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CLINICAL PERSPECTIVES

New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management

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Abstract

New oral anticoagulants (NOAC) are becoming available as alternatives to warfarin to prevent systemic embolism in patients with non-valvular atrial fibrillation and for the treatment and prevention of venous thromboembolism. An in-depth understanding of their pharmacology is invaluable for appropriate prescription and optimal management of patients receiving these drugs should unexpected complications (such as bleeding) occur, or the patient requires urgent surgery. The Australasian Society of Thrombosis and Haemostasis has set out to inform physicians on the use of the different NOAC based on current available evidence focusing on: (i) selection of the most suitable patient groups to receive NOAC, (ii) laboratory measurements of NOAC in appropriate circumstances and (iii) management of patients taking NOAC in the perioperative period, and strategies to manage bleeding complications or 'reverse' the anticoagulant effects for urgent invasive procedures.

Introduction

The prescription of new oral anticoagulants (NOAC) requires an in-depth knowledge of the pharmacology of these drugs, and strategies must be developed in hospitals to ensure optimal care for patients receiving these drugs, especially when they develop bleeding complications or require urgent surgery. The NOAC are renally excreted which requires that patients have their renal function checked prior to initiation of therapy and repeated periodically to avoid inadvertent overdose due to impaired clearance in renal dysfunction. Haematology laboratories should provide basic coagulation tests, such as activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) along with the establishment of specific assays to measure the anticoagulant effect of NOAC in certain circumstances. Development of local guidelines is essential to manage patients receiving NOAC who present with bleeding or require urgent surgery.

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This practical guide comprises of three sections:

1 Selection of the most suitable patient groups to receive NOAC.

2 Laboratory measurements of NOAC in appropriate circumstances.

3 Management of patients taking NOAC in the perioperative period, and strategies to manage bleeding complications or 'reverse' the anticoagulant effects for urgent invasive procedures.

Methods

Experts in thromboembolic disorders representing the Australasian Society of Thrombosis and Haemostasis (ASTH) were invited to join the panel of guideline development. The process included reviewing up-to-date evidence and existing high-quality evidence-based international guidelines for NOAC. We conducted monthly teleconferences from 6 June 2012 to 19 June 2013 during which specific questions, drafting and revisions of the guideline were discussed. Further revisions were made by consensus through email. All eight members of the panel are the authors of this article.

Table 1 Pharmacological characteristics of dabigatran, rivaroxaban and pixaban

	Dabigatran (Pradaxa)[2]	Rivaroxaban (Xarelto)[4]	Apixaban (Eliquis)[6]
Action	Direct thrombin inhibition, free and clot bound	Direct Factor Xa inhibition	Direct Factor Xa inhibition
T_{max}	2 h	2.5–4 h	1–3 h
Half life	12–17 h	5–9 h (healthy) 11–13 h (elderly)	8–15 h
Plasma protein binding	35%	95%	87%
Elimination	Renal 80% Hepatic 20%	Renal 33% Renal metabolite 33% Hepatic 33%	Renal 27%
Metabolism	Substrate for transporter P-gp	Substrate for transporter P-gp CYP 3A4, CYP 2J2 and CYP independent mechanisms	Substrate for transporter P-gp CYP 3A4/5 (major) CYP 1A2, 2C8, 2C9, 2C19, 2J2 (minor)
Weight Impact on pharmacokinetics	<50 kg or >120 kg, less than 25% change in plasma drug concentration, no dose adjustment	<50 kg or >120 kg, less than 25% change in plasma drug concentration, no dose adjustment	<50 kg or >120 kg, less than 25% change in plasma drug concentration, no dose adjustment
Age Impact on pharmacokinetics	AUC for plasma drug concentration up to 2.0 fold higher after 65 years; use 110 mg twice daily if ≥75 years of age	AUC for plasma drug concentration 1.5 fold higher after 65 years, but no dose adjustment	AUC 32% higher after 65 years, but no dose adjustment†

†Apixaban, 2.5 mg twice daily if patient have two out of three of the following: age, ≥ 80 years; weight, ≥ 60 kg; creatinine, ≥ 133 umol/L. AUC, area under the curve; CrCl, Creatinine clearance; P-gp, P glycoprotein.

Consensus recommendations were reached in an equitable manner. Agreement of all members of the expert panel was required in order to proceed with making the recommendation. We acknowledge the lack of evidence in this area and that the recommendations are based largely on expert opinions.

Potential conflicts of interest were declared and recorded. No financial support was received.

Selection of the most suitable patient groups to receive the NOAC

NOAC have been approved in many countries for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF), the treatment of new deep vein thrombosis and pulmonary embolism, and secondary prevention of venous thromboembolism, as well as the prevention of venous thrombosis in hip and knee arthroplasty. Table 1 summarises the pharmacological characteristics of dabigatran, rivaroxaban and apixaban. In Australia, all three drugs are available on the Pharmaceutical Benefits Scheme for the abovementioned indications depending on the drug. Table 2 compares patient suitability for NOAC versus warfarin; and Table 3 suggests which patients should not be prescribed NOAC.

