo-fetal toxicity (post-implantation loss), impaired ossification and an increased incidence of common malformations as well as placental changes observed at clinically relevant plasma concentrations [31]. As with rivaroxaban, studies in animals have shown reproductive toxicity with dabigatran and apixaban, while there are no data on the use of NOAC in pregnant women [6, 38]. It follows that the potential risk in humans is unknown. Currently, all NOAC should be avoided in pregnancy and during breast feeding [6, 31, 38].

Laboratory Monitoring of New Oral Anticoagulants

Routine monitoring of the anticoagulant effect of NOAC are not required due to their predictable anticoagulant effects, but may be desirable in specific clinical settings. These include patients at extremes of body weight, with renal or hepatic impairment, and in the assessment of compliance, the effects of accidental or deliberate overdose, the evaluation of patients with haemorrhagic or thrombotic complications or where emergency surgery or interventions are required [46].

Some of the basic coagulation screening tests can provide a qualitative assessment of NOAC activity. The thrombin time (TT) is very sensitive for dabigatran and shows a linear relationship with increasing dabigatran concentration, and a normal TT excludes the presence of significant dabigatran levels. The activated partial thromboplastin time (aPTT) is prolonged with dabigatran, and the prothrombin time (PT) is least sensitive with little prolongation with clinically relevant doses. Therefore, the aPTT or PT is not suitable to quantitate the level of dabigatran, but the aPTT can be used for urgent determination of the relative intensity of anticoagulation [46]. The Ecarin clotting time (ECT) provides a quantitative assessment of dabigatran activity but is not widely available [47•, 48, 49]. Rivaroxaban leads to

concentration-dependent prolongation of the PT, but this varies depending on the thromboplastin reagent used, and INR monitoring is not appropriate for rivaroxaban [31, 46]. Rivaroxaban also prolongs the aPTT, but its effect on the aPTT is weaker than that on the PT. Rivaroxaban has no effect on the TT. Anti-factor Xa assays can provide a quantitative measure of rivaroxaban activity, but their availability is generally restricted to specialised coagulation laboratories. Whilst coagulation monitoring is not generally required in patients on NOAC, monitoring of renal function, with dose reduction or cessation with severe renal impairment as detailed above, is required as with low molecular weight heparins (LMWH).

Specific Issues in Patients with APS

As with most other available anticoagulants in the context of patients with APS, the detection and monitoring of LA may be affected by NOAC. Limited observations on the addition of rivaroxaban in vitro to plasma from patients with LA suggest that ratios using Taipan/Ecarin, snake venoms which directly activate prothrombin and which can be used to detect LA, are not affected by the presence of rivaroxaban [50•, 51].

Adverse Effects of New Oral Anticoagulants

Bleeding Complications

Bleeding is a risk with any anticoagulant. Based on phase III clinical trials involving 50,934 patients and available clinical experience so far, the risk of bleeding complications with NOAC at therapeutic dose are comparable to warfarin with lower rates of intracranial haemorrhage in the AF studies as detailed below [52, 53]. In the ROCKET-AF study, the incidence of major bleeding with rivaroxaban and warfarin was similar at 3.6 and 3.45 %, respectively. The number of patients who experienced the most severe bleeding, as measured by transfusion of at least 4 units of red cells, was also similar between both treatment groups (49 in the rivaroxaban group and 47 in the warfarin group). Six patients developed fatal bleeding: one in the rivaroxaban group and five in the warfarin group [8]. However, mucosal bleeding (i.e. epistaxis, gingival, gastrointestinal, and genitourinary) and anaemia were seen more frequently during long-term rivaroxaban compared with warfarin treatment [31]. In the rivaroxaban Einstein-Extension Study, there was a lower incidence of major bleeding (0.8 %) with rivaroxaban compared to that with warfarin (1.2 %) [54]. In the RE-COVER dabigatran acute VTE treatment trial, major bleeding occurred in 1.6 % of patients on dabigatran and 1.9 % of those on warfarin with the incidence of any bleeding 16.1 and 21.9 %, respectively (41). In the dabigatran RE-LY AF trial, the rate of major bleeding per year was significantly lower in the group randomized to dabigatran 110 mg compared with that in patients on warfarin (2.71 vs. 3.36 %, respectively; $p<0.001$), and the rate of haemorrhagic stroke per year was significantly lower in patients receiving this and a higher dose of dabigatran (0.38 % in the warfarin group and 0.12 % in the dabigatran 110 mg daily group ($p<0.001$) and 0.10 % in the dabigatran 150 mg daily group ($p<0.001$)). The rate of gastrointestinal (GI) bleeding was increased in the dabigatran 150 mg daily arm compared with that in patients on warfarin (1.51 vs. 1.02 %, respectively; $p<0.001$) [8]. Since there was more GI bleeding in both the dabigatran and rivaroxaban treatment groups, in addition to clinical surveillance, haemoglobin monitoring may be appropriate to detect clinically occult bleeding in patients treated with these drugs [6, 31]. Administration of a PPI may be considered to prevent GI bleeding [6, 31]. In the ARISTOTLE (Apixaban for Reduction In Stroke and other Thromboembolic Events in Atrial Fibrillation) trial, which compared apixaban 5 mg twice daily with warfarin in AF, the annual risks of intracranial as well as other major bleeding were significantly lower in the apixaban arm at 0.33 and 0.80 % ($p<0.001$) and 2.13 and 3.09 % ($p<0.001$), respectively [38].