Laboratory testing and NOAC

The following comments focus on the NOAC dabigatran (*Pradaxa*; direct thrombin inhibitor) and rivaroxaban (*Xarelto*; direct Xa inhibitor) as both agents are available for thromboprophylaxis post hip and knee arthroplasty and anticoagulation for non-valvular AF to prevent systemic thromboembolism. In addition, rivaroxaban is available for treatment of deep vein thrombosis and pulmonary embolism. A third drug apixaban (*Eliquis*; a direct Xa inhibitor) is available for thromboprophylaxis post hip and knee arthroplasty and non-valvular AF to prevent systemic thromboembolism but limited data on laboratory testing are available.

Caution

1 Neither rivaroxaban nor dabigatran should be used in the presence of severe renal impairment (creatinine clearance (CrCl) < 30 mL/min using the Cockcroft-Gault equation). Apixaban should be avoided in patients with CrCl < 25 mL/min. Patients previously stabilised on these drugs may be at risk of bleeding if there is deterioration of renal function since its commencement.

2 Rivaroxaban is metabolised by the liver, and moderate-severe liver impairment will increase drug levels.

3 Overall with NOAC, there are fewer drug interactions than with warfarin. However, with rivaroxaban drugs that interfere with CYP3A4, such as azole antifungal agents, human immunodeficiency virus-protease inhibitors and rifampicin, have significant interaction. For dabigatran, drugs that inhibit p-glycoprotein such as verapamil can increase drug levels. Table 4 shows the clinically relevant drug interactions that will result in

Table 2 Patient selection for anticoagulation initiation with new oral anticoagulants (NOAC) or warfarin

		NOAC	Warfarin
Recent stroke	Disabling (rivaroxaban < 3 months; dabigatran < 6 months) Any stroke < 14 days Or <7 days for apixaban	No†	Yes
Increased bleeding risk	Surgery < 1 month	No	Assess risk versus benefit
	GI bleed < 12 months, ulcer < 30 days	No	Assess risk versus benefit
	Any history of ICH, Intra-ocular, spinal, retroperitoneal or atraumatic intra-articular bleeding	Assess risk versus benefit†	Assess risk versus benefit
	Planned major surgery/procedure	Assess risk versus benefit†	Assess risk versus benefit
	Anaemia Hb < 100g/L	Assess risk versus benefit†	Assess risk versus benefit
	Thrombocytopenia $<100 \times 10^9$/L		
	Recent malignancy or radiation	Assess risk versus benefit†	Assess risk versus benefit
Planned cardioversion		Assess risk versus benefit Excluded from ROCKET-AF only	Yes
Fibrinolytic treatment within 2–10 days		No†	Yes
Dual antiplatelet therapy		No‡	Yes
VTE with active cancer		No	No (use LMWH)
VTE with known APLS		No	Yes
Weight < 50 kg		No	Yes
Practical issues			
	Poor venous access	Yes	No
	Remote patients, INR monitoring inaccessible	Yes	No
	Unpredictable dietary Vitamin K	Yes	No
	Concomitant medications likely to make warfarin management difficult	Yes	No

†Patients with this criterion were excluded from clinical trials evaluating NOAC. ‡Not excluded in RE-LY.[2] However, dual antiplatelet therapy combined with a NOAC likely increases bleeding risk. APLS, antiphospholipid syndrome; GI, gastrointestinal; ICH, intracranial haemorrhage; INR, international normalised ratio; LMWH, low-molecular-weight heparin; VE, venous thromboembolism.

Table 3 Who should not be on NOAC

Active significant bleeding†
Disorder of haemostasis† (e.g. von Willebrand disease or coagulation factor deficiency)
Prosthetic heart valve
Poor renal function (dabigatran and rivaroxaban‡, CrCl < 30 mL/min; apixaban CrCl < 25 mL/min)
Known hypersensitivity to a NOAC preparation
Concomitant medication known to affect pharmacokinetics (refer to Table 4)
Pregnant and breast feeding
Liver disease with an ALT > 2 times upper limit of normal or Child-Pugh Grade B or C§
Stably anticoagulated on warfarin (warfarin time in therapeutic range >65% over a 3-month period)

†Therapeutic anticoagulation, with any agent, usually avoided.
‡Rivaroxaban 10 mg daily can be used with caution in patients with a CrCl of 15–30 mL/min undergoing hip and knee arthroplasty, but is contraindicated with CrCl < 15 mL/min.
§Apixaban may be used in Child-Pugh grade B hepatic impairment, with caution.
ALT, alanine transaminase; CrCl, creatinine clearance; NOAC, new oral anticoagulants.

Table 4 Clinically relevant drug interactions with at least 50% change in the exposure to dabigatran or rivaroxaban and apixaban

Mechanism	Dabigatran		Rivaroxaban and apixaban	
	Interacting drug	Exposure (%)	Interacting drug	Exposure (%)
P-gp inhibition	Ketoconazole†	150	Ketoconazole†	160
	Quinidine†	53		
	Amiodarone	60		
	Verapamil	50‡		
P-gp induction	Rifampicin	–67	Rifampicin	–50
CYP3A4 inhibition			Ketoconazole†	160
			Clarithromycin	50
			Ritonavir (and other HIV protease inhibitors)†	50
CYP3A4 induction			Rifampicin	50

Modified with permission from *Blood* 2012; 119: 3016–23.[8,9]
†Contraindicated. ‡Variable depending on verapamil formulation. HIV, human immunodeficiency virus; ND, not determined; P-gp, P glycoprotein.

at least a 50% change in exposure to dabigatran, rivaroxaban or apixaban and which concomitant medications warrant contraindication to the use of NOAC. We also refer the reader to the product information for a comprehensive list of drug interactions.

NOAC do not require monitoring when used for thromboprophylaxis or for therapeutic anticoagulation; however, routine coagulation tests can be useful as screening tests to determine residual anticoagulant effect. Assay for specific drug level may need referral to a specialised laboratory.

The anticoagulant effect of NOAC should be measured in the following clinical situations:

1 Bleeding: Is there an overdose or is therapeutic anticoagulation due to a NOAC contributing to the bleeding?

2 Change in clinical scenario: Patients requiring urgent surgery, new or worsening renal failure, lack of adherence, and recurrence or extension of thromboembolism.

Recommended Assays in the presence of bleeding:

Since specific assays for quantitation of drug levels may not be available in many laboratories, routine coagulation assays may be utilised to provide qualitative information about the presence of some NOAC.

Dabigatran

The TT is the most sensitive routine coagulation assay for determining if any dabigatran is present.[10–13] A normal APTT suggests that it is unlikely that a high level of dabigatran is contributing to bleeding and a normal TT excludes the presence of dabigatran.

Rivaroxaban

The PT is the most sensitive routine coagulation assay for detecting rivaroxaban.[14] A normal PT value using a thromboplastin that is sensitive to rivaroxaban (such as Triniclot PT Excel S, Neoplastin R and Recombiplastin) suggests that the rivaroxaban level is not high, but does not exclude its presence. As with the low molecular weight heparins (LMWH), the APTT and PT cannot estimate the intensity of the anticoagulant effect. Rivaroxaban does not prolong the TT.

Apixaban

There are limited data available for apixaban. A normal PT and APTT does not rule out significant anticoagulant effect. The drug specific anti-factor Xa chromogenic assay is necessary to estimate accurately the anticoagulant effect of apixaban.[15]

Recommended assays with changes in clinical scenario:

The relatively short half-life of dabigatran, rivaroxaban and apixaban means that recording the time of the last dose taken by the patient will be important in interpreting the assay results.

Dabigatran

A dilute thrombin clotting time assay such as the HEMOCLOT Thrombin Inhibitor assay is the recommended assay to determine dabigatran drug level. The C_{max} 2 h after dabigatran from patients in the RE-LY Study is between 100 and 250 ng/mL.[10,13] Population pharmacokinetic modelling of patients receiving dabigatran 150 mg twice daily demonstrates a median (with 5th and 95th percentiles) peak level of 184 ng/mL (64–443) and trough of 90 ng/mL (31–225).[13]

Rivaroxaban

A drug specific anti-factor Xa chromogenic assay is sensitive for quantitative measurements of rivaroxaban.[14] Population pharmacokinetic modelling of patients receiving rivaroxaban 20 mg once daily demonstrated a median peak level of 290 ng/mL (95% confidence interval (CI): 170 to 400) and trough of 32 ng/mL (95% CI: 0 to 150).[16] The clinical relevance of drug level is unknown and should not be used to modify maintenance drug dose.

Apixaban: A drug specific anti-factor Xa chromogenic assay has been developed but is not yet commercially available.

Table 5 summarises the laboratory tests and patterns when monitoring NOAC. Figure 1 is a suggested algorithm when monitoring of NOAC is necessary.

Perioperative management of patients on NOAC undergoing elective surgery or procedures

Elective surgery

As with all patients receiving other anticoagulant agents, an important factor in determining management in the perioperative period of patients receiving NOAC is the risk of thrombosis if the drug is stopped relative to the risk of bleeding if it is continued. As with warfarin, it may not be essential to discontinue NOAC in patients undergoing minor procedures, although firm evidence to support this practice is not established.[18] Surgery should be timed to avoid peak drug levels.[19] If the bleeding risk with the procedure is high and the NOAC needs to be stopped, advance planning is essential as, unlike warfarin, there are no established strategies for immediate reversal of the anticoagulant effect. The short half-life of

Table 5 A summary of laboratory tests and patterns for measuring new oral anticoagulants (NOAC)