Other Unwanted Effects of New Oral Anticoagulants

The phase III clinical trials showed no significant alteration of liver enzymes (aspartate transaminase/alanine transaminase) in patients treated with NOAC, which was welcomed as hepatic toxicity had limited the development of the previously studied oral DTI ximelagatran in the early 2000s [52, 53, 55]. Dabigatran was associated with a significant increase in GI symptoms such as dyspepsia, nausea, vomiting and upper abdominal pain, compared with warfarin, which was not observed with rivaroxaban and apixaban [6, 31, 52]. The association of dyspepsia with dabigatran may be related to increased acidity as a result of tartaric acid contained in dabigatran capsules [52]. In the dabigatran AF trial (RE-LY), the rate of myocardial infarction was significantly increased in the dabigatran 150 mg daily group compared with that in patients on warfarin (0.74 and 0.53 %, respectively; $p<0.048$), but in the dabigatran VTE trial, the number of patients developing acute coronary syndromes were similar in both arms [53]. Less common side effects associated with rivaroxaban include tachycardia, syncope, pain in the extremities, pruritus and hypotension [53].

Management of Bleeding Associated With New Oral Anticoagulants

There are no properly conducted randomised controlled trials related to the management of patients on NOAC

who experience bleeding or are undergoing surgery. However, with increasing use of NOAC, practical guidance is needed for these situations. The suggested management below is based on current published guidelines, consensus reports and SPC recommendations for the individual drugs.

Because of their short half-lives, stopping the drug, observation and supportive care is the preferred strategy in the patient who develops minor or mechanically controllable bleeding. With normal renal and hepatic function, NOAC are expected to be cleared from the body within a few hours of the most recent dose [45]. Management in the context of major or life-threatening bleeding or emergency surgery is challenging. Dabigatran is predominantly renally excreted and thus can be dialysed with removal of about 60 % of the drug over 3 h, although there are limited supportive data for this approach. Rivaroxaban is highly bound to plasma protein and is not expected to be dialyzable, although the use of activated charcoal to reduce absorption may be considered [45, 56]. Prothrombin complex concentrate (PCC) has been shown to reverse the coagulopathy associated with rivaroxaban but not dabigatran in healthy individuals [57••]. At present, based on national guidance [58] and the manufacturers' recommendations [6, 31], patients on NOAC who experience major bleeding should be generally managed along the following lines, with haematological advice sought at an early stage. The NOAC should be stopped and local measures applied; a full blood count, coagulation screen, and renal and liver function tests should be checked. Supportive measures including blood component support are required. Haemostatic support with PCC, activated PCC (e.g. factor VIII inhibitor bypass activity (FEIBA) or recombinant factor VIIa (rVIIa) as well as antifibrinolytic therapy (tranexamic acid) may be useful for rivaroxaban and dabigatran. Haemodialysis should be considered for dabigatran and activated charcoal for recent ingestion of rivaroxaban or dabigatran.