Test	Dabigatran	Rivaroxaban	Apixaban
Prothrombin time (PT)/international normalised ratio (INR)	Insensitive	Marked variations with different thromboplastins, and low dose response may be poor. Discuss sensitivity with your local laboratory. Conventional INR does not correct for the variations and must not be used. Current INR system not recommended for use	*In vitro* studies indicate the PT is insensitive to accurately estimate the anticoagulant effects of apixaban. No *ex vivo* patient data is available to date. PT and INR not recommended for use
Activated partial thromboplastin time (APTT).	Somewhat sensitive (curvi-linear) but may underestimate high levels	APTT is prolonged dose dependently, but is less sensitive than the PT.	Similarly *in vitro* studies indicate the APTT is insensitive to accurately estimate the anticoagulant effects of apixaban.
Thrombin time (TT)	Standard TT is oversensitive; dilute TT or commercial method (HEMOCLOT) appear suitable options	Insensitive	Insensitive
Chromogenic anti-Xa assay	Insensitive	Standard assay as used for monitoring heparin is too sensitive. Modified anti-Xa rivaroxaban assay is suitable.	Modified anti-Xa apixaban assay is yet to be commercially available
Recommendation	Test with PT, APTT, TT. If any tests prolonged, extend testing and/or refer to algorithm for possible scenarios.		
Expected overall test patterns:			
a. Significant anticoagulant effect unlikely	APTT & TT normal	PT normal (using a sensitive thromboplastin)	PT normal (using a sensitive thromboplastin)
b. Anticoagulant effect present (Screening tests)	TT prolonged or no clot obtained; APTT prolonged	PT prolonged	PT prolonged – apixaban likely present in excess
c. Drug effect likely (confirmatory tests)	Dilute thrombin clotting time assay (HEMOCLOT) prolonged	Modified anti-Xa positive (rivaroxaban level)	Use modified anti-Xa apixaban assay when available

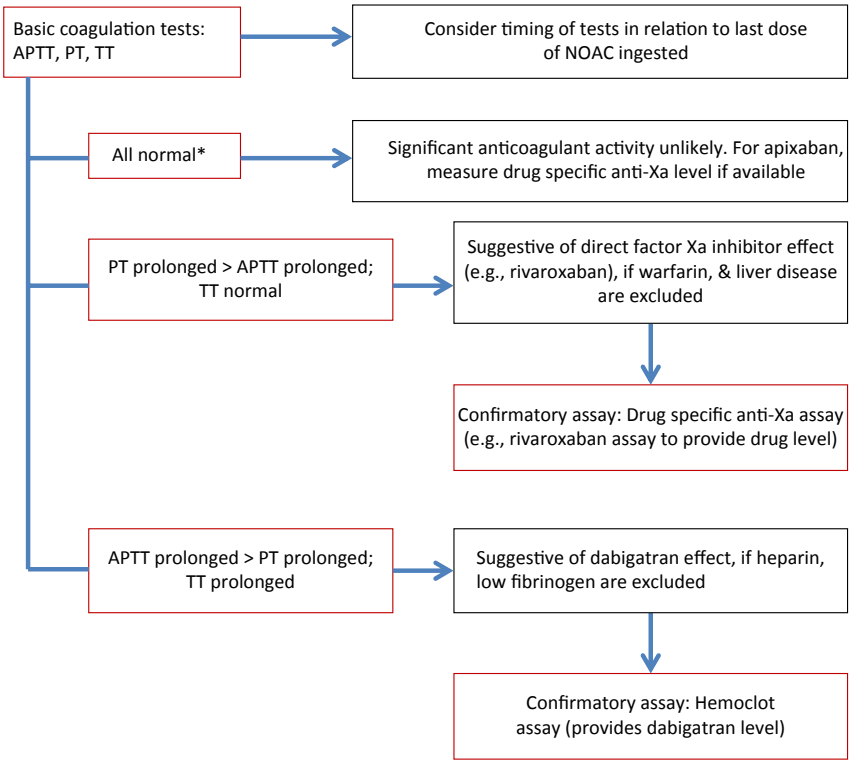

Figure 1 Suggested laboratory algorithm for dabigatran and rivaroxaban evaluation*. (Modified with permission from *Pathology* 2013; 45: 435–7.[17]) *Routine coagulation tests are insensitive to apixaban. APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time.

NOAC with rapid onset and offset of anticoagulant effect should allow for safe and shorter period of drug cessation prior to procedures in patients with normal renal and hepatic function.[8,20]

The timing of preoperative NOAC interruption to ensure a minimal or no residual anticoagulant effect at surgery is based on the elimination half-life of NOAC, patient renal function (based on calculated CrCl) and its effect on NOAC elimination, and the bleeding risk associated with planned surgery and anaesthesia. Table 6 shows the suggested timing for the last dose of NOAC before surgery.

Table 6 Preoperative interruption of new oral anticoagulants: a suggested management approach[21–24]

Drug (doses)†	Renal function	Low bleeding risk surgery‡ (2 or 3 drug half-lives between last dose and surgery)	High bleeding risk surgery§ (4 or 5 drug half-lives between last dose and surgery)
Dabigatran (150 mg twice daily)			
Half-life, 12–17 h	Normal or mild impairment (CrCl ≥ 50 mL/min)	Last dose: 24 h before surgery	Last dose: 48–72 h before surgery
Half-life, 13–23 h	Moderate impairment (CrCl 30–49 mL/min)	Last dose: 48–72 h before surgery	Last dose: 96 h before surgery
Rivaroxaban (20 mg once daily)			
Half-life, 5–9 h (healthy)	Normal or mild impairment (CrCl ≥ 50 mL/min)	Last dose: 24 h before surgery	Last dose: 48–72 h before surgery
Half-life, 9–13 h	moderate impairment (CrCl 30–49 mL/min)	Last dose: 48 h before surgery	Last dose: 72 h before surgery
Apixaban (5 mg twice daily)			
Half-life, 7–8 h	Normal or mild impairment (CrCl ≥ 50 mL/min)	Last dose: 24 h before surgery	Last dose: 48–72 h before surgery
Half-life, 17–18 h	Moderate impairment (CrCl 30–49 mL/min)	Last dose: 48 h before surgery	Last dose: 72 h before surgery

†Estimated half-life based on calculated renal clearance using the Cockcroft–Gault equation. ‡Aiming for mild to moderate residual anticoagulant effect at surgery (<12–25%). §Aiming for no or minimal residual anticoagulant effect (<3–6%) at surgery. CrCl, creatinine clearance.

Table 7 Recommendations for NOAC use for VTE prophylaxis in the setting of neuraxial anaesthesia

	Dabigatran, 150 mg or 220 mg daily	Rivaroxaban, 10 mg daily	Apixaban, 2.5 mg twice daily
Time of last NOAC dose before catheter insertion or removal	24 h	24 h	24 h
Time of NOAC dose after catheter insertion	NR†	22–26 h	26–30 h
Time between removal of catheter and next NOAC dose	6 h	6 h	6 h

†Dabigatran is not recommended in patients undergoing anaesthesia with postoperative indwelling catheters. NOAC, new oral anticoagulants; VE, venous thromboembolism.

Neuraxial anaesthesia in patients receiving NOAC

As with all patients on anticoagulants, those receiving NOAC are at risk of developing epidural or spinal haematoma when neuraxial anaesthesia is used while anticoagulated. Patients should be monitored carefully for symptoms and signs of neurological impairment.

For patients with adequate renal function receiving rivaroxaban 10 mg daily for venous thromboembolism prevention post elective hip or knee arthroplasty, the following strategy is recommended:[25]

1 The last dose of rivaroxaban is 24 h before catheter insertion or removal.

2 The first dose of rivaroxaban is 22–26 h post catheter insertion in case of traumatic puncture.

3 First dose of rivaroxaban is no earlier than 6 h after catheter removal.

Similar strategies have been suggested for dabigatran and apixaban (Table 7).

There is no evidence regarding the safety of neuraxial anaesthesia in patients therapeutically anticoagulated with a NOAC and therefore cannot be recommended. In this situation, neuraxial anaesthesia should be avoided until laboratory testing establishes the absence of its anticoagulant effects where available or five renally adjusted half-lives of the drug have elapsed (refer to Laboratory testing and NOAC section).

Restarting NOAC after surgery[8,20]

Bleeding risk can be minimised after major surgery by adjusting the time when anticoagulant is resumed, according to the anticipated surgical bleeding risk and the extent of intraoperative or immediate postoperative bleeding. This means that for major surgery, therapeutic anticoagulation should be delayed for at least 48 h, preferably 72 h (Table 8). For patients at high risk for thromboembolism, consider administering a reduced dose of dabigatran, 75 mg once daily or rivaroxaban 10 mg once daily, starting the evening after surgery and continue until it is safe to resume therapeutic anticoagulation. Patients who are unable to tolerate oral intake can receive prophylactic LMWH (e.g. Enoxaparin 40 mg once daily). For patients at low risk for thromboembolism associated with a high bleeding risk, therapeutic anticoagulation can be delayed for greater than 72 h, particularly in view of a lack of an antidote for NOAC.

Following minor surgery where the bleeding risk is low, therapeutic doses of NOAC can be started about 24 h after surgery.

Ensure that hepatic and renal functions are normal before recommencing NOAC postoperatively.

NOAC and urgent surgery

Consider delaying surgery, if appropriate, until coagulation screen is normal or until sufficient time has passed for drug clearance. For dabigatran, haemodialysis can be considered to enhance drug elimination.[26] When urgent life-saving surgery cannot be delayed, consult with Haematology Service to discuss measures to control bleeding prior to and during surgery. For dabigatran, no haemostatic agent is known to reverse effectively its anticoagulant effect and evidence of potential benefit, particularly of activated prothrombin complex concentrate

Table 8 Postoperative resumption of new oral anticoagulants: a suggested management approach

Drug	Low bleeding risk surgery	High bleeding risk surgery
Dabigatran	Resume 24 h after surgery, 150 mg twice daily	Resume 48–72 h after surgery, 150 mg twice daily†
Rivaroxaban	Resume 24 h after surgery, 20 mg once daily	Resume 48–72 h after surgery, 20 mg once daily‡
Apixaban	Resume 24 h after surgery, 5 mg twice daily	Resume 48–72 h after surgery, 5 mg twice daily‡

Reproduced with permission from *Blood* 2012; 120(15): 2954–62.[20] †For patients at high risk for thromboembolism, consider administering a reduced dose of Dabigatran (e.g. 75 mg once daily) on the evening after surgery and on the following day (first postoperative day) after surgery. ‡Consider a reduced dose (i.e. rivaroxaban 10 mg once daily or apixaban 2.5 mg twice daily) in patients at high risk for thromboembolism. LMWH such as enoxaparin 40 mg once daily or mechanical prophylaxis such as intermittent pneumatic compression (IPC) can be considered until therapeutic anticoagulation can be re-introduced.