Perioperative Management of Patients on New Oral Anticoagulants

NOACs 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. However, there may be a role for 2–3 days of a low-dose LMWH bridging regimen (e.g. enoxaparin 40 mg or dalteparin 5,000 units once daily) in postoperative patients who are unable to take oral medication. There are no published clinical studies on bridging patients from and to long-acting VKAs with short-acting NOAC during the perioperative phase [59].

Elective Surgery in Patients Receiving Dabigatran

Suggested timings for stopping dabigatran prior to surgery are as follows: with CrCl 80–50 mL/min, dabigatran should be stopped 72 h prior to major surgery or surgery with a high risk of bleeding and 48 h prior to minor surgery or with a standard risk of bleeding. With moderate renal impairment (CrCl 30–50 mL/min), dabigatran should be stopped 4–5 days prior to major surgery or surgery with a high risk of bleeding and 72 h prior to minor surgery or where there is a standard risk of bleeding [6, 60, 61•]

Elective Surgery in Patients Receiving Rivaroxaban

Suggested timings for stopping rivaroxaban prior to surgery are as follows: with CrCl >80 mL/min, rivaroxaban should be stopped 48 h prior to major surgery or surgery with a high risk of bleeding, and 24 h prior to minor surgery or when there is a standard risk of bleeding. With CrCl 50–80 mL/min, rivaroxaban should be stopped 72 h prior to major surgery or surgery with a high risk of bleeding, and 48 h prior to minor surgery or where there is a standard risk of bleeding. With moderate renal impairment (CrCl 30–49 mL/min), rivaroxaban should be stopped 72 h prior to major surgery or surgery with a high risk of bleeding, and 48 h prior to minor surgery or surgery with a standard risk of bleeding. With severe renal impairment (CrCl 15–29 mL/min), rivaroxaban should be stopped 4 days prior to major surgery or surgery with a high risk of bleeding and 72 h prior to minor surgery or surgery with a standard risk of bleeding [31, 59, 62].

Emergency Surgery

For emergency surgery, surgeons should assess the urgency of the surgery against the risk of bleeding complications, with individualised clinical judgement required. In patients without bleeding, prophylactic use of haemostatic blood products such as PCC for reversal of the effects of rivaroxaban is not recommended. However, in cases of severe bleeding, the measures outlined above should be considered.

After the surgical (elective or emergency) intervention or invasive procedure, rivaroxaban or dabigatran should be restarted at the relevant dose for the indication as soon as possible, provided the clinical situation allows and adequate haemostasis has been established [54, 61•, 63].

Epidural/Spinal Anaesthesia, Neuroaxial Blocks

Given the risk of epidural haemorrhage, epidural or spinal anaesthesia should only be performed in patients in whom there is a high degree of certainty that the NOAC has been completely cleared. Dabigatran is not licensed for use with indwelling epidural catheters and should therefore not be administered if ongoing post-operative epidural anaesthesia is planned; LMWH should be used instead, noting the dosing and timings associated with catheter insertion/removal. Once the epidural catheter is out, if appropriate, aim to change to therapeutic dose dabigatran from days 2–3 post-operation onwards, assuming there are no concerns about bleeding, the CrCL is >30 mL/min and oral absorption is assured. With rivaroxaban, an epidural/spinal catheter should be inserted pre-operatively, with the number of hours after the last dose of rivaroxaban before insertion of epidural/spinal catheter as follows; CrCL >50 mL/min: at least 30 h; CrCL 30–50 mL/min: at least 48 h; CrCL <30 mL/min: epidural/spinal should be avoided. If traumatic puncture has occurred, rivaroxaban administration should be delayed for 24 h [61•, 62–64].

Conclusions

The current mainstay of treatment of thrombotic APS is long-term anticoagulation with oral VKA such as warfarin. However, warfarin is limited by a narrow therapeutic range, slow onset/offset of action, variable response, a requirement for frequent laboratory monitoring, and numerous interactions with food, drugs and alcohol. In addition to these limitations, interactions between aPL and warfarin lead to difficulties in patients with APS with monitoring anticoagulant effects. NOAC are potentially a major advance since they do not require routine anticoagulant monitoring, although renal function should be monitored, have no reported interactions with food and alcohol, and few reported drug interactions. These drugs 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, but these trials may not be directly applicable to patients with APS. Prospective clinical studies of NOAC in patients with thrombotic APS are the way forward.

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- • Of importance
- •• Of major importance

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