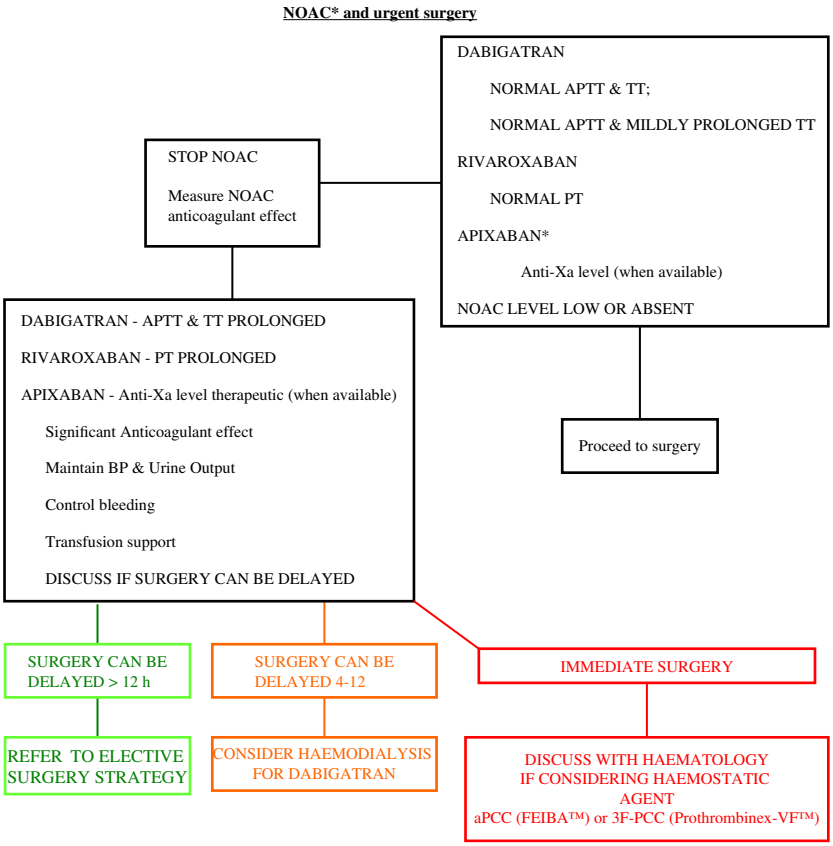

Figure 2 Suggested management of patients receiving NOAC requiring urgent surgery.
*Routine coagulation tests are insensitive to apixaban. Anti-Xa testing for apixaban is not currently available. Refer to Laboratory testing and NOAC section. aPCC, activated prothrombin complex concentrate; 3F-PCC, 3-factor prothrombin complex concentrate. APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time.

(aPCC) such as FEIBA (Baxter, Deerfield, IL, USA), is based largely on animal and *ex vivo* studies.[27–32] Laboratory tests in healthy volunteers suggest that the impact of rivaroxaban on laboratory assays of haemostasis may be reversible with prothrombin complex concentrate (PCC) or aPCC; however, whether this results in a reduction in bleeding risk is unknown (Fig. 2).[33,34] Presently, there is no 'standard of care' for the administration of haemostatic agents to achieve haemostasis with NOAC. Refer to the section on 'General principles in management of patients bleeding while receiving NOAC'.

Switching to or from other anticoagulants

Conversion with a parenteral anticoagulant

- For conversion from LMWH, start the NOAC when the next LMWH dose is due.
- For conversion from a continuous heparin infusion to NOAC, start NOAC immediately when infusion ceased.
- For conversion from rivaroxaban or apixaban, start unfractionated heparin or LMWH 12–24 h after the last dose (1–2 half-lives of the NOAC). No bolus dose of unfractionated heparin is required.
- For conversion from dabigatran, wait 12–24 h where CrCL greater than or equal to 30 mL/min, or 48 h where CrCl less than 30 mL/min, after the last dose of dabigatran before starting the parenteral anticoagulant. When the CrCl is less than 30 mL/min, dabigatran is contraindicated and LMWH are not recommended.

Conversion with warfarin

Conversion from warfarin to a NOAC. Patients who are stably anticoagulated on warfarin may prefer to remain on warfarin. However, the added convenience and the potential for enhanced efficacy and reduced risk for intracranial bleeding of dabigatran, rivaroxaban or apixaban may mean that patients will choose to transition from warfarin to one of the new anticoagulants.[8]

- For conversion from warfarin to a NOAC (dabigatran, rivaroxaban or apixaban), discontinue warfarin and start NOAC the next day when current international normalised ratio (INR) is 2.5 or less.

Conversion from a NOAC to warfarin. Some patients will not be able to continue with a NOAC. When switching from a NOAC to warfarin, it is necessary to take into account

Table 9 Suggested strategy for conversion from new oral anticoagulants to warfarin

Calculated creatinine clearance	Rivaroxaban or apixaban: time from warfarin initiation	Dabigatran†: time from warfarin initiation
Greater than 50 mL/min	Stop rivaroxaban 4 days after starting warfarin	Stop dabigatran 3 days after starting warfarin
31 to 50 mL/min	Stop rivaroxaban 3 days after starting warfarin	Stop dabigatran 2 days after starting warfarin
15 to 30 mL/min	Stop rivaroxaban 2 days after starting warfarin	Stop dabigatran 1 days after starting warfarin
Less than 15 mL/min	Consult with Haematology Service	Consult with Haematology Service

Modified with permission from *Blood* 2012; 119: 3016–23.[8] †Dabigatran is contraindicated when creatinine clearance < 30 mL/min.

that the elimination half-life of a NOAC is affected by renal function, there is a delay in the onset of warfarin effect (typically 5 days) and the INR readout may be affected by both the NOAC and warfarin. Table 9 shows suggested transition strategies.

We recommend starting with a warfarin dose of 5 mg or less. The first INR should be measured on day 3 after starting warfarin, with the main purpose to identify high levels thereby maintaining caution with ongoing warfarin dosing. Point-of-care INR monitors should not be used to assess the INR during transitions between a NOAC and warfarin. Stop the NOAC when INR has been ≥ 2.0 on two consecutive days taking into account the NOAC effect on INR.[8] Discuss with your local haematology laboratory for further advice.

Managing NOAC-related bleeding

General principles in management of patients bleeding while receiving NOAC[13,35–37]

1 Drug discontinuation – Anticoagulant should be ceased at least temporarily in all patients presenting with significant bleeding. The timing of recommencement will be influenced by the severity of the bleeding event, the presence of ongoing risk factors for bleeding (e.g. anatomical lesions, persisting renal dysfunction) and the initial indication for anticoagulant therapy.

2 Baseline laboratory assessment – Baseline assessment of haemoglobin should be performed to assess bleed severity. Standard coagulation testing (APTT, PT and TT) and where available specific drug levels should be performed to assess the contribution of excess drug to the bleeding event and to guide the need for intervention either to reduce drug level or counteract the anticoagulant effect of the drug (see Laboratory testing and NOAC section). Creatinine level should be measured to assess renal function and allow prediction of the expected rate of anticoagulant drug clearance.

3 General supportive care measures – Surgical and radiological procedures to identify the source of bleeding and to limit ongoing bleeding should be performed as appropriate, taking into account the risk of procedure-related bleeding in an anticoagulated patient. Adequate hydration should be maintained to enhance renal clearance of both dabigatran and rivaroxaban. Transfusion of red cells should be administered as clinically appropriate. Platelet transfusion should be considered in patients on concurrent anti-platelet therapy or with significant thrombocytopenia (platelet < 50×10^9/L).

4 Activated charcoal – Administration of activated charcoal should be considered in patients with moderate and severe bleeding who present within 2 h of the last oral dose of NOAC.

5 Administration of haemostatic agents – Current evidence on the use of pro-haemostatic agents in patients with dabigatran, rivaroxaban or apixaban is limited and conflicting. aPCC (FEIBA) and four-factor PCC have been shown to reduce bleeding in animal models with variable effect on coagulation parameters in animals, healthy volunteers and *ex vivo* NOAC patient plasma samples spiked with haemostatic agents, with recombinant factor VIIa (rFVIIa) demonstrating a less consistent effect.[27–34,38–40]

The risk and benefit of administration of such agents should be assessed in each individual patient. Due to the limited data supporting efficacy and potential for thrombotic complications, use of these pro-haemostatic agents should be restricted to patients with life-threatening bleeding unable to be managed with supportive measures alone. FEIBA appears to have a more consistent impact on haemostatic changes associated with dabigatran and the factor Xa inhibitors than other agents,[32–34,38] but clinical evidence for its use in patients with bleeding while on these agents remains limited.[41] PCC have been demonstrated to be able to reverse the laboratory anticoagulant effect of rivaroxaban, but in a small series appeared ineffectual in patients with bleeding on dabigatran.[42] In Australia and New Zealand, only three-factor PCC (Prothrombinex-VF, CSL, Melbourne, Vic., Australia) is available and its efficacy in the new anticoagulant drugs has not been evaluated.

The advice to use either FEIBA or Prothrombinex-VF in patients with active life-threatening bleeding while on the NOAC is therefore opinion rather than evidence based at present. Guidelines are likely to evolve rapidly as more specific measures become available. Generalsupportive measures should not be neglected, and

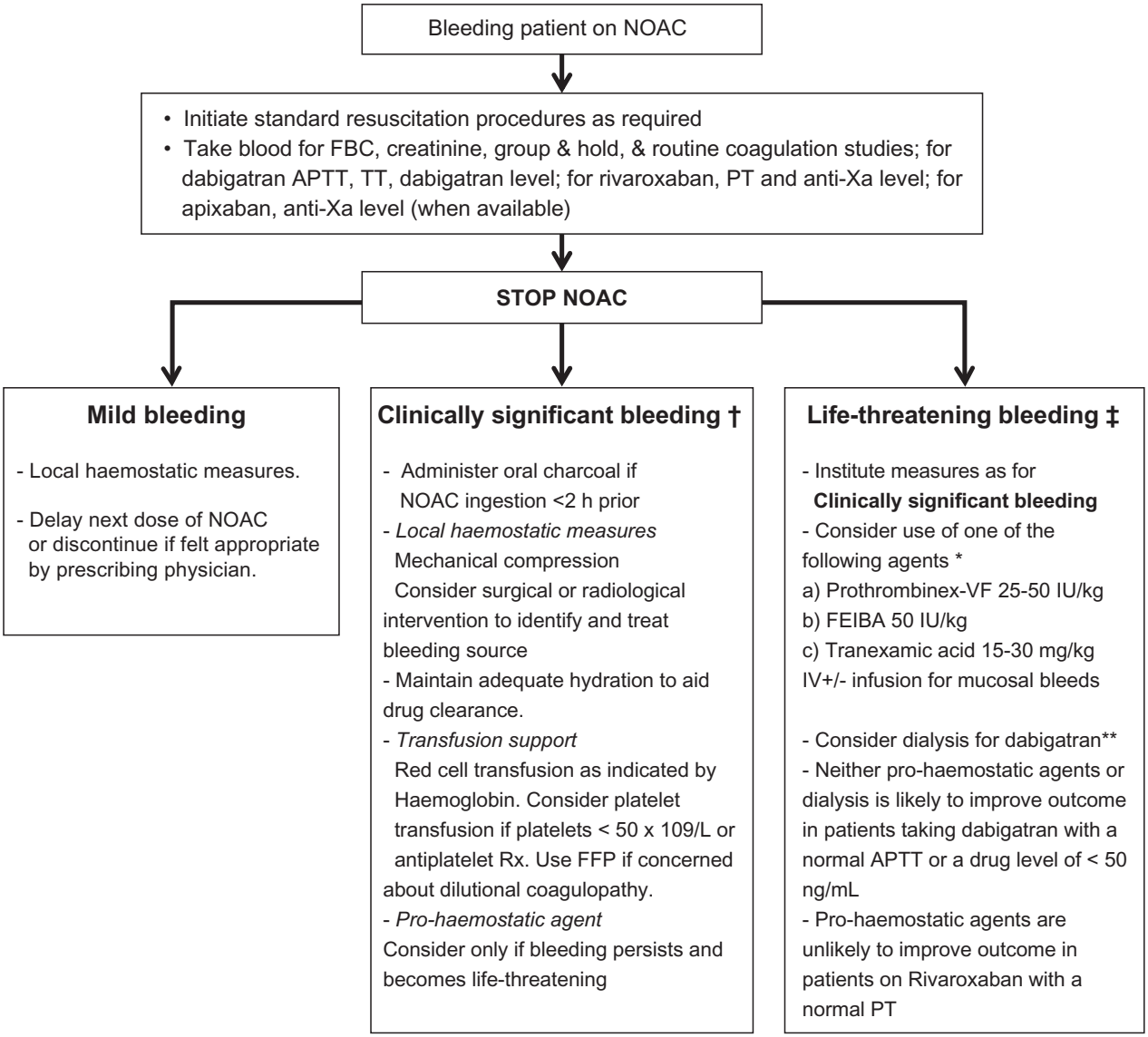

Figure 3 Management of new oral anticoagulants (NOAC)-associated bleeding.[26–31,33,34] †Clinically significant bleeding – reduction in Hb ≥ 20g/L, transfusion of ≥2 units of red cells. ‡Life-threatening bleeding – bleeding in critical area or organ (intraocular, intracranial, intraspinal, compartment syndrome, retroperitoneal or pericardial), hypotension not responding to resuscitation. *This is an off license use of FEIBA and Prothrombinex-VF and the risk of thrombotic complications with these agents when used for this indication is unclear. Their use is supported by laboratory data but clinical evidence supporting an improvement in clinical outcomes is lacking. **Dialysis is indicated if dabigatran level is high as indicated by excessively prolonged activated partial thromboplastin time (APTT) > 80 s or dabigatran level > 500 ng/mL and/or impaired renal function. Four hours of haemodialysis will reduce drug level by ~60%.[26] FBC, full blood count; FFP, fresh frozen plasma.

consideration for dialysis in patients with life-threatening bleeding and high plasma dabigatran concentrations should not be delayed by the use of pro-haemostatic agents (see below). We do not recommend the use of rFVIIa, based on less consistent data on its ability to reverse anticoagulant effect derived from animal and laboratory models, and its association with risk of thrombosis when used outside patients with haemophilia.[43]

6 Dialysis – Dialysis may be considered where available in patients receiving dabigatran with life-threatening bleeding, particularly if renal function is impaired or dabigatran is present in excess (APTT > 80 s or dabigatran level > 500 ng/mL).[26] There is no role for dialysis in rivaroxaban- and apixaban-related bleeding.

Figure 3 shows the suggested algorithms to manage NOAC-related bleeding.

Conclusion

New oral anticoagulants are being used increasingly to manage patients with AF and VTE. A thorough understanding of their pharmacology in conjunction with practical guidance on their usage should lead to ongoing safe implementation.

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